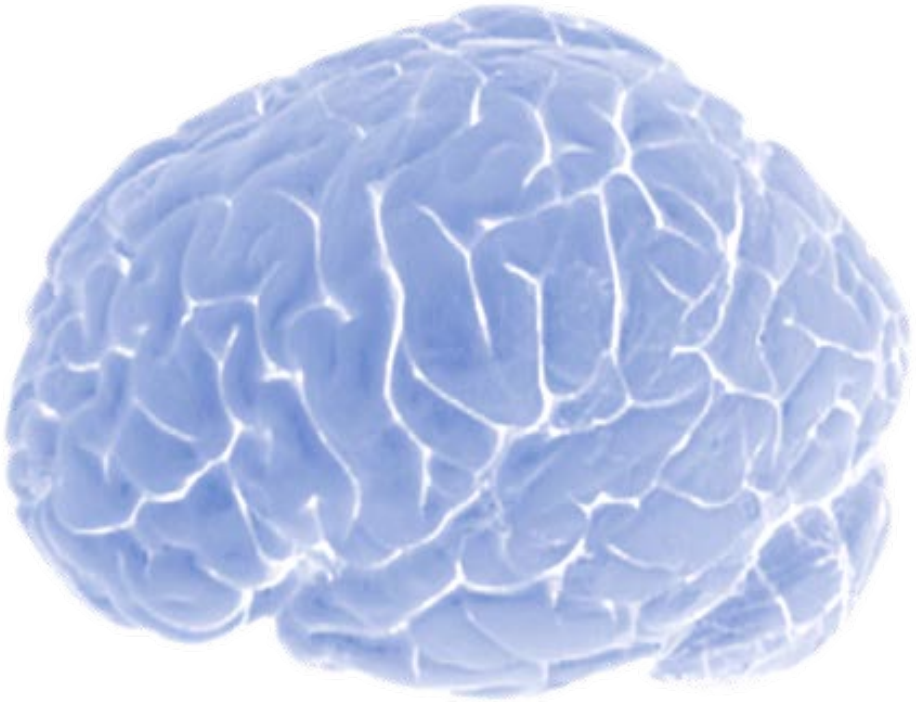
Gray Matter on My Mind

Brains Wired For Survival & Success

Neuroscience for the Health Professions



George E. Carvell, PhD, PT

1st Edition

All humans (and small dogs) are free to read and contemplate the text and figures contained within this ebook. You may use this material in a strictly non-commercial fashion for teaching purposes or for reference as long as you provide the appropriate Creative Commons attribution of this scholarly work (whose writing only took about 2.3 decades to complete). Enjoy!

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Forward

There are many excellent textbooks written for neuroscience instruction. Gray Matter On My Mind (GMOMM) is written for readers who have little or no formal background in neuroscience but want to discover something about the very organ they use to learn.

I'm writing from the perspective of a neuroscience teacher and researcher with a systems level approach rather than a molecular approach to nervous system concepts and principles. Furthermore, I've placed emphasis on information that may be most relevant to those who aspire to be, or are, healthcare professionals that choose rehabilitation as the entry point into patient care. I've included "classic" information as well as more recent discoveries that build on or challenge the "classics." As an instructor, I find teaching neuroscience to be a wonderful challenge to make such information accessible to students at many levels of education: from undergraduate to graduate predoctoral, doctoral and professional doctoral students.

I do not have a mathematical mind although I have great respect for those who understand nature "by the numbers." I use what one might call a "mechanistic" approach. I've found most learners I have encountered can follow and use this approach as an analogy for often complex processes that are likely to be probabilistic (mathematically speaking) in their actual occurrence.

Also you may notice I provide a sprinkling of humor in my writing much as I do in the classroom because an engaged brain retains a sense of humor even if it is not explicitly expressed for others to appreciate. Of course many topics related to nervous system dysfunction are deadly serious for the healthcare provider as well as for the patient and are treated as such. Many students find science to be "dry, abstract, intimidating, irrelevant, boring, esoteric, incomprehensible, etc.' and neuroscience, in particular, to fit all those descriptions and worse.

However, if the nervous system can be presented as a dynamic structural and functional entity, the learner will tend to be more engaged in and out of the classroom. That's why I've included many movies and interactive media to make points about particular dynamic concepts or processes. I may not be the sharpest tack in the pack of neuroscientists but I do have a point that, pushed hard enough by inquisitive students, can attach a memo to their cerebral gray cork boards. Note: I know grey is a classic spelling of this color but as an anatomist I prefer gray.

GMOMM does not tell you everything you need to know about neuroscience; such a book has yet to be written. I'll never be able to provide a comprehensive picture at all levels of research in this enticing field of study. As a researcher I have moments of exhilaration in discovery but everyday I am humbled by the extraordinarily complex "simplicity" of nature.

I hope you learn something about the wrinkled organ in your cranium from this introduction to neuroscience, and that it entices you to continue your investigation and/or the application of your knowledge for the benefit of those individuals who need expert assistance to regain function following assaults to their nervous system due to disease or injury.

Preface

This Gray Matter On My Mind (GMOMM) neuroscience ebook includes links to dynamic media that directly complement the text and static images. Where figures link to the dynamic media (movie or interactive file) web links will be provided in the figure caption. Your web browser must support the particular media type to open it in a separate web browser window. Interactive media files have been converted from a flash format to a Swiffy (Google, Inc.) file that will open in html5 compliant devices, including the iPad. The interactive media web link will open the media in a separate web-browser window.

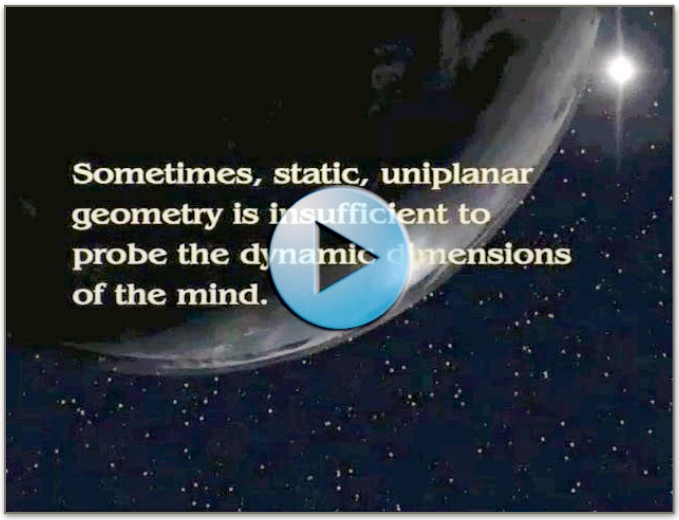
A number of spinal cord and brain anatomy figures are derived from instructional material used in my neuroanatomy lecture and laboratory teaching (past and present) at the University of Pittsburgh.

Smalldog_Introduction_Video

You may open this ebook draft with a pdf reader on a mobile device, laptop computer or desktop computer (Windows or Mac). The **mp4** Videos should play if your web browser supports html5 content. If you use an ebook mobile device you should use an e-reader that does not block web links within the document. Interactive media files were converted using an Adobe extension (Swiffy) created by smart people at Google, Inc. These converted flash files are accessed by links marked as **Interactive Media** files (performance varies across devices). Throughout this ebook any figure image that has the blue play button has a link to open an **mp4_video** (requires html5 enabled web browser). The video player "skin" for the **mp4** movie is dependent upon each device's playback properties of the mp4 videos. Playback of default html5 mp4 video may vary depending upon the operating system of your mobile device, the speed of your web connection and the hardware device's web browser support of this video format. Three dimensional virtual reality (**VR**) movies of the brain, brain models, head and cranial vault have been converted using Object2VR software (Garden Gnome Software ®, Vienna, Austria), from a previous Apple QTVR format. The converted Object2**VR** Movies play on all devices that support html5 compliant web browsers that do not block Java scripts. Download and Playback of **VR** movies may differ across web browsers, devices, operating

systems and internet connection speeds. The local GMOMM search file and all copyright protected movie and interactive media files reside on a University of Pittsburgh secure server location- **http://gmomm.pitt.edu**. The search feature for this web site allows you to choose a particular figure and, where applicable, its media link(s). All media are copyright protected, with a hyperlink related to the appropriate figure in the GMOMM ebook.

The following movie "*Wormholes and 4 Dimensional Space: Expanding the Dynamics of the Mind"* is an example that has both audio and video content. This formatting is repeated throughout this digital GMOMM ebook. The caption for the Wormholes and 4 Dimensional Space image below contains a link that opens a "default" html5/**mp4** video file.



Wormholes and 4 Dimensional Space: Expanding the Dynamics of the Mind (gec,jec,dh). GO TO: gmomm.pitt.edu Dynamic_Brain_Geometry_Video

The following 3D VR Movie is an example of 3D brain VR Movie content. This 3D VR video (movie) link formatting is repeated throughout this digital GMOMM ebook.

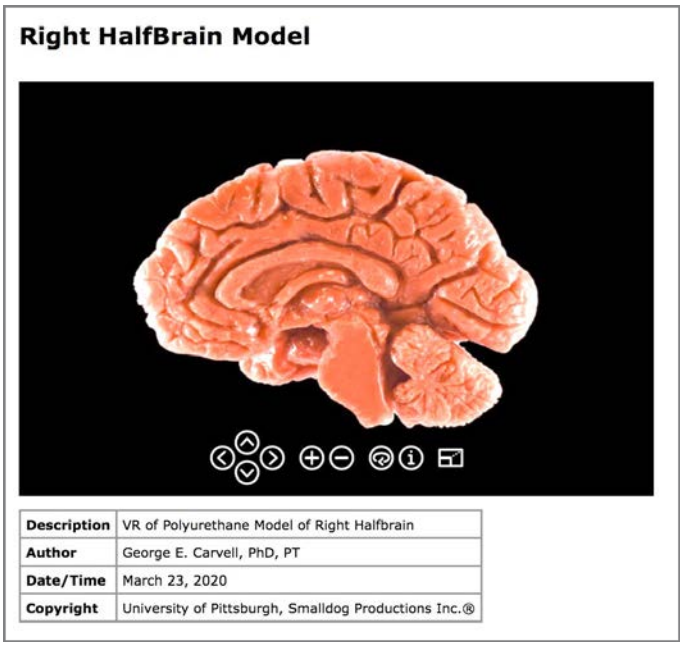


Fig 00-00. Right Halfbrain 3D Polyurethane Rubber VR Movie. The control buttons for the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen.(gec). GO TO: gmomm.pitt.edu Fig1-2VR_MOVIE

Acknowledgements

I first want to thank my former Dean, Clifford Brubaker, PhD, School of Health and Rehabilitation Sciences, University of Pittsburgh who supported my efforts to develop this approach to neuroscience instruction. Dean Brubaker provided assistance to me as I began this endeavor in the 1990s even though I was but a "babe in the woods" in the computer-assisted creation of dynamic electronic content.

I appreciate the fantastic support and interest in my Smalldog Productions, Inc. ® by staff at the University of Pittsburgh Innovation Institute. In particular, I thank Carolyn J. Weber, RPh, MBA. The professionals at the Innovation Institute understand the challenges of intellectual property issues, the transfer of this technology into the private sector and they have supported my efforts even though Smalldog Productions, Inc.® is such a small under-resourced company.

There are a number of individuals who were instrumental to creation of some of the early dynamic rendering when I started building content in 1997. Graphic static images and dynamic media (movies and flash files) have been created by a number of individuals. Dave Hopson (dh) helped create a few of the early 3D animations. Jonathan E. Carvell (jec) assisted in videography in creation of the original 3D QTVR movies: they were converted to html5 compliant 3D VR movies by the author (gec). Jonathan was the subject for a number of movies regarding active touch and kinesiologic EMG. In addition, he assisted in the creation of a number of animations illustrating clinical concepts. Jason A. Carvell (jac) provided the sculpted skull and cranial vault by precisely reconstructing soft tissues with clay placed upon a skull plus cervical vertebrae. Jason provided several other drawings. George E. Carvell (gec) wrote all text, created all interactive media files and created all text-based and graphic-based conceptual representations of information illustrated in all static figures and dynamic movies and he rendered all of these still images and movies. Each figure legend includes the initials of the person or persons who contributed to the construction of the static or dynamic graphic.

Many professional colleagues have kindled my thinking about the vast topic of neuroscience particularly related to applying basic principles to clinical practice. Peer-reviewed publications & texts as referenced in each chapter were vital to my formulation of ideas presented in this book.

Students in my classes ask challenging questions and provide feedback about my classroom or laboratory instruction. These two essential elements help me alter my approach to better present difficult principles and concepts. A "blank stare" by an otherwise alert, oriented, bright student or colleague is a trigger for me to try another way to engage all students and to rethink my explanation of the information by altering text and/or graphics. A reciprocity between engaged brains of students and my presentation of neuroscience in an academic setting maintains a fluid evolution in my teaching and understanding of neuroscience adapted for health professionals.

George E. Carvell, PhD, PT, Professor Emeritus University of Pittsburgh, May, 2022, Pittsburgh, PA, USA

Chapter 1

INTRODUCTION TO THE MAMMALIAN NERVOUS SYSTEM

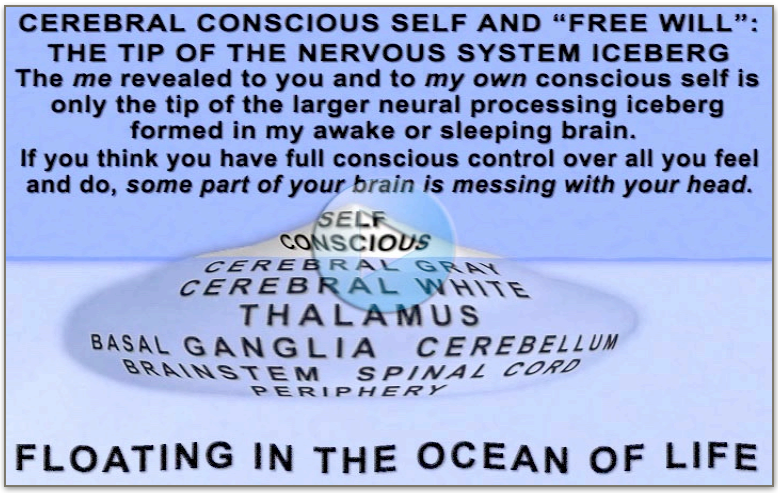


Fig 1-1. Your Conscious Self: Only The Tip of the Neural Iceberg (gec). GO TO: gmomm. pitt.edu *Fig1-1_Video*

A brain sure you have-but is your mind in there?

This question is not meant as an insult, nor is it a trivial query, since a clear majority of neuroscientists describe some equivalence between the brain and the mind, while a minority do not (see references). Rene Descartes is often referenced as a dualist where the mind and the physical being are seen as separate entities. However, Descartes describes a case where a young girl had progressive gangrene of the hand leading to amputation of the arm at the elbow. He states that the amputation was done without her knowledge (how did that happen?) followed by adding cloth bandages lengthened to simulate the missing limb. The young girl complained of pain in various missing fingers following the amputation (what is now known as phantom pain). Descartes uses this example to argue that our senses are not experienced in the body but in the mind. *However*, the mind does seem have a physical location for Descartes: the brain. He summarizes his interpretation of this case in the following way "[And this clearly shows that the pain of the hand is not felt by the mind in so far as it is in the hand, but in so far as it is in the brain.]" Descartes, Part IV, CXCVI, p. 114, Selections From The Principles of Philosophy; Principles of Philosophy originally published in 1644. The mind has a physical location: the brain. By analogy, a code-based digital operating system (software = mind?) is useless unless it is matched to a compatible silicon-based electronic device (hardware = brain?) that "runs" the digital code. Operational System (OS) Codes are matched to the physical device, e.g., Apple iPhones don't run a Google Android OS. *Likewise, shrinking your brain and transplanting it into the cranial vault of a squirrel would likely not go well for you or the squirrel. What does "free will" look like for a squirrel with a shrunken human brain/mind? Is this a story-line for a blockbuster animated movie?*

So, some might suggest your *mind* represents (or is) the product of your remembered experiences, relationships, moods, wants, drives, thoughts, skills and a particular view of the world (with you in it). The *brain* is a real biological structure that resides in a defined physical location transported by the body it comes to know so well.

How brain and mind relate is not *now* easily resolved by currently available physical measurements of brain activity. So your mind may be *in there* or is just simply *there*.

The mind is often characterized as an invisible entity, known to some degree by its owner but becomes apparent to everyone else only by the actions, gestures and thoughts shared by that mind with others. Even then my interpretation of your mind may not be entirely accurate, since my own conscious experiences or subliminal biases outside of consciousness may subtly or substantially flavor my interpretations of the thoughts, actions or gestures of others. Moreover, cognitive neuroscientists suggest that a majority of brain duties are completed without conscious awareness by the brain's owner, e.g., see Custers & Aarts, 2010; Fuster; 2013; Gladwell, 2005; Roskies, 2010. Our conscious self and our expressions of "free will" are but the tip of the iceberg in the complex and often hidden neural processing within our brains. We are *not* consciously aware of most brain activity responsible for engaging our bodies with our surroundings *nor* are we consciously aware of many internally generated decisions *nor* do we consciously attend to the plethora of sensory information associated with our actions.

First impressions may come around only once but they may completely miss the mark and distort one's feelings about a person we are meeting for the first time. Moreover, if injury or disease disrupts your complex neural processes then to some extent altered higher brain structure/function may result in you *losing your mind* to one degree or another. Some would suggest that despite our best efforts to prevent such a tragic state of affairs, it may indeed happen for many of us to some degree as we become eligible for membership in AARP (we hope our expiration date and loss of cognitive abilities will be coincident events in the distant future). Recent research suggests that healthy aging is associated with compensatory biochemical changes that allow the mature owner of the body/brain to live quite successfully even if the brain circuitry and electrochemical links to the more mature body are most certainly different from a younger self (we adapt to age-dependent physical and mental "maturation"). A human mind (brain) regardless of age uses critical neural resources to generate four key processes for individualized success: *creativity, selectivity, initiative and focus*. Age likely influences the brain's strategy for generating and controlling these processes.

So, are you a glass half full, or glass half empty brain/mind owner? Now that you are either charged up to learn more or are totally depressed, you will be introduced to the astounding bio-electro-chemical system that provides the fundamental wiring for mammalian survival and success across the lifespan of the individual and the species.

First, a word (actually many words) about science as an intellectual noncommercial venture. When a scientist is interviewed by the media about an exciting discovery (typically something chosen as "sexy" from the vast expanse of more *mundane* scientific endeavors), you may often come away with this impression: the scientist has great confidence in his or her answer. Although the interview often ends with the caveat "*more research must be done*," this is only the tip of the intellectual iceberg. Watching a

dedicated scientist at work provides an entirely different perspective. **Definitive proof** of a theory or hypothesis is often an elusive target in science. A single study is not proof. Replication of a study's findings strengthens the argument and advances knowledge. A scientist who does not acknowledge this important qualification of our current understanding of nature is overstating his or her conclusions.

Scientists by their very nature are inquisitive people who typically see science as more of a matter of formulating testable questions to advance our understanding rather than providing a *final* answer to complex phenomena in nature *(truth)*. More often than not, research findings lead to *incomplete answers* that, in turn, provide more *refined questions* and *new approaches*. Dedicated scientists and clinician-scholars have repeated "*scratch your head-what does that mean?"* moments in the laboratory or clinic. If the scientist scratches her head but then does nothing, that will not lead to progress. If the head-scratching leads to action, progress may be made. On the other hand, if she scratches someone else's head without permission she may become quite unpopular.

Science is the intellectual "itch" that keeps on returning to the curious. *The cure is not a lotion or potion but is the scientist's incentive driving that curious individual to take demonstrative action and to persevere in the face of daunting challenges, both intellectual and fiscal.*

THREE BASIC PRINCIPLES TO REMEMBER

Here are three fundamental principles to begin your study of neuroscience:

1. ***Normal cell physiology is like "Goldilocks and the Three Bears."*** Typical mid-range use is "just right" while the extremes (too hot or too cool) provide important cues for more "radical" adjustments. Multiple buffers and intrinsic cellular repair mechanisms are critical in this regard providing continuity of function under extreme circumstances. In addition, neural networks appear to use this Goldilocks principle for optimal function, at least in auditory cortex of mice, e.g., see McGinley, et.al., 2015.

2. ***Normal adult mammalian brain function is a tenuous balance between order and entropy.*** Order requires precise but adaptable connectivity. Entropy arises from variability in stochastic "analog" processing and from more diffuse global influences within a distributed system. Many neural networks within our brain have mechanisms that support some degree of self-organization: see Waterfall Order Entropy and Waterfall Whirlpool Movies below.

3. ***Life as we know it appears to be a product of nature's lottery.*** Scientists attempting to unravel nature's "rules" depend on informed 'hunches', hypothesis-driven trial and error investigative processes, rethinking questions based on new data and some luck (some clever individuals turn their luck into serendipity and perhaps a Nobel prize). By definition, nature's lottery introduces a capricious element to the process of discovery. Moreover, the incredible persistence of life itself depends upon

a molecular structure (DNA) which alone is not alive in a biological sense until it is incorporated within a carbon-based living being.

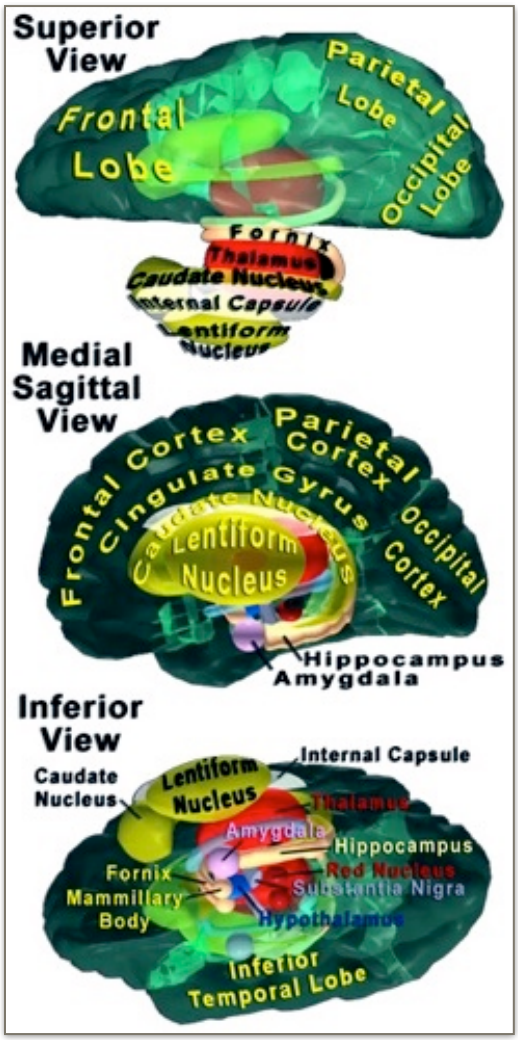
MAMMALIAN NERVOUS SYSTEM: THE SOPHISTICATED MESSENGER

The intact mammalian nervous system functions properly only by cooperative interactions among connected neurons. Excitability by itself is a necessary but not sufficient condition to build an organ that can control the carbon-based mass where it lives; neural communication within that mass provides the necessary means to that end.

Some connections among neurons are restricted to a small local cluster of cells (local network). Other neuronal networks use massive white matter "cables" to link one brain area to another (long-range binding of distributed networks). Connected networks from the top of the brain to the bottom of the spinal cord provide the "bioelectric-chemical" system to interact with, learn about and adapt to a changing world. Despite the enormous progress made over the past 150+ years, neuroscientists have not agreed upon a single unifying construct regarding all neural events leading to human conscious perception. Considering the enormity of the challenge (billions of neurons and trillions of connections) this should not be surprising.

> Consider this illustration:
>
> Pet a dog [one that you can trust and likes to be petted]. When you stroke the dog's fur, where does the touch sensation seem to be coming from? You experience the touch as if it occurs at your fingertips and palm (where contact occurred). However, the actual location of the neural processing that reveals the perception to you is in your brain which has no sensory receptors for touch.
>
> If a neurosurgeon touched your awake brain (not the overlying meninges) you would not know it. If the neurosurgeon applied a 0.5 sec train of brief electrical pulses to the correct part of the brain that interprets touch information, you would experience some sensation from the appropriate body part even if it felt unusual. Although your brain lacks sensory receptors it "feels" what you touch with your hand. For this sensation to rise to conscious awareness some suggest that neural activity within multiple brain areas must be sustained for at least 0.3 to 0.5 seconds before one is fully aware of the event. Others suggest conscious awareness may **begin** to arise within about 0.15 to 0.2 seconds. Despite some apparent delay in awareness, your brain may retrospectively place the event at the actual instance of the tactile contact and "project" the sensation to an inferred skin location, e.g., see Cauller & Kulics, 1991; Engbert, et.al., 2008; Libet, et.al., 1967; Libet, 2004; Mountcastle, 1980. Feeling related to touch is a much richer experience than just a tactile sensation. Many

individuals will experience also some emotional overtone in their brain/ mind when petting a friendly animal. This feeling is layered on the warmth and texture of the fur that you can recognize by active touch. If you deem such an encounter as a pleasant experience, you (and your dog) may have autonomic changes such as a reduced heart rate and lower blood pressure. Besides your sensorimotor systems, your limbic system, insula, brainstem neuro-modulators and neuroendocrine system are involved in biological feelings. Such individual, subjective feelings enrich our lives but are difficult to localize at a high level of resolution to any single structure within our brain circuitry using current methods, e.g., see Craig, 2002, 2009; Damasio & Carvalho, 2013; Solms & Turnbull, 2002. Moreover, your brain is not a blank slate upon which each sensory experience is written anew. Prior experiences influence what you feel in a Bayesian sense such that perceptions are influenced by both external sensory data and by probabilistic intrinsic "expectations", e.g. see Blankenburg, et.al., 2006; Geldard & Sherrick, 1972, 1983; Goldreich & Tong, 2015; Price, 1763.



Your brain "creates" this complex series of neural events from such a simple encounter between two carbon-based biologic entities (man and man's best friend). This is an active process such that one or both entities willingly seek it out, i.e., it is an intentional behavior driven from within your brain(s). Now imagine a neuroprosthetic device (e.g., brain machine interface) that could restore this complex experience following loss of sensation in the fingers and/or loss of voluntary control of the petting hand.

Fig 1-2. Superior, Medial Sagittal and Inferior Views extracted from Deep Visible Brain VR Movie. The control buttons for the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen. There are Three HotSpots; each will open a linear mp4 movie in a separate browser window to label: 1. Diencephalon, 2. Basal Ganglia and 3. Limbic Structures (gec). GO TO: gmomm.pitt.edu Fig1-2VR_MOVIE

To those interested in *studying the organ they use to study*, a full appreciation of the magnificent brain cannot be realized unless you can see it as the dynamic four-dimensional structure (three spatial and one temporal dimension) that it is. Figure 1-2 shows three static views extracted from a 3D VR movie. The figure labels key outer and inner structures of a constructed digital model of the human brain.

BRAINS OF MICE TO MEN: EXPANSION OF NEURAL NETWORKS

The nervous system provides: 1.) a link between you and the external world, 2.) a means of moving within your environment, and 3.) a network of cells that allows you to think, create and interact with others at many levels of sophistication. The Central Nervous System (CNS) includes the brain and spinal cord. The CNS is a floating powerhouse of information acquisition, data interpretation and creator of actions. The brain and spinal cord are surrounded by a clear lake (cerebrospinal fluid) that bathes and protects your mobile "processors": don't try this with your smartphone, tablet or laptop computer. The Peripheral Nervous System (PNS) includes neural components located within the non-neural tissues extrinsic to the CNS plus anatomical connections with CNS nerve cells (neurons). The PNS provides the link between central neural codes for what we do and the peripheral end organs responsible for generating movements and secretions. It also links peripheral sensory organs that transduce non-neural energies into neural codes to inform you about your internal and external world.

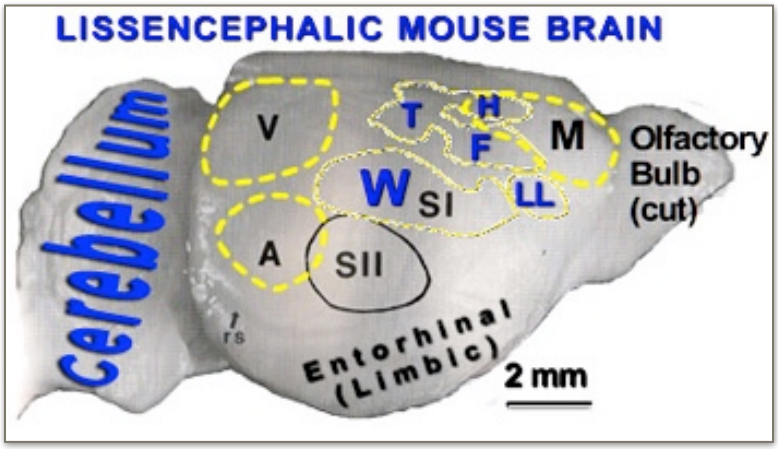


Fig 1-3. Mouse Brain: A = Auditory Area, V = Visual Area, SII = Second Somatosensory Area, SI = Primary Somatosensory Area: F = Forelimb, H = Hindlimb, LL = Lower Lip, T = Trunk, W = Mobile Mystacial Vibrissae (Whiskers), M = Motor Area, rs = rhinal sulcus G.E. Carvell, unpublished photo (gec).

Compared to rodents as small mammals with lissencephalic (smooth surface) brains, higher primate cerebrums represent the dramatic expansion of neural networks contained within big gyrencephalic (folded surface) brains, e.g., you fold your shirt (brain) to fit it into your suitcase (skull).

Note a ten-fold order of magnitude difference in scale bars for the smooth lissencephalic (Mouse) versus the "wrinkled" gyrencephalic (Human) brain figures. Mice and rats have relatively poor eyesight but as nocturnal animals have sophisticated olfactory and tactile sensory organs supporting survival skills. Note the relatively large

area of the rodent brain for smell (olfactory bulb) and somatosensory representation for face, especially the mystacial whiskers in the rodent's limited cerebral cortex.

Primates have excellent vision: many neural networks are wholly or partially devoted to visual processing in the superficial cerebral gray matter. In addition, human cerebrums have greatly expanded "association" cerebral cortical areas that provide the wiring for both survival and success at a level that far exceeds that of sub-primate species. Success here is defined as the individual expression of abstract, creative thoughts and translation of those ideations into highly skilled behaviors, e.g., language, human gestures, manual dexterity and other nonverbal precision actions.

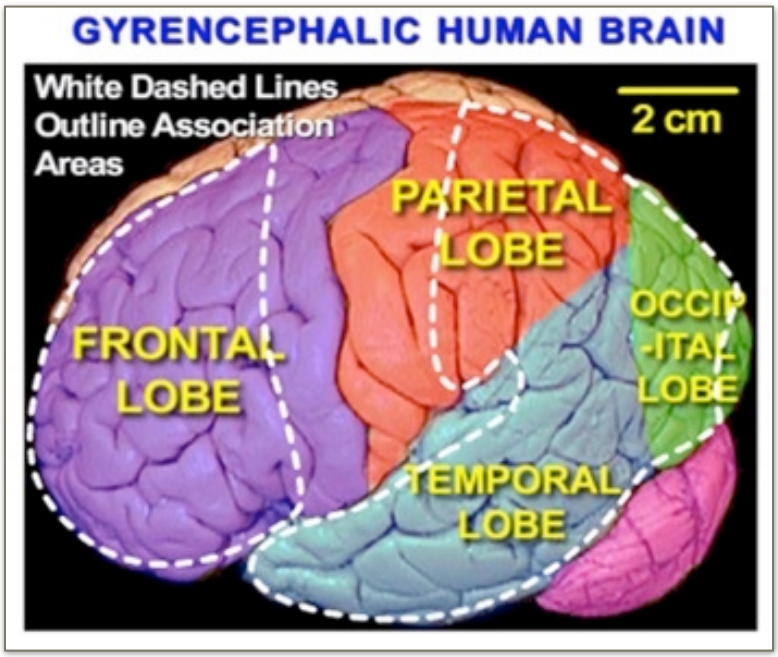


Fig 1-4. Gyrencephalic (folded) human brain: lateral view of cerebrum and cerebellum. The gray matter located within the dashed white line borders is called association cortex for integrating complex neural events. Cerebellum (inferior to cerebrum) is "pink" in this colorful figure. Note the difference in scale for this figure versus the mouse brain figure above (gec).

YOUR NERVOUS SYSTEM IS NOT A COMPUTER BUT IT CRUNCHES NEURAL DATA NONETHELESS

The human brain feels, sees, hears, thinks and does its will. The basic computer detects inputs, "crunches" data & generates logical outputs. Some digital devices have been programmed to be so clever one might be tempted to think they are *alive.* Artificial Intelligence (AI) scientists are attempting to bridge the gap between carbon-based neural processing and silicon-based computational processing.

The nervous system is our "bioelectrochemical" system that:

1. powers our actions, secretions, thoughts, expressions & gestures.

2. makes us aware of ourselves, other living beings & our surroundings; provides an internal "virtual" representation of "reality."

3. defines us as a species, empowers us as individuals, and allows for conformity or change (novelty) based upon judgments of relevant external and internal conditions.

4. provides the neural basis for creativity, abstract reasoning, our personal "history" and the will to "be," to "do" and to "feel."

If our computers functioned like biological neural networks these silicon 'brains' would not put up with the inherent delays, "hidden" data and "best guess" interpretation of afferent inputs or generation of outputs that contain jitter and lag; we expect consistent "behavior" from our desktop or laptop computers and mobile digital devices. By contrast, neural processes creating biological behavior rarely show such digital computational consistency from one trial to another even if the outcome appears to be predictable on its surface. This variability in brain network solutions to life's challenges indeed may be one critical element that makes biology so adaptive and resilient within an environment having unpredictable levels of entropy, e.g., see Deco, et.al. 2011.

Likewise, we might like our brains to do logical sequences and complex number crunching at supersonic speeds, but we would not be happy when in the middle of the day our brain must reboot because our BOS (Brain Operating System) has a fatal error. Nevertheless, our slower brain processors do have adequate time to react to variations in our environment and to alter our internal state within a fraction of a second or, within a different timeframe, to adjust neural processing over a lifetime (see below).

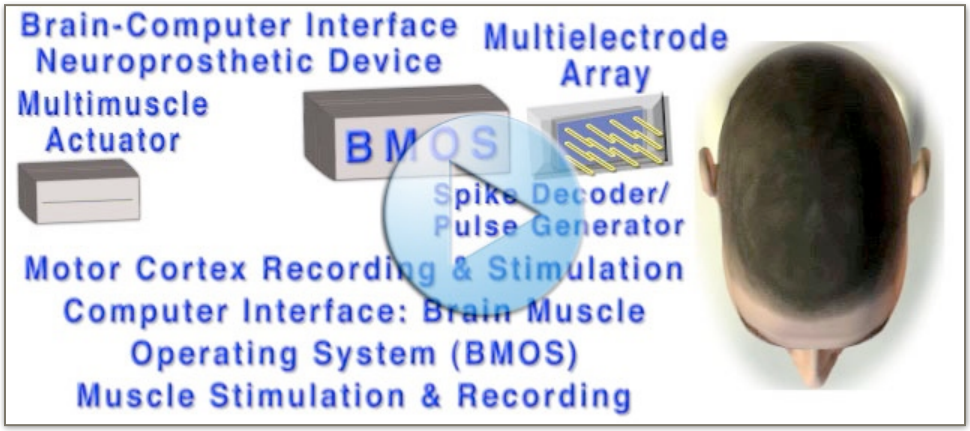


Fig 1-5. Hypothetical Brain Computer Interface Movie (gec). GO TO: gmomm.pitt.edu Fig1-5_Video

We currently upgrade our nervous system by the relatively slow process of development, maturation and adaptation: "exposing" our brain to new experiences and learning opportunities. Most of our neural networks have cellular and sub-cellular mechanisms for neural plasticity. At present, we can't purchase new brain hardware or software, plug-in a thumb-drive nor can we simply download updates to fix bugs in the programming. Perhaps it is for our benefit as a species that the "algorithm" used by my brain is not identical to that used by your brain when complex networking takes place to solve a difficult problem or to be creative. Some level of stochastic processing has allowed biology to evolve and, when conditions are right, to flourish in the face of daunting challenges to our being.

Who knows perhaps in the future there will be an "*app*" on a digital device no larger than a smart phone that literally helps you to move using short-range, secure wireless

connectivity. There is of course a potential downside to this AI technology. The device must be reliable and secure: *you would not want hackers stealing your identity and possibly your very ability to report the incident*.

Today silicon-based computational devices and carbon-based thinking devices are separate entities (with a few exceptions, e.g., cochlear implants, deep brain stimulators, exoskeletal walking devices), but in the future, there is likely to be greater inter-digitation as "man-machine" cybernetic, carbon-silicate and other material composites: a Brain-Machine Interface (BMI), e.g. see Wander and Rao, 2014; Capogrosso, et.al., 2016; Rivnay, et.al., 2017.

LIGHT UP MY BRAIN?: EXPERIMENTAL OPTOGENETIC APPLICATIONS IN NEUROBIOLOGY

It is now possible to experimentally activate neurons in the brain by using light pulses rather than electrical pulses. These experimental procedures in animals take advantage of the genetic manipulations of neuronal DNA and the use of introduction of fiber optic delivery of laser light filtered to emit specific wavelengths. Light-sensitive transmembrane protein complexes that open an ion channel (opsins) can be incorporated into neuronal membranes. One example is channel rhodopsin (CHR2). When activated by light of the appropriate wavelength a Na^+ ion channel is opened in the opsin protein complex. Opening these channels depolarizes the neuron. Alternatively incorporation of halorhodopsins (HR) into a neuron will tend to hyperpolarize the cell due to opening of a Cl^- ion channel when activated by light at a different wavelength. Opsins are typically incorporated into a neuron's membrane due to 'transfection' of the cells with a virus or bacterium that has been genetically altered to express the opsin. By injecting the opsin-containing virus or bacteria into a particular brain region the microorganism is incorporated into the cell, activates the neuron's DNA to replicate the virus and thus provide an abundant supply of the opsin. The opsins are incorporated then into the neuronal membrane. Such infected neurons will then respond to light pulses of the correct wavelength. Many of these opsins have fast-acting ion channel kinetics. The opsin channels may be expressed in different neuronal components. By injecting the correct virus in one area of the brain the opsins will be expressed in the axons and axon terminals in other brain areas to which the infected cells project. For example, one could inject a deep brain nucleus such as the thalamus and then apply light pulses via a fiber optic probe in the appropriate region of the cerebral cortex to activate the opsin-containing thalamic axons/axon terminals. Tagging specific cell markers allows scientists to target specific cell types as well. Currently, there are many limitations in these methods that preclude application in humans. For example, depending upon the wavelength, most light pulses do not penetrate brain tissue more than ~ 0.5 mm with any appreciable degree of light power. Introducing the opsins requires genetic manipulations of "foreign" microorganisms that are injected into the brain. This all suggests that the future could include such optogenetic manipulations

applied to human neuropathological conditions. Other techniques use Ca^{++} imaging to detect depolarizing influences in single cells and neural networks. However, it may not be time yet for me to offer my brain for such experimental procedures (don't light up my brain just yet)! Optogenetic approaches are well established in the mouse model but such techniques are just emerging for other species, e.g, marmosets (small "primitive" primates), see Kim, et.al., 2017 for recent review. Such technology may provide high resolution mapping of specific neuron types, e.g., see Furth, et.al., 2018.

NEUROEMBRYOLOGY: AN ONTOGENETIC OVERVIEW OF NERVOUS SYSTEM ORIGINS

The nervous system is differentiated early *(many of these cells define their life's work and often their place of employment before they go to school)* and is derived from the ectoderm of the embryonic disk.

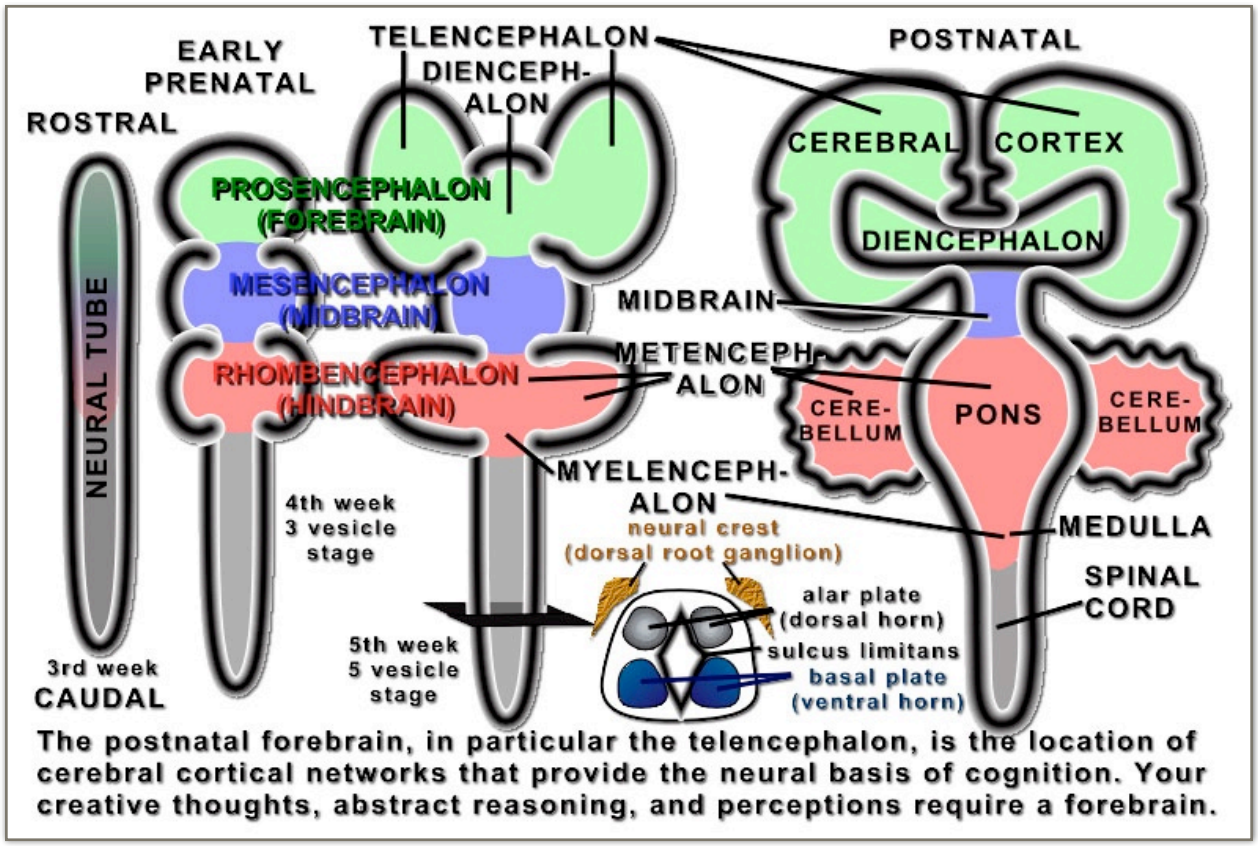


Fig 1-6. Neuroembryology Basics (gec).

The embryo observed from above contains three layers: the ectoderm (top), the mesoderm (middle) and the endoderm (bottom). The endoderm will develop into visceral structures, the mesoderm will develop into musculoskeletal structures and the ectoderm gives rise to the skin and the nervous system (neurectoderm). The nervous system at this early stage is composed of the neural plate which curves to form the neural tube as cells are rapidly added due to mitotic activity. As it grows some of these

cells split to become neural crest cells. The formation of the neural tube may occur even before the mother may be aware of her pregnancy (about 3 weeks gestation). The neural tube grows rapidly to form three rostral vesicles: prosencephalon (forebrain), the mesencephalon (midbrain) and the rhombencephalon (hindbrain). This three vesicle stage of development quickly morphs into the five vesicle stage of neural tube development. The five vesicles are: the telencephalon & the diencephalon derived from the prosencephalon, the mesencephalon which changes little from the three vesicle stage, and the metencephalon + myelencephalon which are derived from the rhombencephalon of the three vesicle neural tube.

The major adult brain derivations are listed below.

- Telencephalon = Cerebral Cortical Gray & White Matter, Basal Ganglia, Basal Forebrain, Lateral Ventricles
- Diencephalon = Thalamus, Hypothalamus, Subthalamus, Retina, Optic Nerve/Tract, Third Ventricle
- Mesencephalon = Midbrain-Superior Colliculus, Inferior Colliculus, Substantia Nigra, Ventral Tegmental Area, Crus Cerebri, Red Nucleus, Sulcus Limitans, Cerebral Aqueduct
- Metencephalon = Pons & Cerebellum-Pontine Nuclei, Cerebellar Peduncles, Facial Colliculus, 4th Ventricle, Vestibular Trigone (Area), Sulcus Limitans
- Myelencephalon = Medulla Oblongata-Medullary Pyramid, Inferior Olive, Cuneate & Gracile Tubercles, Fourth Ventricle, Sulcus Limitans
- Peripheral Neural Crest cells will become Dorsal Root Ganglion Cells, Autonomic Post-ganglionic Cells, Cranial Nerve Ganglion Cells, Chromaffin Cells (Adrenal Medulla), Schwann Cells

Nervous system cells often have help in their migration to their final location. These guiding cues may be both physical and chemical in nature and may attract or repulse. Think of the youngster that is just beginning her schooling and is guided by her parents, crossing guards and teachers who assist in her transition from home to school. *Come here, go this way not that way, wait for the light before crossing the street.* Supportive cells in the CNS may provide physical barriers or scaffolds for migration of neurons. For example, at the appropriate time, radial glial cells seem to provide a guiding path for cells in the deep telencephalon to migrate along a radial (vertical) path in the developing cerebral cortex. Neurons follow this path and stop at the appropriate layer within the gray matter to do their job with “predictable” consequences-appropriate access to the information they need, crunching of data and then distribution of the processed information to appropriate targets (those elements willing and able to listen). These physical (cellular) cues **plus** chemical cues are vital to organizing the central nervous system. Physical and chemical cues are required to acquire as well as maintain the appropriate peripheral nervous system relationships with the head and body organs that

are non-neural in their function. Peripheral nervous system neurons are the adventurous components since they experience the body in which they reside at the "margins" in a "foreign" and potentially "hostile" environment (we're not within the meninges anymore). By contrast, neurons in the deep gray matter of the brain within a group called the Basal Ganglia (BG) are "homebodies" that never let their neurons or neuronal projections stray into unknown territory since they make only local connections with nearby neighbors (see below). Their view of the body in which they live is somewhat insular and their "world" view is somewhat abstract. They may have "*read about*" but never experienced the external (real) world in its gritty detailed reality. As you will learn later, the basal ganglia take on some of the most important roles in human behavior. The basal ganglia may provide a critical neural substrate for choosing one behavior out of many to devote precious neural resources for reaching a goal. BG do not do this alone since they have direct or indirect access to needed information upon which decisions are made. Fortunately (for their owner) BG are well-connected to other nervous system areas which *DO* receive reports from and send messages to those more adventurous components of the nervous system. In addition, BG have substantial reciprocal connections with association cerebral cortical areas responsible for higher cognitive functions. *Does this remind you of organizations such as universities, for-profit businesses or certain governments?*

Our nervous system needs a variety of elements to make it a viable entity that typically does its part to keep its host (body) engaged and adaptable. The intact human nervous system seems to be particularly adept at limited "multitasking" since it attends to and reacts to its owner's self-centered internal milieu while also experiencing and engaging the external world beyond the *me*. Nervous system pathology then has serious consequences for one's ability to maintain normal or extraordinary bodily and "out-of-brain" functions. Dedicated health professionals serve a critical role in helping others retrieve or resume a higher quality of life after such devastating incidents.

NERVOUS SYSTEM LEVELS

The Nervous System can be parsed into four clinically relevant levels: three Central Nervous System (CNS) levels (Supratentorial Brain, Posterior Fossa Brain and Spinal Cord) and one Peripheral Nervous System (PNS) level.

1. CNS Supratentorial Brain Level: Gray and white matter associated with the Cerebral Hemispheres and Supratentorial Brainstem (Telencephalon, Diencephalon) located above the tentorium cerebelli.

2. CNS Posterior Fossa Brain Level: Gray and white matter associated with the Posterior Fossa Brainstem (Midbrain, Pons, Medulla Oblongata) and Cerebellum located beneath the tentorium cerebelli.

3. CNS Spinal Level: Spinal cord gray matter (dorsal horn, intermediate gray and ventral horn gray) where neurons and synapses are found plus surrounding white

matter where axons transmit information to another location (spino-spinal, ascending, and descending long tracts).

4. PNS Peripheral Level: Cranial Nerves, Peripheral Nerves, dorsal roots (sensory/afferent), ventral roots (motor/efferent), ganglia (dorsal root ganglia, autonomic sympathetic & parasympathetic ganglia), plexi and supportive cells. The peripheral level provides a mechanism to activate effectors (glands, smooth muscle, cardiac muscle and skeletal muscle) and transmit data from a variety of sensory receptors that convert non-neural energy into neural impulses.

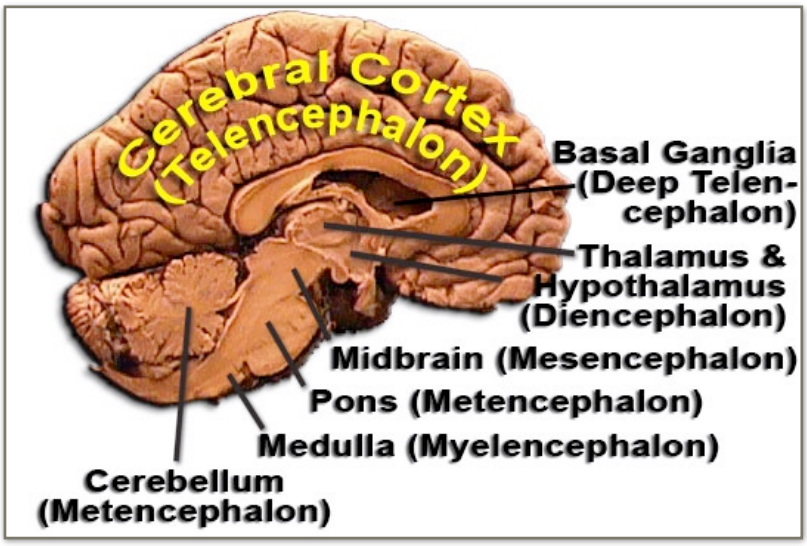


Fig 1-7. Rostral Neural Tube Adult Brain Derivatives of Forebrain (Telencephalon, Diencephalon); Midbrain (Mesencephalon); and Hindbrain (Metencephalon and Myelencephalon) (gec).

THE BRAIN IN 3D: RELATIONSHIP OF SUPERFICIAL TO DEEP STRUCTURES

Fig 1-8. Central Nervous System Brainstem 3D Label Movie; Cerebral Cortex, Cerebellum are Removed (gec). GO TO: gmomm.pitt.edu Fig1-8_Video

The cerebral cortex is a thin gray matter mantle covering deeper white matter and gray matter structures. Basal Ganglia are deep gray matter nuclei important in cognitive and sensorimotor behaviors and include: 1. Striatum = Caudate Nucleus + Putamen, 2. Globus Pallidus, 3. Substantia Nigra and 4. Subthalamic Nucleus. Thalamus is a gray matter structure that serves as the gateway for information ascending to the cerebral cortex from subcortical structures and monitors our intentions and actions derived from cerebral cortical networks. It includes a number of separate nuclei that relate to sensory, motor, limbic, consciousness & integrative functions.

The Internal Capsule is a white matter structure that contains axons originating from pyramidal cells in the cerebral cortex that travel to brainstem and spinal cord structures plus thalamocortical & corticothalamic axons that link the thalamus to the cerebral cortex.

Pituitary Gland in conjunction with the hypothalamus is the major hormonal controller for the brain and endocrine system.

Amygdala is a gray matter nucleus involved in limbic functions including anxiety, fear & reactions to highly charged affective stimuli, memories, or events.

Red Nucleus in midbrain contributes to control of dexterous limb movements (Rubrospinal Tract). It is well connected: Motor Cortex, Cerebellum, Inferior Olive.

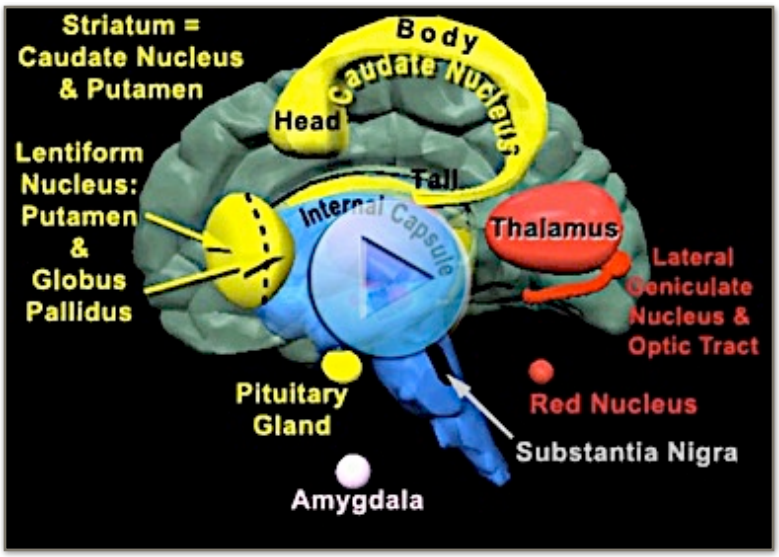


Fig 1-9. Brain Explode Movie (gec): GO TO: gmomm.pitt.edu *Fig1-9_Video*

BRAIN LOBES: CEREBRAL SUPER-STRUCTURE MEETS SUPER-FUNCTION

The brain of mice and men contains four anatomical lobes (frontal, parietal, temporal and occipital) and one "functional" lobe (limbic).

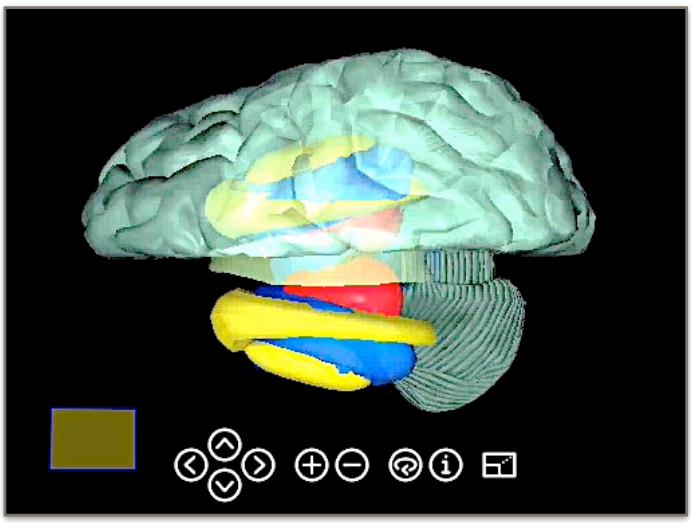


Fig 1-10. Visible Brain: Digital Model of Cerebral Cortex and Subcortical Brainstem Structures in 3D. Control buttons for the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. Arrow buttons allow you to move in a single direction. Curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen. Rectangle (lower left) is a Hotspot to open a movie with an "exploded", labeled view of deep structures in separate browser window (gec). GO TO: gmomm.pitt.edu *FIG1-10VR_MOVIE*

Each of the brain lobes contains cerebral gray association areas that integrate information arising from a.) nearby and distant cerebral cortical areas (corticocortical), b.) from the thalamus (thalamocortical), and c.) from brainstem nuclei that provide widespread modulatory effects on the cerebral cortex (Dopaminergic, Noradrenergic, Cholinergic, Serotonergic [5HT] Nuclei). Regulation of these neuromodulatory influences may be critical to optimize cerebral neural network function, e.g., see Bennett, et.al., 2013 and McGinley, et.al., 2015.a

These lobes in the human brain include substantial collections of neurons in areas that are not related to primary sensory or motor function. Evidence supports the idea that these association (non-primary) areas provide the neural basis for higher functions in humans, non-human primates and perhaps some other species (see below).

Higher level association cortical areas include:

1. Anterior Association Cortex includes Dorsolateral, Ventrolateral Prefrontal Areas (See **UPFRONT "ME, BE, DO")**

2. Posterior Association Cortex includes Posterior Parietal, Parieto-Occipito-Temporal and Lateral, Inferior Temporal Areas (See BACKUP/Superior **"OBJECTS & ME IN WORLD"-ACTION ORIENTED** plus **BACKDOWN/Inferior "YOU & WORLD"-CONSCIOUS PERCEPTIONS & CREATIONS**).

3. Limbic Association Areas include inferior and medial limbic cortical plus deep subcortical limbic areas (See Fig 1-11 and **INNER DEPTHS [LIMBIC] "VALUE-ADDED FLAVORING FOR ME, YOU & WORLD"**).

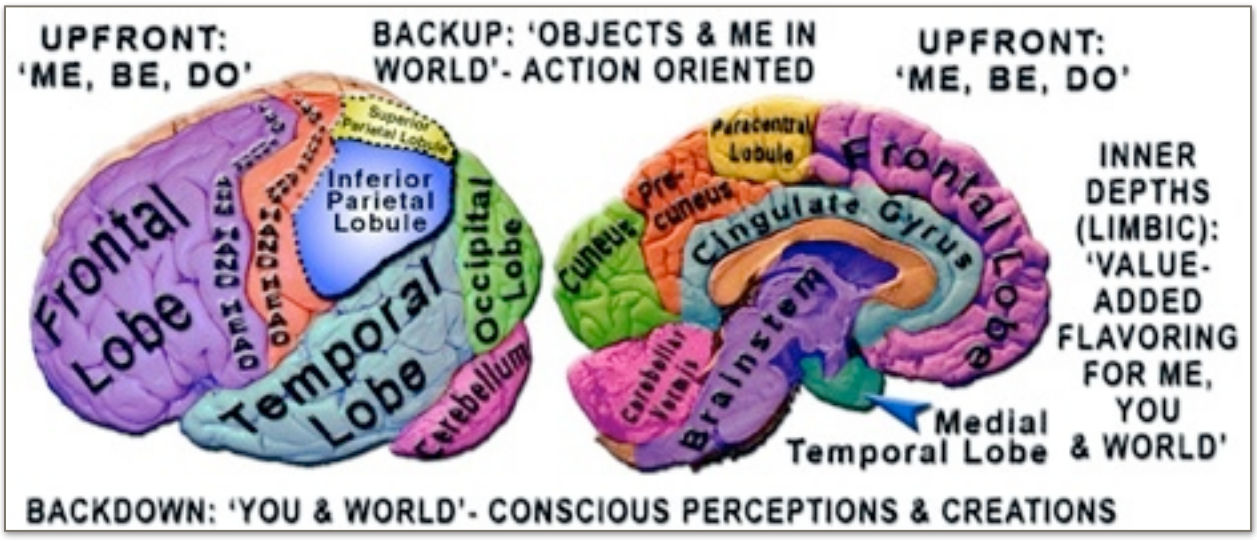


Fig 1-11. Anterior, Posterior-Superior, Posterior-Inferior & Limbic Association Areas (gec).

WHY WE HAVE SO MUCH GRAY MATTER ON OUR MINDS!

The adult human cerebral cortex is 1.5 to 4.5 mm thick depending on the cortical area. If we strip this thin outer mantle of cerebral gray matter from the underlying white

matter, iron out the wrinkles and lay it out flat, the gray matter would cover the surface area of a large computer monitor; *this, of course, is not recommended*-use this as a figurative reference only. The total surface area of the adult human cerebral cortex has been estimated to be about 2.5 square feet containing ~20-30 billion (or more) neurons along with many more supportive cells: glia (astrocytes, oligodendrocytes, microglia), blood vessel cells (pericytes, endothelial cells, vascular smooth muscle cells), etc.

Astronomers estimate that the Milky Way Galaxy in which we reside is composed of perhaps 250-300 billion stars (no one has really counted) plus much more invisible dark matter. Neuroscientists estimate that the entire adult human brain has perhaps 90-100 billion neurons plus ~150-200 billion glial cells. Thus, if one could compress the Milky Way into the space of the human cranial vault (skull), the number of stars might be just right to replace these brain cells. After such a substitution, perhaps we would all be star-studded celebrities with a small part of the universe guiding our way.

Fig 1-12. Brain Galaxy Movie. Your Star-Studded Brain (gec). Professional Milky Way Photograph Courtesy of Hannah Marchant, BS, CSCS (hm, gec). GO TO: gmomm.pitt.edu
Fig1-12_Video

However, while each star may be a solitary bit of the universe with only gravity, photons and perhaps some ethereal "stuff" (dark matter, dark energy, hydrogen clouds, "Big Bang" debris?) linking one star to another, our brain cells cannot do their job alone in a vacuum. Brain cells must be interconnected within networks to be functional. Moreover, brain cells like other living cells in our body utilize energy derived from ATP to accomplish their biochemical missions (our brains tend to be energy hogs-see later). For normal nervous system function our brain cells must communicate with one another and work together as a cooperative system. Brains do *NOT* operate well as a loose collection of self-absorbed "celebrity stars" although astrophysicists tell us that at the atomic or subatomic level we all indeed are derived from stardust, e.g. see Tyson, 2017. Nonetheless, such stardust does not guarantee us fame and fortune within the wide expanse of dark matter. Fame and fortune require talent, dedication, luck, access to the "right" people and quite often a healthy dose of expensive marketing.

Neurons are excitable cells that provide the anatomical basis for integrative processes that we understand to be the bases for our thoughts, feelings, actions.

Ultimately neural networks are the origins for our capacity to both survive and succeed as human beings. Neurons generate Action Potentials (APs). Patterns of APs become the “language” for rapid communication between neurons. Electrophysiologists are neuroscientists who study this language and try to translate it for us into our native languages: no small task for us humans as non-AP linguists. Other neuroscientists study the biochemical, molecular, computational, and genetic “languages” of brain function. My brain is multilingual even if my communicative mind is not, i.e., don’t ask me to explain to you all of the detailed intricacies of my molecular brain.

Glial cells are traditionally thought of as supportive cells that do not generate APs although such glial cells are responsive to neurochemical cues and communicate with each other, with neurons and with blood vessels. Such supportive roles are critical to the mission: brain metabolism & blood flow regulation, “sinks” for neurotransmitters and certain ions, myelination of central nervous system axons, regulation of neural network activity, regulation of synaptic function. In addition, reaction to injury and other protective roles are performed by a variety of abundant glial cells, i.e., a mixture of microglia, oligodendrocytes and a variety of astrocytes.

KEEP THE GRAY & WHITE MATTER: COLORS of SUCCESS

Through extensive intrinsic and extrinsic connections, the *human* cerebral cortex extends our perceptual and behavior repertoire to include:

1. FRACTIONATION - the ability to move body parts independently and to localize motor actions to a limited set of appropriate muscles.

2. ENHANCED SPEED, AGILITY, ACCURACY, AND ADAPTABILITY IN GOAL-DIRECTED MOTOR BEHAVIOR.

3. REFINED MOTOR LEARNING AND ENHANCED MOTOR PERFORMANCE IN SKILLED TASKS.

4. THE ABILITY TO DEFINE AND TO REFINE THE PERCEPTIONS OF as well as THE MANIPULATIONS OF OUR ENVIRONMENT

- by superb manual dexterity & eye-hand coordination in use of tools

- by improved control of communication skills and expressions of one's being: e.g., reading, writing, drawing, painting, sculpting, dancing, sports, music, computations and myriad expressions of abstract reasoning.

5. CREATION AND TRANSFORMATION OF OUR IDEAS, THOUGHTS, AND WILL INTO IMMEDIATE OR DELAYED ACTIONS/GESTURES AS APPROPRIATE FOR THE SITUATION; this requires planning, programming, and judgement for the generation & regulation of goal directed purposive behavior.

6. THOUGHTFUL SELECTION OF REWARD-BASED “POSITIVE” BEHAVIORAL CHOICES WHILE PURPOSEFULLY SUPPRESSING BEHAVIORS HAVING POTENTIALLY “NEGATIVE” OUTCOMES.

STRUCTURE/FUNCTION ARE RELATED: “SHADES OF GRAY AND WHITE”

Korbinian Brodmann in 1909 published a “map” of the cerebral cortex gray matter based upon the cytoarchitectonic differences from one portion of the cerebral cortex to another. This map of ~50 separate areas has been used as a “template” for relating structure to function. The map has been reproduced here as an introduction to structure-function relations “by the numbers.” Brodmann’s original map, like the living brain is not this colorful. Brodmann areas have been used as identifiable landmarks for many anatomical, physiological and brain imaging studies in monkeys that have similar cortical regions to us and for brain imaging studies in us humans.

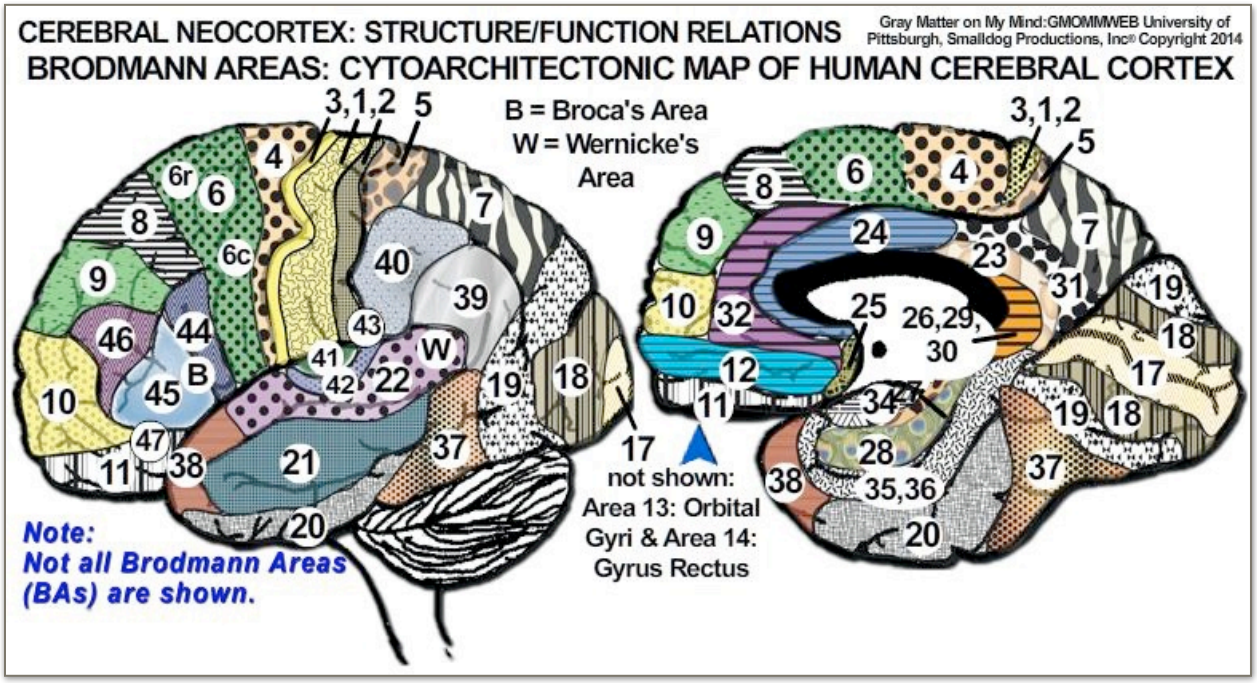


Fig 1-13. Brodmann Areas (BAs) of the Human Cerebral Cortex. Interactive Media File shows relationships of BAs to function according to the area(s) that you choose (gec). GO TO: gmomm.pitt.edu *Fig1-13_Interactive Media*

HUMAN BRAINS ARE WELL WIRED FOR SURVIVAL AND SUCCESS.

Traditionally ascending tracts from spinal cord to brain have been regarded as sensory channels and descending tracts from brain to spinal cord as motor channels of brain function. However, this view may be an artifact of our need to categorize and link structure to function. Advances in methodology to trace pathways across synapses and to precisely measure neural activity in these pathways in behaving beings suggest we have oversimplified tracts as currently professed in neuroscience and neurology texts.

If we think of the nervous system as the "electrical" system that sparks the life of an organism, then perhaps we must reconsider ascending and descending tracts as part of a larger network that cannot be constrained to having only "sensory" or "motor" properties. What if these ascending and descending tracts merely provide circuits that are part of a "grander" mission related to the organism's "raison d'être." For humans, in particular, these tracts may have evolved to wire us for both survival and success.

Survival includes behaviors common to all mammals and those behaviors particular to all members of a species (*Homo sapiens*, in this case). Survival does not equate to unrefined actions. Many survival actions are sophisticated and unique to the behavioral repertoire of the species; some may be inherited through a long line of human ancestry.

Success here refers to human behaviors defined by an individualized neural representation of abstract ideation that is supported by the skills necessary for its expression. Success infers an ability to take precise action upon internalized perceptions and intentions individualized to our goal. This may be expressed at the tips of our fingers, the tip of our tongue, at the junction of our vocal folds or telescoped through an instrument linked to our action. The gray and white matter that underlies these two entities (*survival and success*) may be partially segregated or more likely, success is fleshed out upon the skeleton of survival. Improvements in pathway tracing and network activity monitoring should reveal the extent of any such separation in the future. This dialogue does not represent an elitist attitude about human behavior nor is it a treatise on Darwinian principles. It *is* meant to be an argument that encourages us to think about our brains from a more pragmatic view of how our electrical system's wiring supports our biology; a dialogue about how each brain interacts with the body it inhabits and the world in which it lives. This dialogue occurs with or without a full cognizance of all that "*sparks*" in the cranium (see below).

HOW MUCH DO WE REALLY KNOW ABOUT OUR OWN THOUGHTS?

To what extent are we consciously aware of our brain's hard work of deep thought? Do we have full conscious control over the amazing cognitive powers of our forebrains? This is a basic question regarding the neural basis for self and self-control, e.g., see Brass & Haggard, 2007; Custers & Aarts, 2010; Haggard, 2008. We think of free will as our ability to do, say or think what we want (usually within bounds of societal and moral constraints). What if most of the hard work of thinking, like that for skilled actions, really goes on behind the scenes, out of the "reach" of consciousness? Perhaps it becomes available to our conscious brain only when we add sense to the thought. Sense here may be related to activation of receptors for those energies that we recognize in the world around us ("bottom-up") and/or an internal representation of the world ("mind's eye") built upon previous experience from the "top-down." Maybe it makes no "sense" for the cognitive brain to bother (engage) our consciousness unless we must make some decision that potentially will involve us interacting with the outside world. What if

we are unaware of what our brain is cogitating for most of our waking hours? After all, I can't read your mind, so what makes you think that you have full-access privileges to all of your own forebrain's information?

Does this strike you as a bit "unnerving"? Does this sound like the raving of a brain whose clutch is not fully engaged? Not really. Many well-respected neuroscientists are dealing with these very issues of self-consciousness: see references. Invasive single cell electrophysiological recordings in human subjects are not routine measures for fine-grained study of cognition (this may occur during neurosurgery or in identification of the source of seizures using implanted microelectrodes), but global assessments of brain activity are more commonly done using brain imaging, e.g, functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) and electro-encephalography (EEG). Critical regions of our brain must read between the conscious explicit lines of our being to keep our biology humming along (silently of course).

IS THE FRONTAL LOBE REALLY UPFRONT WITH *FREE WILL*? DO WE REALLY HAVE FULL CONSCIOUS CONTROL OF ALL OF OUR THOUGHTS & ACTIONS?

Human brains have expansive cerebral cortices. We like to think that all this gray matter is under our full conscious control; we control all thoughts and actions through our self-awareness and volitional commands that fulfill our most treasured wants and needs. Alas, such is not the case according to cognitive neuroscientists. Portions of our cerebral cortex, in particular our massive prefrontal cortex (PFC) churns through neural processes that apparently are not brought to our conscious attention, i.e., many thoughts and actions occur outside of our full awareness. Full transparency in PFC governance may not be the norm; portions of the PFC may take advantage of privileged access to information and communicate such data on a "*need to know*" basis to our consciously aware selves. For example, rapid "automatic" movements, such as rapid postural adjustments or rapid precision grip force adjustments often occur outside of consciousness. It has been suggested that until we receive sensory information resulting from an action, we have no conscious awareness of the action and even so much of that data may be utilized subconsciously and out of our explicitly reportable experience. Moreover, studies suggest that first impressions or quick "gut feelings" about an event or another person may be based primarily on subconscious, implicit preconceived notions or stereotypes, e.g. see Custers & Aarts, 2010; Gladwell, 2005. Goals based upon such processing may serve our survival behaviors. However, rational thoughts may require a suppression of such fast, biased "survival instincts"; this extra neural effort demands more time & greater neural resources.

Nevertheless, access may be limited to background processing and many of our goals may be substantially influenced by neural decisions that do not "rise" to our full conscious awareness. Perhaps circuitry responsible for conscious decisions have signed non-disclosure agreements with these frontal lobe networks regarding

proprietary information. Therefore, if you are one of those individuals who takes pride in your ability to gain full conscious control of your life, a portion of your brain may be "*messing with your head.*"

The expression of a person's will in a civilized democratic society seems to be based upon a combination of aspiration, inspiration and "desiration" that *in toto* do not lead to incarceration (allow me a little "poetic license" here). The mixture is not a simple mathematical sum since each component may be weighted differently depending upon the situation and personality of the owner of the will. The will may be an expression of one's individuality at the brain-mind interface, e.g., see Fuster, 2013.

NERVOUS SYSTEM ORGANIZATION: CONCEPTUAL HYPOTHESES

The nervous system is organized according to a central and peripheral division of labor. The Peripheral Nervous System (PNS) provides connectivity between non-neural portions of the organism with the neural portion the Central Nervous System (CNS) that controls many of our bodily functions and interprets sensory data transduced and gathered by the PNS. The way these PNS and CNS structures interact with one another has important implications regarding what scientists pay attention to when designing research, how we regard the altered nervous system following damage due to disease or injury, and how we plan rehabilitation approaches to recovery of function following such nervous system injury.

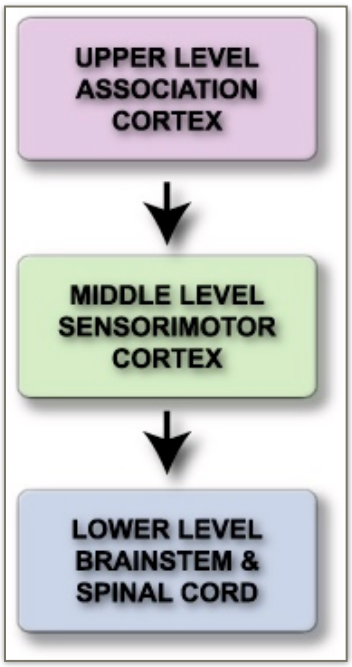


Fig 1-14. Traditional Jacksonian Top-Down, One-way Hierarchy (gec). GO TO: gmomm.pitt.edu [Fig1-14_Video]

HIERARCHY: A hierarchical control model has been proposed by a number of scientists. A one-way, top-down control model was proposed by John Hughlings-Jackson at the end of the nineteenth century. Jackson parsed the CNS into three levels. The Upper Level corresponding to "Association" Cortex is the least automatic and provides the commands to implement one's will to the Middle Level. The Middle Level corresponds to the Sensorimotor Cerebral Cortex that as a "middle manager" provides the orders to the Lower Level to implement the action. The Lower Level includes the Brainstem and Spinal Cord. Thus, according to this view, a ONE WAY, TOP-DOWN Organization has evolved to add higher level control over more "primitive" lower brain & spinal levels. Since the nineteenth century hierarchical control has been revised according to anatomical and physiological findings that suggest a more flexible information flow. Nonetheless, even these recent modified hierarchical models suggest that information builds through

stages that require a serial flow from simple to more complex (e.g., bottom-up for sensory processing) or from highly integrated commands to targeted executioners of such commands (top-down control of volitional movements), e.g., see Hughlings-Jackson; 1884; Davis, 1976; Walshe, 1961.

HETERARCHY: By contrast, a more recent proposal by some neuroscientists suggests that the nervous system uses a heterarchical or modified hierarchical control that distributes the “signing of the will” and the “execution of the will” across multiple neural networks located within “higher” and “lower” regions of the neuraxis. Legally, a person’s final will cannot be executed unless it already has been signed by the one that composed it and by authorized witnesses to the signing. Such distributed control is made possible in our advanced nervous system by reentrant connectivity and multitasking of neurons that share responsibility for neural representation of intentions, actions and perceptions (this is a “living” will: we do not have to die to implement the process). Thus, neurons in a network may function differently depending upon the timing of events in an evolving process. Parallel and serial processing may occur but the critical factor is reciprocity of connectivity that, given time and access to information, dynamically regulates network participation in neural processing. This model suggests that function is derived, for the most part, as an emergent property of a coalition (group) not the fixed property of individual members (neurons). Some coalitions may be highly structured and relatively “hard-wired” e.g., highly evolved sensory & motor pathways, while others may be quite transient and emerge only when a particular need arises, for example, in decision-making, perceptual judgments and cogitation within cerebral structures, e.g., see Cisek, 2012; Cisek & Kalaska, 2010; Davis, 1976; Kalaska & Crammond, 1999.

The will to do appears to be implemented by a distributed network using reciprocity of connectivity. Function is not restricted to individual structures but is distributed among many cell assemblies at many levels of the CNS. Cortical and Subcortical Structures are heavily interconnected and once one's will is set in motion, information flows in multiple directions. "Cognitive" aspects **(PLANNING, PROGRAMMING, PREPARATION and DECLARATION of One's INTENT)** are not restricted to association cortex. Recent evidence shows that some spinal interneurons adjust their activity during "mental" aspects of decision making before movement begins. Function is distributed and most information flow is not polarized. Likewise, implementation of one's Action **(COORDINATION, EXECUTION, REVISION, & PERFECTION)** is not simply an order from the "CEO" but a cooperative feedforward and feedback interplay amongst multiple neurons at many levels of the CNS. Reciprocity of information sharing is a critical aspect of intelligent biological communication as happens for non-biological digital networks.

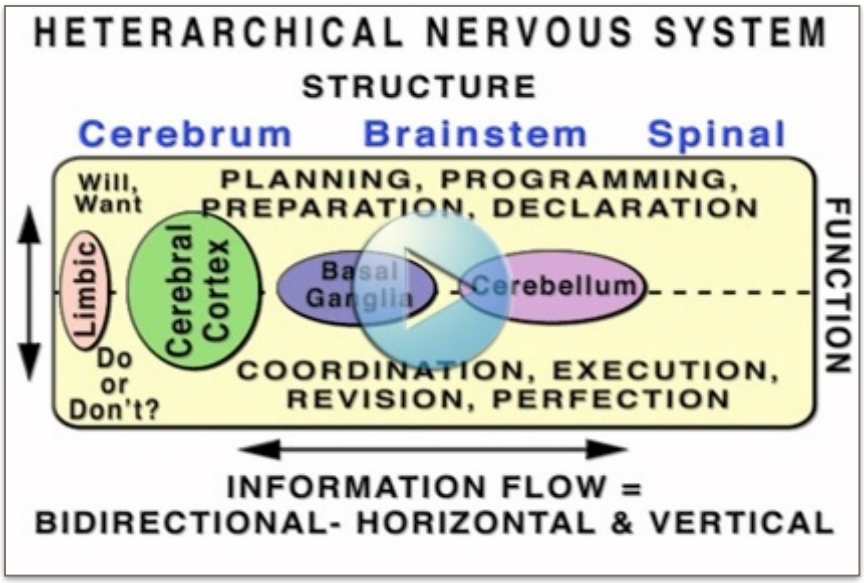


Fig 1-15. Heterarchical Nervous System Organization Movie (gec). GO TO: gmomm.pitt.edu Fig1-15_Video

It has been well established that portions of the subcortical Basal Ganglia (BG) and the Cerebellum (CBM) have loop connections with Cerebral Cortical Motor Areas (that project to spinal motor centers). BG and CBM also project to brainstem structures that are directly involved in sending signals to spinal centers responsible for "Execution of the Will." Moreover, recent neuroanatomical tracing studies in higher primates suggest that portions of BG and the Lateral Cerebellum have loop connections with "cognitive" Prefrontal Cortical Areas (see references). These loop connections provide a distributed network that is responsible for the "Compiling and Signing of the Will." As such, models that look only to higher level corticocortical connections for cognitive processes appear to be shortsighted. A posterior view of a transparent model of right cerebral cortex, cerebellum, thalami and bilateral basal ganglia is illustrated below.

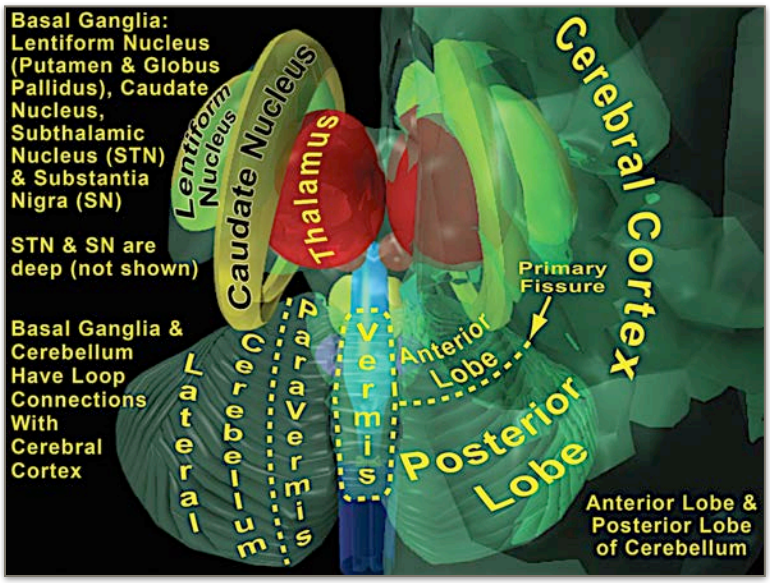


Fig 1-16. Posterior view of Right Cerebral Cortex, Cerebellum, Thalami and Bilateral Basal Ganglia (gec).

For several thought-provoking comparisons of a hierarchical versus a heterarchical nervous system organization see Davis, 1976 for a heterarchy based upon fundamental survival behavior circuitry in invertebrates and see Kalaska & Crammond, 1992 plus Cisek & Kalaska, 2010 for a distributed "heterarchical" organizational model related to

skilled cerebral sensorimotor control in primates. Self-organizing neural representations may require a brain heterarchy or a substantially modified hierarchy.

THE BRAIN IS ALL ABOUT MOTION

Our brains provide the neural basis for voluntary (willed) motor control including locomotion. Neuropathology that interrupts neuronal interactions within CNS sensorimotor control centers and/or interrupts signal transmission along central or peripheral sensorimotor pathways produces deficits in our ability to move in a precise, reward-based and goal-driven fashion. At this macroscopic level of motion analysis, only the outcome of movement is obvious to the naked eye of an untrained observer (see Walking Your Brain Movie). To understand the neural events leading to the motor outcome one must use additional (and often sophisticated) instrumentation to measure events within the machinery of the brain that lead to such body motion.

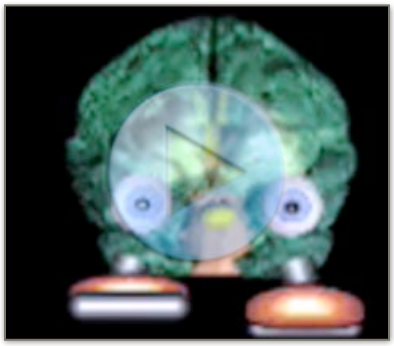


Fig 1-17A. Walking Your Brain Movie: A Wandering Mind (gec). GO TO: gmomm.pitt.edu *Fig1-17A_Video*

Using sophisticated instrumentation, neuroscientists can "see" (measure) relationships between brain processes and motion at the cellular, sub-cellular and molecular level. At a microscopic or finer level, motion of ions & molecules provides the basis for the electrochemical events that underlie basic intracellular and intercellular signaling.

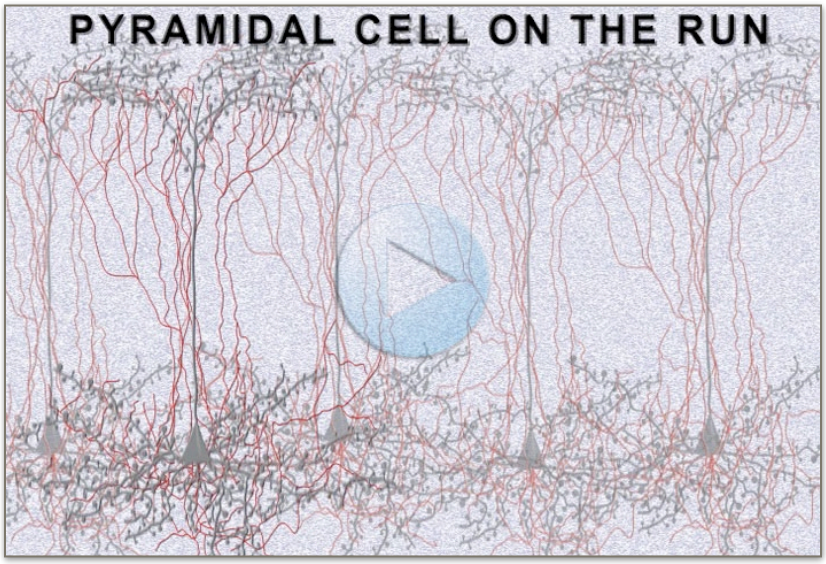


Fig 1-17B. Pyramidal Cell On The Run Movie (gec). GO TO: gmomm.pitt.edu *Fig1-17B_Video*

One important neuron within the cerebral cortex critical for perception, cognition and volitional action is the pyramidal cell. While the Pyramidal Cell On The Run Movie provides an unrealistic expectation for such microscopic motion in your brain, neurons and glia indeed survive and succeed as living cells due to motion of the cell's membrane or motion within the molecular constituents that form the cell membrane. In addition, motion occurs within and among organelles and ultrastructural "highways" for molecular transport, e.g. microtubules inside the extended protoplasmic extensions of these cells.

For example, under certain circumstances, axons may grow due to long-term plastic adaptation or in response to injury. Synapses may “wiggle”, grow in size, or even disappear in response to electrochemical signals that influence dynamic actin. Protein complexes inside the axons and dendrites of neurons provide highways and “delivery vehicles” for active transport of membrane-bound proteins either to or from the neuron’s cell body. Protein complexes within different compartments of either a neuron or a glial cell provide a channel for ions to pass through the channel’s aperture to produce a depolarizing or hyperpolarizing effect on the membrane. Other protein complexes may bind a signaling chemical to activate other regulatory proteins as second messengers within the membrane and messenger proteins inside the cell and thus change the cell’s structure/function. Molecular motion is a hallmark of signaling at a submicroscopic level, e.g., nucleotide-dependent coding of amino acid aggregation and construction of peptides/proteins according to a precise amino acid sequencing code.

Later chapters will focus on the dynamic pathways and processes necessary for normal brain function at the system, cellular and sub-cellular levels.

DO WE SENSE TO MOVE, MOVE TO SENSE OR JUST ACT?

Sir Charles Sherrington and colleagues at the end of the nineteenth and beginning of the twentieth century did experiments to reveal reflexive neural control circuitry. Such investigations suggested that particular sensory stimuli are both ***necessary and sufficient*** to produce simple to complex evoked responses in reduced (lesioned) nervous systems. Such spinal or brainstem reflexes were suggested to be a framework for functional activities such as locomotion and postural control. By chaining reflexes together complex, integrated multilimb actions would be triggered by the appropriate stimuli.

However, a contemporary of Sherrington, Graham-Brown (1914) performed a series of experiments that suggested no such requirement for sensory stimuli to generate complex rhythmic actions.

Graham-Brown showed that immediately following a thoracic spinal cord transection, the hindlimbs would step on a treadmill even after complete lumbosacral dorsal rhizotomy (all lumbosacral dorsal roots were transected). Graham-Brown suggested that stepping was due to a centrally generated rhythm based upon agonist-antagonist mutual inhibitory cycling: half-centre hypothesis for internally generated rhythmic movement. Since then, many experiments have supported the concept of central pattern generators (CPGs) for rhythmic motor output and have suggested that while sensory inputs may certainly modulate CPG output, many motor activities do not require specific sensory input to either trigger or guide such actions. While reflexes may play a role in daily activities such actions are not likely to be the building blocks for complex behaviors even in invertebrates, e.g., see Davis, 1976. Sensory input does appear to be very important for informing the organism about its immediate or distant environment but such sensory inputs may just as often be used in a feedforward context

(predictive control) manner as in a reactive, feedback context. Sensory inputs may be critical for periodic updating of behaviors that require precise control of sustained force and/or position.

Recent studies suggest that many actions designated as reflexes are not invariant and may represent only a fraction of those mechanisms responsible for stereotypical patterns (e.g., gait) and more sophisticated skills (e.g., reaching and grasping). So, we use our senses to guide or trigger some movements. We also move so we can gather data from our environment when we interact with the objects and people in our world; active touch is a prime example that will be discussed in later chapters. Based on an informed choice we act when a volitional goal is to be fulfilled and either preprogrammed or newly programmed complex sequences of movements will generate the rewarded behavior. For a review of these movement control issues see: Prochazka et.al., 2000; Haggard & Lau, 2013; Frith, 2013. A separate but related issue is the origin of actions: nature or nurture? Some species-specific behaviors may have a significant genetically endowed basis while others seem to be learned as we experience and interact with our world. Even inherited behaviors may be modified by learning.

N. A. BERNSTEIN'S CIRCULAR "SERVO LOOP" HYPOTHESIS

Early in the twentieth century, Nicholai A. Bernstein proposed an organization of the nervous system quite different from his contemporaries: for English translation of "The Coordination and Regulation of Movements" see Bernstein, 1967; see also Latash, 2021.

Bernstein envisioned a circular servo "reflex" loop where the required signal (the intended action,"DO THIS") is compared with the actual signal (feedback from afferent, re-afferent & efferent signals from sensors or motors: "DID THAT") as the task unfolds.The Comparator in Bernstein's loop generates an error signal that drives neural processing (see diagram). The circular process may be either continual or reiterative to reduce error; energy & the error signal keep the loop active. Note that the "Will-Command" center is isolated from the loop and that all connections are one-way. Bernstein believed that practice is essential for the nervous system to solve the problem of motor control through repetition of the task to reduce the error signal. The solution is an emergent property that changes according to a process of problem-solving: the nervous system searches for an optimal successful solution; a "dynamical systems" approach. Modern modifications of this hypothesis include reciprocally connected neural components that are less functionally segregated. The change in color and size of the looping signal simulates the reduced error and improved control as the task is repeated. With practice, actual output more closely matches the idealized "Will." Bernstein and others suggest hundreds to thousands or hundreds of thousands of repetitions are required to perfect skill (reduce errors and better match the idealized implicit plan).

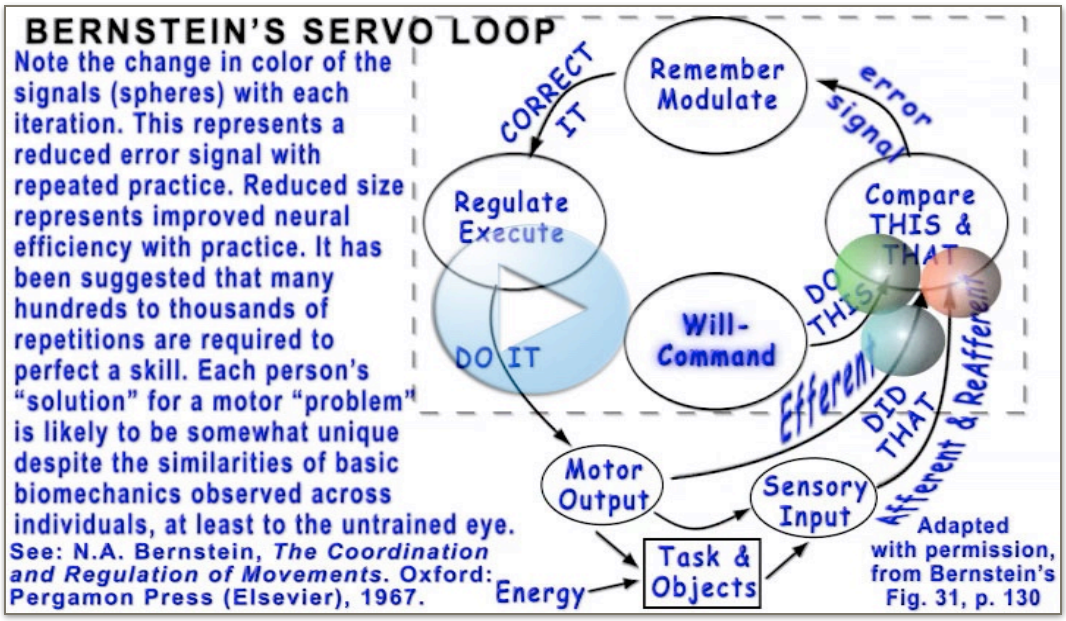


Fig 1-18. Bernstein's Servo Loop Distributed System Hypothesis (gec). GO TO: gmomm.pitt.edu Fig1-18 Video

DISTRIBUTED NETWORK-MODIFIED HIERARCHY: DISTRIBUTED FEEDFORWARD & FEEDBACK LOOPS

Anatomical, physiological and lesion studies suggest that the mammalian nervous system can operate in an efficient manner only when neural circuits distributed across multiple levels and areas of the neuraxis communicate in a feedforward and feedback manner. Information flow is rarely a one-way process. This process may require significant preparation (think of hosting a dinner party) or a more casual process (think of popping into a deli for a sandwich).

Motor Control is really a story about sensorimotor control unless the individual is totally deafferented and has no access to information from any other senses.

The Modified Hierarchical Distributed System: Sensorimotor Loop Movie illustrates the relationship between supraspinal (brain) & spinal levels of the CNS and the periphery (afferent & efferent). Some or all of our senses may provide information about peripheral events. If the sensory input is generated by our actions it is called re-afferent. Both afferent and re-afferent information is shared with neurons at spinal & supraspinal levels (on-line feedback or periodic knowledge of results). However, afferent impulses are not the sole source of information. Central gray neurons provide efferent information about ongoing motor events (central events in the animation).

A motor (efferent) copy of what is going out of the system is critical information ascending to the brainstem (& eventually the cerebral cortex by way of the thalamus) and to the cerebellum. Information is shared within & among spinal levels via the propriospinal tract (double arrows in spinal level).

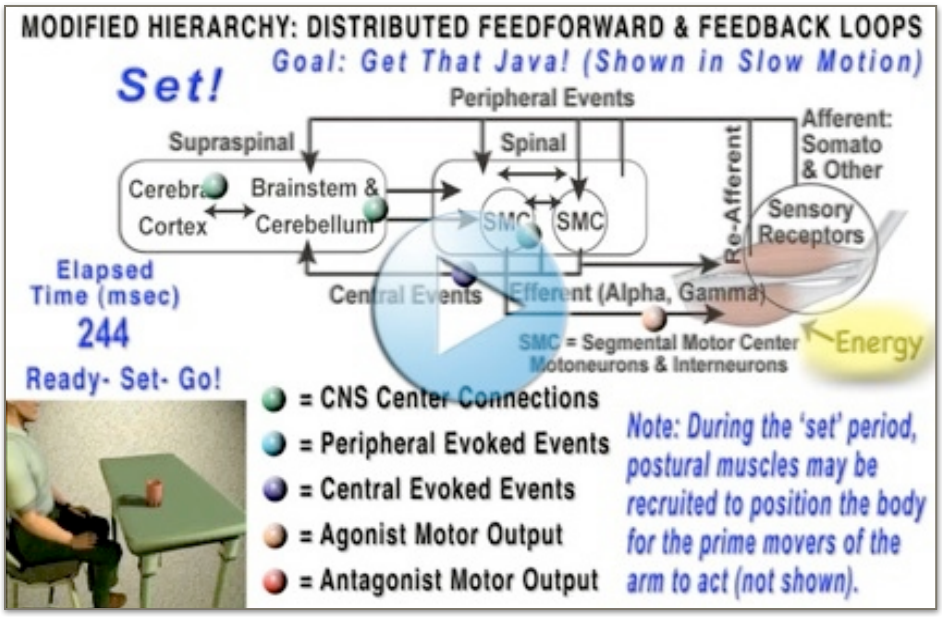


Fig 1-19. Modified Hierarchical Distributed System: Sensorimotor Loop Movie (gec). GO TO: gmomm.pitt.edu [Fig1-19_Video]

While information from the periphery and from central neuronal sources may provide ongoing feedback, this may be also a source of feedforward signals as predictive data so that we can anticipate what motor signals soon will be required (forming internal models compared to external/internal updates).

Indeed classic neuroscience teaching and experimental laboratory protocols typically assign sensation/perception, thought/cognition and motor/action to different portions of the nervous system. A different view suggests a more overlapping function for neurons within both local and more global networks to allow us to interact with our world using a principle of selecting the most appropriate behavior from among several concurrent possible choices, e.g., see Cisek, 2012 and Cisek and Kalaska, 2010.

CNS BENEATH THE BRAIN = SPINAL CORD: SEGMENTED INPUTS, OUTPUTS AND BRAIN CONNECTION HIGHWAYS

The adult spinal cord begins at the medulla-spinal cord transition at the foramen magnum and ends as the conus medullaris at the L1-L2 vertebral level. Below the conus, spinal roots continue caudally as the cauda equina. Lumbar and sacral roots of the cauda equina exit at the appropriate orthopedic level. Like the Brain in the cranial vault, the spinal cord and the cauda equina are surrounded by the three meninges (dura, arachnoid, and pia mater) and cerebrospinal fluid (CSF). A spinal tap at the L4-5 level is used to measure the pressure and constituents of the CSF. There are 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal segments in the human spinal cord.

The Spinal Cord has gray matter where neurons live and work (communicating and integrating information sent to, and received from the Brain, the Periphery, and other Spinal Cord segments). This circuitry incorporates Relay (Projection) Neurons, Propriospinal Neurons (spinospinal connections) and local interneurons (excitatory and inhibitory) and motoneurons to innervate muscle.

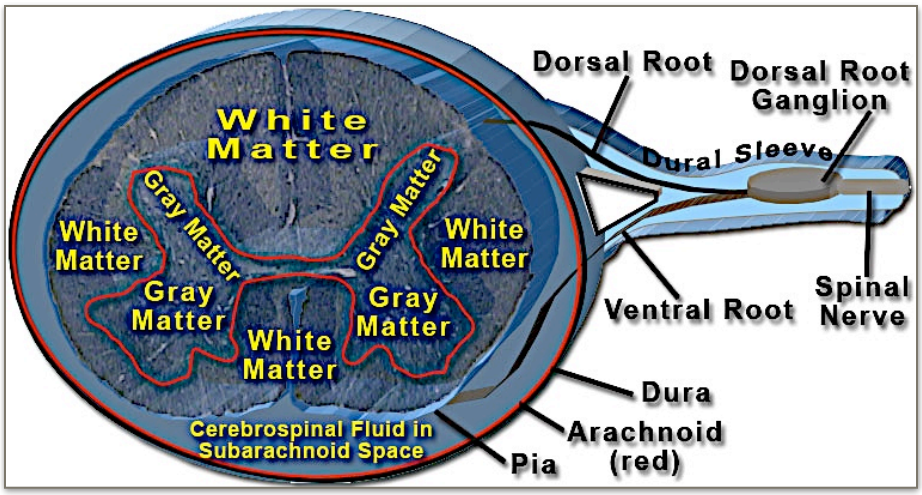


Fig 1-20. Spinal Cord basic structure (gec).

White matter surrounds the spinal gray to provide highways for Action Potential signals among segments of the Spinal Cord, for signals that ascend from the Spinal Cord to the Brain (Ascending Tracts/Pathways), and for descending signals from the Brain to the Spinal Cord (Descending Tracts/Pathways). Dorsal horn gray neurons are typically associated with sensory function and ventral horn gray with motor. While this distinction is generally true, normal function may draw no such distinct structural boundaries. The intermediate gray is often referred to as an integrative and visceral region. The Spinal White surrounds the gray.

The Spinal Gray develops from the mantle layer of the neural tube. It is divided in half (both right to left and dorsal to ventral). The dorsal median sulcus and ventral median fissure draw the line right to left. The sulcus limitans (seen as a midline groove in the developing neural tube) divides dorsal from ventral. Dorsal gray (DG) is derived from the alar plate, the ventral gray (VG) from the basal plate of the developing neural tube.

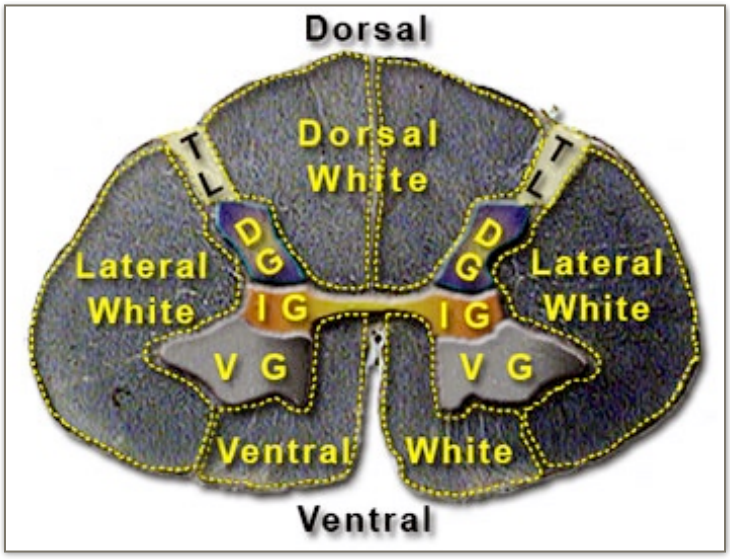


Fig 1-21. Spinal Gray and White Zones (gec).

The intermediate gray (IG) contains integrative and visceral projection neurons. Dorsal horn neurons are typically associated with sensory function and ventral horn with motor. While this distinction is generally true, normal function may draw no such distinct structural boundaries. For example, gamma motoneurons in the ventral horn modify the sensitivity of the muscle spindle to changes in muscle length and thus modify the sensory signal. The Dorsal Nucleus of Clarke located at the base of the

dorsal horn contains projection neurons that send ascending signals about the consequences of movement (proprioception, kinesthesia) to the cerebellum to guide and/or modulate movement.

The gray matter contains local excitatory and inhibitory interneurons that influence neural networks within one or several segments. Propriospinal (spinospinal) neurons in the gray interconnect spinal segments: within a local region (e.g., short propriospinal neurons at the cervical level) or across regions (long propriospinal neurons interconnecting multiple levels). Motoneurons in the ventral horn innervate extrafusal and intrafusal skeletal muscle.

Projection Neurons in the dorsal and intermediate gray send information from the spinal level to the brain. Alpha Motoneurons in the ventral gray (VG) innervate extrafusal skeletal muscle to move our articulated skeleton. Gamma Motoneurons innervate intrafusal muscle in the muscle spindle to alter sensitivity of the proprioceptive endings. Preganglionic Autonomic Motoneurons in the lateral portion of the thoracolumbar Intermediate Gray (IG) innervate smooth muscle, and glands by way of a two neuron chain (output to sympathetic chain ganglia).

Fig 1-22. Spinal Cord Over-view Interactive Media File (gec). GO TO: gmomm.pitt.edu [*Fig1-22_Interactive Media*]

The Spinal White develops from the marginal layer of the neural tube, and surrounds the gray matter. It is divided into three funiculi (columns): dorsal, lateral and ventral (anterior) white matter. Axons in the white matter provide continuity between spinal segments (Propriospinal Tract) and between the brain and spinal cord levels of the CNS (ascending and descending tracts). In addition, peripheral (sensory) afferents enter the spinal white at the dorsal root entry zone. Dorsal root ganglion cells send central axons into the dorsal funiculus (dorsal column) via the medial division of the dorsal root afferents or into the Tract of Lissauer (TL) via the lateral division of the dorsal root afferents. TL is located at the juncture of the dorsal and lateral funiculi. Dorsal gray (DG) neurons receive multiple synapses from these peripheral inputs. The Spinal Cord Overview Interactive Flash File provides an introduction to the spinal level of the CNS including gray and white matter.

PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system (PNS) is the portion of the nervous system that wanders into “foreign” non-neural cellular territories (the skin, deep subcutaneous structures, internal organs, sensory receptor organs, muscles and glands).

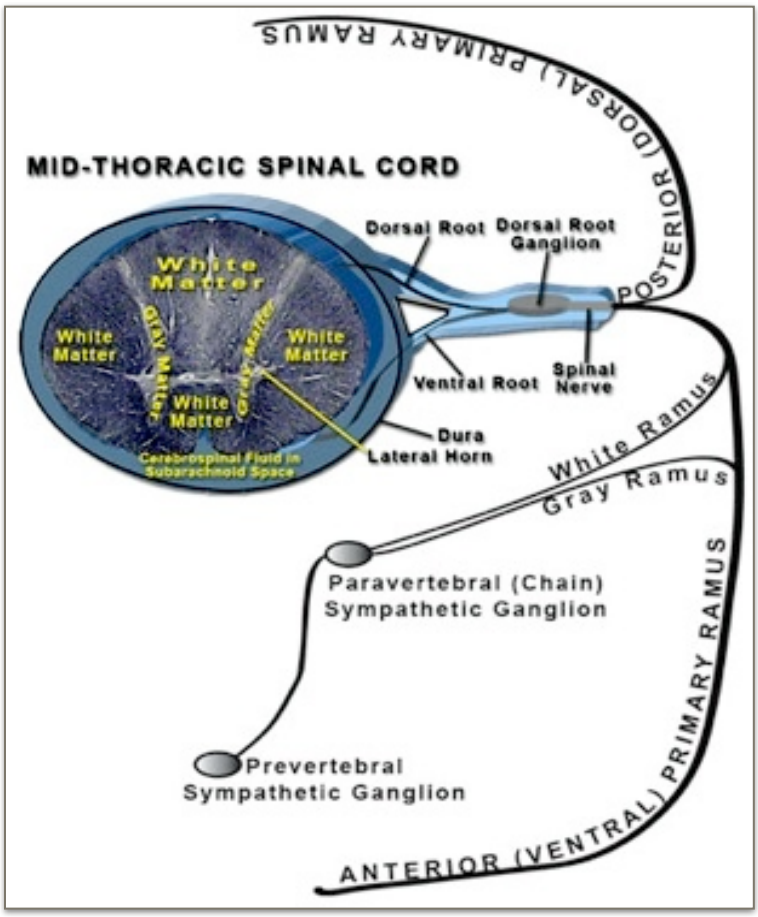


Fig 1-23. Peripheral Nervous System Basic Architecture (gec).

The PNS provides: 1.) a link between you and the external world, 2.) sensory and motor data for control of homeostatic mechanisms that keep fundamental physiological processes responsive to changing needs and 3.) a means to move within your environment in a controlled fashion.

The PNS includes dorsal & ventral roots, dorsal root ganglia, autonomic ganglia, mixed spinal nerves, plexi, and peripheral nerves. As shown in the figure, the spinal nerve gives rise to a posterior (dorsal) primary ramus and an anterior (ventral) primary ramus. At the spinal levels responsible for innervating the

upper limb the anterior rami form the brachial plexus. The lower extremity is innervated by peripheral nerve roots that form from the lumbosacral plexus.

Autonomic components of the PNS includes autonomic ganglia, the white ramus that contains myelinated B sized autonomic motor axons from preganglionic motoneurons, the gray ramus that contains unmyelinated C sized autonomic axons arising from postganglionic autonomic motoneurons in the chain ganglia plus sympathetic and parasympathetic afferent and efferent axons within peripheral nerves innervating the visceral organs in the head, neck, thorax and abdomen, glands, vascular organs and blood vessels.

Sympathetic (paravertebral) chain ganglia and sympathetic or parasympathetic end organ (prevertebral) ganglia are locations of autonomic synaptic interactions between preganglionic motoneuron axon terminals and postganglionic motoneurons in the periphery. Along with motor axons, the motor periphery includes the Alpha Motoneurons in the ventral horn, the neuromuscular junction and most clinicians include skeletal muscle (as part of the motor unit).

Sensory (afferent) axons within peripheral nerves provide long range signals as action potentials (APs) that arise from transduction of non-neural energy into a language understood by the nervous system: volleys of APs sent at different speeds according to the conduction properties of those afferent axons. The Peripheral Axon Conduction Velocity Properties Interactive Flash File shows relationship of AP conduction speed to axon size & simulates effects of cooling on conduction velocity.

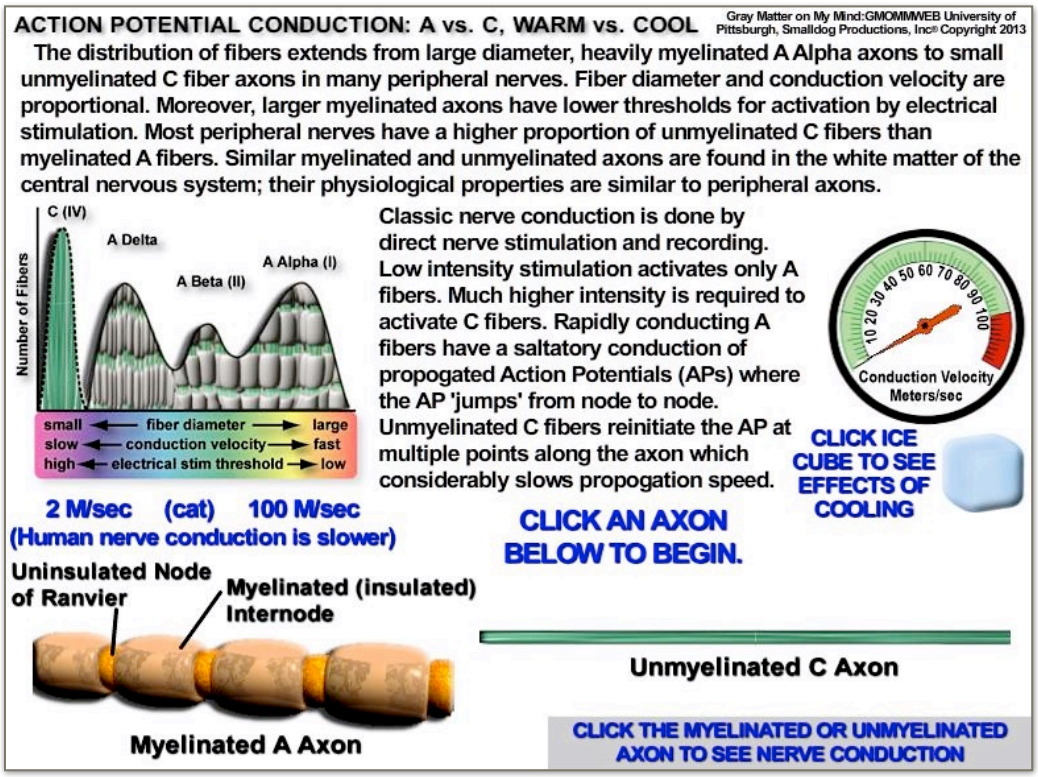


Fig 1-24. Peripheral Axon Conduction Velocity Properties Interactive Media File (gec). GO TO: gmomm.pitt.edu

[Fig1-24_ Interactive Media]

Transduction into these messages is

dependent upon sensory receptors distributed within most tissues and specific organs of the body that respond to such stimuli by producing local generator potentials. General somatic sensations arise from cutaneous and subcutaneous tissues plus deep non-contractile and contractile tissues associated with the musculoskeletal system. Visceral afferents arise from organs deep within the thorax, abdomen, blood vessels and glands. Special senses provide afferents from the sensory organs within the head: eyes, ears, nasal cavity, tongue and pharynx.

The special sensory organs for sight, sound, balance, taste and smell involve relatively complex anatomical receptor organs that are activated by unique non-neural energies that are limited to a relatively narrow spectrum among the many energies that exist in nature. For example, only a small portion of the electromagnetic spectrum is transduced by our eyes (visible light) while the rest of the spectrum in bandwidth frequencies above or below visible light can only be appreciated if we produce man-made devices that can measure those energies. My human sense of smell is responsive to a fraction of the aromatic chemicals that are exciting to the nose of my beagle (26 pounds of olfactory mucosa mounted on four legs) even when (for the beagle) the concentration of those chemicals is miniscule. Perhaps, we are fortunate to not be bombarded by all those energies that would require massive energy expenditure to transduce and perceive. We must recognize there is much more in nature than we can ever appreciate by direct biological access.

Motor (efferent) axons within the PNS innervate organs of action: smooth muscle, glands, cardiac muscle and skeletal (striated) muscle. Our ability to interact with our environment and the inanimate and animate objects within it is limited by our biology. I can flap my arms as hard as I can but cannot fly like an eagle. Excellent human swimmers cannot match the grace, speed and adaptability of a dolphin (another big-brained mammal). I might wish to jump vertically from a standing start up to twice my height like a cat but I cannot. However, the eagle, dolphin and cat cannot hammer out a message on a keyboard to translate their thoughts into a written message for others to read (although I am not particularly facile at typing like others I see texting like mad with their thumbs on a small digital device).

Our anatomy provides both affordances for and constraints on our actionable intentions. Some motor axons provide not direct action but indirect control of sensory receptors, e.g., gamma motor axons that innervate the special (intrafusal) muscle located within the muscle spindle proprioceptive organ. The gamma innervation alters the sensitivity of the muscle spindle sensory transduction that, in-turn, may alter our skeletal muscle actions. Likewise cochlear nerve efferent axons do not directly transduce sound waves but may alter the sensitivity of the sensory transduction within the cochlear organ of the inner ear. Innervation of the smooth muscle in the gut, airways or blood vessels may not help us to get from one place to another or maintain a particular posture but they do support those aspects of mammalian physiology that keep

us going from a dynamic bodily physiology standpoint, e.g., I need more oxygen, more blood, more nutrition or less gaseous, liquid or solid byproducts of metabolism. Cardiac motor innervation is special from the standpoint that without it our hearts still pump blood due to the intrinsic impulse conduction system within the heart but without the cardiac parasympathetic and sympathetic innervation our hearts are unresponsive to changing demands of blood delivery as we burn more or less ATP by action-oriented organs within the cranium, body wall, limbs or viscera.

Glands provide more broadly distributed responses to biological need. For example, sweat glands provide a mechanism to cool bodies who's core temperature is rising, release of chemicals from visceral glands help us digest the foods that provide energy for basic and special biological processes. The adrenal glands in particular provide chemicals for big responses to life experiences where "action as usual" will not suffice. Blood cortisol and adrenalin are responses to real or perceived conditions where homeostasis is being significantly challenged perhaps to an extent that a live-or-die response is engaged. One could see how such an actionable system would be vital in an unpredictable world. However, too often for modern humans it is only that one person's perspective (not that of all others) that evokes such *emergency* responses: think of personal stress in a civilized society! Nevertheless, there are those occasions where a collective response to a real or perceived threat engages many nervous systems to prepare for or react to large-scale emergencies. All of this suggests that the *peripheral* nervous system is *central* for us to continue to exist as complex living animals (humans) that can both appreciate and interact with a changing world in such an extraordinary fashion.

CELLULAR BASIS OF NERVOUS SYSTEM INTEGRATION

The nervous system is composed of cellular components. These cells are classified as neurons or glial cells. A population of these cells are of non-neural origin, e.g, vascular cells, pericytes that support physiological demands of neural cells. Other cells in the meninges cover the brain and spinal cord (dura, arachnoid and pia), while others form an intrinsic plumbing system known as the cerebrospinal fluid (CSF) system. Cells in the choroid plexus of the CSF system are located in the ventricles (internal fluid filled caverns) and arachnoid granulations are located in the superior sagittal sinus (subarachnoid space meets venous system). All the cells above plus a special group of intrinsic supportive cells called glial cells are non-spiking cells (they do not generate action potentials). Glial cells include astrocytes, oligodendroglia and microglia.

The cells capable of generating all-or-none spikes (action potentials) are called neurons. Neurons provide the unique communication system within an organism that allows it to rapidly interact with and often alter its environment and the life-forms contained therein.

The human nervous system is a highly sophisticated biological communication "device" that, compared to other species, provides its owners a complex array of

adaptive features to generate a maximal impact on themselves and on nature. As will be discussed later, neurons and astrocytes communicate with each other and their blood supply to provide a dynamic architecture responsive to changing levels of brain activity.

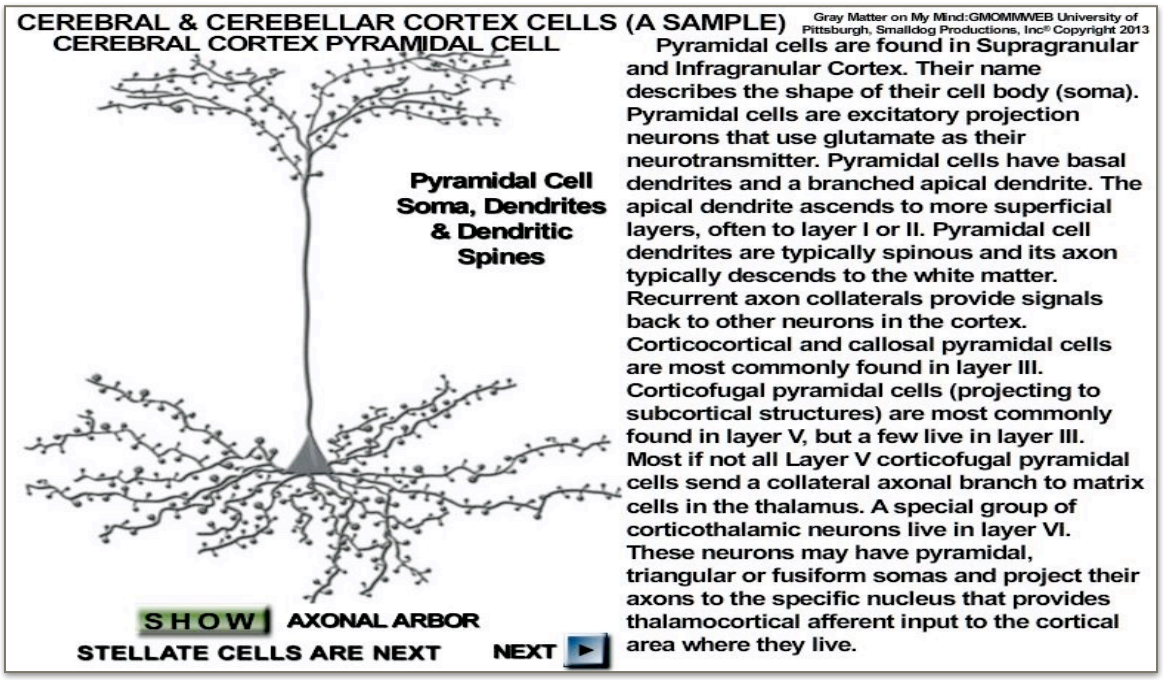


Fig 1-25. Cerebral and Cerebellar Cortex Cell Type Sampler Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig1-25_Interactive Media]

A sampling of neurons present in the cerebral and cerebellar cortex (accounting for ~ 75-80% of all brain neurons) are shown in the Cerebral & Cerebellar Cortex Cell Sampler Interactive Flash File. These cell types will be revisited in detail in later chapters.

Neurons communicate with one another primarily through extensions that protrude from the cell body or soma. These cytoplasmic extensions are called neurites. Some neurites act primarily as collectors of information from other neurons (dendrites).

Each neuron typically extends from its soma a neurite called an axon that may then branch many times to deliver signals to other cells. The major way that neurons talk to one another is by way of synaptic junctions. The presynaptic portion of the synapse (typically an axon terminal of the presynaptic cell) releases a chemical (neurotransmitter) that binds to a receptor protein complex that recognizes the chemical on the postsynaptic portion of the synapse. The postsynaptic membrane may be located on a dendrite, a dendritic protrusion (dendritic spine) or on the soma of a postsynaptic cell. Less frequently the axon of one neuron may provide an axon terminal that synapses on the axon of a second neuron providing an axo-axonal synapse. Thus most

communication within the nervous system requires electrochemical signaling with chemical messenger release at the junctions among many neurons.

Some cell-cell connections utilize signals with no chemical release (electrical gap junctions). Gap junction synapses are fast and may occur between two neurons, between two glial cells, between glia and neurons or between glia and blood vessel endothelial cells. Compared to modern digital devices, chemical and gap junction information transmission in the nervous system is a relatively slow process consuming many microseconds to milliseconds compared to the nanosecond to picosecond information transfer in an electronic integrated circuit.

The "Classic" Pyramidal Cell Activation Movie illustrates incoming messages (orange glows) that sum at the pyramidal cell's soma (green pyramid) to produce an outgoing message in the form of an action potential (AP) that jumps from node to node along the myelinated axon (bright flashes). Nodes are periodic excitable interruptions in the "insulating" myelin sheath.

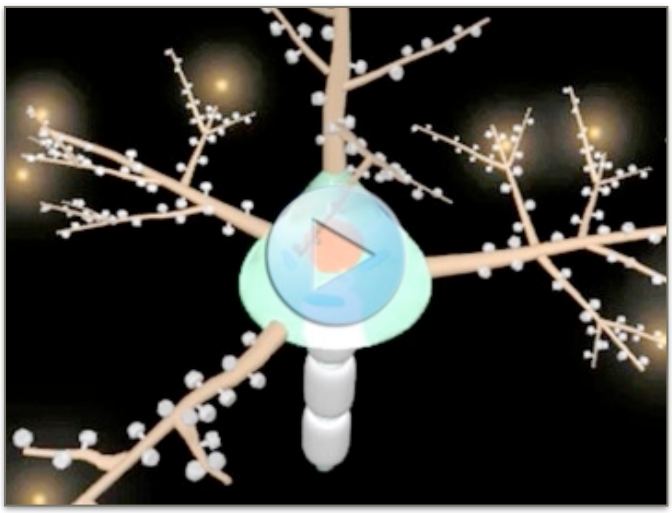


Fig 1-26. "Classic" Pyramidal Cell Activation Movie (gec). GO TO: gmomm.pitt.edu *Fig1-26_Video*

Although digital devices are becoming astonishingly "clever," their adaptive intelligence pales in comparison to the carbon-based humans who created (and almost all who use) these "smart" silicon-based devices which *currently* lack 1. a conscious will, 2. self-referential feelings, 3. morals, 4. highly adaptive communication and 5. adaptive manual task management (sci-fi cyborgs excluded). Note: artificial intelligence folks might disagree with this list.

So, if you happen to have a bright teen son or daughter who is more proficient than you are with their thumbs on a smartphone don't fret, you have other talents and skills that are very critical: e.g., you are probably paying for it.....

.....Does that contradict my argument?

Some neurons are contacted by thousands of synapses which may represent relatively redundant information from one or a few input sources. Alternatively, neurons may collect data from inputs representing varied types of information some of which may already be processed from prior integrative procedures. The "default" method of data collection by a neuron is thought to be a straightforward accumulation of inputs and an algebraic summation: an "*integrate and fire*" or "*rate*" coding of data. By contrast,

neurons which receive powerful temporally synchronized synaptic inputs may use a "*coincidence detection*" coding where relatively few correlated inputs rapidly sum (s*parse spike coding*). This coincident firing may occur due to massive convergence of strong inputs from a single source such as is found in many sensory pathways or such coincident firing may be due to the emergence of a learned cooperative processing among neurons in a circuit that is repeatedly activated in a similar fashion from one iteration to the next for a repeated task. Such learning may be due to neural network plasticity correlated with perfecting a skill. The Pyramidal Cell Activation Movie shows simultaneous inputs to a number of synaptic spines on many branches of the dendritic tree (orange glows). This relatively synchronous input results in an integration of local depolarizing potentials known as Excitatory PostSynaptic Potentials (EPSPs). The soma is depolarized above threshold to initiate an AP.

A subset of pyramidal neurons are capable of repetitive firing due to dendritic ionic channels opening or closing. These neurons have a persistent firing mode thought to be important in supporting working memory within certain regions of the brain.

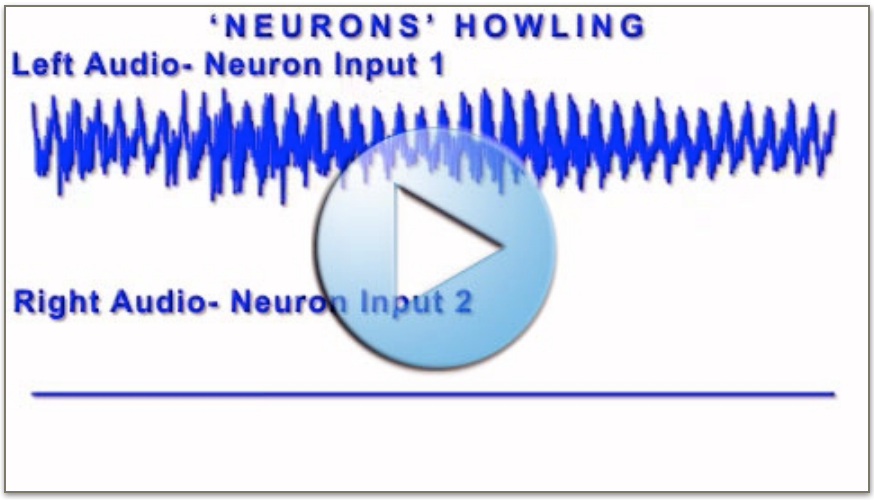


Fig 1-27. Neurons Howling- Neuronal Integration: A Simple Simulation of a Complex Process (gec,jec). GO TO: gmomm.pitt.edu
Fig1-27_Video

An example of a simulated "neuron" listening to two separate inputs (Right Audio & Left Audio) is presented in the Neurons Howling Movie. Each channel has similar but not identical data that are spatially and temporally separated (right versus left). The final audio represents an example of an integrate and fire mode of processing by neuron 3 of inputs from neuron 1 (left audio) & neuron 2 (right audio). The right and left audio channels are integrated (mixed in this example). This simple audio simulation representing such limited input is a simplified version that is virtually never found in a complex brain. Each neuron in a mammalian brain is more like a person sitting in an acoustically magnificent venue listening to a live symphonic presentation. You appreciate the rich score not the individual notes. Play the movie for a highly simplified version of neuronal integration. Although most messages in the brain may not be so dramatic, the movie simulates one neuron's capacity to listen to subtle (or not so subtle) differences in the tales being told by different actors (neuron 1 and neuron 2) trying to get the attention of postsynaptic neuron three.

Although not simulated here, the output of neuron three would be a series of action potentials: a *digital* signature of the *analog* integrative process. ***Of course, neurons downstream that receive this digital signature may or may not be interested in the "howling," i.e., the processed data may have a small or a large impact upon other neural networks***.

The lone wolf's impact depends significantly upon other messages being transmitted at the same time from other places. Combined data may be integrated, or other alternative "exciting" information may win the day. Excitatory information competes with influences from inhibitory neurons that suppress or "stifle" the circuitry (*turn down that loud music, I'm trying to think here!*). Local membrane fluctuations combined with particular ion channels add an unpredictable element (entropy) to data transmission.

CELL ASSEMBLY: NEURON NETWORKS DO THE WORK OF THE BRAIN -"NO NEURON IS AN ISLAND UNTO ITSELF"*

Brains work correctly and efficiently when neurons interact in either a cooperative or a competitive fashion (these are not mutually exclusive within a group of connected cells). Groups of neurons that have local interactions to code a specific function may be called a cell assembly, an ensemble, a cellular aggregate, a nest of cells, a node, a cell colony or a column. The concept "no neuron is an island unto itself" is a play on the words of J. Donne, "Devotions Upon Emergent Occasions," *Meditation* 17, 1623.*

A neuron in isolation emits but a whisper until many cells form cooperative coalitions. Then as a group the ensemble's voice is very powerful. Moreover, unlike hard-wired groups of components in an electronic integrated circuit, brain circuits tend to be more fluid in their structure and function: a critical capacity of their biology & chemistry that produces molecular, sub-cellular and cellular plastic changes according to use and experience, e.g., see Dias, et.al., 2015. Contrary to earlier thoughts about age-restricted brain maturation & plasticity, more recent evidence supports the notion that brains can and do adapt and learn at any age, e.g., see Katz & Schatz, 1996; Kempermann, 2008.

Many cells in the Motor Cortex (MI) hand area are well-suited to code even the lowest force levels of distal muscles when measured on a cell by cell basis. Precise force control is robustly coded by individual MI neurons. However, no such robust relationship exists for Motor Cortex single cell activity regarding the direction of reaching movements. Single cell directional specificity coding has not been seen despite an obvious engagement of motor cortex circuitry for fine motor control of multiple muscles involved in complex reaching and grasping synergistic tasks.

Since the 1980s, research by A. P. Georgopoulos, A. Schwartz and others (e.g., see Georgopoulos, et.al., 1988) have approached this problem using more sophisticated computational methodology to describe a directional coding mechanism for reaching an arm into either 2D or 3D space.

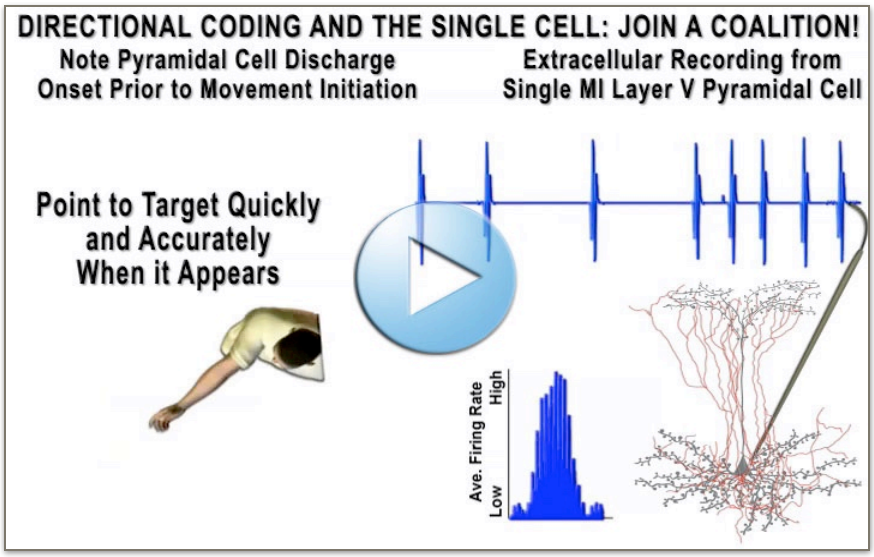


Fig 1-28. Simulation of MI Neurons and Population Coding of Movement Direction Movie (gec). GO TO: gmomm.pitt.edu
Fig1-28_Video

Directional coding appears to be an emergent property of a neuronal ensemble (population code) not an elemental feature of individual, segregated single cells. In addition, multiple cerebral and subcortical sensorimotor areas are involved in this distributed network function, e.g. see Kalaska & Crammond, 1992.

The Simulation of MI Neurons and Directional Coding of Movement Direction Movie above allows you to see & hear the simulated response from a Motor Cortex Pyramidal Cell as a subject reaches for that target. Note the movement directions associated with either high, medium or low firing rates of the selected neuron; note the relatively broad directional tuning of individual MI cells. This appearance of the yellow target is the GO signal for the subject to reach for the target. You should hear the modulated neuronal discharge begin slightly ahead of the movement after the target appears which simulates the known property of MI Neurons related to Motor Set. The Pre-movement modulation of activity (Motor Set) typically begins several hundred milliseconds before movement onset in MI (mental preparation to move). Precise coding of movement direction is due to increased discharge of a subpopulation of neurons while inhibiting others that code opposite directions: an emergent property of the cell assembly.

THE BIG PICTURE: LARGE SCALE NETWORK ACCESS WITHIN A BIG BRAIN - CONNECTING CELL ASSEMBLIES

High quality signal transmission among widely separated areas of the brain supported by healthy white matter bundles is thought to be a necessary condition for higher level cognitive functions of the primate cerebrum.

> Consider the following scenario:
>
> Think of yourself as standing among a throng of people in Times Square, New York City at 1 minute before midnight on December 31 of a year of your choosing. You use your smartphone to let your friends (located in another state or another country) share in the experience. Of course you are not the only person who has thought of this. Your data transmission is

> "spotty" at best and when you do connect, all your friends hear is barely audible garbled sounds and all they see is uneven, choppy low resolution images. Your audio and video data are immersed within a sea of chaotic AV noise. On the other hand, if your phone has circuitry that blocks all ambient noise, your friends may wonder if the connection has been lost when you are not talking. Some electrophysiological studies suggest a small amount of background noise may optimize neural network function (I know we are still connected). Now you can appreciate the scale and complexity of the data handling required of individual neurons in generating reliable long-range communication in the human brain, i.e. why we need coalitions (well-connected neural networks) that filter and optimize meaningful signals embedded within a noisy background.

Brains do not have "Wi-Fi" so the axons of projection neurons that provide these long-range connections must have reproducible, "guaranteed" signal transmission. This faithful nerve impulse transmission is a necessary but not sufficient condition for normal brain function. A unified function such as conscious perception of a visual scene depends also upon a distributed parsing of the components that, when bound together, lead to normal perception. In addition, some neuroscientists suggest that these higher functions rely upon genetic history built upon a long-standing empirical learning process by our species. The visual system in primate brains utilizes many different cerebral cortical and subcortical brain areas to code the different aspects of visual signals. It has been proposed that due to the numerous and widely separated areas participating in perception, neuronal activity must be transiently and functionally bound together to create a relative synchrony of firing across separate networks (the binding problem).

Cell assemblies such as cerebral cortical columns provide "integrated circuitry" to accumulate data, transform those data into a neural image and then share that integrated information with other cell assemblies from which meaning is derived. A physical analogy of integrating separate sensory data into a more unified multisensory perception is illustrated by the Waterfall Order Entropy Movie. While data streams begin as separate entities they eventually flow into a common pool where mixing of data occurs. Such later processing is influenced by top-down cognitive and limbic processes. Note the less predictable nature of flow for individual bits (drops) of data within each data stream.

Cerebral cortical cell assemblies may be combined at different scales, e.g., at a macro-columnar scale providing a broader "Standard Definition (SD)" image or in the case of evolved primates a finer grained "High Definition (HD)" neural image that rescales data by fracturing the macrocolumnar representation into selective minicolumnar neural images (see SD to HD Movie). Slow-motion simulation of this hypothesized processing shows the transition from SD to HD neural image that in your brain would occur within a fraction of a second (e.g., recognizing a familiar face).

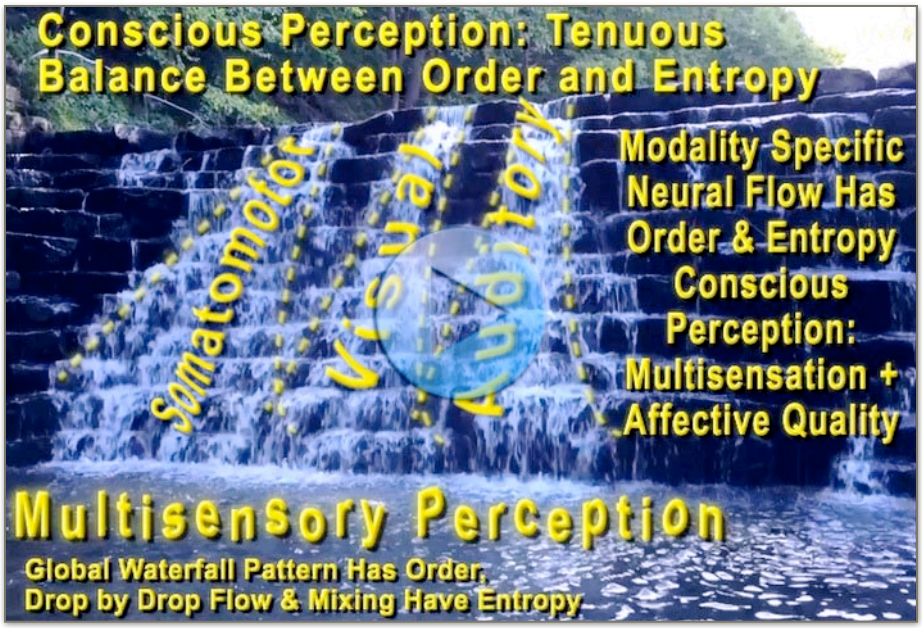


Fig 1-29. Waterfall Order Entropy Movie (gec). GO TO: gmomm.pitt.edu *Fig1-29_Video*

Evidence for such a fracturing into HD neural images in humans is yet to be documented and may only be tested when technology advances to allow measurements at this fine-grained level of spatial and temporal detail *in-situ*.

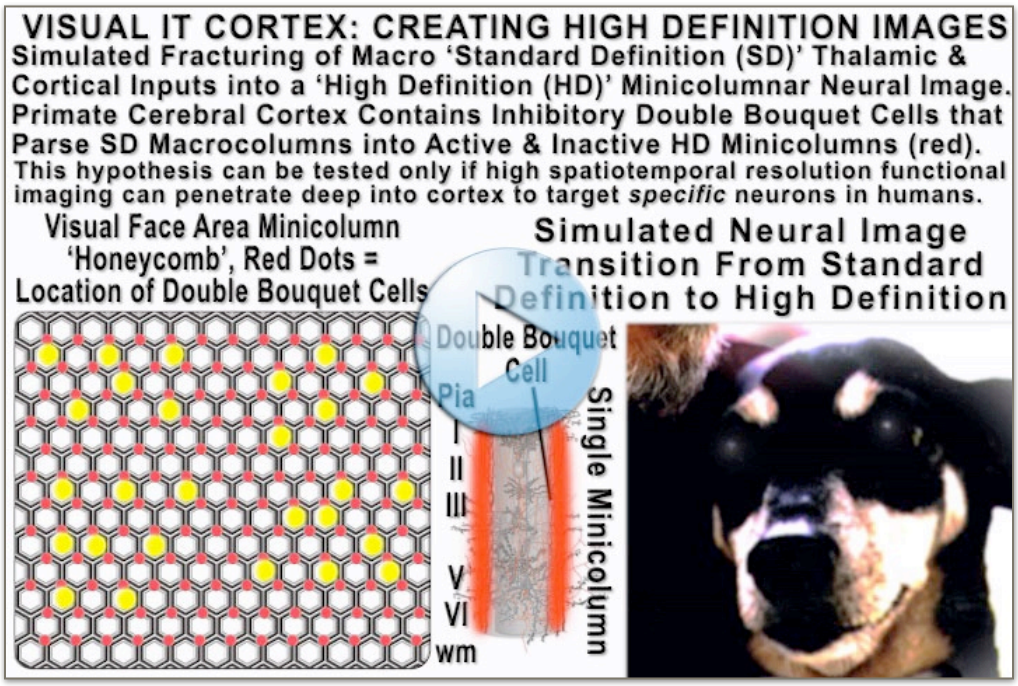


Fig 1-30. Creating High Definition Minicolumnar Images From Standard Definition Macro-columnar Images Movie (gec). GO TO: gmomm.pitt.edu *Fig1-30_Video*

MEASURING LARGE SCALE BRAIN ACTIVITY PATTERNS: ELECTROENCEPHALOGRAM (EEG)

Multiple scalp macroelectrodes are used to measure large-scale brain waves from different portions of the human cerebral cortex. These electroencephalogram (EEG) electrodes provide a glimpse into large populations of neurons working in a collective fashion often with one or more underlying rhythms in the EEG recordings.

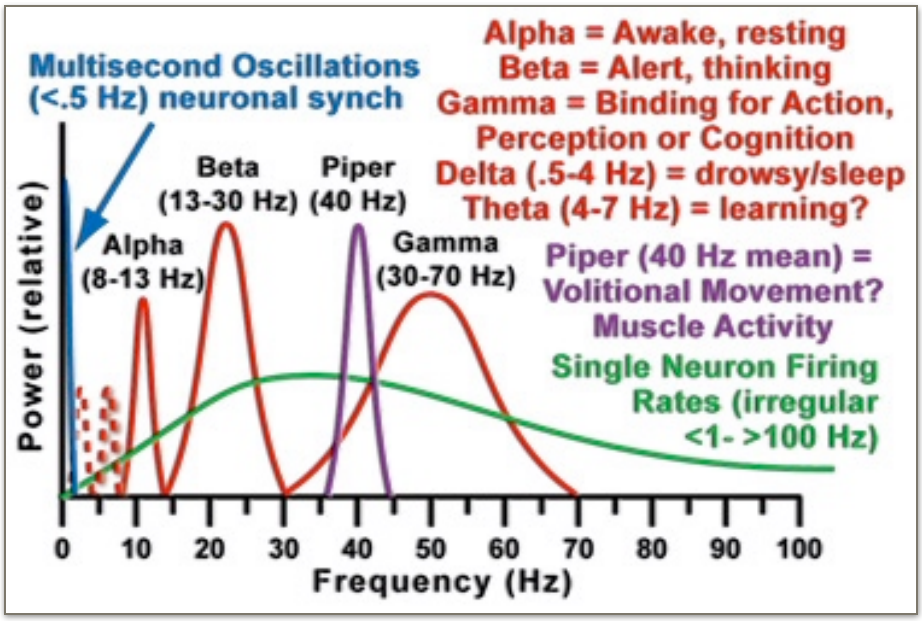


Fig 1-31. Electro-encephalogram (EEG) and Neuronal Firing Frequency Spectrum (gec)

Sophisticated algorithms have been developed to decipher patterns of activity within these EEG recordings. EEG potentials represent the summed subthreshold and suprathreshold activity of many thousands of neurons that form local cell assemblies connected to many other nearby and distant cell assemblies. The EEG therefore represents large scale not small scale brain activity. The different frequency bands within the EEG spectrum are shown in the figure above. The proposed relationship of each band of activity to function is included. While you are reading this information we would anticipate substantial portions of your cerebral cortex to be generating Alpha, Beta, Gamma and Theta rhythms.

Certain EEG rhythms are associated with cognitive mental processes, e.g., Gamma (30-70 Hz) rhythms.

A. Lutz and colleagues (see A. Lutz et.al., 2004) measured EEG activity in 8 veteran practitioners of objective-less meditation (mean age 49) versus 10 young novices (mean age 21). The young subjects had one week of instruction before the EEG measurements during meditation. Compare this to the experts who had 10,000 to 50,000 hours of practice over 15-40 years. Experts showed profound differences in gamma band (25-42 Hz in this study) EEG activity compared to novices.

Activity within “hotspots” of prefrontal and posterior parietal cortex showed high levels of synchronized gamma oscillations (binding?) for expert but not for novice meditators.

According to the authors, Objectless Meditation is a form of mental training where practitioners contemplate no specific object or person but self-induce a cognitive/ emotional state of well-being. This *altered state of consciousness* is accompanied by a significant change in EEG oscillations within frontal and parietal association areas. For the meditation experts, but not novices, even when the individuals are in a “resting” premeditation state the gamma band amplitude is elevated in portions of the frontal and

parietal lobes. The “hotspots” of synchronized gamma band oscillations seen in these areas suggest a binding of cerebral areas involved in perception, intention and executive decisions.

Fig 1-32. Meditation: Gamma Rhythms correlate to intense intrinsic cogitation (gec). GO TO: gmomm.pitt.edu Fig1-32_Video

In addition, a “horseshoe” shaped inter-hemispheric corticocortical gamma activity across parieto-occipital and prefrontal EEG recording sites suggest shared function between right brain and left brain. Binding is thought to be one method of getting networks within different brain areas “on the same page” during cognition and other higher level cerebral functions. The lack of such a significant increase in gamma band activity in younger rookie meditators implies either a training effect, age effect or lack of specific talent for this mental processing. The strong correlation between the level of gamma activity and the hours of experience with meditation but not age shown in this study is consistent with a training effect. It would be instructive but technically tedious to follow changes in EEG patterns in novice subjects as they gain experience with meditation.

Perhaps filtering out external stimuli and “concentrating” on an internal state of calm accesses our deepest thoughts of contentment that would otherwise be hidden from our cognitive self, e.g., see Tang, et.al., 2015. These EEG results do not address the issue of defining a mechanism for generation of and the purpose for the gamma band rhythms. It is not clear whether Gamma Band Cerebral Oscillations are responsible for cogitation or if these oscillations are only an epiphenomenon of underlying neural mechanisms responsible for correlated firing of relevant cell assemblies. See “EEG Rhythms: Intense Brain Buzz in Expert Cogitators” simulation above and an introduction to binding below.

EVENT RELATED POTENTIALS: READINESS POTENTIAL - READY TO GO BEFORE YOU KNOW

The EEG waves at various frequency bands indicate rhythmic activity that may correlate to ongoing brain activity associated with the functions described in the EEG spectrum figure above. In addition, non-rhythmic event related activity may be recorded at certain electrode locations. For example, a “readiness potential” may be recorded at the vertex of the skull (C_z) when an individual is about to perform a voluntary action, e.g., see Cunnington, et.al., 2003; Deecke, et.al., 1976; Haggard, 2008 and refs below.

The readiness potential may begin one to 1.5 **seconds** ***before*** conscious awareness of the neural machinery that initiates this mental process and the onset of the action being contemplated (W-Judgement). The W-Judgement is taken as first awareness of the urge to move. This C_z EEG location lies above several midline cerebral cortical brain areas that appear to be related to a neural signal of an intent to act and perhaps the action coupled to awareness of that will.

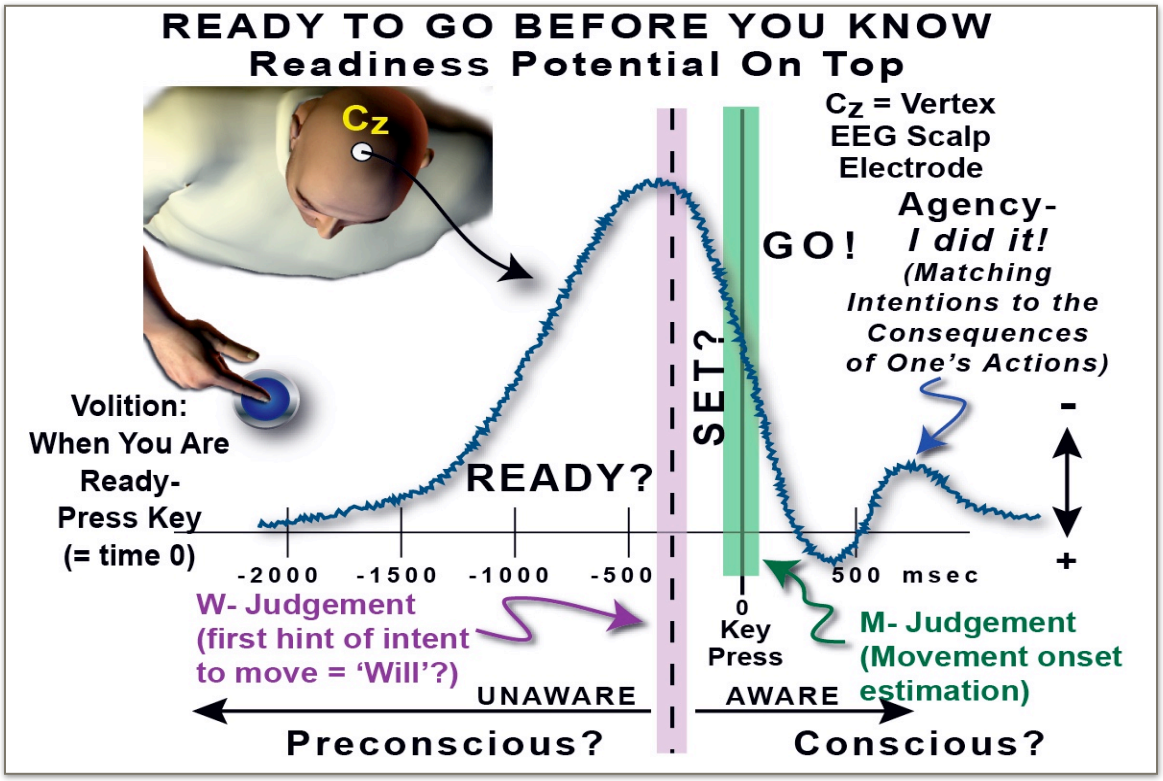


Fig 1-33. Readiness Potential (ERP): Ready To Go Before You Know. (gec) GO TO: gmomm.pitt.edu *Fig1-33_Video*

Lateralized EEG potentials over the frontal motor areas have been recorded before contralateral arm movement onset. Such lateralized potentials typically begin ~0.6 to 0.8 second before movement suggesting that they reflect the brain’s preparation to move in a volitional fashion. A simulation shows these central and lateralized Event Related Potentials (ERPs) recorded by EEG scalp electrodes: see Readiness Potential (ERP) Movie. Subjects normally appear to be aware of their first intent to act ~200-250

milliseconds before movement (W-Judgement) onset despite the fact that the scalp recorded ERP may begin hundreds to thousands of milliseconds before the "awareness" of one's own actions. Preplanning or "intentional deliberation" to move in the near future seems to initiate and prolong the duration of the ERP before movement onset. Subjects place the actual movement onset (M-Judgement) quite closely in time to the beginning of action: e.g., see Libet, et.al., 1983, Libet, 2004, and Haggard, 2008.

Considering the delay in awareness of a volitional act relative to the brain's initiation of neural resources to produce the act and the delay in neural awareness following the onset of a sensory signal (see pet a dog scenario above) it would appear my conscious self is *living on borrowed time and in a derived virtual space* (my brain's neural resources). Preconscious or non-conscious brain activity may lead to conscious awareness but such delayed sharing of information does not prevent me (portions of my brain) from vetoing an action before it is unleashed. As will be illustrated in later chapters many rapid actions occur without the need for conscious awareness and when conscious control is required details regarding me as the agent may occur after the fact.

BINDING: GETTING DISTRIBUTED NETWORKS ON THE SAME PAGE AT THE SAME TIME - WHY WE NEED COHERENT CONVERSATIONS IN OUR BRAIN

Cerebral cortical networks have local and global connectivity. These networks may "read" and "write" information in back and forth data streams. It has been suggested networks are most efficient in neural processing when they are bound together. Such binding is suggested to be associated with oscillatory activity and re-entrant connectivity. There are a number of rhythms that may accomplish such high level data translation. One important frequency range is called gamma band (40-70) Hz frequency as recorded by EEG or local field potentials in awake "thinking" brains. Gamma binding has been implicated in higher level processing: e.g., see Pritchett, et.al., 2015 & below.

Other lower frequencies are critical for higher level processing as well. For example, a recent study (Helfrich, et.al., 2018) has provided evidence that slow oscillations < 1.5 Hz (SO) plus sleep spindles (12-16 Hz) are synchronized during Non-REM sleep. This synchronization is different for young vs.older adult subjects during a night's sleep. This slight shift in synchrony of these two rhythms for older adults was correlated with greater forgetting of "nonsense" words learned on the previous day (as compared to younger adults). The authors suggest that the medial prefrontal cortex (mPFC) is a critical cortical area involved in synchronization of SO and sleep spindles leading to memory consolidation. They show a correlation between age-related mPFC gray matter loss and decreased function: see Helfrich, et.al., 2018. While this is an intriguing study, one wonders if the older adults (70+) are simply forgetting nonsense information (that has no importance to them) while the twenty year olds (who own slightly less "mature" prefrontal networks but robust hippocampi) have no compulsion to forget anything. The No-Binding Vs. Gamma Oscillation Binding Simulation Movie is an attempt to illustrate

an oversimplified solution to the binding problem inherent in a distributed network. The scenario as shown in the movie below is artificial.NO BINDING: Neurons in the Posterior Parietal Cortex (Dorsal Visual Stream = Where/How processing) discharge ~10 Hz when an object is within their receptive field (green 10 Hz Sine). The Inferior Temporal Cortex Neurons (Ventral Visual Stream = What processing) discharge at ~15 Hz (blue 15 Hz Sine). There is rarely a coincident discharge between the two areas (sines out of phase & light flashes are asynchronous). BINDING: If a small 60 Hz Sine (small central red sine) is mixed with both signals the resultant waveforms have periodic coincident activity as shown by the "ugly" green & blue waveforms and synchronous flashes. The scenario will work only if the two areas are interconnected and are equally influenced by a common source of the "binding" 60 Hz input.

The source (central red glow) of the 60 Hz (40-70 Hz Gamma Frequency oscillations) is unknown. The Thalamic Reticular Nucleus, Pulvinar, Claustrum, Intrinsic Cortical Circuits have been suggested as potential candidates. Not all neurons have properties allowing for such synchrony. A subset of neurons may produce/induce the binding, e.g., certain inhibitory GABAergic interneurons synching discharge of pyramidal cells. Some neuroscientists suggest the synchronous oscillations are an epiphenomenon (not the cause) of network interactions. Moreover, additional rhythms (not simulated here) may be involved in binding, e.g., alpha, beta or theta band oscillations. Some evidence suggests that gamma oscillations may be most important within local networks while other slower rhythms are more evident with longer range network connections. Sleeping brains may use other rhythm binding frequencies as related to memory consolidation, see above and Helfrich, et.al., 2018.

Fig 1-34. No-Binding Vs. Gamma Oscillation Binding Simulation Movie (gec). GO TO: gmomm. pitt.edu Fig1-34_Video

This simulation has serious limitations (see references). 1. Actual mechanisms for binding are likely to be more complex and may utilize more than one frequency band to accomplish the task, e.g, alpha, beta and theta bands. 2. Neurons discharge discrete action potentials not continuously varying voltage fluctuations as simulated here (sinewaves). 3. Cortical Neurons are seldom so consistent in their discharge periodicity. 4. Biology is seldom this straightforward or so "simple." For reviews of these complexities in brain rhythms see Steriade, 2006; Buzsaki, 2006,; Buzsaki & Wang; 2012; Freeman, 2015; Siegle, et.al., 2014 and Kim. et.al., 2016.

SELF-ORGANIZING PRINCIPLES FOR NERVOUS SYSTEM FUNCTION

While brain anatomy has many consistent features from one brain to the next based upon species-dependent genetic and epigenetic ordered developmental rules, any such precise form may not necessarily predict function at the brain/mind interface. Coalitions of neurons reciprocally connected within local and long-range networks may show functions that may not be predictable on a cell-by-cell basis as neural processing unfolds over time. Populations of neurons may show probabilistic emergent properties not self-evident when investigating the nervous system on a cell by cell basis, e.g., see Georgopoulos, et.al., 1988; Pouget, et.al., 2003; Ma et.al., 2006 and Yuste, 2015.

These emergent properties are based upon classic excitatory-inhibitory interactions and more fluid global neuromodulatory and recurrent connectional influences. Such limits in predictability may drive neurobiologists crazy when attempting to reveal consistent rules and logical mechanisms to account for behavior. Alternatively, such natural fluidity in biology may offer surprises in data obtained by experimentation. Such revelations may lead to new experimental approaches and perhaps reveal those mechanisms nature has selected to solve neural control problems in complex biological entities: see Waterfall-Whirlpool Movie. Adaptability to changing circumstances layered upon some basic structural rules together form the essence of a plan for both survival and success of evolved or evolving organisms, e.g. see Edelman, 1987; Edelman & Tononi, 2000; Damasio, 2010; Damasio & Carvalho, 2013.

Fig 1-35. Waterfall-Whirlpool Movie (gec). GO TO: gmomm.pitt.edu
Fig1-35_Video

So, if you are a person who *above all else* treasures logical predictable outcomes to life's challenges, you probably should not consider a career as a neurobiologist and you should consider consulting an experienced, trusted financial advisor to plan for your retirement rather than dabble in stocks and bonds on your own.

A BRAIN FOR ME AND A BRAIN FOR YOU: A MEETING OF THE MINDS

It has been said you must love yourself before you can love another.

Some individuals appear to be well-wired for the former (which on occasion is blatantly obvious) while other people seem to be well-wired for making friends, family and colleagues the center of their attention. Each of us is different. While the following

discussion is not intended to address such a specific philosophical issue related to love of others versus love of self, there is some indirect evidence suggesting that portions of your cerebrum are primarily devoted to the self while additional cerebral areas provide circuitry to allow *you* to interact with the outside world & relevant biological entities in it. Both brain "views" appear to be essential for humans to become self-aware, socially engaged and to form a personal theory of mind consistent with reality (the multidimensional physical world), e.g., see Churchland, 2011; Schilbach, et.al., 2012.

These distinctions are not absolute since an intelligent nervous system must be capable of integrating "in here" with "out there". Such an inference regarding potential separation of neural processing of endogenous and exogenous behaviors is supported, in part, by results of human brain imaging studies, primate neuroanatomical and neurophysiological studies and the functional deficits accompanying localized cerebral cortical lesions, e.g., see Baluch & Itti, 2011; Churchland, 2002; Damasio, 2010; Damasio & Carvelho, 2013; Dehaene, et.al., 2014; Frith & Frith, 2010; Haggard, 2017; Kjaer, et.al., 2002; Northoff & Bermpohl, 2004; Raichle, 2015; Rothschild & Mizrahi, 2015; Solms & Turnbill, 2002.

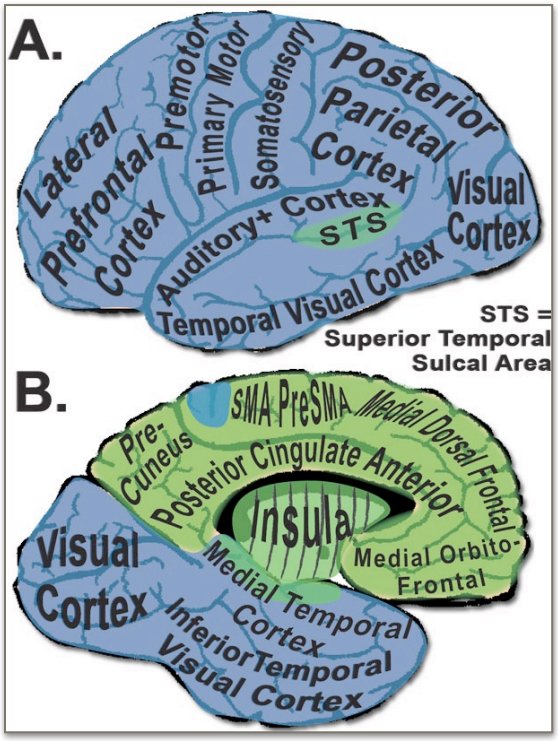


Fig 1-36. "In Here" (green) and "Out There-Related to In Here" (blue) Cerebral Cortical Areas. A. Lateral View; B. Medial View of Cerebral Cortex (gec). GO TO: gmomm.pitt.edu *Fig1-36_Video*

Self-referential processing appears to be linked substantially to areas along the medial wall of the cerebral cortex plus the insular cortex deep within the lateral sulcus (panel B green areas in the figure) and a limited portion of the lateral temporal cortex (panel A green area). On the other hand, the much larger "outer" regions of the lateral, superior and inferior cortex (blue areas in the figure) provide a means to engage and understand other biological or non-biological entities in the outside world (with the self in it). Human brain imaging studies suggest a portion of the Superior Temporal Sulcal Area (green on blue [STS] in panel A of the figure) is involved in identification of motions unique to a person or to another species versus motions of inanimate objects: a key feature supporting a "social" brain. The "In Here" and "Out There-Related to In Here" movie simulates: first a limited local activation of the visual cortex when the visual stimulus is of no relevance or interest to the subject and second, by contrast, a global cerebral cortical activation including both feedforward and

reentrant (feedback) connectivity when there is a visually captivating experience to be emulated and remembered. The normal mature human brain becomes well attuned to the biological cues and gestures of others to infer intention of the brains (beings) demonstrating those signs of life. These cues are compared to our own personal experience to provide us a best guess regarding the intentions and feelings of others, e.g., see Deco, et.al., 2011; Frith & Frith, 2010; Kjaer, et.al., 2002; Haggard, 2017. Some humans are better at reading both obvious and subtle social cues than others. Individuals within the Autism Spectrum are often poor at reading many (but not all) subtle or obvious social cues, e.g., see T. Grandin, 2008.

One significant evolutionary advantage of this "mind-reading" would seem to be the enabling of individuals to amicably engage with others so that human civilization may flourish. Alternatively, the ability to read social cues may mitigate potential hazards associated with threatening behaviors of others.

While competitive pressures certainly influence our interactions with one another, at times of relative peace and prosperity, a "cooperative" brain would seem to be better suited than a highly competitive one for socializing large groups of people who must interact in a symbiotic fashion to survive and succeed. War and various real or perceived threats of violence or even an epidemic of a life-threatening disease add substantial conscious & non-conscious biases to a competitive vs. cooperative balance.

Nonetheless, even in times of relative peace and tranquility, competition seems to trump cooperation as a reward structure for many public or private institutions/ corporations, social organizations and some individuals having big-headed egos. A mind torn between a competitive bent and a cooperative one leads to some level of tension within the reward system of the brain. As such, one might consider the composite historical record of the human race to be an enigma. Perhaps the sustained history of human existence is an example of the "Goldilocks" principle *including* extremes on a global biological scale (see beginning of this chapter).

> Concepts regarding a brain linked to a self and to the rest of the world will be revisited often in the following chapters. A healthy brain/mind balances the interface between internal processes and the appropriate external links to the physical world. For example, there is mounting evidence that your brain and your viscera are linked in a reciprocal fashion. This infers that your gut and its diverse microbiome influence some of the circuitry in your brain/mind and vice-versa. This may be especially true for your emotional/feeling brain/mind such that glad gut = glad gyri or sad sacs = sad sulci. It has been suggested that your overall state of mind related to anxiety, stress and your diet is malleable; some preliminary experiments (primarily in rodents) using fecal transplants (that is not a misspelling) may alter your mood (if you were a rodent)! In addition, inflammatory and immune reactions may link your internal milieu to your mind in a

pathologic fashion. Much of this understanding has come about quite recently due to advanced technology allowing researchers to make appropriate measurements to substantiate their hypotheses (see refs). So if you are anxious and stressed but you have a relative or friend who is easy going, totally laid back, and seems to have their s*** together (so to speak) you might consider asking them for a special **gift** on your birthday. Such visceral-mind interactions are not limited to the gut. For example, as a precocious toddler once pronounced: *"To pee or NOT to pee that is the question. Whether 'tis nobler to pee in the potty or suffer the slings and arrows of peeing in one's training pants"*. We all learn self control of body and mind at different stages of development (my apologies to W. Shakespeare). I could go on but it might get gross(er) (see refs). Indeed, Antonio Damasio's hypothesis for our conscious being is called "The Somatic-Marker Hypothesis" where body (all of it) and brain/mind cannot be treated as separate entities (Damasio, 1994, 2010).

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Chapter 2

NEURONS, NEURITES, GLIA AND MICROVASCULATURE

Cells are complex carbon-based building blocks of living biological entities. Neurons and some glial cells in the nervous system are excitable cells. Neurons "talking" to one another provide the basis for rapid neural communication. Glial cells use relatively slow signals to form glial networks and communicate with neurons, neurites and blood vessels. Unlike neurons, glia do not generate "all-or-none" Action Potentials (APs). "Fast" communication takes place by neuronal signaling where APs carry the message from one neuron to another. Peripheral Nervous System (PNS) Neurons provide a mechanism to transduce non-neural energy to neural energy (sensory) or to evoke actions by neurotransmitter release at glands or muscle due to motor axon impulses (motor). Fast communication to or from peripheral structures with the Central Nervous System (CNS) is coded by APs. Slower biochemical signals use intracellular transport mechanisms, glial-neuron interactions, and messages carried by the bloodstream, e.g, hormones. CNS Neurons provide a mechanism to gather information from one or more source(s), integrate that information ("analog" processing) and then "decide" whether information is to be sent to other neurons as a "digital" signal (axonal APs).

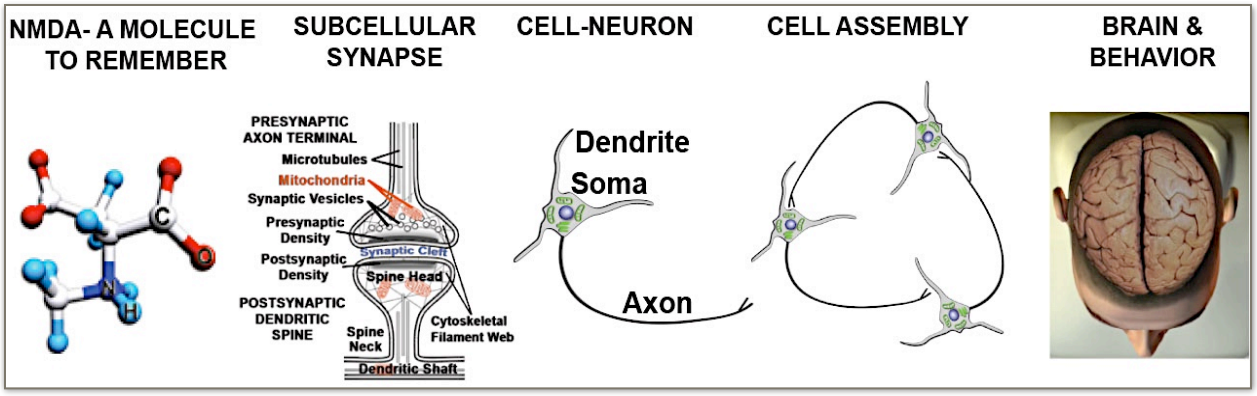


Fig 2-1. Molecule To Man. The nervous system is studied at many levels from the molecular basis of nervous system organization to behavioral studies of brains within their owners. Studies using computational networks and those combining computational and biological networks-brain machine interfaces or neuroprosthetic research are not represented in the figure. Play Many Faces of Neuroscience Movie (gec). GO TO: gmomm.pitt.edu Fig2-1_Video (LARGE MOVIE-BE PATIENT).

Neurons may accomplish the analog to digital sampling in different ways, e.g, a neuron may sum the inputs as they arrive in an integrate and fire mode or rapidly collect temporally coherent "first-in" signals in a coincidence detection mode. Most neurons use both coding mechanisms and more sophisticated methods with the selected coding dependent upon past-history and often upon the intensity of signals being accumulated.

In some instances data must be held in mind for some time, e.g., working memory and short-term memory.

Discrimination tasks most certainly require greater neural processing than simple detection tasks.

None of our brain circuitry approaches the speed of digital integrated circuits that operate at nanosecond or picosecond speeds. Biological communicators take longer to process data (typically milliseconds to seconds). Of course utilization of accumulated information may be expanded over much longer time frames, from seconds to an entire lifetime (reuse of historical “engrams” or *de-novo* use of stored data).

Neuroscientists investigates the nervous system using a broad range of methods; from a small scale, e.g, molecular to large scale, e.g., neural basis of behavior. The scale selected for study by the investigator is related to the questions to be asked in the research endeavor and the tools available to the investigator to do the work.

NEURON DOCTRINE

Two major theories formulated in the nineteenth century attempted to describe the fundamental organization of the central nervous system. One theory proposed a global lattice of continuously connected cells into a reticulum. The reticular theory was championed by J. von Gerlach and C. Golgi.

A contemporary of Golgi, Santiago Ramon y Cajal proposed an alternative hypothesis. Cajal developed a modification of Golgi's staining technique to microscopically visualize and manually render the histological details of neurons and glia. Although light microscope magnification provides limited resolution of fine detail (at micrometer level), Cajal argued that each neuron is a separate entity that connects to other neurons indirectly, i.e., an unseen physical gap exists between cells: the Neuron Doctrine, see: S. Ramon y Cajal, 1995, Lopez-Munoz, et.al., 2006 and L. Swanson, 2017. Moreover, Cajal asserted that neurons have a specific directional flow of information. Dendrites & Dendritic Spines collect information from other neurons that “flows to” and is integrated at the soma. Output from the soma occurs by way of branches of an axon that has multiple axonal swellings (synaptic boutons). Recently, neuroscientists have provided convincing evidence to show that information flow, at least for some neurons, is less polarized than that represented by Cajal’s classic Neuron Doctrine (see later chapters).

We have substantial evidence to show that neurotransmitters are released by axon boutons to provide signal transmission between excitable cells.

Chemical transmission at central nervous system synapses was not widely accepted until the latter half of the 20th century, e.g., see Katz, 1966. Charles Sherrington, at the end of the nineteenth century, named the cell to cell junction a synapse (see Fulton, p. 55, 1938).

The synaptic cleft is ~20-30 nanometers wide (as revealed in mid twentieth century by electron microscopy). Neurites include branched dendrites and branched axons. Astrocytes interact with neurites including synapses (tripartite synapse: presynaptic & postsynaptic neural membranes plus glial membrane).

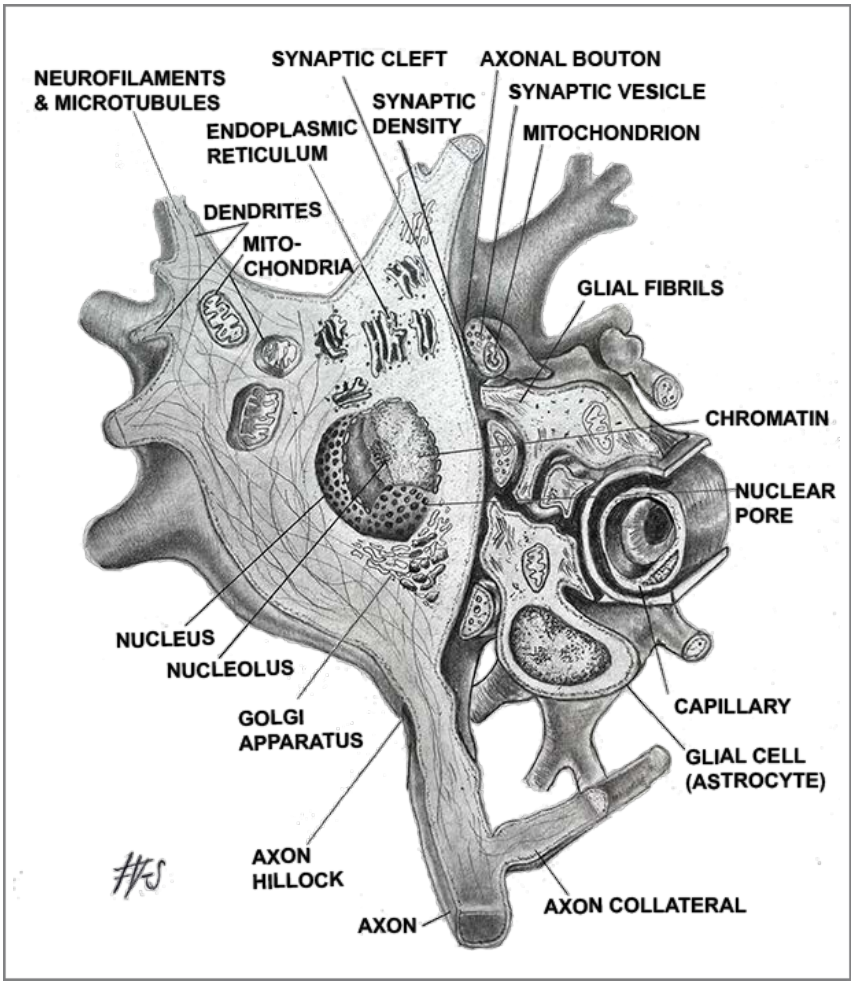


Fig 2-2. A Neuron like other cells of the body has organelles to manufacture and regulate proteins and biochemicals for normal function. It contains mitochondria to provide energy for the high metabolic demands of these excitable cells. A neuron extends its cytoplasm from its body (soma) by way of neurites (dendrites and axon). This requires special cytoskeletal proteins (neuro-filaments) and protein transport tubules (microtubules). Neuron Ultrastructure drawing courtesy of Francesca Varela-Seri, AB, BS, (fv-s, gec).

The neuron is a post-mitotic cell incapable of replicating itself. There is evidence that stem cells capable of maturing into neurons are found in certain locations within the brain that last into adulthood. Stem cells have been identified in the phylogenetically older hippocampal and olfactory brain areas although no such stem cells have been identified in the phylogenetically "younger" cerebral neocortex (cerebral gray mantle). The trigger(s) for activation of this stem cell conversion to a functioning neuron is currently being studied. Hippocampal adult stem cell neurogenesis may be critical for memory, learning and spatial navigation and may be significantly attenuated with aging and certain brain pathologies or possibly augmented by certain lifestyle or "training" factors: e.g., see Kempermann, 2008; Inoue, et.al., 2015; Anacker and Hen, 2017.

NEURON ORGANELLES

Microtubules provide highways for active transport of vesicles containing proteins and biochemicals. Anterograde transport = soma to axon or dendrite terminals, retrograde transport = axon or dendrite terminals to soma. Axonal terminations (boutons) typically form synaptic connections with another excitable cell's membrane (a neuron or muscle fiber). Nuclear DNA in neurons as in other cells provides the code necessary for the cell to sustain its structural, regulatory plus metabolic proteins and regulate gene expression. Intracellular triggers (e.g., enzymes or viruses) induce DNA to transcribe specific RNA. RNA provides the template necessary for selecting and linking amino acids to form peptides and protein molecules with the aid of the endoplasmic reticulum (ER) and ribosomes. Ribosomes and ER has been identified in portions of the dendritic tree as well as the soma. The Golgi Apparatus packages proteins into vesicles for delivery to distant locations by way of active transport: think moving truck. Mitochondria are found in soma & neurites and synapses where energy is required. Mitochondria contain their own separate DNA (mDNA) that can replicate even though the nuclear DNA of the neuron in which they reside cannot. Mitochondria use aerobic metabolism (oxidative phosphorylation) as a primary mechanism to produce the critical molecular energy source: Adenosine Triphosphate (ATP). Mitochondrial function and mDNA may be altered by aging or pathology with effects on energy production and perhaps effects on the survival of the neuron itself, see references.

ACTIVE TRANSPORT OF BIOCHEMICALS & ORGANELLES

Microtubules provide highways for axonal trafficking of vesicles containing proteins, organelles and biochemicals (neurotransmitters or precursors, neurotrophins, viruses, etc). Fast axonal transport requires ATP to energize motor molecules (dynein & kinesin) that provide the “wheels” to interface the molecular “cargo” to the microtubule highway (see animation). Vesicles are membrane bound packages of biochemicals that may be transported in either direction (see blue sphere). Viruses, large proteins may be transported in either direction (see gray particle). Axonal transport mechanism disorders may lead to “sick” neurites (distal axonal dystrophy or dying-back phenomenon) in chronic diseases, e.g., diabetic neuropathy.

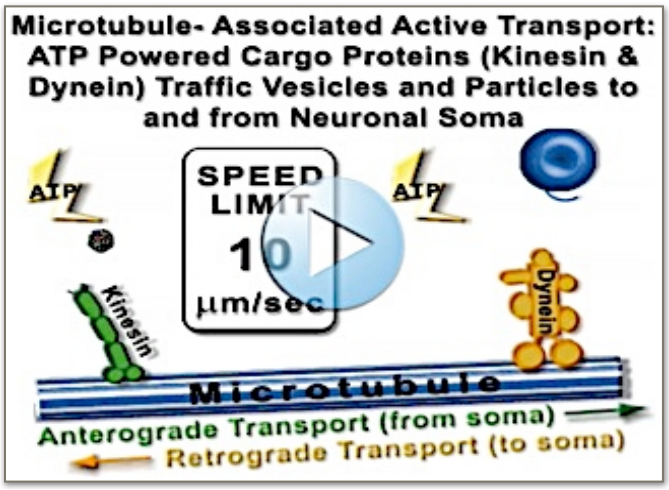


Fig 2-3. Active Axonal Transport Animation Movie (gec). GO TO: gmomm.pitt.edu *Fig2-3_Video*

Dysfunction of transport physiology or abnormal neurite infrastructure may impede or even block transport in progressive neurodegenerative diseases e.g., Alzheimer’s Disease,

Amyotrophic Lateral Sclerosis or Parkinson's Disease e.g., see: Koleske, 2013; Maeder, et.al., 2014; Millecamps & Julien, 2013.

Neuroscientists take advantage of active transport to label neurons and neurites or trace pathways in the nervous system. For example, rabies virus injected into a muscle infects motor axon terminals. Retrograde axonal transport of the virus infects (labels) motoneurons in the spinal ventral horn.

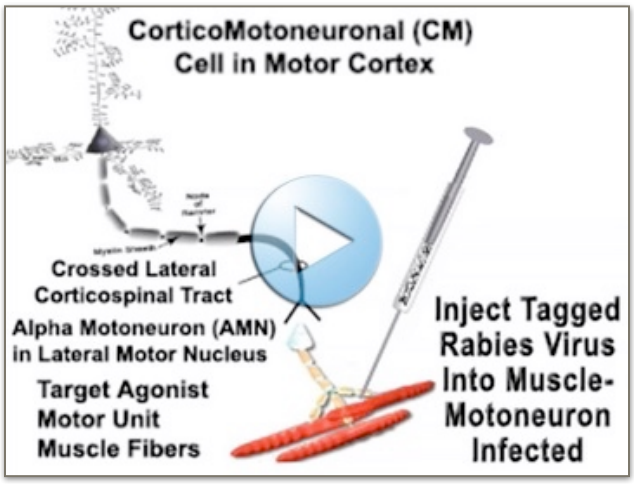


Fig 2-4. Retrograde Transport of Rabies Virus: Tracing Cerebral Cortex projections to spinal motoneurons (gec). GO TO: gmomm.pitt.edu *Fig2-4_Video*

The virus next infects those axon terminals that synapse on the motoneurons. From the spinal cord, the rabies virus is transported back (retrograde axonal transport) by way of the lateral corticospinal tract to pyramidal cells in the cerebral cortex. The Retrograde Transport of Rabies Virus animation simulates such a use of retrograde tracing to define the origin of corticomotoneuronal cells in the motor cortex that provide direct monosynaptic connections to those specific alpha motoneurons in the spinal cord that innervate the particular muscle targeted by the Rabies injection.

NEURON COMPONENTS-SOMA, DENDRITES, DENDRITIC SPINES, AXONS, AXONAL BOUTONS AND SYNAPSES

Neurons are excitable cells that have the capacity to generate large depolarizing potentials that are propagated in an all-or-none fashion from their point of initiation along an axon to the target cell(s). This self-regenerating depolarization is called an Action Potential (AP) which is critically dependent upon high densities of voltage-gated Na+ channels. The Soma and Initial Segment of the axon (axon hillock) are the normal points for suprathreshold initiation of the AP as the result of summation of accumulated depolarizing currents due to multiple excitatory inputs (EPSPs). Some dendrites also contain voltage-gated Na^+ channels that propagate plateau potentials from the soma into the dendrites and/or voltage-gated Ca^{++} channels that may generate depolarizing plateau potentials which propagate from dendrites to the soma. Excitatory inputs may be suppressed by hyperpolarizing influences from inhibitory synapses (IPSPs) and/or by voltage-gated K^+ channels or other ion channels in dendrites and soma of the neuron.

SOMA-CELL BODY

The membrane of the soma or somata or cell body is the classic location of an integration of multiple excitatory and inhibitory potentials. When the soma and axon

hillock are depolarized above threshold, the cell will initiate one or more Action Potentials (APs). Dendritic shafts may be capable of propagating a dendritic plateau potential. Back-propagated (soma to dendrite) or forward-propagated (dendrite to soma) plateau potentials may influence synaptic potentials (Synaptic Potentiation or Depression). Organelles within the soma are responsible for protein production and biochemistry that keeps the neuron viable, and responsive to alterations in its microenvironment (see above).

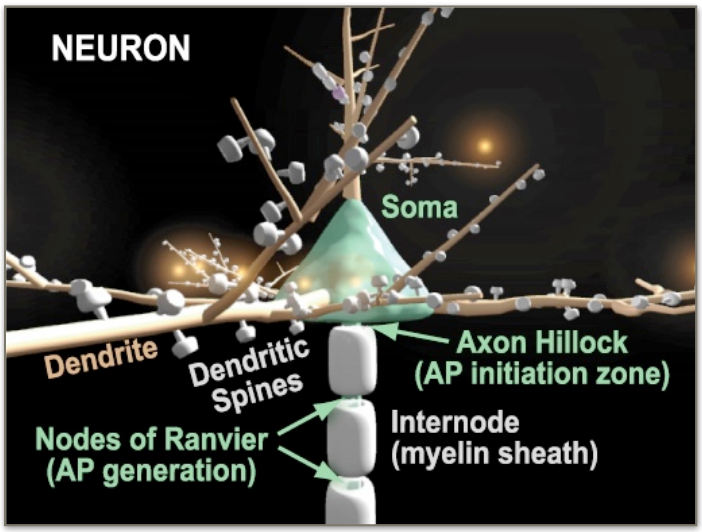


Fig 2-5. Basic Compartments of the Typical Neuron Interactive Media File(gec). GO TO: gmomm.pitt.edu
Fig2-5_Interactive Media

DENDRITES

The dendritic tree provides a distributed network of neurites that collect information from a number of sources by way of excitatory and inhibitory synapses on the dendritic shaft or on dendritic spines. The dendritic tree provides one mechanism to summate membrane potentials that will be distributed to the soma. Some dendrites may propagate Sodium or Calcium potentials (spikes) from or to the soma when sufficiently depolarized. Voltage-gated Potassium channels may influence membrane conductance. Their distribution appears to be activity-dependent. Patch clamp recordings of thin dendritic branches *in-vitro* suggest that small populations of NMDA glutamate receptors may generate “propagated” NMDA potentials. The pyramidal cell, as illustrated here, has a single apical dendrite with many branches and several basal dendrites emerging from the base of the soma's pyramid. The apical dendrite traverses a number of cortical layers in a vertical fashion, while the basal dendrites tend to have a more restricted laminar distribution. Apical versus basal dendrites may be influenced by synaptic inputs originating from different intrinsic or extrinsic sources (compartmentalization).

DENDRITIC SPINE

Dendritic spines provide a distinct point of contact for axospinous synapses which invariably are excitatory synapses. Ionotropic (AMPA, NMDA) and metabotropic glutamate receptors populate the spines. Many researchers have investigated the plasticity of these special synapses. There is increasing evidence to suggest that repetitive activation of axospinous synapses changes their morphology and efficacy; this may be one type of morphological alteration responsible for learning and memory in the CNS. Spines have a variety of sizes and shapes. Recent *in-vitro* and *in-vivo* studies

have shown an amazing mobility of the spine head and neck in response to altered glutamate, NMDA receptor or Ca^{++} levels. This rapid mobility may be due, in part, to activation of dynamic actin & other contractile/elastic proteins that form the cytoskeletal architecture of the spine. Protein manufacture may be due to local ribosomes/ER and/or proteins transported to the spines from the soma; signals for nucleic acid activation are sent from the spines to the nucleus in the soma.

AXON HILLOCK-INITIAL SEGMENT OF AXON

Action Potentials (APs) represent non-graded, all-or-none, faithful transmission of signals from the soma to the axon termination at some distance from the cell body. The AP is generated at the axon hillock (initial segment) and regenerated at each Node of Ranvier in a myelinated axon. The axon hillock represents a transition from "analog" to "digital" signals: an "analog" integration of somal graded depolarization that meets the threshold for generation of the "digital" Action Potential. A "guaranteed delivery" of AP messages ensures that if the summed local depolarizing events at the soma meet or exceed threshold and the axon hillock is not inhibited, information will be passed on to other neurons or peripheral end organs without fail. The axon hillock marks the first super high density collection of voltage-gated Na^{+} channels in the neuron, i.e., the normal site of axonal AP initiation for the neuron. The precise anatomical location of this AP initiation varies by neuron type and perhaps by the neuron's activation history, e.g., see Bean, 2007; Debanne et.al., 2011 and Yoshimura & Rasband, 2014.

AXONAL NODES OF RANVIER

Action Potentials (APs) are self-regenerative depolarizations of the axon. In a myelinated axon this regenerative process occurs at each successive Node of Ranvier (saltatory conduction). The current generated by an AP (named action current) is typically far in excess of threshold required for each Node under "normal" physiological conditions (~5x threshold safety factor for transmission). This safety factor provides a margin for continued function despite less than optimal conditions, e.g., cooled nerve. AP generation is dependent upon a high density of voltage-gated Na^{+} channels that are clustered at each Node. Nodes have few voltage-gated K^{+} channels so repolarization is different for myelinated versus unmyelinated axons.

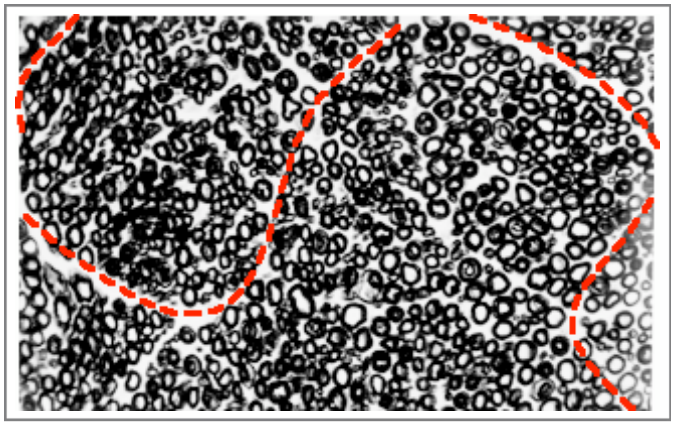


Fig 2-6. Photomicrograph (x125) of a portion of sciatic nerve in cross-section. Heavy metal stain (Osmium Tetroxide) reveals the myelin sheaths ("donuts") surrounding axons of different diameters. Unmyelinated axons are not visible. Axons are grouped into fascicles (see dashed red lines drawn on photo separating axon bundles) (G.E. Carvell & W.D. Letbetter, unpublished data).

Myelin is produced by Oligodendroglia in the CNS and by Schwann Cells in the PNS. Central or peripheral demyelinating diseases may slow or block AP conduction due to a dispersing of Na^+ channels to paranodal regions, frank loss of Na^+ channels, expression of non-native Na^+ channels and/or alterations in K^+ channels in paranodal regions.

SYNAPSE-POST YOUR MESSAGE HERE!

The synapse is the location of information transfer from one neuron to another. There are many types of synapses that have been physiologically and anatomically characterized. Protein complexes provide voltage-gated and chemically-gated channels for information transfer from a presynaptic to a postsynaptic cell. Synapse structure/function and synaptic integration will be discussed in detail in a later chapter.

Fig 2-7. Signpost for Information Transfer: Synaptic Voltage-Gated and Chemically-Gated Ion Channels (gec).

EXCITATORY AXOSPINOUS SYNAPSE-EXCITATORY POSTSYNAPTIC POTENTIAL (EPSP)

EPSPs are small depolarizing potentials that individually are inadequate to depolarize the CNS neuron's membrane to threshold for generation of an AP; many EPSPs must sum to create an AP. Summation may occur within both a spatial domain and a temporal domain. In reality summation is typically a combination of the two: a spatialsummation of EPSPs arriving at the cell at about the same time. Axospinous synapses are typically excitatory.

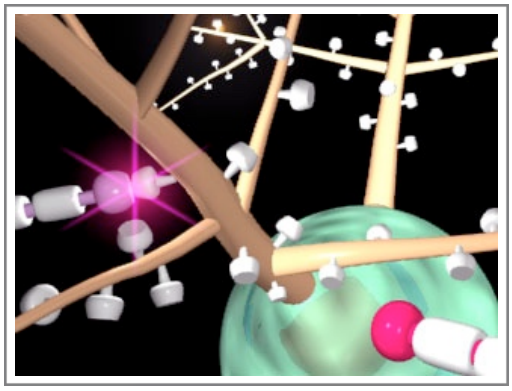


Fig 2-8. Activation of an excitatory axospinous synapse (glutamatergic excitatory axon terminal bouton synapsing on dendritic spine: see purple starburst) (gec).

These excitatory synapses are glutamatergic (use glutamate as neurotransmitter) and many axospinous postsynaptic membranes include both NMDA and non-NMDA (AMPA/Kainate) Glutamate Receptor Types. They will be discussed again in a later chapter.

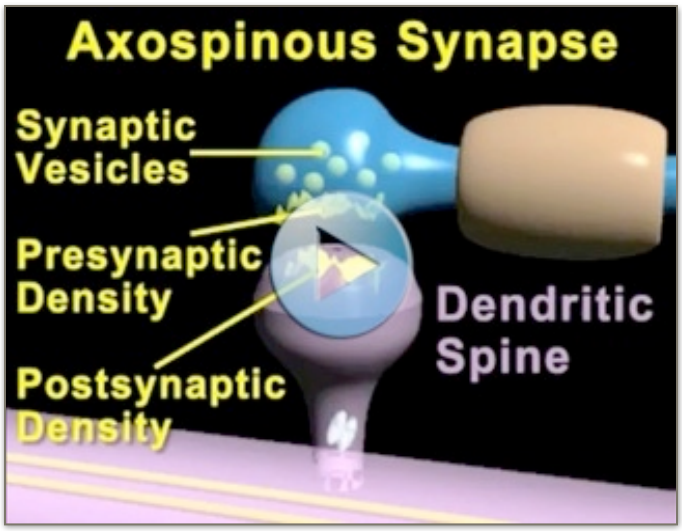


Fig 2-9. Axospinous Synapse Movie: Typical Excitatory Synapse. Watch presynaptic and postsynaptic sequence of events (gec). GO TO: gmomm.pitt.edu Fig2-9_Video

INHIBITORY AXOSOMATIC SYNAPSE-INHIBITORY POSTSYNAPTIC POTENTIAL (IPSP)

Inhibitory synapses have a key role in controlling levels of neuronal excitability. Inhibitory synapses are located along dendritic shafts (especially at branch points), are axosomatic (directly on soma) and are even found at the axon hillock (axoaxonic synapse). Thus, inhibitory synapses are in key positions to counteract the depolarizing influences of excitatory synapses on dendrites and dendritic spines.

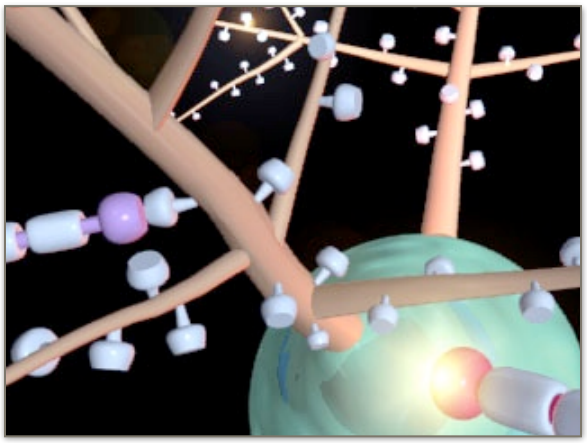


Fig 2-10. Activation of an inhibitory axosomatic synapse (inhibitory axon terminal bouton synapsing on soma: see yellow glow) (gec).

Mature Active Inhibitory Synapses may cancel all but the most potent excitatory inputs. $GABA^A$ receptors on the Soma or Dendritic Shaft hyperpolarize membranes that are relatively depolarized due to excitatory synapses, or "clamp" more hyperpolarized membranes to the Cl^- equilibrium potential (-60 mV). GABAergic synapses may provide one form of a "shunting" inhibition. Lack of GABAergic connections would be disastrous for the brain. GABAergic synapses on the axon hillock of excitatory neurons (inhibitory axo-axonic synapses) will prevent that excitatory cell from generating APs as long as the inhibitory influence lasts.

GABA MAY ENTICE YOUNG NEURONS TO DEVELOP EXCITATORY CONNECTIONS

The prenatal and early postnatal brain is a beehive of activity. Early in prenatal life precocious neural tube and neural crest cells are replicating and some are forming appropriate connections with targets in the periphery or within the developing CNS. Most of these cells will define themselves as either neurons or glial cells while a minority

may put off such a decision and remain as neural stem cells in a few regions of the developing brain even into adulthood. Some cells will not match with an appropriate target and undergo naturally occurring cell death (apoptosis). Patterns of cell migration and pathway development continue within the prenatal and early postnatal period.

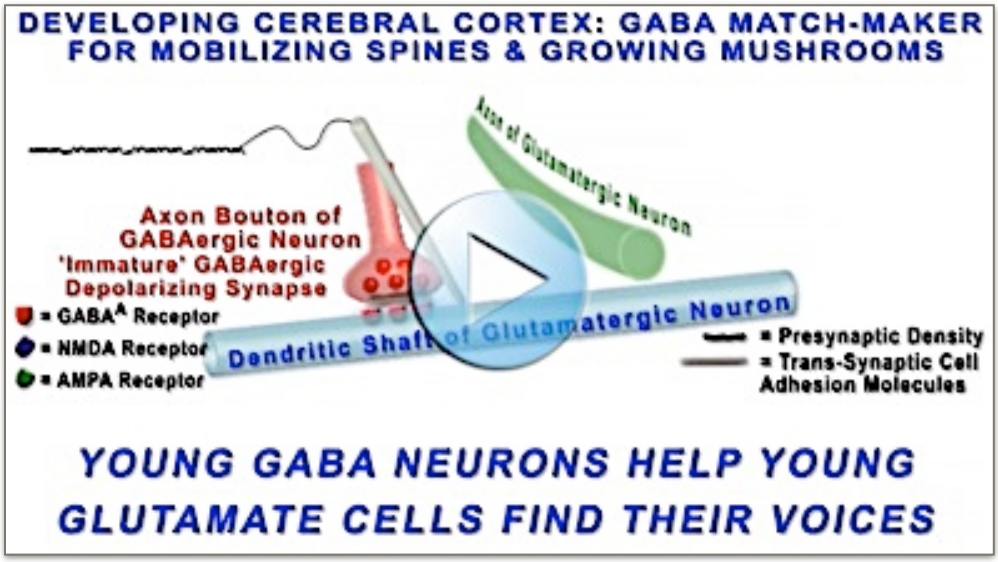


Fig 2-11. GABA Enhances Immature "Silent" Glutamatergic Synapses to find their voices (develop functional connections) (gec). GO TO: gmomm.pitt.edu Fig2-11 Video

During postnatal development, cells may decide early what they will be when they grow up while others put off this decision until greater experience with the outside world is obtained. Development of synaptic connectivity is intense in the young brain. Many genetic, molecular and activity-dependent cues appear to be important in creating, eliminating or stabilizing synaptic connections. This appears to be a "mutual admiration society" where some level of consensus is reached between the presynaptic and postsynaptic neuron. This "mating" may be dependent upon chemical cues alone or in many cases the match requires some more work in the form of patterns of neural activity (Hebbian plasticity).

Some of these relationships do not last and the synapses are eliminated while others go on to a more permanent bond as secure synaptic "marriages." One of the most common types of synapses in the cerebral cortex is the glutamatergic axospinous synapse (axon bouton to dendritic spine). Most dendritic spines start out as filopodia. If "*Mr. Right*" axon bouton meets the filopodia, trans-synaptic adhesions form, pre-synaptic and post-synaptic densities form and NMDA (but not AMPA) receptors are active. However, such nascent synapses are called "silent synapses" since the NMDA receptor requires not only glutamate binding but depolarization of the post-synaptic membrane to open the ion channel. One mechanism proposed to depolarize the post-synaptic membrane in the immature brain is $GABA^A$ receptor activation. Immature neurons are said to have a Cl^- gradient that unlike mature neurons supports depolarization not hyperpolarization of the membrane. Increased Ca^{++} conductance by

way of NMDA receptors may then activate AMPA receptor insertion so the synapse is no longer silent.

Initially, GABA neurons may be the “matchmakers” for budding excitatory synapses. Once the postsynaptic GABAergic cell matures the Cl^- gradient changes and an inward Cl^- conductance produces hyperpolarization. GABA neurons now become the “mature” constraining influence on highly excitable cells (the honeymoon is over). Play the movie.

BRAIN IS PLASTIC THROUGHOUT ITS LIFETIME

Recent evidence suggests that many connections in the brain do not become hard wired as we become adults. Brain cells contain sophisticated chemical laboratories that attempt to maintain a balance of potentially volatile biochemical reactions.

Production of new proteins is critical to long-term plastic changes. This chemistry maintains the general health of the cells and provides the extraordinary communicative functions defining sophisticated mammalian nervous systems.

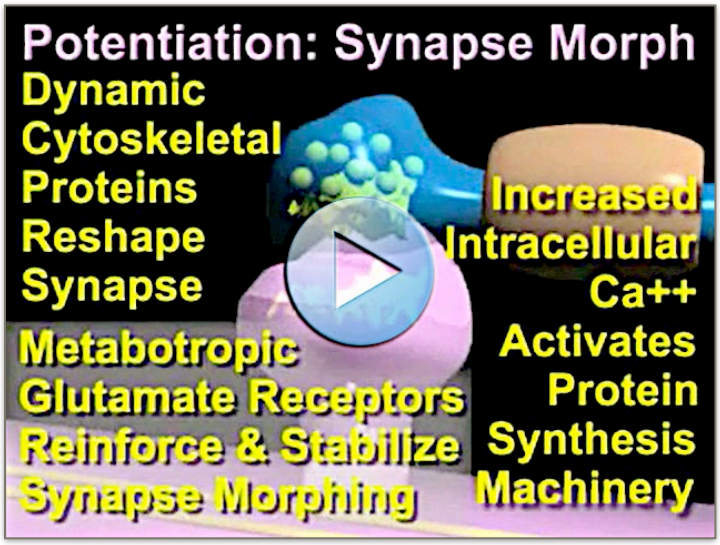


Fig 2-12. Axospinous synaptic growth (morphing) - Long Term Potentiation (LTP) Movie (gec). GO TO: gmomm.pitt.edu Fig2-12 *Video*

Early studies showed that communication between neurons requires synapses with chemically gated receptors. Recent research suggests a more diverse and complicated interaction among neurons using both autocrine and paracrine chemical messengers having both short-term & long-term effects on individual cells and cell assemblies. Activity related changes may be specific to certain synapses and/or to the overall activity of the organism (e.g., exercise may influence certain neurotrophin levels in multiple brain areas). The movie shows synaptic growth due to increased use. In addition, plasticity may result from typical maturation of the brain, brain injury, neuropathological insults. Changes occur in both neurons and glia (see below).

MICROGLIA, PERICYTES, OLIGODENDROCYTES & ASTROCYTES: BLUE COLLAR WORKERS & UNSUNG HEROES

Microglia, oligodendrocytes and astrocytes (glia) are supportive cells in the central nervous system (CNS). These supportive cells reach out to touch other CNS elements.

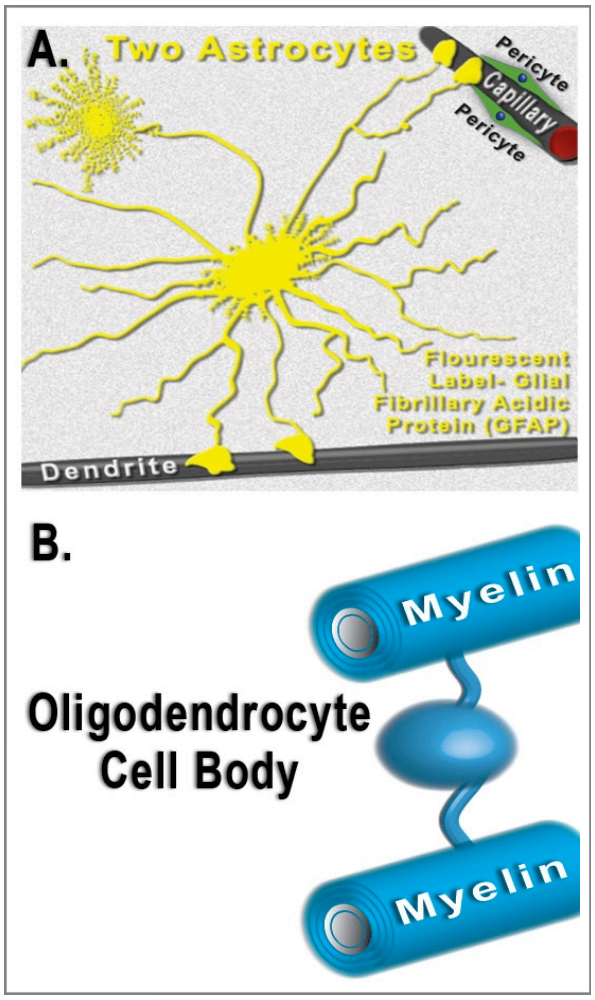


Fig 2-13. A. Astrocyte with end-feet on a Dendrite and a Capillary; another astrocyte and two pericytes along the capillary. Actual Structural Relationships are more complex than illustrated here. B. Each Oligodendrocyte myelinates multiple CNS axons (gec).

While they do not have roles in neural communication in the traditional sense (origin of excitability and synaptic interactions), these cells are critical to brain function. For example, Oligodendrocytes are glial cells responsible for myelinating CNS axons. New oligodendrocytes arising from progenitor cells may increase in number as a result of aging, disease or even motor skill learning. Action potentials may trigger release of factors that influence astrocytes and oligodendrocytes (see references). A change in CNS myelination due to age-related maturation, use-dependent cues and as reaction to injury provide examples of nervous system plasticity. Early work suggested that glial cells associated with capillaries have a passive physical and nutritive supportive role (blood brain barrier and blood flow regulation). Recent studies propose a broader and more active relationship of glia to neurons and their blood supply. Astrocytes are implicated in functions as diverse as neurotransmitter and K^+ uptake, modulating neurotransmitter release, regulating synaptogenesis & synapse plasticity, regulating extracellular biochemistry, acting as sentinel cells for homeostasis, responding to injury & aging, responding to hyperemia, and providing nutritional support of brain cells.

Recent evidence suggests that astrocytes have evolved in size, diversity and complexity as the sophistication of neural processing has evolved; human brains have well developed populations of astrocytes, e.g., see Glaume, et.al., 2010; Haim & Rowitch, 2017; Oberheim, et.al., 2006. Astrocytes are not the cells that come out on stage to take a bow at the end of a performance. However, the show will not go on without them. One study of Albert Einstein's brain showed that in Brodmann Area 39 (Posterior Parietal Cortex) there are more glia (but not neurons) than that found in control brains: see Diamond, et.al. 1985. Pericytes are contractile cells that are juxtaposed to brain capillaries (see below).

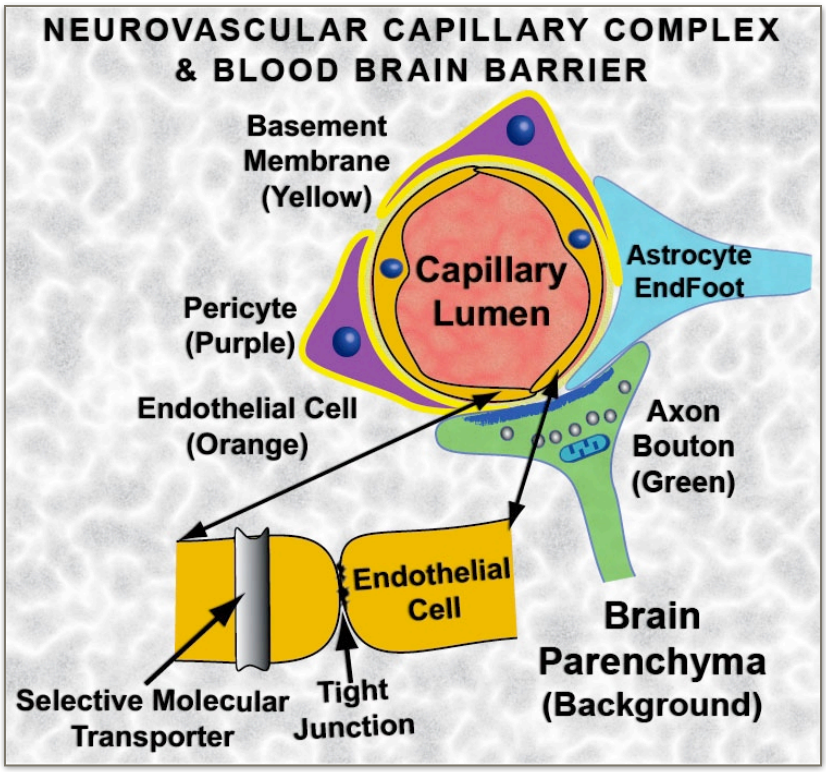


Fig 2-14. Pericyte, Astrocyte, Neuronal Input and Microvasculature: Key Elements for Normal Blood Brain Barrier and Proper Brain Perfusion (gec).

Pericytes have a role in maintenance of a restricted permeability (H_2O and molecules) in the blood brain barrier, see Armulik, et.al., 2010. When pericytes contract they constrict the capillary or when they relax the capillary dilates. Increasing levels of noradrenaline causes pericyte contraction while increasing levels of glutamate results in pericyte relaxation. Brain ischemia appears to be associated with pericyte contraction and their demise, see Hall, et.al., 2014 and Fernandez-Klett, et.al., 2010. Pericytes along with Astrocytes may play a key role in normal neurovascular coupling; dysfunctional neurovascular coupling is associated with degenerative and blood system brain disorders, e.g., see Sweeney, et.al., 2016.

Fig 2-15. Microglia In Action Movie-Rapid Response to Brain Injury (gec). GO TO: gmomm.pitt.edu Fig2-15_Video

Microglia (that invade the early developing CNS) & some astrocytes, e.g., reactive astrocytes, react within minutes to hours in response to brain injury due to physical, biochemical or molecular triggers. They attempt to contain the injury site and assist repair for extended time periods. Microglia and Reactive Astrocytes have a key role in response to inflammatory stimuli, degenerative pathology, biochemical stressors and hormonal changes within the brain. Overactivity in these glial cells with certain conditions may actually increase pathology, e.g., see Deczkowska, et.al., 2018; J. Ulrich and D.M. Holtzman, 2021. Glia may also

have a key role in regulating synaptic transmission, e.g., see Martin-Fernandez, et.al., 2017.

Microglia and Astrocytes may send protoplasmic “fingers” to separate presynaptic and postsynaptic elements at synapses during plastic events (developmental or pathologic). Play Microglia In Action movie and see references at end of movie to see rapid response “wall off” injury site due to physical or biochemical triggers. Neurons are “married” to microglia- “for better or for worse”. Recent studies suggest that microglia assist astrocytes in removing extracellular Beta Amyloid plaques in brains of individuals with early onset Alzheimer’s Disease. However, later in the disease, abnormal tau proteins (neurofibrillary tangles) accumulate inside neurites and microglia attack. Normal tau protein anchors microtubules within axons providing a highway for fast axonal transport. Abnormal tau configurations no longer do their duty and the highways crumble destroying neurites and synapses, for review see J. Ulrich and D.M. Holtzman, 2021.

PYRAMIDAL CELL DENDRITIC POTENTIALS, TRIPARTITE SYNAPSES AND NEURAL PLASTICITY

Recent technological advances have provided sophisticated tools to investigate specific compartments of the dendritic tree of pyramidal neurons. Two-Photon microscopy, laser-activated release of caged glutamate at single dendritic spines, identification of specific ion channel proteins and optogenetic techniques have shown a complex interaction of synaptically-mediated and ion-channel-mediated integration and propagation of depolarizing and hyperpolarizing events within the dendritic tree. Most data are derived from i*n-vitro* brain slices but some findings have been confirmed for *in-vivo* brains.

Both forward-propagated and back-propagated dendritic potentials are thought to be due to voltage-gated Ca^{++} or Na^{+} channels respectively. These transmembrane ion channel proteins may be altered by use-dependent redistribution and/or altered density of these channels within different compartments of the dendritic tree. There is some evidence to suggest that dendritic potentials contribute to “Hebbian” and perhaps non-Hebbian synaptic plasticity either locally or over broader expanses of the neurites. In addition, Various types of K^{+} channels and hyperpolarization-activated cyclic nucleotide gated (HCN) channels have been identified that could alter the dendritic membrane potential and contribute to shunting hyperpolarization much as inhibitory axo-dendritic synapses contribute to a shunting inhibition. If these ionic channels function in a similar manner in mature, intact brains then the mechanisms that a neuron uses to adapt to new information processing extends beyond its synapses and beyond classic spatiotemporal integration of currents derived from summation of EPSPs and IPSPs at the neuron soma.

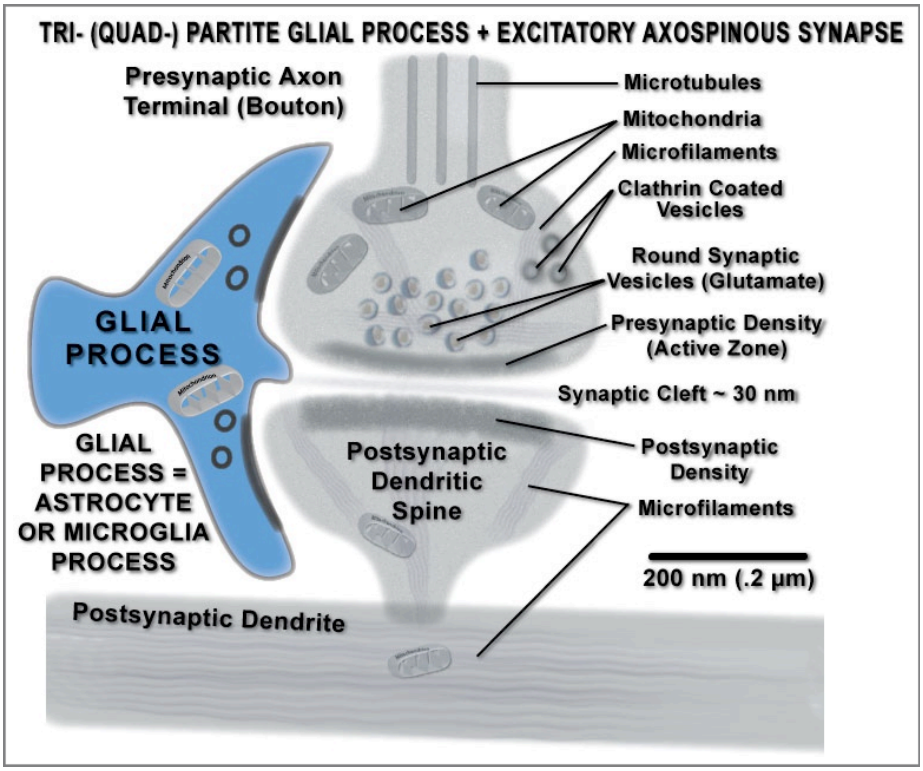


Fig 2-16. TriPartite (Quadripartite) Synapse- Relationship of Neuronal Synapse to Astrocyte and Microglia (gec)

Neuroscientists have described a robust interaction between astrocytes, microglia and neurons including tripartite (quadripartite) synapses: pre- and post-synaptic neural elements flanked by an astrocytic and microglial processes (see figure); but compared to most neural membrane potential events, glial-neural interactions are slower and are not confined to a single cell (e.g., a human astrocyte "oversees" a 200-300 micrometer microdomain). Such glial-neuron bidirectional interactions are critical components in synaptic plasticity. the relationship changes with age, is altered in degenerative brain disorders and brain trauma.

A neuron, like the human brain it inhabits can be seen as a consumer of information. Access to data on the internet is not limited to an ethernet wire connected to a desktop computer: there are other "wireless" options to get data, filter it and perhaps send it to others (if high speed is not critical then synapses are not the only option for data transfer). Astrocyte domain signaling may have an important role in more indirect "slower" brain processing.

MICROVASCULATURE: PERFUSING AN ACTIVE BRAIN

Microvasculature within the gray and white matter provides the constant supply of blood nutrients (glucose) and transport of blood gases oxygen (O^2) and carbon dioxide (CO^2) required for an organ that has little capacity for anaerobic metabolism.

While slight changes in blood flow follows cardiovascular and respiratory cycles, increased demand by elevated neuronal activity is related directly to more substantial changes in local blood flow.

The classic view is that elevated blood flow is directly correlated with increased neuronal firing: a typical supply demand relationship. However, recent investigations

suggest that elevated cellular activity (neurons and glia) is related in a complex fashion to the demands of increased metabolic requirements and hyperemia (excessive elevated blood flow). Recent evidence suggests there is no simple one-way pathway among neurons, glia and capillaries. Multiple signals from all of these elements and pericytes (see above) interact. Such interactions may provide a critical contribution to brain function beyond the basic structural or metabolic roles traditionally assigned to astrocytes and blood supply: for recent review of normal and dysfunctional blood flow regulation mechanics see Kisler, et.al., 2017; play Cerebral Neurovascular Blood Flow Regulation movie.

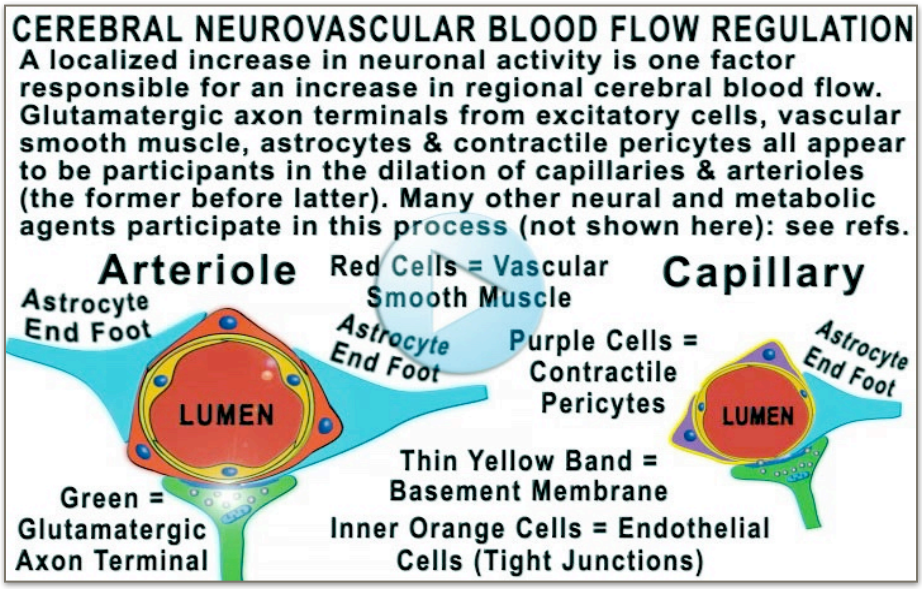


Fig 2-17. Cerebral Neurovascular Blood Flow Regulation Simulation (gec). GO TO: gmomm.pitt.edu *Fig2-17_Video*

Microvasculature-Neural-Glial Relationship Movie shows a localized arterial (red), venous (blue) and capillary network within a portion of a cortical column in the cerebral cortex. Yellow spots represent increasing levels of neural activity (subthreshold and suprathreshold synaptic events) within a number of small neuronal networks: note change when thalamic input excites many neurons. Cerebral Blood Flow, density of microvasculature and levels of neural activity are highest in the middle cortical layers (layer IV and lower layer III), at least for those sensory cerebral cortices studied: see references. Vessel pulsations mimic cyclic cardiovascular and respiratory effects on blood flow. Remember that the brain surrounded by meninges, cerebrospinal fluid and a bony cranial vault "floats" within a pressurized closed compartment (normally a low pressure).

Mechanical micropulsations are transmitted through the semisolid brain tissue. Recent direct measurements of localized blood flow suggest that as neuronal activity increases there is a localized hyperemia. Astrocytes with direct access to microvessels (arterioles and capillaries) are highly active during hyperemia. However, the level of hyperemia appears to be far in excess of actual requirements: i.e., blood supply exceeds metabolic demand. While some might argue that this represents a "safety factor," others have suggested that the observed hyperemia represents a real signal of

altered brain function beyond a simple summation of sub-threshold and supra-threshold synaptic events. Local blood flow change is assessed in functional Magnetic Resonance Imaging (fMRI) of the brain. Thus the fMRI Blood-Oxygen-Level Dependent (BOLD) signal is at best an indirect measure of neuronal function (see below).

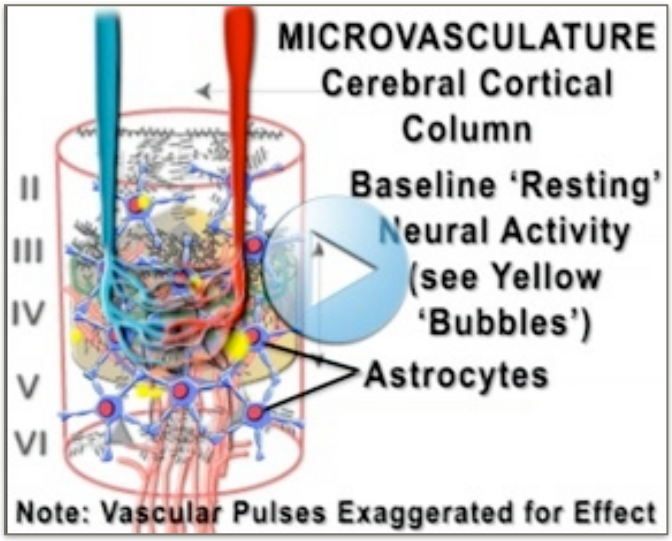


Fig 2-18. Microvasculature-Neural-Glial Relationship to Increased Metabolic Demand (gec). GO TO: gmomm.pitt.edu Fig2-18_Video

BRAIN IS AN ENERGY HOG: YOU PAY DEARLY (ATP CURRENCY) FOR ENHANCED NEURAL COMMUNICATION

While the brain is typically 2% or less of your body weight, it is a greedy organ since it utilizes ~17% of your cardiac output and ~20% of the oxygen supply: see Carpenter and Sutin, 1983. Perhaps there is a reason why some individuals look forward to "couch-potato" time watching mind-numbing TV shows or web videos at the end of a long and challenging work day. If an individual utilizes cognitive resources for a significant time throughout the day their brain has "burned" through huge quantities of Adenosine TriPhosphate (ATP), oxygen (O^2) and blood glucose. High rates of Action Potential propagation is akin to your brain running a marathon (or perhaps a speedy sprint). It should not then be surprising that neuroscientists who do "spike counting" have suggested that sparse spike coding is a network's "best friend." Efficient (neurophysiological and metabolic) neural network activity occurs when connections have been well established (repetitive practice) and "coincidence detection" replaces an "integrate & fire" mode of synaptic integration to initiate an action potential in a post-synaptic cell. This suggests an "efficient" brain opts for sparse but synchronous spiking among a sub-population of neurons within a distributed grouping of cells, e.g., within a cerebral cortical macrocolumn or microcolumn.

When information must be kept "in mind" for periods of seconds to minutes, e.g., working memory, special burst firing patterns may emerge for certain cells in the cerebral cortex. This value-added markup in energy consumption to support a burst of action potentials in a network of neurons is the price we pay for data storage and retrieval. ***Thinking is hard work even though the brain rarely lets you see it sweat.***

The Thinking Brain Is an Energy Hog movie illustrates the expected energy requirements for the cerebral gray matter as estimated for a rat brain: see Laughlin,

et.al., 1998; Attwell and Laughlin, 2001. Such requirements for your brain may differ. Aging and/or brain pathology may compromise the mitochondrial efficiency and/or reduce the number of mitochondria available to the energy hungry brain. In addition, mitochondrial dysfunction compromises metabolism and altered biochemistry could trigger pathways responsible for apoptosis, e.g., see Kujoth, et.al., 2005; Sahin & DePinho, 2010; Sahin, et.al., 2011.

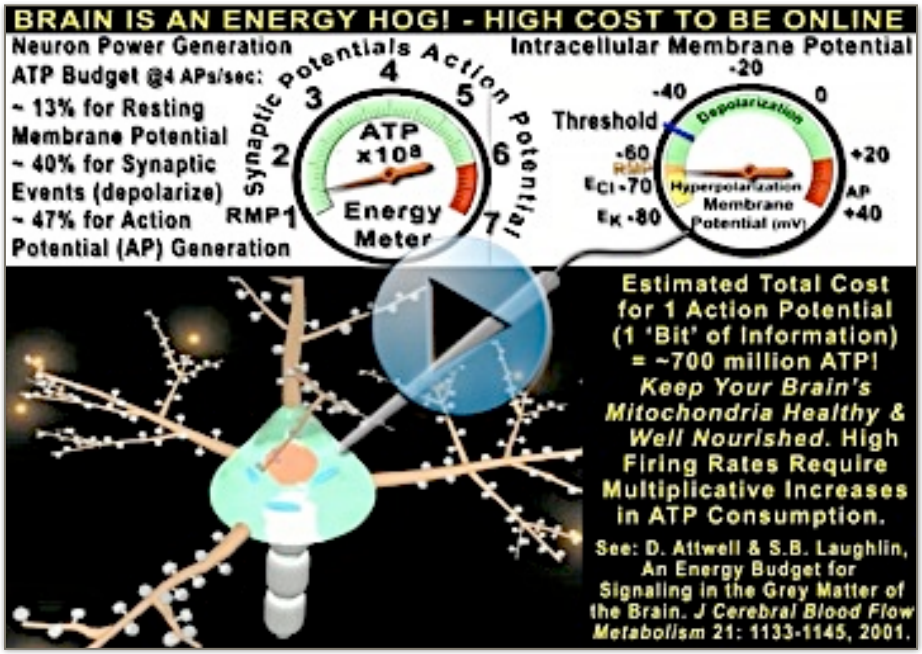


Fig 2-19. Thinking Brain is an Energy Hog-Burning ATP by the bucket loads (gec). GO TO: gmomm.pitt.edu *Fig2-19_Video*

It is suggested that the human brain may have even higher energy demands due to more complex circuitry at least in some cerebral cortical areas. Play the Thinking Brain Is an Energy Hog movie to see the large ATP budget that the brain submits to the local mitochondria and cardiovascular system for normal high-level function. It should not be difficult to imagine the critical role of optimized cerebral blood supply (plus the nutrients that it delivers to neurons and glia) in keeping ATP production at a high level. An increase in blood flow associated with increased neuronal activity has been demonstrated at least since the 19th century, e.g., see Roy and Sherrington, 1890.

FMRI BOLD SIGNAL BEST REFLECTS LOCALIZED NEURAL ENSEMBLE'S NET INTEGRATION NOT ITS ACTION POTENTIAL OUTPUT

The Blood Oxygen Level Dependent (BOLD) signature from functional Magnetic Resonance Imaging (fMRI) of the brain is a spin-echo signal due to the paramagnetic properties of deoxyhemoglobin as hemoglobin gives up its oxygen. The BOLD signal represents a localized hyperemic response where blood flow exceeds oxygen demands. It is still unclear exactly how this blood signal relates to the activity of the cells beneath the “glow.” While limited studies have suggested that the BOLD signal, like more direct measures of local circulatory or metabolic changes is related to neural activity within the brain, this is not a simple linear signal of neuronal function. For example, the BOLD

signal is significantly delayed relative to rapid, brief, transient network activation due to a relatively synchronous thalamocortical volley into layer IV of the primary somatosensory cortex. In addition, any output from this cortex tends to have few Action Potentials (APs or spikes) representing the sensory data. The BOLD signal correlates better with intrinsic network activity than with transient input or output spikes. Recordings of Local Field Potentials (LFPs) appear to be well correlated to the BOLD signal although the BOLD is delayed and far outlasts the LFP signal in most cortical areas. The LFP represents subthreshold and suprathreshold synaptic events and dendritic currents of hundreds to thousands of interacting neurons. The LFP duration exceeds the front-loaded APs that initially drive the ensemble currents, see Logothetis, et.al., 2001; Lauritzen, 2001; Heeger and Ress, 2002. By analogy, the BOLD may not represent the bolus of guests arriving at a party, nor the reflections on the party by guests who have left the party. Is the BOLD signal the lingering guest that doesn't know when to leave the party or some “re-ciphering” (echo) of the many diverse conversations that took place during the party? If BOLD represents integrative efforts but is poorly related to output APs then what is the function of the “chattering” among excitatory and inhibitory neurons reflected in the BOLD signal? Perhaps this synaptic/ionic activity contributes to more subtle interactions that represent memory, learning or some other recurrent image of integrative “history” within the network (after “talking” to other networks). If the brain uses sparse spike coding as an energy-efficient mechanism of communication then the BOLD may be a poor indicator of any inter-areal communication since output APs seem to contribute little to the BOLD signature. A further complication is the relative role of astrocytes in metabolism and blood flow regulation: all that “glows” may not be neuronal in origin, e.g., see Zonta, et.al., 2003. Brain injury/disease involving mitochondria, ion channels, synapses, neurites, glia or microvasculature will alter the BOLD signal and brain function. Any compensatory extension of the neural/glial conversation in these brains = increased amplitude and/or duration of the BOLD signal.

BRAIN FREEZES, ASTROCYTES & “AEROBIC GLYCOLYSIS”

Have you ever had a “brain freeze” and forgotten your PIN as you attempted to withdraw cash from an ATM? Did your brain ever have a “dropped call” when a passerby asks you the ages of the three dogs that you are walking? Perhaps you should blame your “tired” astrocytes not the neurons “holding” the specific information. Astrocytes are subject to aging like neurons. Neurodegenerative CNS diseases may alter astrocyte function substantially which degrades neuronal function (see references). Recent studies of brain metabolism as related to neuronal processing, blood flow and functional imaging (see references) suggest the relationship of blood flow, oxygen consumption, glucose utilization, neurons and glia to metabolic demand is much more complex than previously considered in many physiology and neuroscience textbooks.

There is accumulating evidence that blood flow and oxygen utilization lags behind an initial increase in neuronal activity for cerebral cortical neural networks. “Aerobic”

Glycolysis (production of 2 ATP due to anaerobic steps along the way in the metabolic pathway to oxidative phosphorylation producing 30 ATP) may play a crucial role in supplying needed ATP when neural network activity is suddenly increased for rapid brain responses. Thereafter, oxidative phosphorylation may provide a much greater supply of ATP for maintained brain activity. While blood flow, glucose utilization and oxygen supply increase in a relatively proportional manner, oxygen utilization may not.

As stated above astrocytes may play a key role in metabolic regulation. What glycogen there is in the brain appears to be in astrocytes. Astrocytes may use both glucose and glycogen to generate ATP. Astrocytes interact with neurons, microvasculature (in particular vascular endothelium) and synapses. There are a number of signaling molecules being investigated related to regulation of vasculature volume and pressure. Thus, astrocytes and pericytes may be well positioned to respond to glycolytic and oxidative changes related to metabolic demand for neurons *and* glia.

NEURON TYPES
PYRAMIDAL CELLS, MOTONEURONS & PURKINJE CELLS: PROJECTION NEURONS - AXONAL "TAKE OUT"

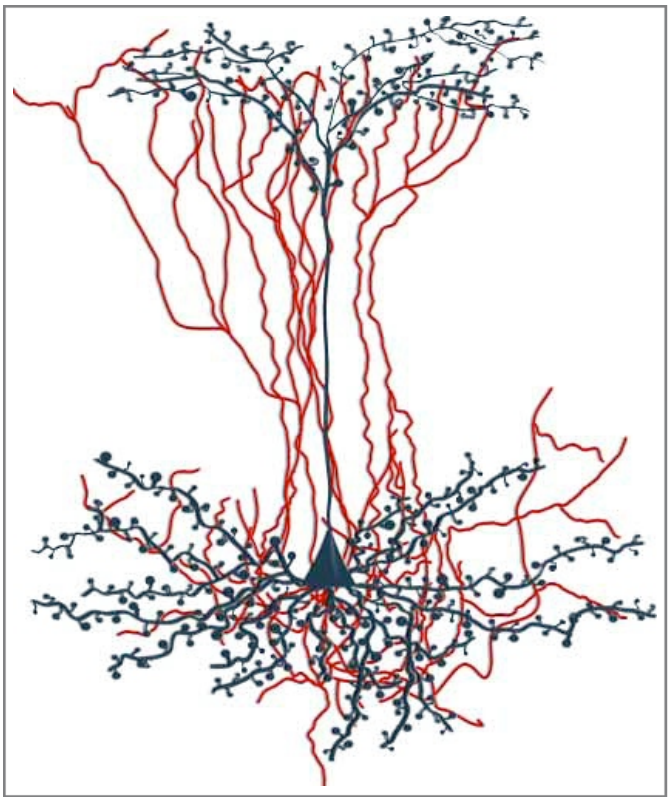


Fig 2-20. Pyramidal Cell-Projection Neuron in Cerebral Cortex. Soma and dendrites are dark; Note axon (red) projecting into white matter as well as an extensive pattern of axonal collateral projections to superficial cortical layers (gec).

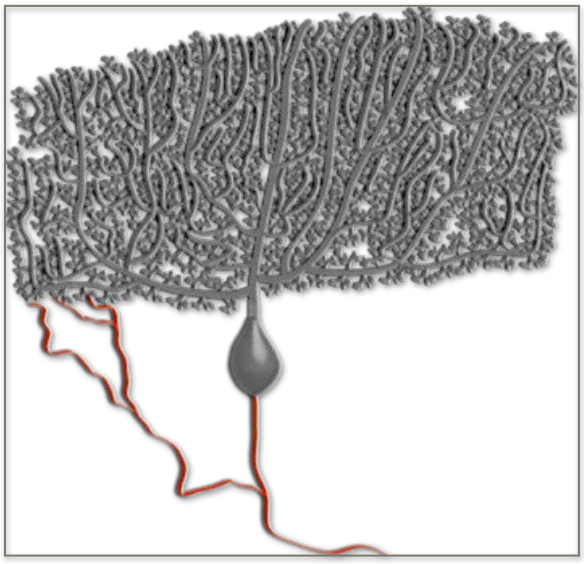
Pyramidal cells are excitatory (glutamatergic) neurons found in Supra- and Infra-granular Cerebral Cortex. Their name describes the shape of their soma (somata). Pyramidal cells have basal dendrites and a branched apical dendrite. The apical dendrite often ascends to more superficial layers, often to layer I or II. Pyramidal cell dendrites are typically spinous and their axon (red in figure) usually descends to the white matter. Recurrent axon collaterals provide signals back to other neurons in the cortex (see figure).

These excitatory projection neurons provide local or distant communication for neural networks. Corticocortical & callosal pyramidal cells are most commonly found in layer III (supragranular layers). Corticofugal pyramidal cells (projecting to subcortical brain and/or spinal structures) are typically found in layers V, VI (infragranular layers); these infragranular pyramidal neurons also have local axonal collateral projections to nearby gray matter neurons.

Motoneurons (MNs) located in the brainstem and spinal cord are projection neurons that send an axon into a cranial or peripheral nerve to innervate muscle (smooth, cardiac or skeletal) or glands. C. S. Sherrington described the alpha motoneuron and its innervated muscle fibers as the motor unit: the functional unit of contraction in skeletal muscle, see Sherrington, 1947.

Fig 2-21. Motoneuron and Innervation of Skeletal Muscle-The Motor Unit (gec). GO TO: gmomm.pitt.edu *Fig2-21_Video*

Once an action potential is conducted from the motoneuron's axon hillock to the muscle, all the muscle fibers synaptically contacted by the axon collateral terminals at the neuromuscular junction will contract (assuming the peripheral motor axon is intact and both nerves and muscles are healthy and unfatigued). Motoneurons release Acetylcholine at the neuromuscular junction to depolarize muscle fibers. Thus, the alpha motoneuron is the final common pathway for control of all movements involving skeletal muscle, see Sherrington, 1947.



Purkinje cells in the cerebellar cortex have a broad dendritic arbor that is confined to a single plane. Dendrites have large spines that receive excitatory inputs from granule cells in the cerebellar cortex. Granule cell axons ascend to the cortical surface where they bifurcate and are called parallel fibers.

Fig 2-22. Purkinje Cell-GABAergic Output Neuron of Cerebellar Cortex (axon in red) (gec).

The Purkinje cell axon (red) projects to deep gray matter in the cerebellum (deep cerebellar nuclei) or to vestibular nuclei in the brainstem.

Purkinje cells are excited by a group of parallel fibers, forming an “on-beam” for inhibition of Deep Cerebellar Nuclei (DCN) or Vestibular Nuclei (VN) cells. The inhibitory output of the GABAergic Purkinje Cells (and therefore of the Cerebellar Cortex) provides a mechanism to modulate the discharge pattern of the post-synaptic DCN or VN cells; these nuclear cells are rarely silent since they are driven by excitatory mossy fiber inputs. Thus the Purkinje cell may add precise “pauses” in this flow to increase the fidelity of the ongoing activity patterns. It is the Purkinje Cells that provide precise regulation of firing that is critical for the accurate timing inherent in coordinating movements & expediting cognitive outcomes.

NON-PYRAMIDAL CELLS: CEREBRAL CORTICAL LOCAL CIRCUIT INTERNEURONS - SPINY STELLATE EXCITATORY INTERNEURON

The soma of a spiny stellate cell is small, dendrites are spinous, and the axon (red in figure) ramifies within a relatively narrow radius around the soma.

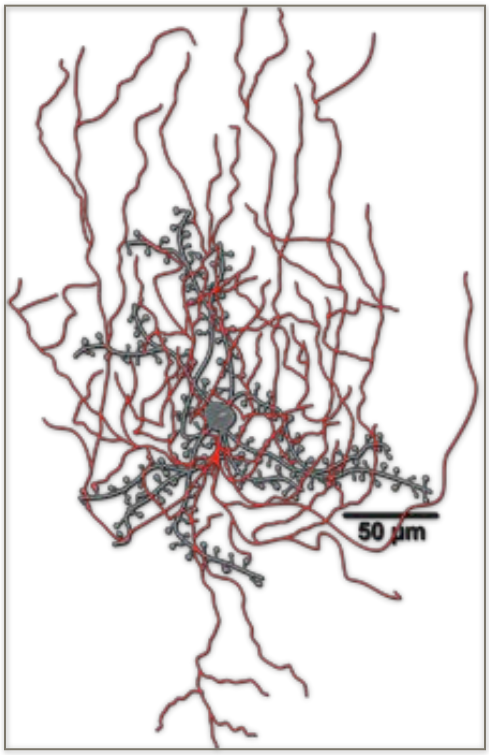


Fig 2-23. Spiny Stellate Excitatory Glutamatergic Interneuron in Cerebral Cortex (axon in red) (gec).

Spiny stellate cells are glutamatergic excitatory neurons found in Layer IV of granular cortex. Layer IV Spiny Stellate Cells receive a major excitatory input from thalamocortical afferents and from other nearby spiny stellate cells. Inhibitory inputs come from local smooth stellate (basket) cells. Other varieties of spiny cells have different dendritic arbors and axon profiles (not shown). Spiny and Smooth Stellate neurons form an important network that provides integrated output to Supragranular and Infragranular Pyramidal Cells. Spiny stellate cells in the rodent barrel somatosensory cortex are embedded within a network of these excitatory cells and another smaller group of inhibitory interneurons. Spiny to spiny stellate excitatory synapses outnumber thalamocortical excitatory synapses by an ~10:1 ratio. Inhibitory connections onto spiny stellate cells appear to be even sparser but these GABAergic synapses occur on proximal dendrites and the soma of spiny stellate cells where their hyperpolarizing effect is very potent.

CEREBELLAR CORTEX EXCITATORY GRANULE CELL

The cerebellar cortex contains millions of small excitatory interneurons called granule cells. These neurons receive input from excitatory mossy fiber axons that originate from cells external to the cerebellum. Granule cells are small cells with sparse dendritic trees that have synaptic connections in distal tufts of dendritic branches. Such synapses are complex with currents flowing in multiple directions. Granule cells are inhibited by cerebellar Golgi cells. The axon arises from the top of the granule cell soma and projects to the surface of the cerebellar cortex. The granule cell axon then bifurcates in a specific plane in the superficial cerebellar cortex. The bifurcated axon is called a parallel fiber since it runs in parallel with the many other granule cell axons that are its neighbors and travel in the same direction.

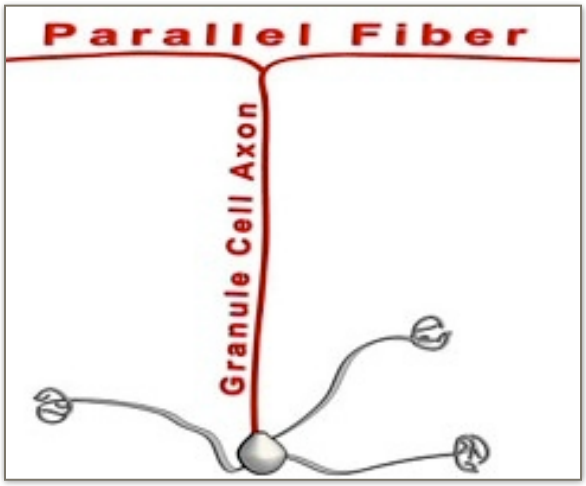


Fig 2-24. Granule Cell-Excitatory Interneuron in Cerebellar Cortex (gec).
The parallel fiber provides excitatory drive to the GABA interneurons in the cerebellar cortex as well as providing an intense source of excitatory drive to the output cell of the cerebellar cortex-the Purkinje Cell.

A stylized illustration of the granule cell is shown in the accompanying figure. Purkinje cells and granule cells tend to have a relatively high tonic background discharge in the awake resting brain. The cerebellar cortex must have its neuronal network firing rate modulated to perform its duties as a precision regulator of connected brain structures. The granule cell is the most numerous of all neuron types in the human brain.

SUPERB GABA INHIBITORY INTERNEURON DIVERSITY

Cortical excitatory cells lack diversity. Excitatory neurons in the cerebral cortex are few in type (pyramidal cells & Spiny stellate cells) and granule cells in the cerebellar cortex are the sole cortical excitatory interneuron. By contrast, inhibitory, GABAergic neurons are diverse in their morphology and connectivity: for review see Kawaguchi and Kubota, 1997; Markram, 2004. GABAergic interneurons provide local inhibitory connections to other stellate cells (spiny and smooth) and to pyramidal cells within a restricted column in the cerebral cortex. Numerous GABA neurons are found also in the basal ganglia and cerebellar cortex. One particular GABA projection cell, the Purkinje cell, provides the sole output from the cerebellar cortex to deep cerebellar nuclei or to vestibular nuclei. For most GABAergic Interneurons the soma (somata or cell body) is large, dendrites are aspinous (or sparsely spiny), and the axon is “beaded” in many GABA interneurons. The “beads” are thought to be locations of “*en passant*” inhibitory synapses. Examples of GABAergic cerebral cortical interneurons having different

morphologies include: Chandelier Cells, Bitufted Cells, Basket Cells, Double-Bouquet Cells, Single-Bouquet Cells, Martinotti Cells, Neurogliaform and Cajal Retzius Cells. GABA neurons modulate excitatory cells' discharge rate and recruitment in cell assemblies. Some GABA cells prevent the production of action potentials in excitatory cells due to soma and axon hillock inhibition; others may be critical to synchronize activity among a population of cells or provide shunting inhibition of pyramidal cell dendritic arbors. Some GABA neurons provide a mechanism to separate influences of excitatory inputs to different portions of a postsynaptic projection neuron, e.g., pyramidal cell. Evidence suggests that normal GABA cell function prevents chaotic electrical brain storms. Some GABA neurons inhibit other GABA neurons: a source of disinhibition. Both genetic and epigenetic “activity-dependent” mechanisms influence GABA neuron diversity: for recent review see Wamsley and Fishell, 2017.

A number of investigators have attempted to classify the many types of GABAergic interneurons using electrophysiological properties, morphology and/or expression of specific biochemical cell markers (see references). A recent classification based on study of somatosensory cortex in mice (Rudy, et.al., 2011) suggests neocortical GABA cells can be classified as Parvalbumin (PV) expressing cells including Basket and Chandelier cells (40%), Somatostatin (SST) expressing cells, e.g, Martinotti cell (30%) or Serotonin (5HT3aR) expressing cells, e.g., Bitufted and Neurogliaform cells (30%). The distribution of each of these groups differs according to depth within the six-layered neocortex. Within superficial layers 5HT3aR cells inhibit SST cells producing disinhibition of pyramidal cell dendrites. It is not certain that this classification is applicable to primate neocortex since the primate cortex has a greater variety and number of GABAergic interneurons.

BASKET GABA NEURON: STRONG SUPPRESSION OF PYRAMIDAL CELL OUTPUT - ENOUGH APS ALREADY!

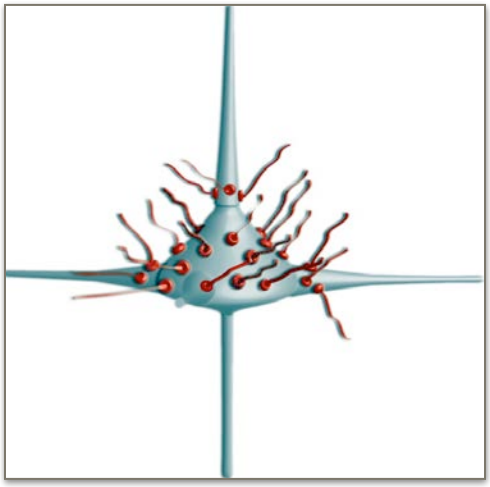


Fig 2-25. Basket Cell Axon Terminals (red) clustered on the Pyramidal Cell Soma: Influential Inhibitory Connections in Cerebral Cortex (gec).

Basket cells are Parvalbumin positive (PV) fast-spiking GABAergic inhibitory interneurons. Basket cells have aspiny dendrites that travel both vertically and horizontally within the cerebral cortex: see Basket Cell figure.

Basket cell GABAergic axon boutons (red) target pyramidal cell somas and proximal dendrites (see Basket Cell Axon Terminals figure). Basket cells come in several sizes from large to small. Each pyramidal cell receives many axosomatic synapses

from multiple GABA interneurons. The pattern of these GABA axon terminations form a basket-like appearance in high-power light microscopy.

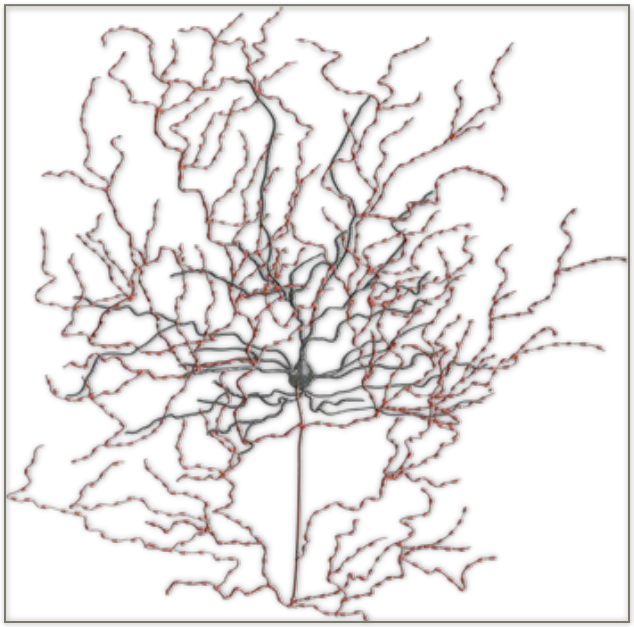


Fig 2-26. Basket Cell Soma and Dendrites are dark, axon in red. Beaded axon. Beads (axonal swellings) = loci of presumptive inhibitory synapses (gec).

This inhibitory interneuron may provide strong hyperpolarizing currents on pyramidal cell or spiny stellate cell somas that would inhibit depolarizing summation from reaching critical threshold for firing an action potential from the targeted cells.

Tonic activation of basket cells would tend to suppress excitability in many pyramidal cells reducing corticocortical and/or corticofugal outputs. Phasic activation of basket cells may increase the synchrony of firing of a select population of pyramidal cells due to periodic instantiation + release of GABA inhibition.

Basket cells have membrane properties and channels producing fast-spiking characteristics and high discharge rates. These firing properties coupled to the strong axosomatic inhibition of excitatory neurons makes these PV cells ideally suited for promoting rhythmic oscillatory network activity, e.g., see Salkoff, et.al., 2015 and Kim, et.al., 2016.

CHANDELIER GABA NEURON: HEY PYRAMIDAL CELL - BE QUIET!

Chandelier neurons have been identified as Parvalbumin positive (PV) fast-spiking GABAergic inhibitory interneurons. Chandelier cells typically have aspiny dendrites that ascend and descend from the soma within a restricted zone.

The axon arbor (red) has a distinct branching pattern where multiple *en passant* axonal cartridge boutons are clustered vertically like a candlestick. Thus the multiple candlesticks attached to this cell's axonal arbor form a “chandelier.” Synaptic axonal boutons of the chandelier cell target the initial axon segment of pyramidal cells (axo-axonic synapse).

The chandelier cell can veto any suprathreshold depolarizing summation in the pyramidal cell (PC) such that no action potential will be initiated as long as GABA is

being released from chandelier axon boutons synapsing on the pyramidal cell axonal initial segment.

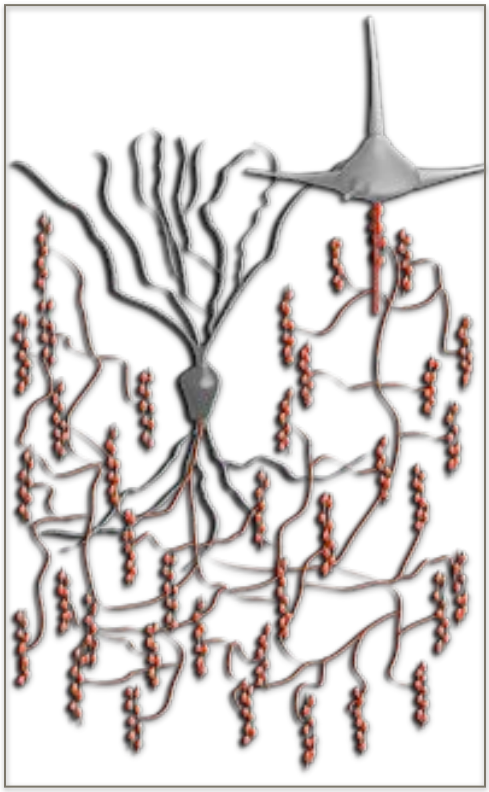


Fig 2-27. Chandelier Cell. Soma and dendrites are dark, axon branches and terminations in red. Note the vertical orientation of 'candelabra' axon boutons from the Chandelier cell that are associated with the initial segment of the pyramidal cell (light gray). This cluster of axo-axonic synapses represents a powerful mechanism for control of pyramidal cell activation in the cerebral cortex (gec).

Thus, the chandelier cell provides a "*cease & desist*" order that quiets postsynaptic active PCs, e.g., see Zhu, et.al., 2004; Lu, et.al., 2017, while also promoting discharge of quiet PCs, see Woodruff, et.al., 2011, but see also Szabadics, et.al., 2006. When the brain is awake, alert and highly active this is a source of potent inhibition. This GABAergic interneuron may be particularly well suited to prevent some pyramidal cells from firing while others continue to influence a local network or a distant target in the brainstem or spinal cord: a method of selective suppression and a process ideally suited to fine-grained, sophisticated "high definition" cortical control, see Lu, et.al., 2017. Multiple Chandelier cells innervate each PC: see Inan, et.al., 2013; each Chandelier cell may synchronize many PCs. Pathophysiology of Chandelier cells has been linked to epilepsy, e.g., see DeFelipe, 1999.

BITUFTED GABA NEURON

Bitufted neurons like smooth stellate cells are GABAergic inhibitory interneurons. Bitufted cells have sparsely spiny dendrites that ascend and descend from the soma within a very narrow distribution (vertical in the cerebral cortex-see figure). The axon arbor however, has a much broader vertical and horizontal distribution and many *en passant* axonal boutons where GABA is released.

Most of the synaptic boutons of the bitufted cell target pyramidal cell dendritic shafts. Thus, while relatively few cells within a vertical column will excite (or inhibit) the dendrites of the bitufted neuron, its inhibitory output will *quiet* a relatively broad network of neurons.

This inhibitory interneuron may be particularly well suited to regulate patterns of activity, prevent excessive spread of excitation within the brain and balance depolarizing and hyperpolarizing influences on pyramidal cell apical dendrites. This inhibitory influence is distributed across a larger macrocolumnar extent of cortex.

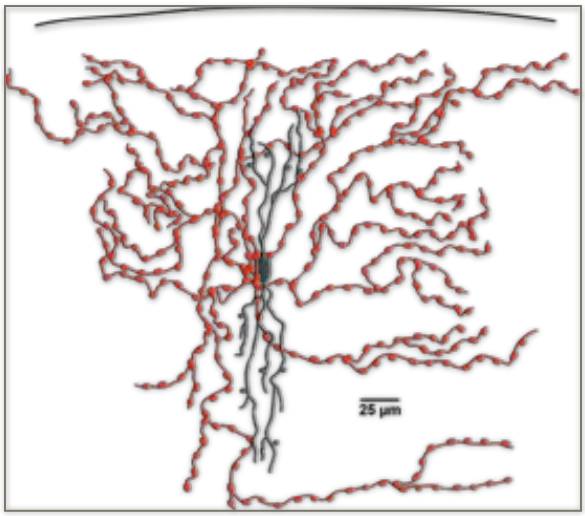


Fig 2-28. Bitufted GABAergic Cell: Dendritic Targeting Inhibition. Soma and dendrites are dark, beaded axon branches in red. Line at top = pia (gec).

MARTINOTTI GABA NEURON: PYRAMIDAL CELL APICAL DISTAL DENDRITE INHIBITION

Martinotti Cell axon terminals target primarily apical dendrites of pyramidal cells. Many of these inhibitory synaptic connections are found in the most superficial layers (layers 1 & 2) of the cerebral cortex.

Martinotti cell somata have been found in supragranular to infragranular layers although more than half of the GABA interneuron somas in layer 5 belong to Martinotti cells (see Markrum, et.al., 2004).

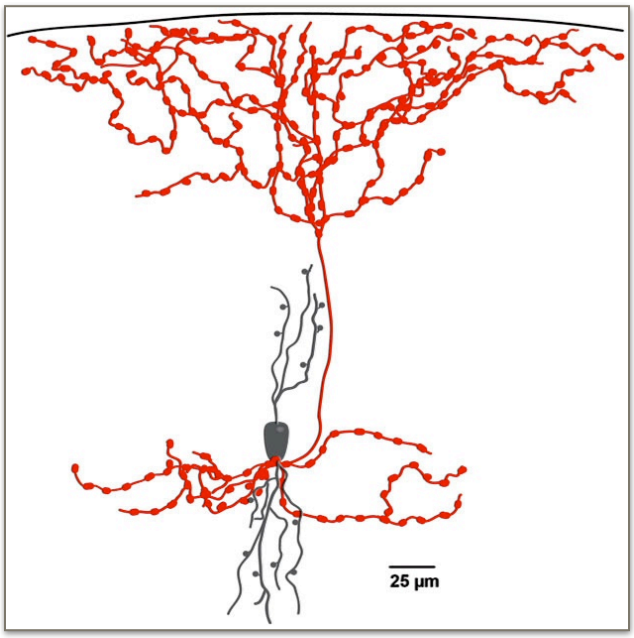


Fig 2-29. Martinotti GABAergic Cell: Dendritic Targeting Inhibition. Soma and dendrites are dark, beaded axon branches in red. Line at top = pia (gec).

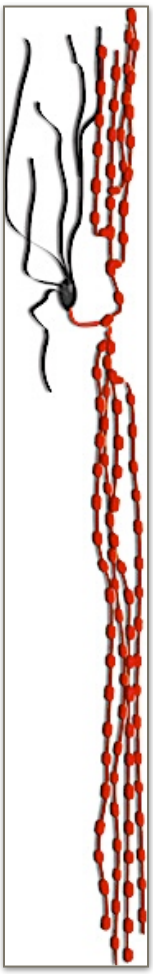
Like Bitufted cells the dendrites are few, are sparsely spiny and localized within a restricted vertical region. Martinotti cells may synchronize a select group of pyramidal cells that fire in a burst mode, e.g. see Berger et.al., 2010; Higley, 2014; Silberberg and Markram, 2007.

Martinotti cells, Bitufted cells and Rose Hip Cells in the superficial layers of the human cerebral cortex (not illustrated) provide an inhibitory control to balance the extensive excitatory inputs to pyramidal cell apical dendritic tufts in layers 1 & 2. Smaller inhibitory interneurons, e.g., Neurogliaform or Single Bouquet cells (not shown) may inhibit these inhibitory Bitufted and Martinotti cells: a disinhibitory network, e.g., see Lee, et.al., 2013; Rudy, et.al., 2011; Tremblay, Lee and Rudy, 2016; Boldog, et.al., 2018.

DOUBLE BOUQUET GABA NEURON: RENDERING HIGH DEFINITION NEURAL "IMAGES"?

Double Bouquet Cells (DBCs) are GABAergic inhibitory interneurons. DBCs have relatively few aspiny dendrites that ascend and descend from the soma within a short vertical & very narrow horizontal distribution. The long vertical but horizontally restricted axon arbor has a distinct branching pattern where multiple *en passant* axonal boutons are extended in a clustered manner that has a "horsetail" appearance.

Fig 2-30. Double Bouquet Cell (DBC) GABAergic Inhibitory Interneuron. Cell soma and dendrites are dark, axon "horsetails" are red. These "horsetails" may provide "high definition" (HD) neural images in your cerebral cortex (more "nixels" per square inch). A "nixel" is my word for a neural image pixel: think high definition flat screen display (gec)



Inhibitory synaptic boutons of the double bouquet cell's axonal arbor target the dendrites and even some dendritic spines of excitatory pyramidal & spiny stellate cells within an ~25-30 micron diameter vertical microcolumn (minicolumn). These cells may also have inhibitory inputs to Martinotti cells, e.g., see Tremblay, Lee and Rudy, 2016. Thus, DBCs may have both restricted inhibitory and disinhibitory influences in the cerebral cortex.

The minicolumn may represent a fine-grained functional unit "carved" out of a larger macrocolumn within the cerebral cortex. Within a minicolumn a small group of vertically (radially) organized cells and their neurites are aligned and interconnected across most or all cortical layers to perform a specific functional task. This task may extract, decipher and "reprocess" information about a particular subset of data originating from the thalamus (as thalamocortical afferents to the minicolumn) or from other cortical areas (as corticocortical afferents to the minicolumn).

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Most often the thalamocortical and corticocortical data are integrated within the columnar network. The minicolumn then sends a refined data set to subcortical structures by way of an infragranular (typically layer V) pyramidal cell which projects its axon into the white matter. Such axonal projections often have multiple subcortical targets. Minicolumns (and double bouquet cells) are well developed and numerous in the primate as compared to any sub-primate cerebral neocortex. Whether the minicolumn represents a refined cell assembly that offers an evolutionary advantage to primate cerebral cortex has been debated among various neuroscientists., e.g., see Casanova, et.al., 2003; Peters and Sethares, 1997; Yanez,et.al., 2005. Double Bouquet Cells (DBCs), in cooperation with other GABA cells, may provide a dynamic regulation of columnar resolution. DBCs may limit processing within discrete minicolumns creating focused "high definition" (HD) networks that are fractionated subcolumns within a larger macrocolumn. HD brain circuits may make neural images *sharper* with an improved

sense of *depth or vividness* in the representation of neural data; a diverse inhibitory population is a critical component, e.g., see Gupta, et.al., 2000; Tremblay et.al., 2016; Yoshimura and Callaway, 2005.

> Consider this scenario (role of strategic inhibition in higher functions):
>
> You are in a meeting with the "big brass" where they are discussing a strategy for moving the organization forward. Most of what they are saying is "foreign" to your usual take on such matters. You say nothing! As the discussion progresses you ascertain they have not considered a potential pitfall to their plan. Now you "release" that suppression of your brain's "voice" and provide an insightful idea (that they see as superb).
>
> Inhibitory interneurons regulating excitatory pyramidal neurons within executive brain circuitry allows us to hold our "cerebral tongue" until just the right moment. For other scenarios, the right time to speak your mind with the "big brass" might be the 24th of never - whereby your brain holds your tongue thanks to high functioning GABA cells controlling any unduly overexcitable pyramidal neurons in your frontal lobes. With aging there is increased risk for insufficient suppression of all that sparks in a "mature" brain, which could get you into trouble: NO "off the cuff" remarks!

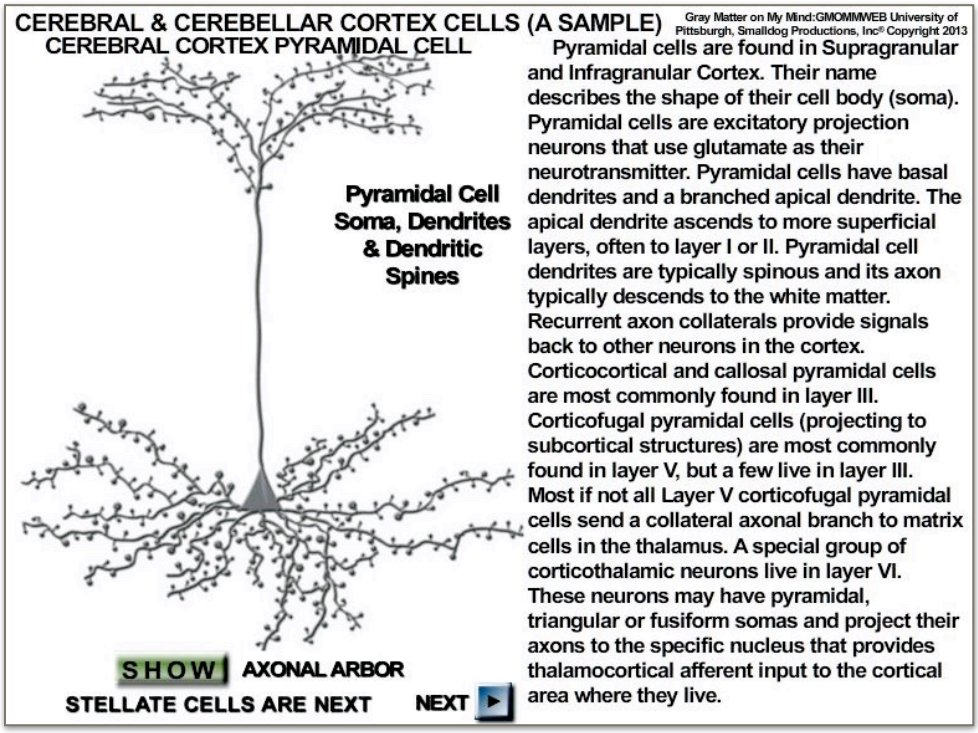

Fig 2-31. Interactive Media File. Cerebral & Cerebellar Cortex Cells. Compare Cerebral and Cerebellar Excitatory and Inhibitory Interneurons and Two Projection Neuron Types (gec). GO TO: gmomm.pitt.edu Fig2-31_Interactive Media

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Chapter 3

EXCITABILITY

Neurons and many glial cells in the nervous system are excitable cells. Glial cells use relatively slow signals to form glial networks and communicate with neurons and blood vessels. Glial cells do not generate “explosive” action potentials (APs). APs are generated by most neurons. “Fast” communication takes place by neuronal signaling that use APs. Peripheral Nervous System (PNS) Neurons provide a mechanism to transduce non-neural to neural energy (sensory) or to evoke actions by transforming APs to gland secretion or muscle contraction (motor). Central Nervous System (CNS) Neurons provide a mechanism to gather information from more than one source, integrate that information (analog processing) and then “decide” whether to send information to other neurons as a “digital” signal (axonal APs). Neurons may code the analog to digital sampling in different ways, e.g, sum the inputs as they arrive in an integrate and fire mode or rapidly collect temporally coherent “first-in” signals as a coincidence detector. Most neurons make a “decision” to initiate an AP using either coding mechanism with the selection of the code dependent upon past-history and often the intensity of signals being accumulated. None of the biological signals approach the speed of electronic digital integrated circuits that transfer information at nanosecond or picosecond speeds. Biological communicators take a longer time to process data (many milliseconds to multi-second timeframe). Such data may be optimized over durations ranging from sub-second intervals to long-lasting alterations in circuits due to memory consolidation or learning.

NEURON MEMBRANE (HIGH FAT, ADEQUATE PROTEIN, AND LOW CARB “DIET”) - RESTING MEMBRANE POTENTIAL

Most of our cells that are alive and healthy have a polarized cell membrane (a biological battery). This polarization is negative inside and is called the Resting Membrane Potential (RMP). Typically, intracellular concentrations of Na^+ and Ca^{++} are low compared to K^+ (see Ion Table below). Excitable cells such as those in the nervous system have the additional property of allowing signal generation & transmission (neural processing). The RMP is due primarily to the selective permeability of the phospholipid cell membranes to K^+. These K^+ ion pores in a transmembrane protein complex (K^+ leak channels) provide the mechanism to create a membrane potential (internal negative 65 mV) between the inside and outside of the cell due to an ionic gradient “charging” the battery. A high concentration of negatively charged large molecules (typically intracellular proteins), labeled Anions (A^-) in the figure, are trapped inside the cell. This thin line of potential difference (RMP) due to K^+ permeability exists along the membrane surface but does not extend into the heart of the cytosol nor the extracellular fluid. Because cell membranes are leaky, like a battery, the RMP would eventually lose its charge with repeated excitation (depolarization) that produces an influx of Na^+. The Na^+-

K^+ ATPase Pump actively maintains this charge by pumping ions against their concentration gradient at the expense of energy consumption powered by Adenosine TriPhosphate (ATP).

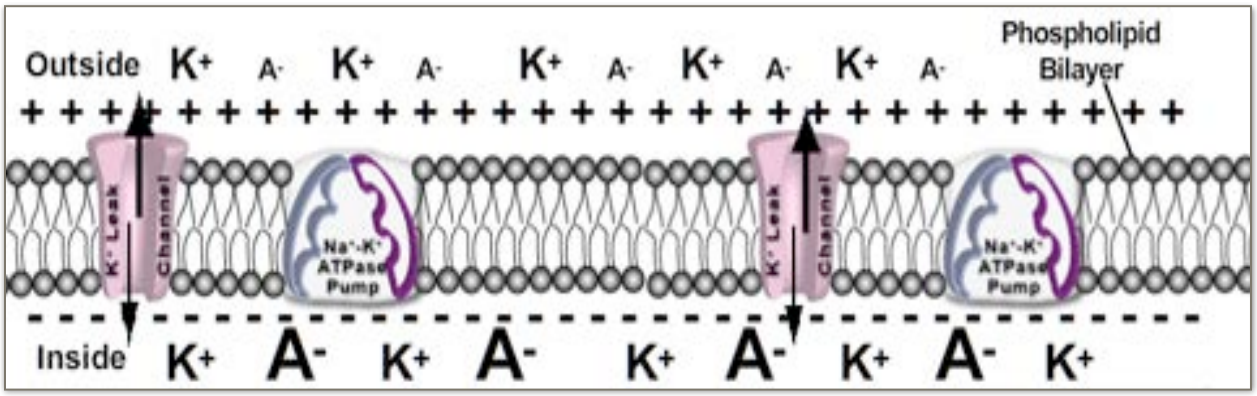

Fig 3-1. Transmembrane Proteins in Excitable Phospholipid Bilayer Membrane (gec).

ION CONCENTRATIONS AND ELECTROMOTIVE FORCE OF CRITICAL IONS FOR "TYPICAL" MAMMALIAN NEURON				
Ion	**Outside Concentration**	**Inside Concentration**	**Ratio Outside: Inside**	**Equilibrium Potential**
Potassium (K^+)	**5 mM**	**100 mM**	**1:20**	**-80 mV**
Sodium (Na^+)	**150 mM**	**15 mM**	**10:1**	**+62 mV**
Calcium (Ca^{++})	**2 mM**	**.0002 mM**	**10,000:1**	**+123 mV**
Chloride (Cl^-)	**150 mM**	**13 mM**	**11.5:1**	**-70 mV**

Fig 3-2. Transmembrane Ion Concentrations and Equilibrium Potentials (gec).

The milliMolar (mM) concentration of ions inside and outside a healthy neuronal cell membrane are shown in the table. Their ratio determines the relative electromotive force. The Equilibrium Potential in milliVolts (mV) represents the cell's membrane potential at which the diffusion gradient and electrical forces are equal and opposite for that particular ion. For example, if the Na^+ level was measured and equilibrated across the membrane, the membrane potential would be +62 mV (i.e., in an unsustainable highly depolarized state). When Cl^- ion concentration is at equilibrium the membrane will be at or close to the typical Resting Membrane Potential (-65 mV to -70 mV). When Cl^-

passes through the membrane via a Cl^- ion channel, the membrane tends to be clamped (held) at the Cl^- equilibrium potential. Actual values vary according to location, e.g., axon versus soma or dendrite, according to cell type and may differ by species, e.g., invertebrate versus vertebrate animals.

SODIUM-POTASSIUM ATPASE PUMP

Sodium-Potassium ATPase Pump Animation shows sequence of events for the K^+ leak channel and the Sodium-Potassium ATPase Pump (Na^+-K^+ ATPase Pump). The Na^+-K^+ ATPase Pump actively maintains or restores a resting membrane potential of an internal -65 to -70 mV by pumping ions against their concentration gradient at the expense of burning energy (ATP). Three Na^+ ions move to a high affinity binding site. ATP energizes the pump and a conformational change occurs in the Na^+-K^+ ATPase Pump. After ATP activation Na^+ ions are pumped outside and two K^+ ions move to a high affinity binding site. The ATPase pump changes shape and delivers the K^+ inside.

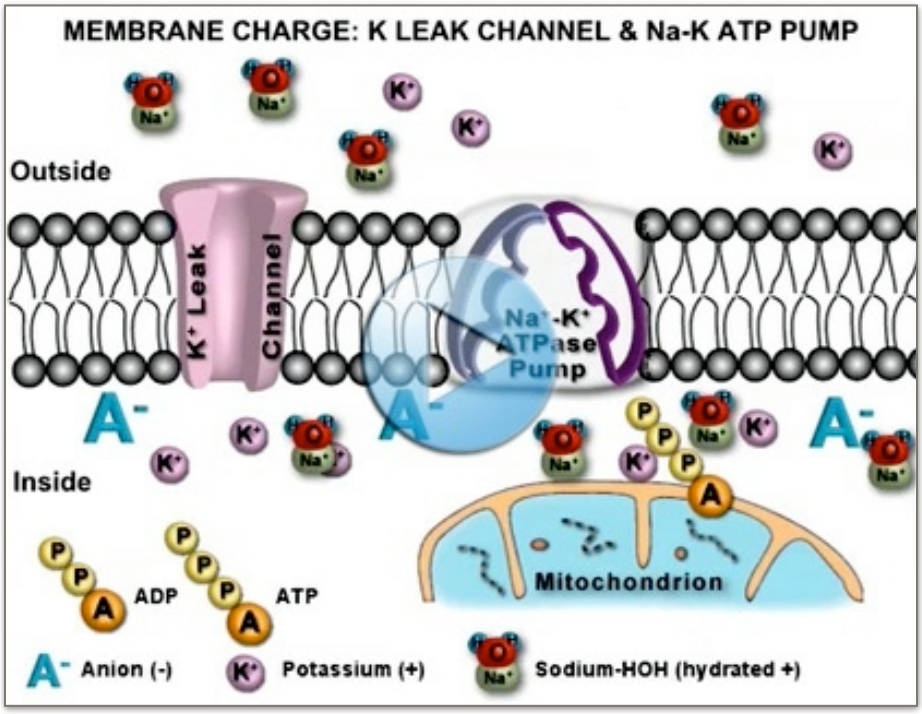

Fig 3-3. Sodium-Potassium ATPase Pump Animation Movie (gec). GO TO: gmomm.pitt.edu *Fig3-3_Video*

VOLTAGE-GATED SODIUM CHANNEL: ACTION POTENTIAL

Neurons are excitable cells that can generate large depolarizing potentials that are propagated in an "all-or-none" fashion from their point of initiation along an axon to the axon terminal(s). This self-regenerating depolarization is called an Action Potential (AP). The critical ion channel for this depolarization is the voltage-gated Na^+ channel (**NaV**). Nine subtypes of the **NaV** channel have been identified for the mammalian nervous system, e.g., see: Yu and Catterall, 2003; Dib-Hajj, et.al., 2013. The **NaV** has two gates: an activation gate and an inactivation gate. At rest, the inactivation gate is open & the activation gate is closed. During the depolarizing (rising) phase of the AP, the activation gate opens & Na^+ rushes IN before a slower inactivation gate closes. During the repolarizing (falling) phase of the AP, the inactivation gate is closing to prevent further

Na^+ influx. When the resting membrane potential has recovered, the Na^+ inactivation gate opens and the activation gate closes. The Na^+ inactivation gate is critical in myelinated axons since paranodal voltage-gated K^+ channels do not repolarize normal Nodes of Ranvier (see figure). Repolarization (falling phase) is due to a combination of Na^+ inactivation (closing inactivation gate of Na^+ channel and K^+ efflux through the open voltage-gated K^+ channel (unmyelinated axon only). An After-Potential is a brief period of hyperpolarization when threshold is raised for generation of a second spike.

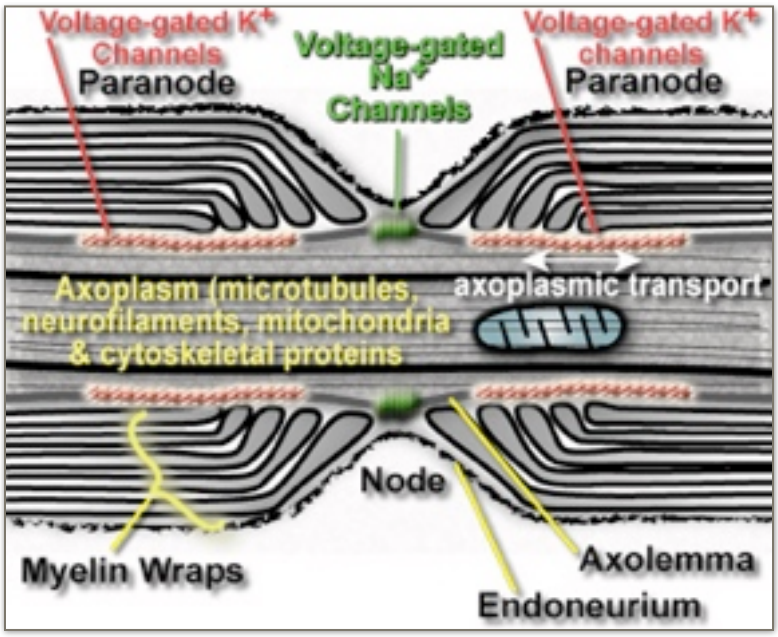

Fig 3-4. Node of Ranvier in Myelinated Axon. Sodium & Potassium Voltage-Gated Channel Separation for Node versus Paranode (gec).

The Voltage-Gated Sodium (Na^+) Channel (NaV) and Action Potential Movie shows the sequence of opening and closing for the Activation and Inactivation Gates of the **NaV** channel related to the depolarizing, rising phase and repolarizing, falling phase of an Action Potential. The voltage-gated K^+ channel is not included in this simulation.

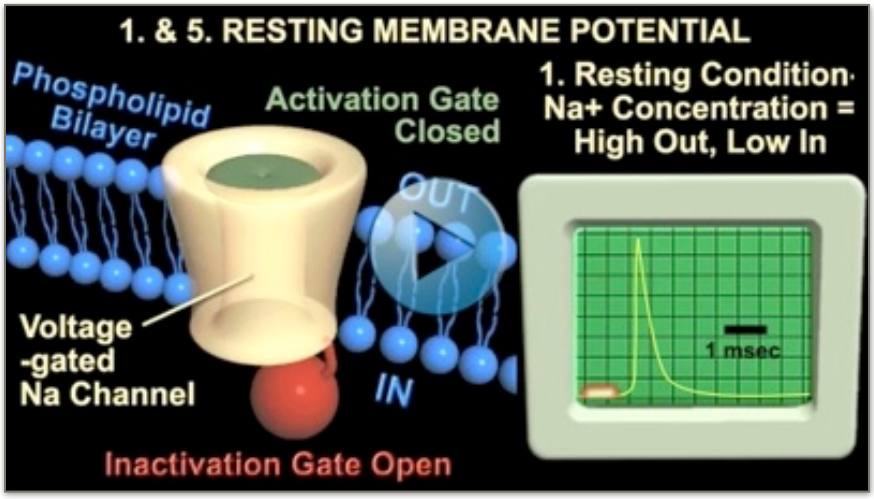

*Fig 3-5. Voltage-Gated Sodium Channel (**NaV**) and Action Potential Movie (gec). GO TO: gmomm.pitt.edu*
Fig3-5_Video

(1) At rest, the Na^+ inactivation gate is open, the Na^+ activation gate is closed and the voltage-gated K^+ channel is closed. (2) During the rising phase of the AP, the activation gate opens and Na^+ rushes IN before the slower inactivation gate has a chance to close. The K^+ channel remains closed. (3) During the falling phase, the inactivation gate is closing to prevent further Na^+ influx and the K^+ channel opens. (4) The Na^+ Activation Gate Closes & K^+ channel remains open and the

membrane remains relatively refractory for a short period of time after the spike. (5) When the resting membrane potential (RMP) is recovered, the Na^+ inactivation gate is open and activation gate is closed. The voltage-gated K^+ channels are again closed.

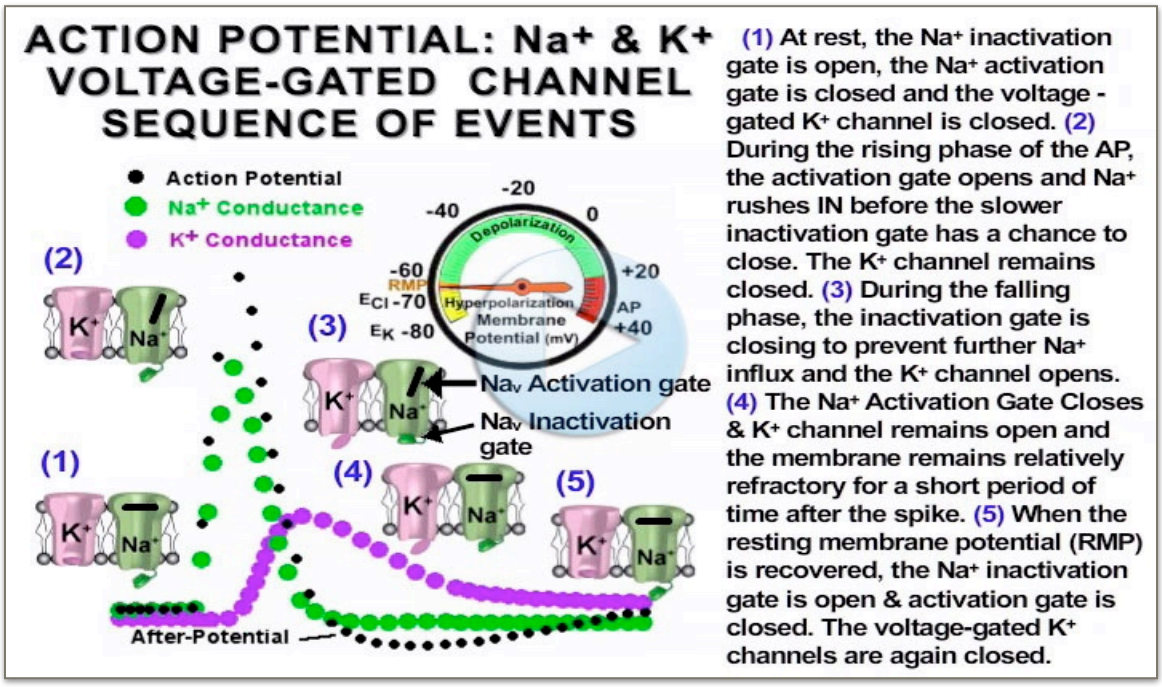

Fig 3-6. Voltage-Gated Sodium and Potassium Channel Conductance in Unmyelinated Axon Movie (gec). GO TO: gmomm.pitt.edu [Fig3-6_Video]

REFRACTORY PERIOD

An Action Potentials (AP) is the product of the opening and closing of gates in a population of Na^+ voltage-gated channels (**NaV**) at a Node of Ranvier in a myelinated axon. Both **NaV** and the slower voltage-gated K^+ channels (**Kv**) are responsible for the rising and falling phases of the spike in an unmyelinated axon. Action Potentials are "explosive" events where **NaV** channels alter their conformation to open and close gates rapidly. Nonetheless, the axon has a short time when it is unresponsive after a spike has been generated. This is the Absolute Refractory Period (ARP) and lasts for the duration of the spike. Large diameter heavily myelinated axons have spike durations of ~0.40 msec while the smallest unmyelinated axons have spike durations ~1.5 msec. Thus, large myelinated axons theoretically can be activated at > 2000 times per second though this rate of spiking typically does not occur in the brain. Short bursts of high frequency APs occur for some neurons *in-vivo* under certain conditions.

Following a spike is the after-potential where the membrane is more hyperpolarized and threshold for reactivation is elevated. This produces a Relative Refractory Period (RRP). Like the ARP the RRP is shortest in duration for myelinated axons but may be quite long for unmyelinated axons due to the relatively slower **Kv**. There may be an increased conduction delay of the AP during the RRP. Watch four animations in the

Refractory Period Movie that show spike responses to one or more stimuli. The time of each stimulus is seen as a stimulus artifact (see S arrows). When two stimuli are far enough apart in time there is no refractoriness. As the second stimulus occurs closer in time to the first stimulus, the RRP is seen as a slightly smaller second spike. When two stimuli are very close in time there is no response to the second stimulus = ARP.

Fig 3-7. Refractory Period Movie (gec). GO TO: gmomm. pitt.edu [Fig3-7_Video]

COMPOUND ACTION POTENTIAL (CAP) REFRACTORY PERIOD

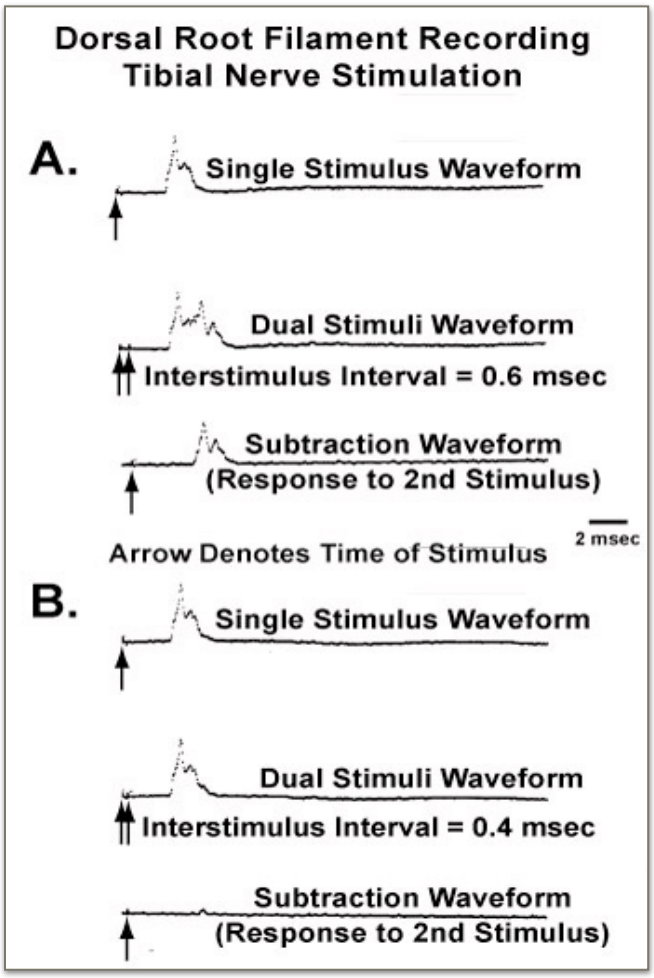

Fig 3-8. Dorsal Root Filament Monophasic CAP Refractory Period: Digitized Monophasic Waveforms (A/D sampling @ 20 KHz) G.E. Carvell & W.D. Letbetter, unpublished data (gec).

The dorsal roots enter the spinal cord as segregated filaments each of which is composed of a very small population of myelinated and unmyelinated afferents.

The figure shows a monophasic CAP recording from a single L7 dorsal root filament in a cat. Dual stimuli reveal a relative refractory period at 0.6 msec (panel A) and an absolute refractory period at 0.4 msec (panel B) interstimulus intervals for this small group of rapidly conducting, large myelinated A sized axons (maximal Conduction Velocity ~90-100 M/sec). Compare the single stimulus waveform to the delayed subtraction waveform due to the second stimulus at a 0.6 msec interstimulus interval (relative refractory period) but absence of the

subtraction waveform when paired stimuli are temporally separated by a 0.4 msec interval (absolute refractory period).

ALTERED NERVE CONDUCTION AND REFRACTORINESS IN REGENERATING MYELINATED SENSORY AXONS

If a peripheral nerve is damaged by crushing or transecting the nerve a series of events ensues. Initially the axons and myelin degenerate distal to the lesion (Wallerian Degeneration). Provided the local environment is conducive to regeneration, a single axon sprout will regrow to its distal target (sensory receptor or muscle).

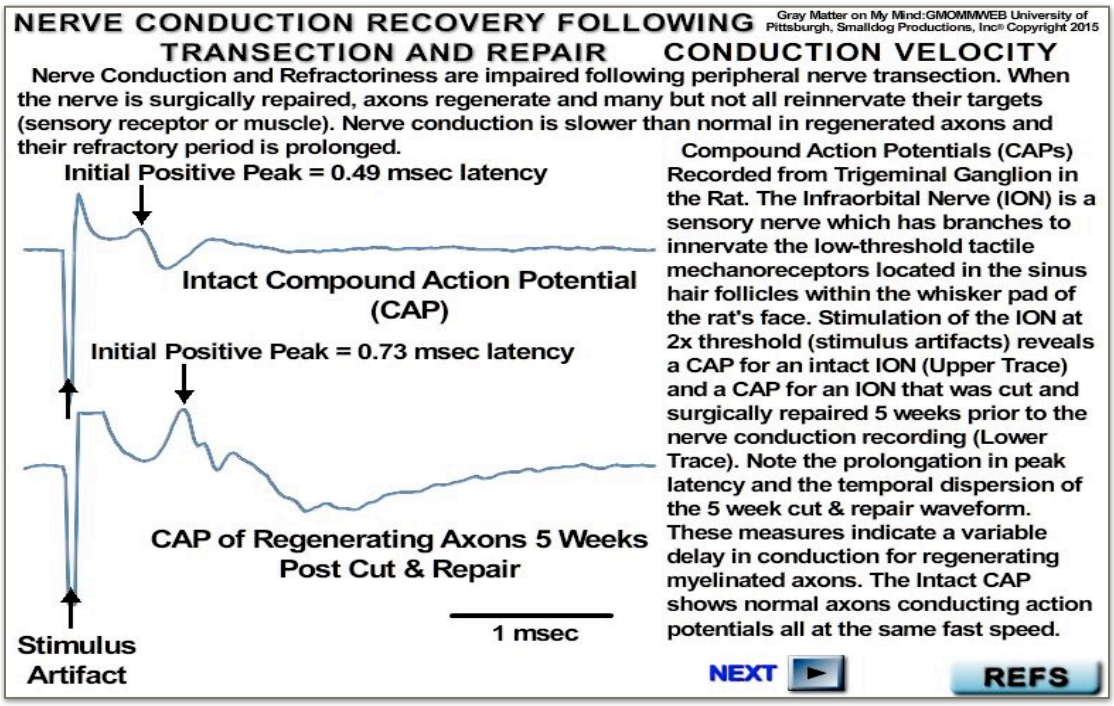

Fig 3-9. Nerve Regeneration Nerve Conduction and Refractoriness Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig3-9_Interactive Media*

If there are no physical or biochemical barriers to regeneration, most but perhaps not all axons will reinnervate their targets. The process includes remyelination of regenerated axons. A more complete consideration of this regenerative process will be discussed in a later chapter: Motor System: Introduction-Peripheral & Spinal. The Interactive Flash File: Nerve Regeneration Nerve Conduction and Refractoriness shows Compound Action Potentials in intact and regenerating Trigeminal Ganglion Cells evoked by stimulation of Infraorbital Nerve in the rat in control animals and in rats at various time points following complete nerve transection and surgical repair of the Infraorbital branch of the trigeminal nerve.

MYELINATED AXONS: SALTATORY CONDUCTION

Myelinated axons conduct Action Potentials (APs) in a saltatory fashion, that is, the AP is said to jump from one Node of Ranvier to the next.

Saltatory conduction was described in some detail by Ichiji Tasaki in the early twentieth century who teased out individual myelinated motor axons from a nerve of a Japanese toad or bullfrog, see: Tasaki, 1938, 1953. Using primarily homemade equipment, Tasaki described action current in a single axon localized to the Node of Ranvier that is generated when an AP discharges at the Node. The AP's action current spreads to the next Node and generates a *new* AP at that Node. We now know that Voltage-gated Na^+ Channels (**NaV**) are localized in very high density at normal Nodes of Ranvier with few or no **NaV** in the internodal or paranodal regions covered by myelin: see Bean, 2007; Caldwell, et.al., 2000; Catterall, 2000; Dib-Hajj, et.al., 2013; Goldin, 2002; Waxman, 2006; Waxman, et.al., 2000; Yu & Catterall, 2003. The highly concentrated population of nodal **NaV** are responsible for the AP and Tasaki's action current. Distribution of the nodal **NaV** channels may differ at axonal branch points where there may be an increased chance of conduction failure: see Debanne, et.al., 2011.

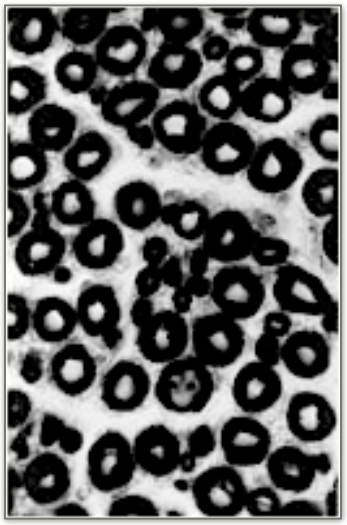

Fig 3-10. Cross-section of a portion of the cat sciatic nerve. Myelin sheaths (black 'donuts') are stained with Osmium Tetroxide (x320 magnification). Axon contained within the myelin is unstained. Unmyelinated axons are not visible. (G.E. Carvell & W.D. Letbetter, unpublished data).

There are a number of subtypes of **NaV** and **Kv** found in peripheral or central myelinated axons. **NaV** are the critical proteins to generate the all-or-nothing AP in a myelinated axon. While unmyelinated axons have **NaV** and voltage-gated K^+ (**Kv**) channels mixed along the axon, voltage-gated K^+ channels are localized to paranodal regions in myelinated axons and normally do not repolarize the axon at the Node. Myelin is produced by oligodendrocytes in the Central Nervous System (CNS) and by Schwann Cells in the Peripheral Nervous System (PNS). Normal nerve conduction in myelinated axons is called saltatory conduction: the AP "jumps" from Node to Node.

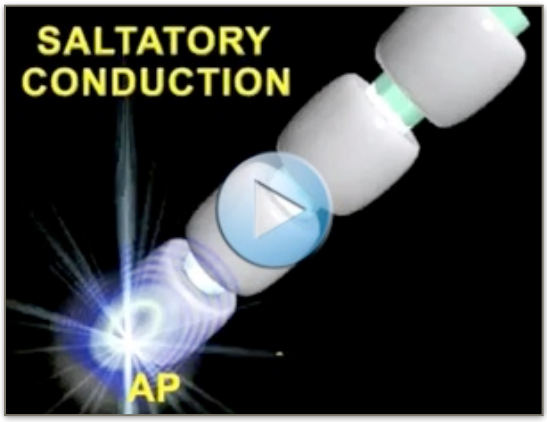

Fig 3-11. Saltatory Nerve Conduction Movie. An AP produces action current (zap) that spreads to next Node to initiate a new AP (explosive event). The action current generated at each node is 5-8x minimal depolarization required to generate an AP (safety factor) (gec). GO TO: gmomm.pitt.edu Fig3-11_Video CAUTION AUDIO IS LOUD!

DEMYELINATION AND REMYELINATION

Segmental Demyelination/Remyelination may result in slowing or failure of nerve conduction through the pathologically denuded (unmyelinated) portion of the axon. Figure shows cross section (x320) of Tibial Nerve at site of an acute nerve compression lesion. Myelin sheaths are stained with Osmium Tetroxide (OsO^4). Nerve Conduction Studies revealed conduction slowing across the lesion site for large axons; see numerous abnormal myelin sheaths-blue arrows. Pressure on peripheral nerves has the greatest effect on large myelinated axons: production of segmental demyelination/ remyelination with little or no axonal degeneration.

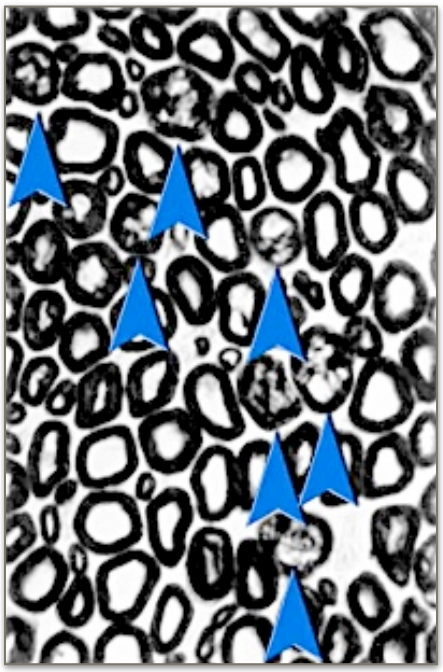

Fig 3-12. Cross-section of peripheral nerve with abnormal myelination following pressure lesion. OsO^4 *Stain (x320). Abnormal myelin is demarcated by blue arrows; unmyelinated axons are not visible.(G.E. Carvell & W.D. Letbetter, unpublished data).*

Severe acute demyelination of long expanses of the fiber often results in nerve conduction failure (physiological conduction block) in the unmyelinated portion of the nerve fiber. Conduction abnormalities appear to be related to dispersion or frank loss of the voltage-gated Na^+ (**NaV**) channels at the Nodes of Ranvier. Normally these receptors are densely packed in the axonal membrane at the Node with few of these channels found in paranodal regions. Peripheral nerve pathology may result in a dispersion of the (**NaV**) channels or removal of the channels from the membrane. Chronic demyelination/remyelination alters axonal conduction properties; such pathology may result in "continuous" conduction or slowed saltatory conduction across affected axon areas.

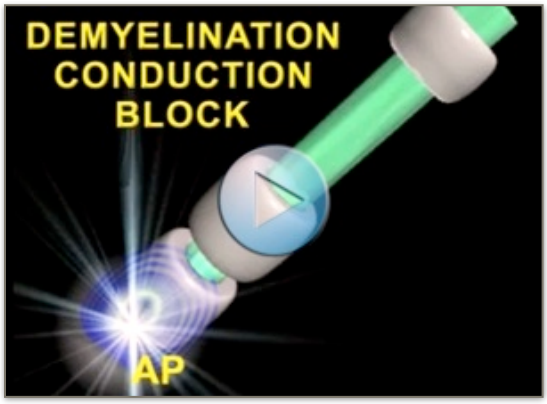

Fig 3-13. Physiological Conduction Block Movie. Action current (zap) fails to spread across extensive 'exposed' portion of the injured axon; AP conduction block in demyelinated portion of axon (gec). GO TO: gmomm.pitt.edu Fig3-13_Video CAUTION AUDIO IS LOUD!

Central Demyelinating Diseases result in loss of myelin and possibly destruction of the Oligodendroglia responsible for myelinating these axons in the CNS white matter. Effects may include clinically silent plaques (plaques = zones of demyelination), higher function loss, sensory/perceptual deficits, cerebellar, and a variety of motor deficits.

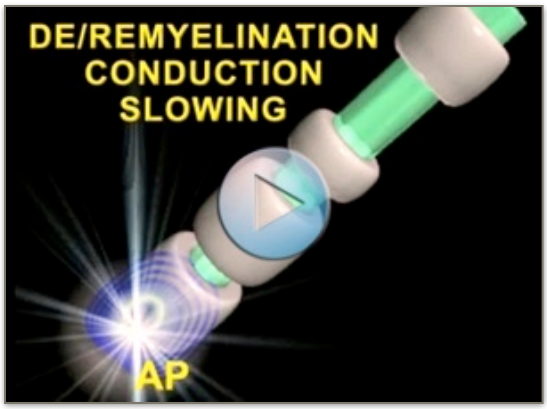

Fig 3-14. Physiological Conduction Slowing Movie. Action current can spread across short gaps in myelin; Action Current is sufficient to trigger AP but with a temporal delay (gec). GO TO: gmomm.pitt.edu Fig3-14_Video CAUTION AUDIO IS LOUD!

The most common central demyelinating disease is Multiple Sclerosis (MS). Recent studies of myelin changes in Multiple Sclerosis have shown that conduction through demyelinated regions of axons may recover despite the absence of remyelination.

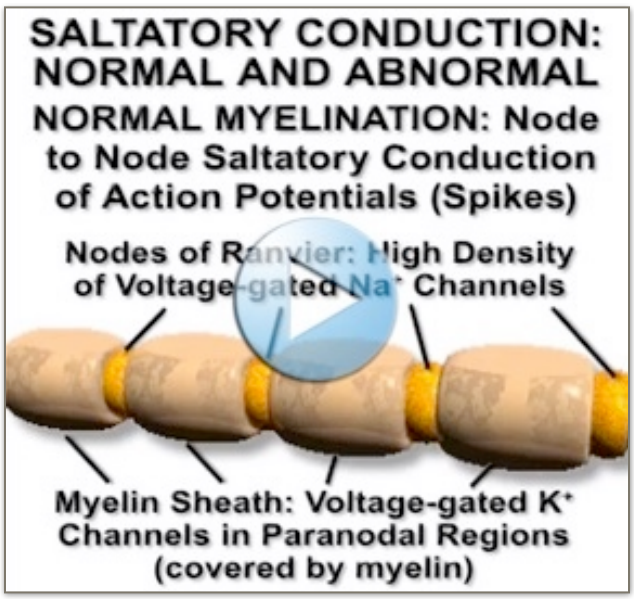

Fig 3-15. Demyelinating/Remyelinating Movie: Progressive Recovery (gec). GO TO: gmomm.pitt.edu Fig3-15_Video

Biomarkers specific for different subtypes of Voltage-gated Sodium Channels (**NaV**) show a redistribution of some **NaV** proteins and insertion of other subtypes within the denuded axon membrane in chronic demyelination. There are at least 8-9 subtypes of **NaV** proteins associated with either peripheral or central axons. Some subtypes are found only in specific locations.

At least one **NaV** subtype appears to be inserted in the denuded portion of the axon that is typically not found at Nodes of Ranvier in CNS axons. This subtype can restore propagation of action potentials but at a reduced speed and lower rates through the denuded region. Since a number of neural processes depend on both high temporal fidelity and/or high spike rates for optimal function, conduction through these plaques may provide limited capacity for full restoration of function. Since demyelination and remyelination appear to be a common aspect of normal aging in cerebral white matter, a similar suboptimal spiking may lead to reduced capacity for coherency in spike coding necessary for rapid network integration as we age. Cognitive processing may decline in speed & sophistication with aging.

AXON DIAMETER & DEGREE OF MYELINATION INFLUENCES CONDUCTION SPEED OF APS

The distribution of fibers extends from large diameter, heavily myelinated A Alpha axons to small unmyelinated C fiber axons in many peripheral nerves. Fiber diameter

and conduction velocity are proportional. Moreover, larger myelinated axons have lower thresholds for activation by electrical stimulation. Most peripheral nerves have a higher proportion of unmyelinated C fibers than myelinated A fibers. Similar myelinated and unmyelinated axons are found in central nervous system white matter; their physiological properties are similar to peripheral axons.

Fig 3-16. Relationship of Fiber Size, Myelination and Electrophysiology of A and C sized axons. Distribution shown is for a mixed peripheral nerve (gec).

Classic nerve conduction is done by direct nerve stimulation and recording. Low intensity stimulation activates only A fibers. Much higher intensity is required to activate C fibers. Rapidly conducting A fibers have a saltatory conduction of propagated Action Potentials (APs) (AP "jumps" from node to node). Unmyelinated C fibers have a re-initiation of the AP at many points along the axon which considerably slows propagation speed.

Fig 3-17. Low Intensity Electrical Stimulus Pulse: Compound Action Potential - A fiber Activation only Movie (gec). GO TO: gmomm.pitt.edu *Fig3-17_Video*

The Low Intensity Electrical Stimulus Pulse Movie illustrates the effect of a low intensity electrical stimulation pulse that activates only large A myelinated axons in a peripheral nerve. The A fibers have fast nerve conduction velocities and the lowest threshold for electrical stimulation. The compound action potential (CAP) includes all A fibers in the nerve.

Fig 3-18. High Intensity Electrical Stimulus Pulse: Compound Action Potential- Activation of A and C fibers Movie (gec). GO TO: gmomm.pitt.edu *Fig3-18_Video*

The High Intensity Electrical Stimulus

Pulse Movie illustrates the effect of high intensity electrical stimulation pulse that activates both large, fast conducting A fiber axons (A fiber CAP) and small, slower C fiber unmyelinated axons (C fiber CAP), i.e., all viable axons in the peripheral nerve.

Temperature has a significant effect on nerve conduction. Nerve conduction velocity decreases by ~3% for each degree Centigrade drop in temperature. Cooling Slows Transmission & broadens the Action Potential Duration. Very cold temperatures will cause a reversible physiological block of nerve conduction. Prolonged freezing produces permanent structural damage.

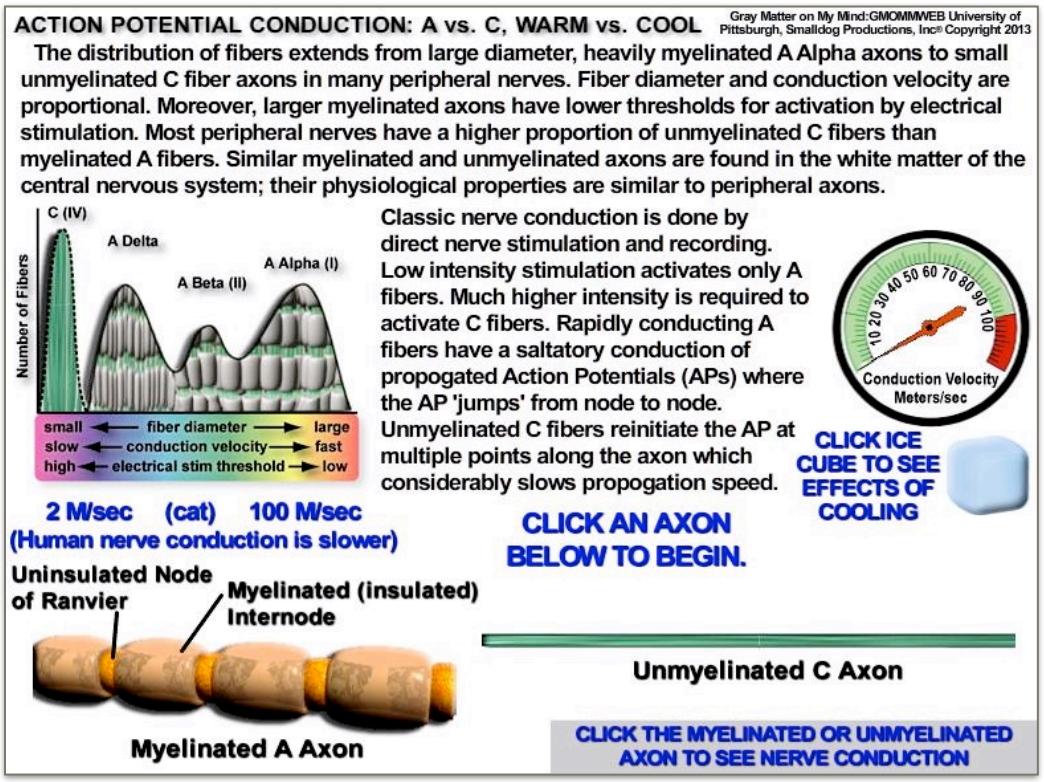

Fig 3-19. Nerve Conduction for Warm and Cool Mammalian Axons Interactive Media File (gec). GO TO : gmomm.pitt.edu

Fig3-19_ Interactive Media

Likewise an abnormally high temperature may block nerve conduction. Peripheral or central demyelinating diseases may be associated with an increased risk for conduction failure for temperature changes within more physiological ranges suggesting an attenuated safety factor for these impaired nerve fibers. Often there is a change in density, specific location, total number or even sub-types of voltage-gated Na^+ and K^+ channels at the nodes and paranodes of axons undergoing demyelination or remyelination, e.g., see Craner, et.al., 2005; Waxman, 1990, 2002, 2006; Waxman, et.al., 2000.

PRESSURE NEUROPATHY ALTERS AP TEMPORAL CODE

Pressure on a nerve produces a demyelination of large myelinated axons with little effect on unmyelinated fibers. This causes a conduction delay through the involved portion of the nerve. The effect is seen not only as a reduced conduction velocity but as

a reduction in the ability to faithfully conduct impulses in rapid bursts, e.g., see Ochoa, 1971; Lehmann, 1973.

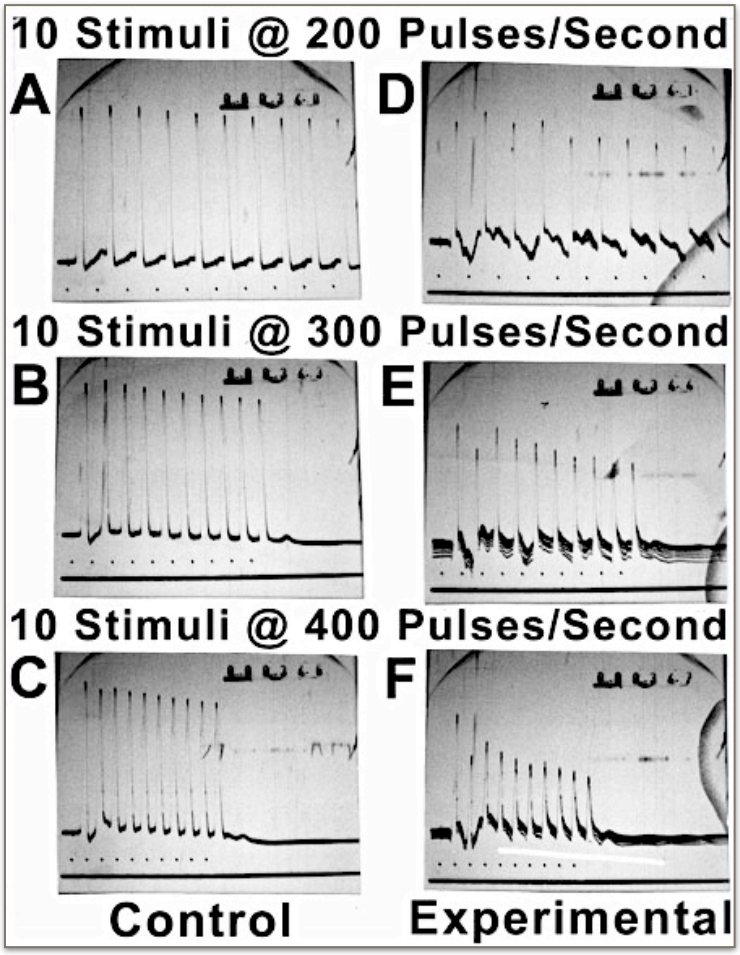

Fig 3-20. Oscilloscope Waveform Photographs: Effects of Local Pressure Neuropathy on Repetitive Conduction of Compound Action Potentials (CAPs). Panels A, B, C = Control Tibial Nerve CAPs (top traces); Panels D,E,F = Experimental Tibial Nerve CAPs (top traces). Lower traces in all panels = stimulus timing of ten 0.1 msec monophasic stimulus pulses. Each photo shows ten consecutive overlaid traces for each of the 10 pulse stimulus trains. G.E. Carvell & W.D. Letbetter, unpublished data (gec).

High frequency bursts of APs are seen in proprioceptive afferents and some afferents innervating low-threshold tactile mechano-receptors. An example of reduced temporal fidelity in coding is illustrated in the figure below. A localized pressure neuropathy was present at the distal thigh between the location of stimulating site at the proximal sciatic nerve and recording site at the distal tibial nerve. Compound action potentials (CAPs) evoked by trains of ten stimuli delivered at 200 Hz (panels A & D), 300 Hz (panels B & E) and 400 Hz (panels C & F) were recorded (photographs of ten consecutive oscilloscope traces in upper traces for each of the three train frequencies). Recordings done several weeks post-pressure. Lower traces in each photograph shows the times of each of the ten stimuli.

The data illustrate the decrement in transmission for the experimental versus the control tibial nerve. Note the reduced amplitude and temporal dispersion of responses in the burst for the experimental nerve which is most evident as frequency of stimulation increases. These changes may be due to temporal delays and/or conduction failure at the lesion site in pressurized axons. As the frequency of stimulation increases there is a greater likelihood for encroachment upon the safety factor for normal transmission of APs. Pressurized axons may be in various states of demyelination and remyelination in this post-lesion recovery state. Consequences of a pressure neuropathy on temporal

coding is greater for sensory than for motor function. Motoneurons do not generate AP frequencies above ~50 Hz. Unless there is conduction failure in motor axons, muscles should be well innervated. However, muscle proprioceptor afferents plus discrete touch and vibration sense afferents routinely discharge short bursts of APs at frequencies equal to or greater than 500-1000 Hz (interspike intervals of 2 msec to 0.1 msec, respectively). Thus some deep and superficial sensations may be distorted. Small myelinated and unmyelinated axons are little affected or unaffected in a pressure neuropathy: crude touch, pain and temperature sensations should be spared.

RECORDING ACTION POTENTIALS FROM SINGLE CELLS IN THE CNS.

Action Potentials (APs) are recorded in the CNS using microelectrodes. Some glass microelectrodes have a small diameter, sharp tip that can impale a neuron (intracellular recording). Intracellular APs have a typical "monophasic" waveform shape. Microelectrodes with larger diameters (glass or metal) can record APs from neurons that are close to (but not impaled by) the electrode. These extracellular recordings show biphasic or triphasic Action Potentials. Neurons do not all fire APs (spikes) in the same way. Some neurons fire few spikes, while others fire long trains of spikes. Still others fire spikes in short bursts of activity. APs travel to axonal terminals of a presynaptic cell's axon to influence postsynaptic cells by way of synaptic transmission.

EXTRACELLULAR RECORDING: RECORDING ACTION POTENTIALS ONLY

Extracellular recordings of APs provide a mechanism to study individual neurons in isolation or, if multiple electrodes are used, one can study how these neurons interact within a neural network.

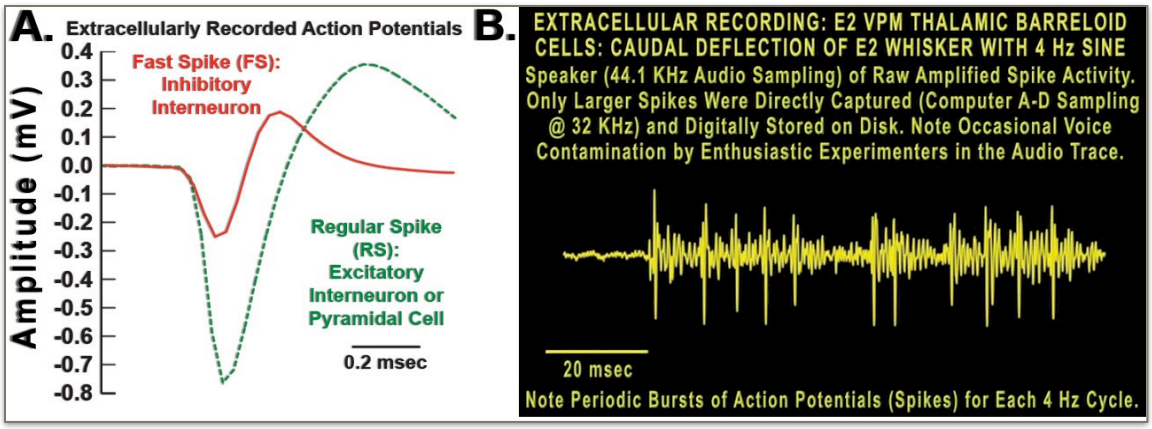

Fig 3-21. Panel A shows extracellular cortical fast spike: AP recorded from an inhibitory interneuron (red waveform) and a cortical regular spike from an excitatory neuron (green waveform). Panel B shows a recording of extracellular neuronal APs in the rat somatosensory thalamus (gec). GO TO: gmomm.pitt.edu Fig3-21_Video

Some Inhibitory interneurons have membrane properties and ion channels that allow them to fire many spikes and such neurons discharge APs that have a fast time-course (brief AP duration). Excitatory neurons typically discharge APs having a slower time-course. Examples recorded in rat somatosensory cortex are shown as waveforms in the following figure (Panel A) and a movie of thalamic neuron extracellular Action Potential discharge in-vivo as a response to a 4 Hz Sinewave tactile stimulus (Panel B and GMOMM movie link). The stimulation here is accomplished by a controlled whisker deflection. The different characteristics of excitatory and inhibitory neurons as related to optimal function within the sensory and motor systems will be discussed in greater detail in later chapters. Single cell APs are often isolated by on-line or off-line spike sorting process where the characteristic features of a particular cell's AP (spike) can be isolated from other spikes of other cells recorded close to the tip of the recording electrode.

INTRACELLULAR RECORDING: RECORDING BOTH LOCAL POTENTIALS & ACTION POTENTIALS

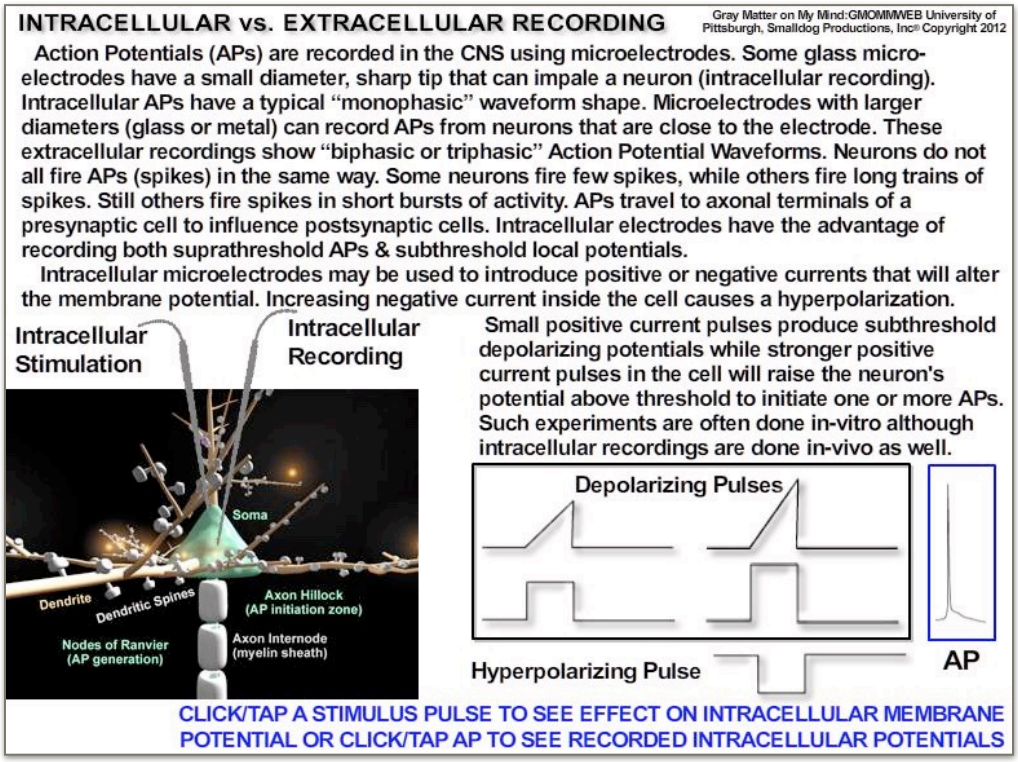

Fig 3-22. The Intracellular versus Extracellular Recording Interactive Media File shows the effect of depolarizing or hyper-polarizing currents on the membrane potential (gec). GO TO: gmomm.pitt.edu

Fig3-22_ Interactive Media

Intracellular electrodes have the advantage of recording both suprathreshold APs & subthreshold local potentials: Resting Membrane Potential (RMP) fluctuations, graded excitatory subthreshold depolarizations such as Excitatory PostSynaptic Potentials (EPSPs) and graded inhibitory hyperpolarizing potentials such as Inhibitory PostSynaptic Potentials (IPSPs). Such intracellular recording experiments include both

in-vitro and *in-vivo* studies. This figure shows an *in-vitro* patch-clamp intracellular recording in the supragranular layers of the somatosensory cortex of an 11 day old rat. Patch-clamp recordings are done by advancing the micropipette to touch the cell membrane and then apply a negative pressure pulse to open the membrane. The electrode now has access to the subthreshold depolarizing or hyperpolarizing voltage/ current fluctuations and suprathreshold action potentials recorded from within the cell. The patch-clamp recording technique was originally perfected by Bert Sakmann and colleagues, e.g., see Neher and Sakmann, 1976, 1992; Stuart, et.al., 1993; Stuart and Sakmann, 1994. This technique is currently being applied to both *in-vitro* single cell recordings in brain slices and *in-vivo* recordings of individual neurons in anesthetized or head-fixed awake animals.

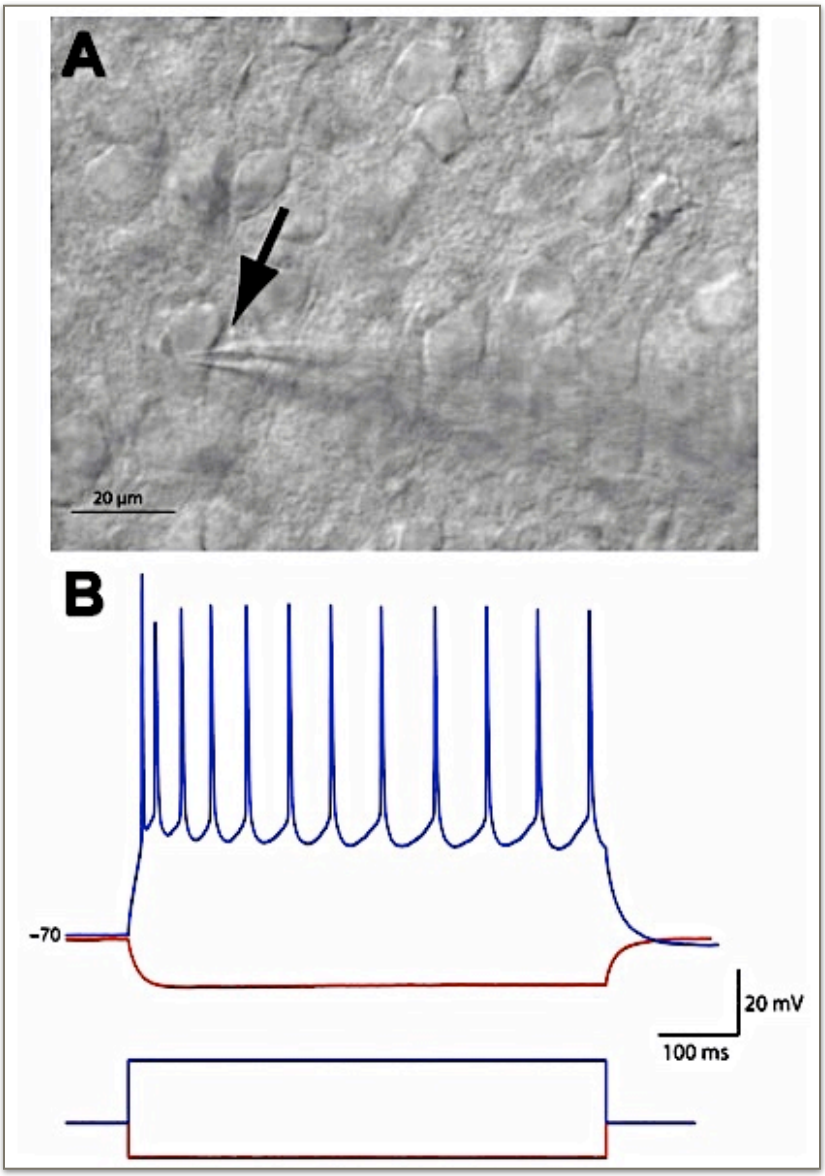

Fig 3-23. ***A.*** *Intracellular Recording performed with glass micropipette: patch recording of pyramidal cell soma in-vitro. Shadow of electrode and 1-2 micron tip that patches soma (arrow) are visible.* ***B.*** *Waveforms show an initial -70 mV resting membrane potential, then 12 APs (upper blue trace) atop a sustained excitation due to a 600 msec suprathreshold depolarizing pulse (lower blue trace) applied to the cell followed by a hyper-polarization of the cell (upper red trace) due to an applied 600 msec hyper-polarizing pulse (lower red trace). Photograph and neuronal patch clamp recordings courtesy of Amanda Kinnischtze, PhD in the Department of Neurobiology, School of Medicine, University of Pittsburgh.*

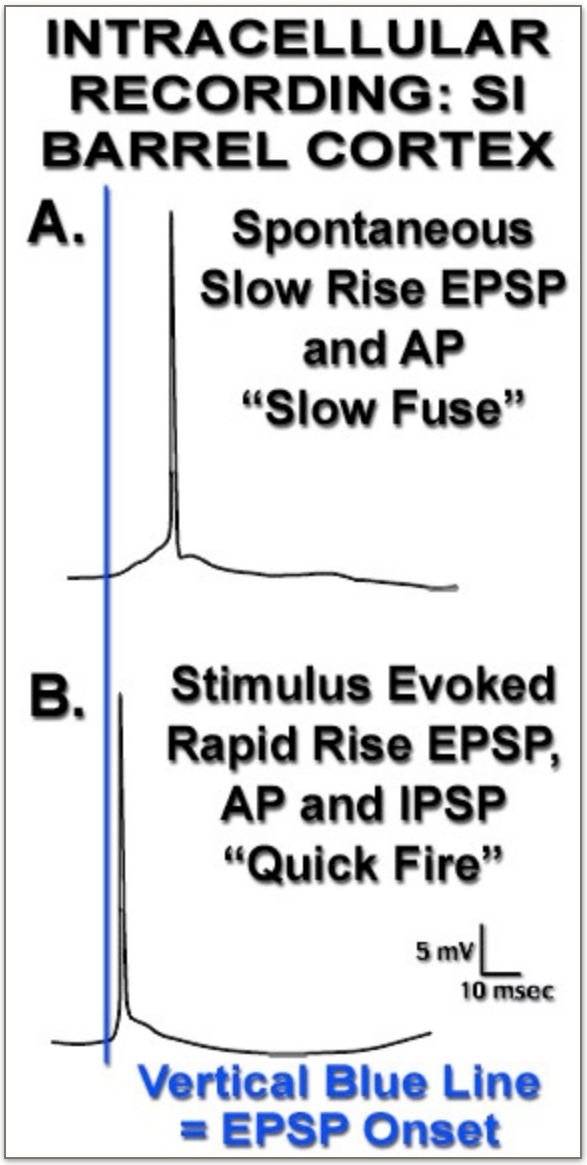

Fig 3-24. Intracellular Recording from Single Cell in Rat Somatosensory (Barrel) Cortex. A. Cell Discharges AP in a Spontaneous Fashion. B. Cell Fires AP Due to Whisker Evoked Stimulus. Note Differences in slope, and time-course of EPSP in A vs. B. and an IPSP following the AP in Panel B only: See also Carvell and Simons, 1988 (gec).

SLOW-FUSE (INTEGRATE & FIRE) VERSUS QUICK-FIRE (COINCIDENCE DETECTION) NEURONAL ACTIVATION

Synchronous input of EPSPs produces a rapid rise in depolarization of the soma. A rapid rise time of the summed EPSP generates an Action Potential (AP) soon after the onset of the summed EPSP (see QUICK-FIRE AP). Asynchronous excitatory input is seen as a slow rise of the summed EPSP at the soma with a delayed onset of AP generation (see SLOW-FUSE AP). The timing and synchrony of EPSPs has a significant effect on the postsynaptic cell: coincident or cumulative EPSP summation.

Neural processing requires cooperation from a distributed network of neurons (cell assemblies). Each cell assembly is a colony of interconnected cells. Networks of neurons may interact in one of several ways. The "default" mechanism is thought to be an Integrate & Fire coding where an increased rate of firing within a colony determines its output to other colonies of cells. An alternative model suggests that a sparse spike code may provide rapid efficient cell assembly coupling. This is called Coincidence Detection coding and requires a temporal precision (synchrony) of spike discharge among colonies of cells. The latter sparse spike coding = a more efficient mechanism for some well rehearsed processes to form an internal representation of the task.

The actual number of synaptic inputs required to depolarize the postsynaptic cell to threshold for initiation of an Action Potential may be ~20-100x greater than the axonal inputs shown in the Quick-Fire versus Slow-Fuse Interactive Flash file. Moreover, the

actual location of the synapses is likely to be on the basal and apical dendritic spines not on the apical dendritic shaft of the postsynaptic pyramidal cell as simulated here.

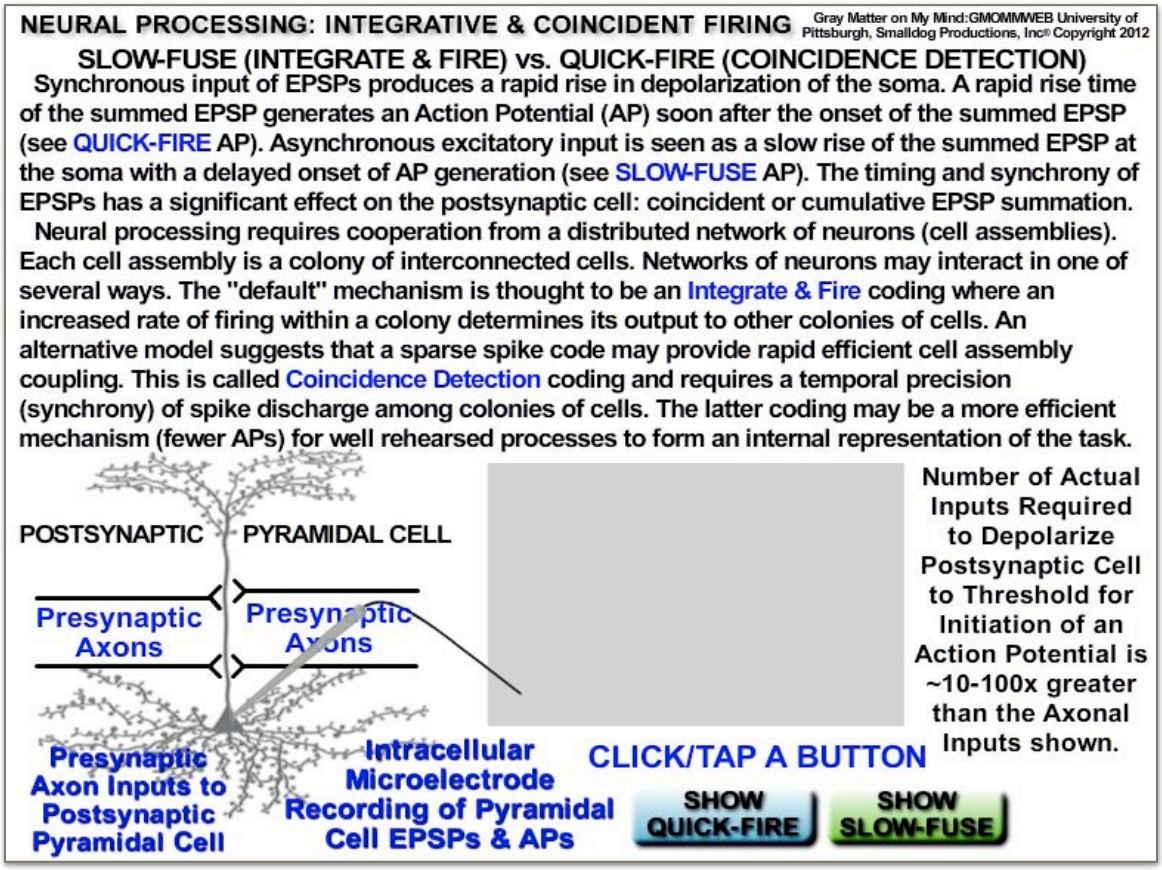

Fig 3-25. Quick-Fire versus Slow-Fuse Neuronal Activation Interactive Media File. (gec). GO TO: gmomm.pitt.edu *Fig3-25_Interactive Media*

LOCAL FIELD POTENTIALS: SUMMED SUBTHRESHOLD & SUPRATHRESHOLD ACTIVITY OF NEURONAL POPULATION

Local Field Potentials (LFPs) are extracellular recordings of summed subthreshold and suprathreshold neural activity from large populations of neurons. LFPs may be recorded with surface macroelectrodes, e.g. epidural or epipial electrodes or using scalp electrodes as in EEG recordings. LFPs are recorded also using depth microelectrodes.

Recordings include the slow-wave components of neural activity by opening filters to include low frequency aspects of neural activity. These responses may represent intrinsic brain activity as in EEG recordings or LFPs may be evoked by central gray or white matter stimulation or by peripheral nerve stimulation (Stimulus Evoked Potential: see figure). LFP responses represent a summation of subthreshold dendritic and synaptic activity plus action potentials due to suprathreshold activation of neurons. Thus LFPs provide a snapshot of electrical activity of networks of many neurons having

extrinsic inputs, local connectivity and long-range longer latency influences. LFPs are correlated to the fMRI BOLD signal: e.g., see Logothetis, et.al., 2001. The early component in the evoked LFP shown here represents the primary somatosensory (SI) cortical response to extrinsic peripheral nerve activation relayed through the thalamus. Later components represent corticocortical and corticothalamocortical recurrent influences on the SI columnar network.

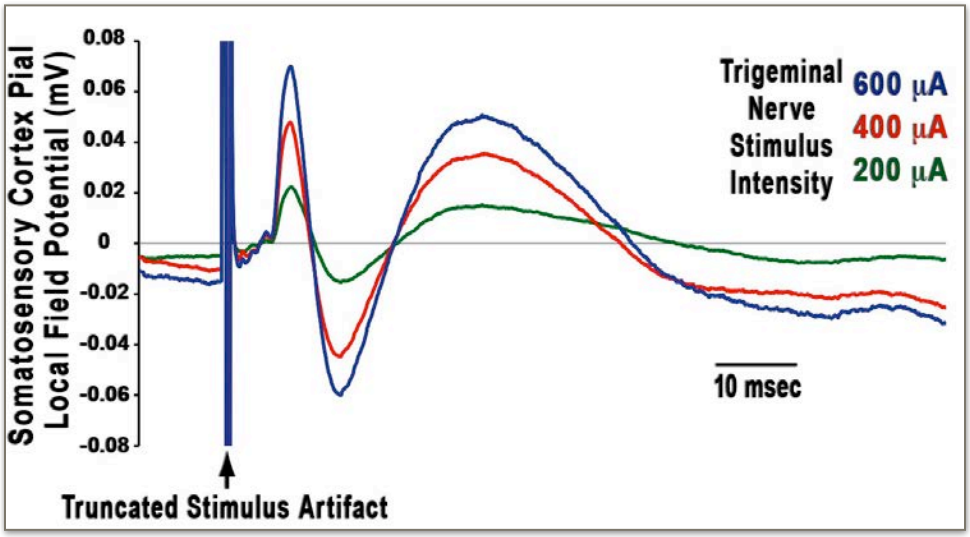

Fig 3-26. Somatosensory Cortex LFP Evoked by Trigeminal Nerve Stimulation: Note Early and Late Components of the Cerebral Cortical Population Response to Peripheral Nerve Stimulation in anesthetized rat. (gec).

CLINICAL ELECTROPHYSIOLOGY: NERVE CONDUCTION (NCV) AND MUSCLE ACTIVITY (EMG) STUDIES

Clinical electrophysiologists can record nerve conduction in sensory and motor nerves in human subjects by way of transcutaneous stimulus and recording (surface stimulating and recording electrodes). Such studies are typically preformed to rule-in or rule-out peripheral nerve pathologies. Sensory Median Nerve Conduction Testing is simulated in the Normal Clinical Sensory Nerve Conduction Movie.

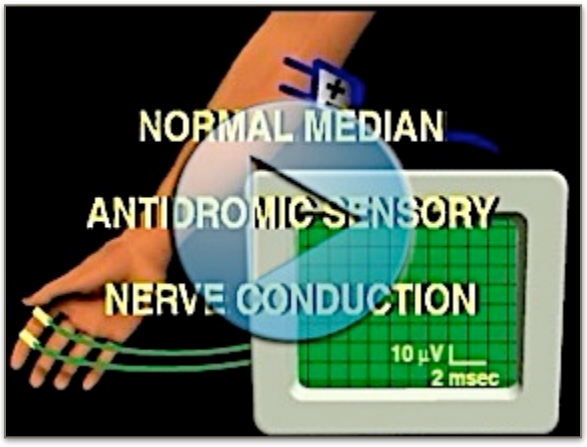

Fig 3-27. Normal Clinical Sensory Nerve Conduction Movie. Methodology to perform a clinical antidromic sensory nerve conduction study of the digital nerves of the index finger recorded using ring electrodes encircling the index finger. Stimulation of median nerve at the elbow and wrist (gec). GO TO: gmomm. pitt.edu *Fig3-27_Video*

Skeletal muscle motor unit electrical activity can be recorded using fine indwelling microelectrodes for selected muscles, e.g. see Basmajian, 1974. Electromyographic

(EMG) needle exams are performed to rule-out muscle denervation due to nerve injury or disease or to rule-out primary muscle disease such as a muscular dystrophy. An entire section devoted to clinical electrophysiology is found in later chapters.

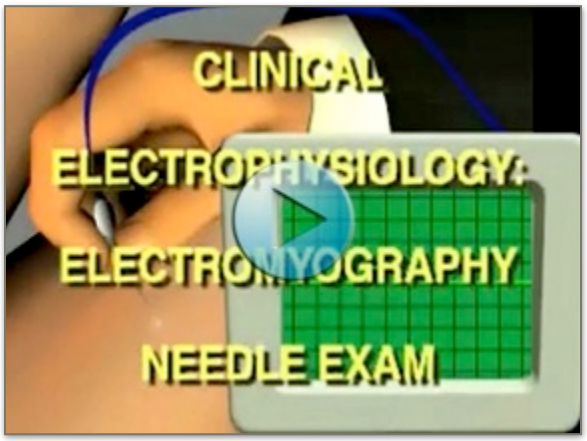

Fig 3-28. Clinical Electromyographic (EMG) Needle Exam Methodology Movie (gec). GO TO: gmomm.pitt.edu *Fig3-28_Video*

INTRODUCTION TO NEURAL NETWORK INTERACTIONS

Networks typically include both excitatory (E) and inhibitory (I) neurons. The ratio of E to I differs according to the anatomical location of the cells. For example, in sensory cortex, E cells far outnumber I Cells (I Cells = 20-30% of total). The I element in the network below is represented by two gap-junction coupled GABAergic Inhibitory Neurons.

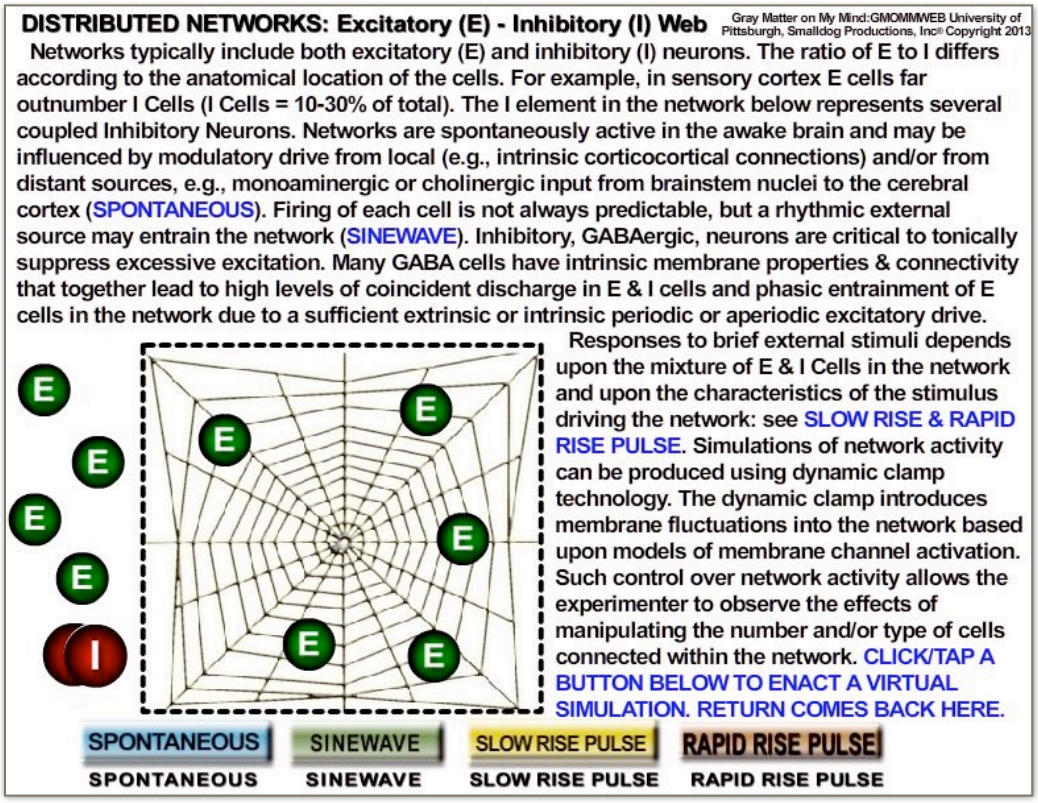

Fig 3-29. Excitatory and Inhibitory Neurons network-ed to generate neural patterns: E-I Network Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig3-29 Interactive Media*

Networks are spontaneously active in the awake brain and may be influenced by modulatory drive from local (e.g., intrinsic corticocortical connections) and/or from distant sources, e.g.,

glutamatergic corticothalamocortical and monoaminergic or cholinergic input from brainstem nuclei to the cerebral cortex (SPONTANEOUS).

Firing of each cell is not always predictable, but a rhythmic external source may entrain the network (SINEWAVE). Inhibitory, GABAergic, neurons are critical to tonically suppress excessive excitation. In addition, some GABA cells have intrinsic membrane properties and connectivity patterns that together lead to high levels of coincident discharge in E & I cells and phasic entrainment of E cells in the network due to a sufficient periodic or aperiodic extrinsic or intrinsic excitatory drive to both E & I cells.

The response to brief external stimuli depends upon the mixture of E & I Cells in the network and upon the characteristics of the stimulus driving the network: see SLOW RISE & RAPID RISE PULSE. Simulations of network activity can be produced using dynamic clamp technology. The dynamic clamp introduces membrane fluctuations into the network based upon models of membrane channel activation. Such control over network activity allows the experimenter to observe the effects of manipulating the number and/or type of cells connected within the network. Cooperation amongst a collection of interconnected cells (network) appears to be critical for normal nervous system function. Special properties are attributed to the collective that may be either weakly represented by individual neurons or invisible in any cell by cell analysis. For example, a population code of some property may emerge when one studies the group of cells as a whole. Such neural network webs merge depolarizing influences of excitatory neurons and hyperpolarizing influences of inhibitory interneurons to determine network firing patterns. Interactions between and among E & I cells is most often nonlinear and depends upon statistical probabilistic integrative factors: see Chapter 4 below.

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Chapter 4

SYNAPSE & SYNAPTIC INTEGRATION

The ability of the brain to operate in a normal fashion depends upon a balanced level of electrical and chemical signaling among many neurons connected within regulated networks. Our brains contain sophisticated chemical laboratories that attempt to maintain a physiological balance among potentially volatile biochemical reactions. Early studies showed that communication in the peripheral nervous system utilizes synapses with chemically-gated receptors. However, chemically-gated neurotransmission was not generally accepted for the central nervous system until the latter half of the 20th century, e.g., see Katz, 1966. More recent research suggests a quite diverse and complicated interaction among neurons utilizing both autocrine and paracrine chemical messengers having both short-term & long-term effects on individual cells and cell assemblies, e.g., see Sudhof & Malenka, 2008. Research from the systems to the molecular level of investigation supports the concept of synaptic plasticity from infancy into adulthood. Enriching the environment and providing novel, challenging and engaging behavioral interventions produce changes at the molecular, synaptic and network levels of neural processing. Both neurons and glia participate in this process, e.g. see Newman, 2003; Perea, et.al., 2009; Stogsdill & Eroglu, 2017.

SYNAPSE INTRODUCTION

Local Potentials are non-propagated, graded potentials found at a number of locations. Depolarization of axon terminals induce presynaptic local potentials at synapses which lead to subsequent interactions between cells (synaptic transmission). Dendrites and the soma are other locations of post-synaptic local potentials that may be either depolarizing or hyperpolarizing.

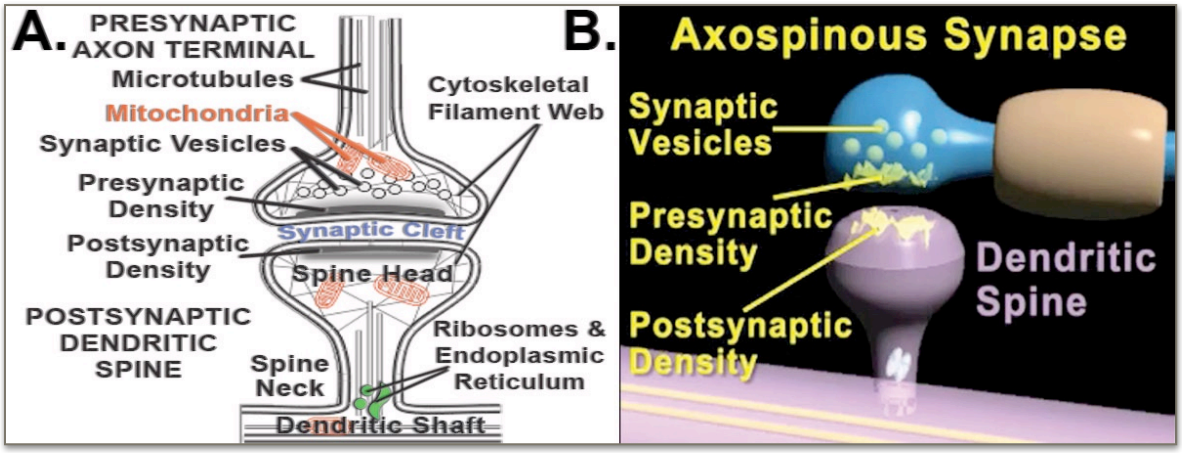

Fig 4-1. A. Ultrastructural Elements of a Typical Axospinous Synapse, B. Movie simulating presynaptic and postsynaptic events for a typical excitatory axospinous synapse (gec). GO TO: gmomm.pitt.edu Fig4-1_Video

Local graded potentials are generated also peripherally where sensory transduction leads to a generator potential in a sensory organ (e.g., skin, muscle, eye, ear).

Neurons communicate rapidly with one another by way of synapses. There are many types of synapses. One classification separates chemical synapses according to post-synaptic ionic membrane potential changes (ionotropic) or to alterations in metabolic properties in the post-synaptic cell (metabotropic) due to activation of 2nd messenger regulatory proteins. Ionotropic synapses are subdivided into Excitatory (E) (depolarizing ion flow) or Inhibitory (I) (hyperpolarizing ion flow). The local graded membrane potential produced in the postsynaptic cell is called an Excitatory Postsynaptic Potential (EPSP) or an Inhibitory Postsynaptic Potential (IPSP) respectively. Increased Conductance but not decreased conductance synapses are covered here. Synapses may be classified also according to location: axospinous = axon to dendritic spine (E), axodendritic = axon to dendritic shaft (E or I), axosomatic = axon to soma (I, rarely, E), axon to axon = axo-axonic (E or I).

NEURON COLLECTS DATA FROM SYNAPSES ON DENDRITES, DENDRITIC SPINES, SOMA & AXON

DENDRITES collect data (excitatory & inhibitory synapses on dendritic shafts, excitatory on spines) & provide a substrate for use-dependent modification of synaptic activity (plasticity). SOMA integrates inputs from dendrites, manufactures metabolic, cytoskeletal & membrane proteins and responds to use (levels of activity) by regulating RNA synthesis. AXON provides final decision point for neuron (axon hillock) to fire an Action Potential (AP) or not. AP signal is faithfully transmitted to the axon terminal to synapse on a target cell (postsynaptic neuron or muscle). When the axonal AP is initiated a Na^+ back propagated dendritic plateau potential (BAP) is generated as well.

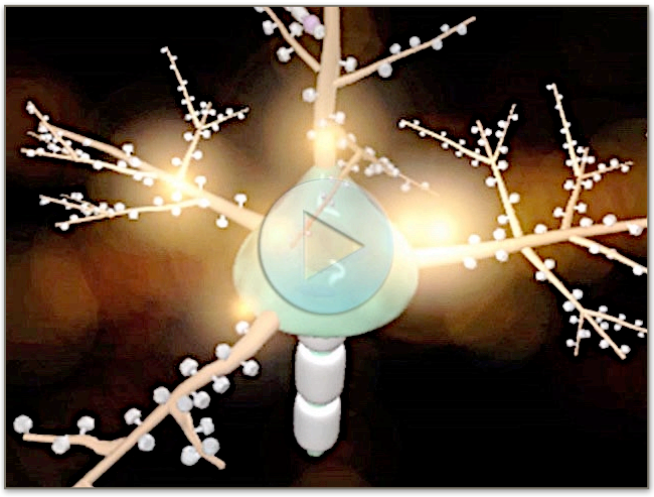

Fig 4-2. "Modern" Pyramidal Cell Activation Movie (Compare this movie to Fig1-26_Video found in Chapter 1). Simultaneous depolarizing inputs to a number of synaptic spines on many branches of the dendritic tree (orange glows) produces a spatiotemporal integration of EPSPs. An Action Potential (AP) is initiated at the axon hillock at the base of the pyramid due to suprathreshold depolarization of the cell. AP is propagated along myelinated axon in a saltatory fashion (bright flashes). A Na^+ plateau action potential that travels back through the dendritic tree (BAP) is illustrated as well (gec). GO TO: gmomm.pitt.edu Fig4-2_Video

Axo-axonic synapses may provide a final arbitrator of signal transmission. Such axo-axonic synapses alter release of neurotransmitter from synaptic axon terminals. The effect may be excitatory or inhibitory.

SYNAPSE ULTRASTRUCTURE: ANATOMY OF NEUROTRANSMISSION.

Currently the only way to see the ultrastructural details of a synapse is by electron microscopy of fixed tissue (see Panel A Ultrastructural Elements of a Typical Axospinous Synapse Figure 4-1). Stylized details of both presynaptic and postsynaptic components are shown in the figure as they might be seen in an electron micrograph. Note the presence of ribosomes and endoplasmic reticulum at the base of the synaptic spine; such organelles are thought to be involved in local production of certain proteins.

Recent methodology provides a dynamic view of synaptic changes related to use-dependent mechanisms of plasticity. Two-photon microscopy of living neurons combined with laser activation of caged glutamate reveals individual synapses made visible by fluorescent dye labeled proteins, e.g., Green Fluorescent Protein (GFP) Actin. Actin is one of the components of the cytoskeletal filament web that provides mobility and stability to the synaptic elements. Glutamate is a common neurotransmitter released from synaptic vesicles at an excitatory axospinous synapse. Play Caged Glutamate movie: see references at end of movie.

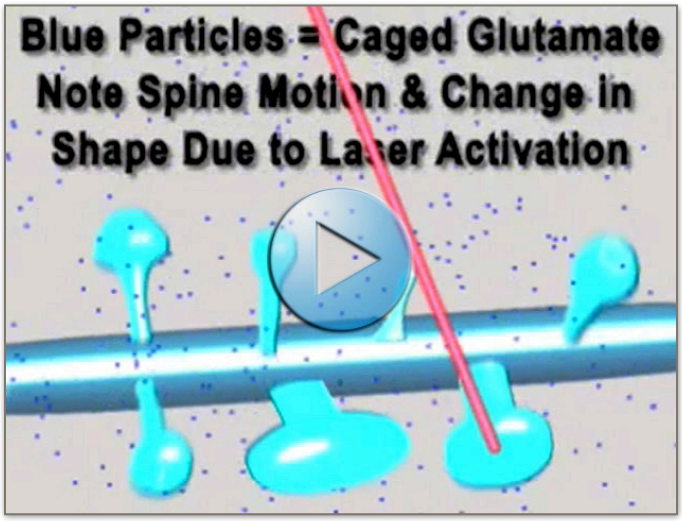

Fig 4-3. Caged Glutamate: Depolarization of Dendritic Spines Animation Movie. Note the dendritic spine motion for all but the largest of the spine heads; (gec). (LARGE MOVIE-BE PATIENT.) GO TO: gmomm. pitt.edu *Fig4-3_Video*

DENDRITIC SPINE MOTILITY: MOBILIZING SPINES AND GROWING MUSHROOMS

Neurons fixed and stained on a slide look lifeless under the microscope. However, in living tissue, neurites, dendrites in particular, are anything but static lifeless processes. Recent technology allows scientists to image living neurons *in-vitro* and *in-vivo*. Using markers for glutamate, dynamic actin, or other key elements found at dendritic spines plus two-photon confocal microscopy, high resolution images can be obtained from these living synaptic sites over periods of seconds to weeks or longer. Actin and other cytoskeletal proteins are found in dendrites and dynamic actin appears to be highly concentrated in dendritic spines where excitatory synapses are found.

Dynamic actin is thought to be responsible for rapid motility where dendritic spines: A.) “wiggle,” B.) appear (synaptogenesis) or disappear (synapse elimination); C.) grow in size and alter their glutamate receptor types in the postsynaptic density of the spine. Dynamic but not static actin responds to changes in levels of glutamate, levels of Ca^{++} and levels of certain neurotrophins. D.) The least mobile spines are big spines (“stubby” or “mushroom” spines) that may remain stable for months to years (long-term memory?). Synapse formation & stability of big spine synapses is enhanced by transsynaptic protein bridges. It has been estimated that about 50-60% of a neuron's dendritic spines are big, stable spines, e.g. see Abraham, 2008; Bourne & Harris, 2007; Dunaevsky & Mason, 2003; Fischer, et.al., 1998; Halpain, 2000; Kasai, et.al., 2003; Koleske, 2013; Song & Huganir, 2002; Star, et.al., 2002; Tada & Sheng, 2006; Trachtenberg, et.al., 2002; Yuste & Bonhoeffer, 2001. Smaller mobile spines may be lost to a greater extent than larger spines in certain portions of the prefrontal cortex with aging. Such loss may be associated with reduced ability to recruit/alter cognitive network processing working memory, see: Morrison & Baxter, 2012; Peters, et.al., 2008.

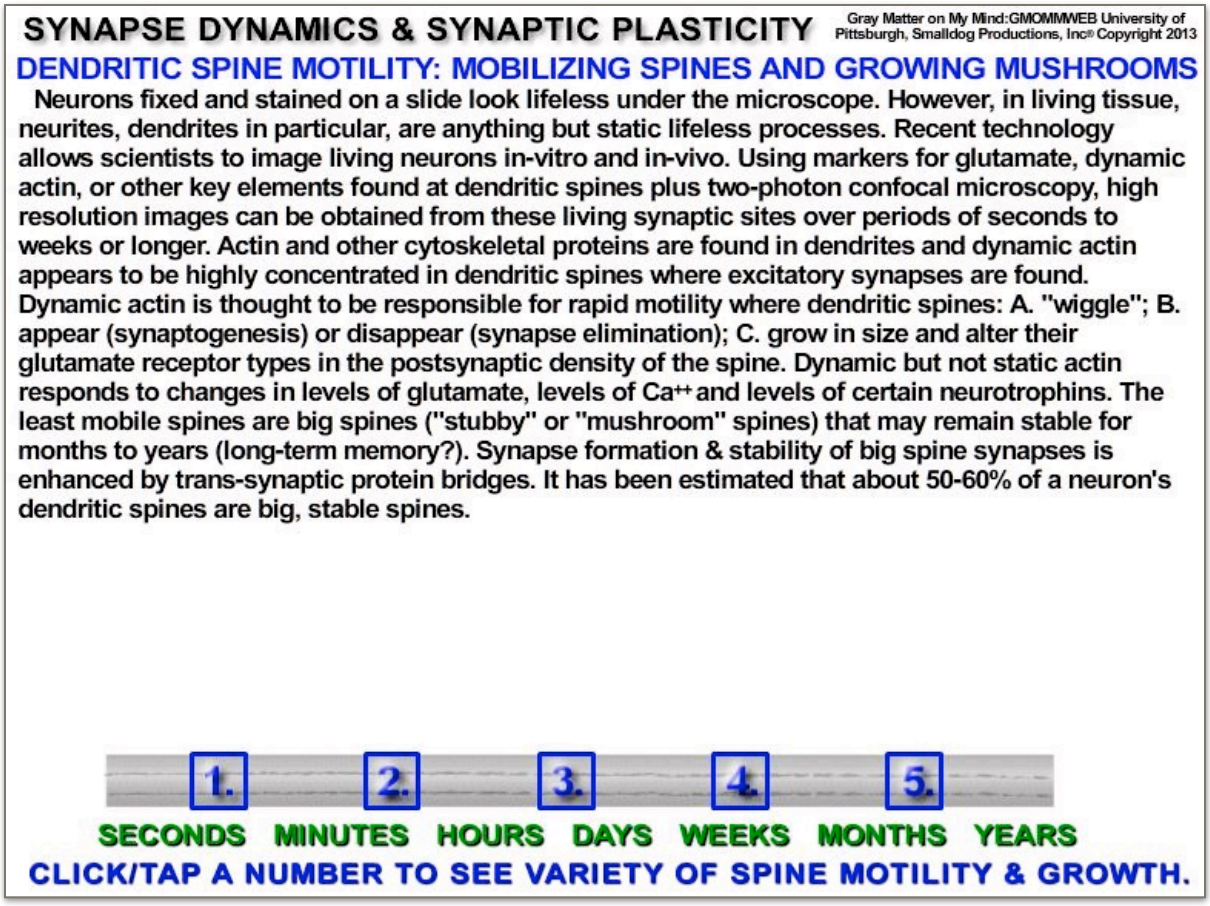

Fig 4-4. Dendrites in Motion Interactive Media File simulating dendritic motility, dendritic spine growth and dendritic spine stability (gec). GO TO: gmomm.pitt.edu
Fig4-4_Interactive Media

NEUROMUSCULAR SYNAPSE: SPECIAL CHOLINERGIC EXCITATORY SYNAPSE IN SKELETAL MUSCLE

The Neuromuscular Junction (NMJ) is a special excitatory synapse. Unlike most excitatory synapses in the CNS, the connection between an Alpha Motor Neuron in the spinal cord and the target muscle fibers in the periphery provides a “guaranteed” transmission of a signal to move. A Nerve Action Potential (NAP) produces a Muscle Action Potential (MAP) by action of a chemical messenger passed between the nerve and muscle. The chemical messenger at the NMJ is Acetylcholine (ACh). ACh is stored in synaptic vesicles in the presynaptic axon terminal. A NAP causes the vesicles to bind to the axon terminal and release ACh into the synaptic cleft. ACh receptors localized to the NMJ on the muscle membrane bind the neurotransmitter. This chemically-gated process opens ion channels in the nicotinic ACh receptor protein complex to allow Na^+ and K^+ ions to pass through the ion pore. The Na^+ influx results in a large depolarization that triggers the MAP. Under normal physiological conditions, the MAP always results in a contraction of the innervated, unfatigued muscle fibers (motor unit contraction). Acetylcholinesterase is an enzyme within the synaptic cleft that quickly inactivates the ACh after it binds to the nicotinic receptors.

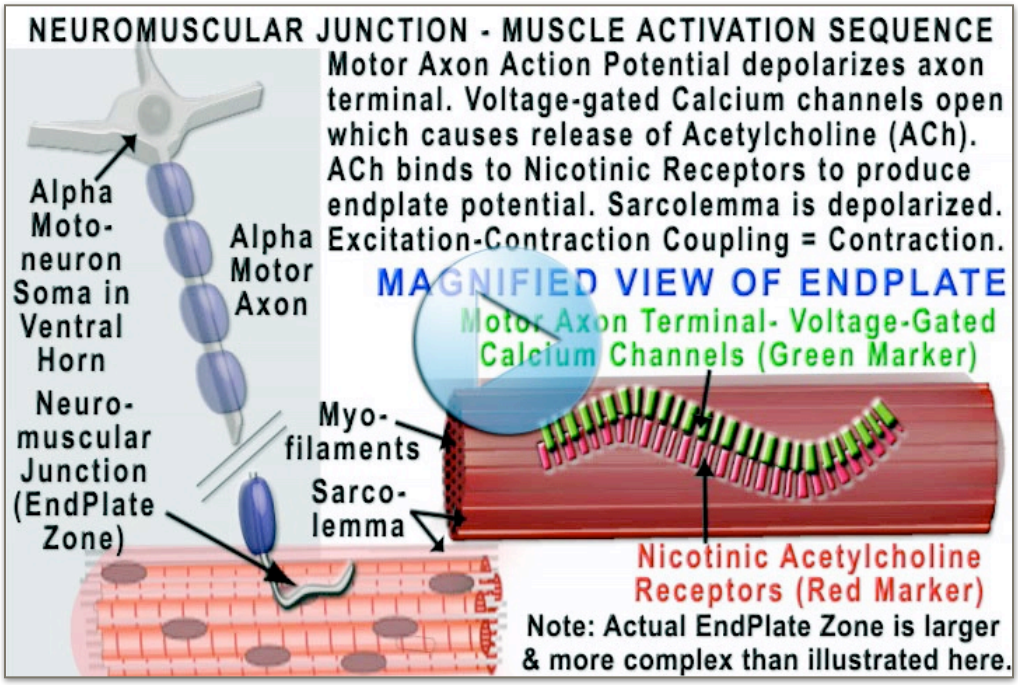

Fig 4-5. Neuro-muscular Junction: ACh Neuro-transmission for skeletal muscle contraction (gec). GO TO: gmomm.pitt.edu Fig4-5_Video

Voltage-Gated Calcium (Ca^{++}) Channels can be labeled by binding ω Conotoxin to these proteins genetically modified to express green fluorescent protein. Nicotinic Acetylcholine (ACh) endplate receptors are labeled with alpha Bungarotoxin (a powerful paralytic snake toxin) that binds specifically to the Nicotinic ACh proteins. Alpha Bungarotoxin blocks the nicotinic ACh receptors. These receptor proteins can be genetically modified to express red fluorescent protein. The following animation simulates the sequence of events at an endplate zone in striated (skeletal)

muscle. Note the mirroring of the Ca^{++} Channels in the alpha motor axon terminal (location of synaptic vesicles filled with ACh) and the location of the nicotinic ACh receptor proteins at the endplate zone on the muscle fiber sarcolemma in the magnified view of the neuromuscular end-plate zone.

GRAY'S TYPE I ASYMMETRIC, TYPE II SYMMETRIC & AXO-AXONIC SYNAPSE

Ultrastructural detail of neurons and their processes at the sub-micron level are revealed when viewed at the electron microscope level (~15,000-20,000x magnification). Cells must be *stained* with a heavy metal to make the proteins electron dense. Synaptic ultrastructure at this level of magnification suggests a structural-functional relationship between the presynaptic and postsynaptic components.

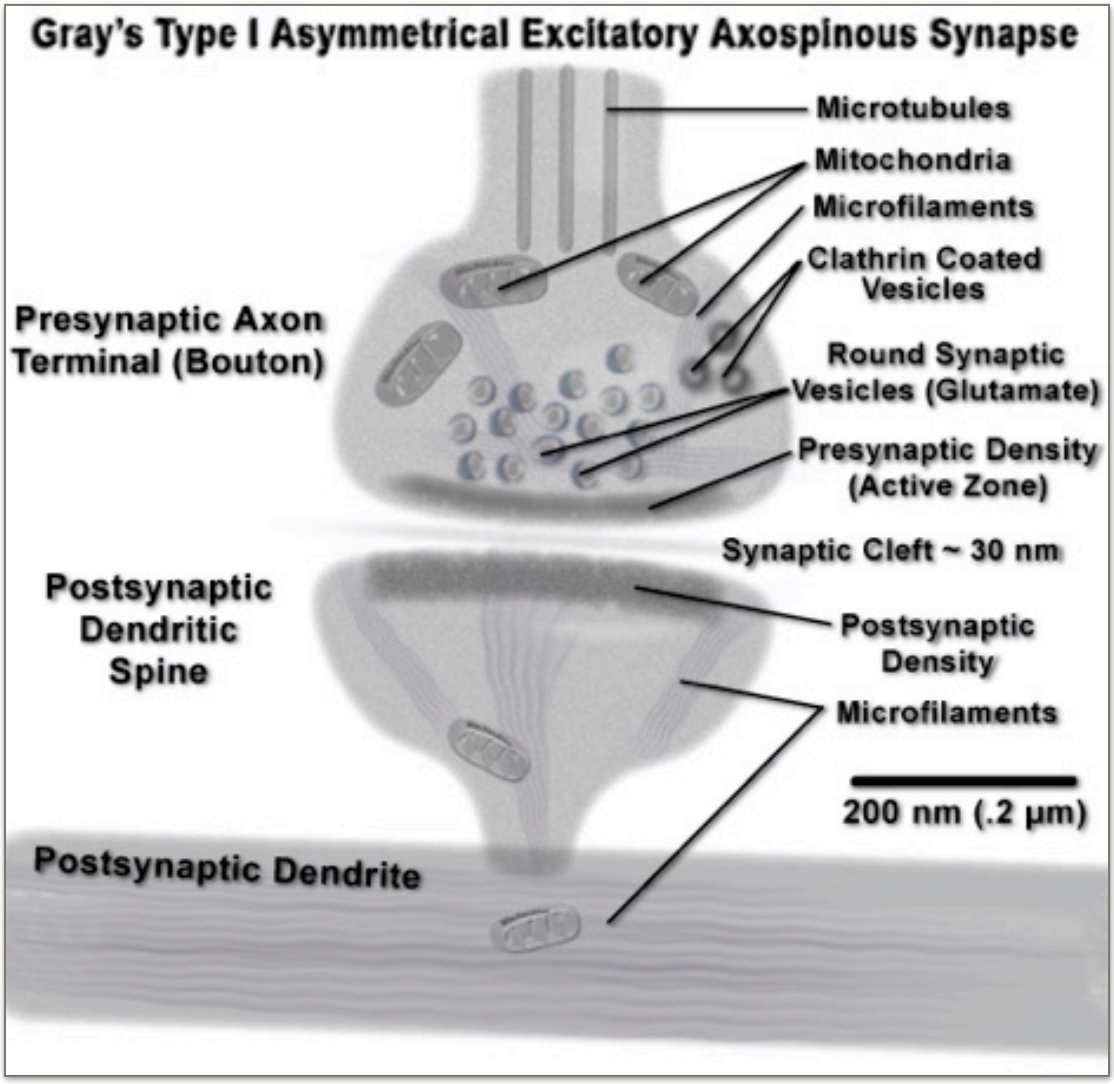

Fig 4-6. Gray's Type I Synapse with an asymmetrical profile (excitatory synapse) (gec).

A Type I Synapse (above) typically has an asymmetric profile (postsynaptic density thicker than presynaptic density), has round vesicles presumably filled with glutamate and a synaptic cleft of ~30 nanometer (nm). This synapse is an axospinous synapse although the major elements would be found also at excitatory axodendritic synapses.

A Type II Synapse (below) typically has a symmetric profile (postsynaptic and presynaptic densities have similar thickness), has pleomorphic vesicles presumably filled with GABA and a synaptic cleft of ~20 nm. Shown in the figure is an inhibitory axosomatic symmetric synapse i.e., the presynaptic axon terminal synapses on the soma of the postsynaptic cell. Axodendritic or axo-axonic inhibitory synapses have similar ultrastructural morphologies.

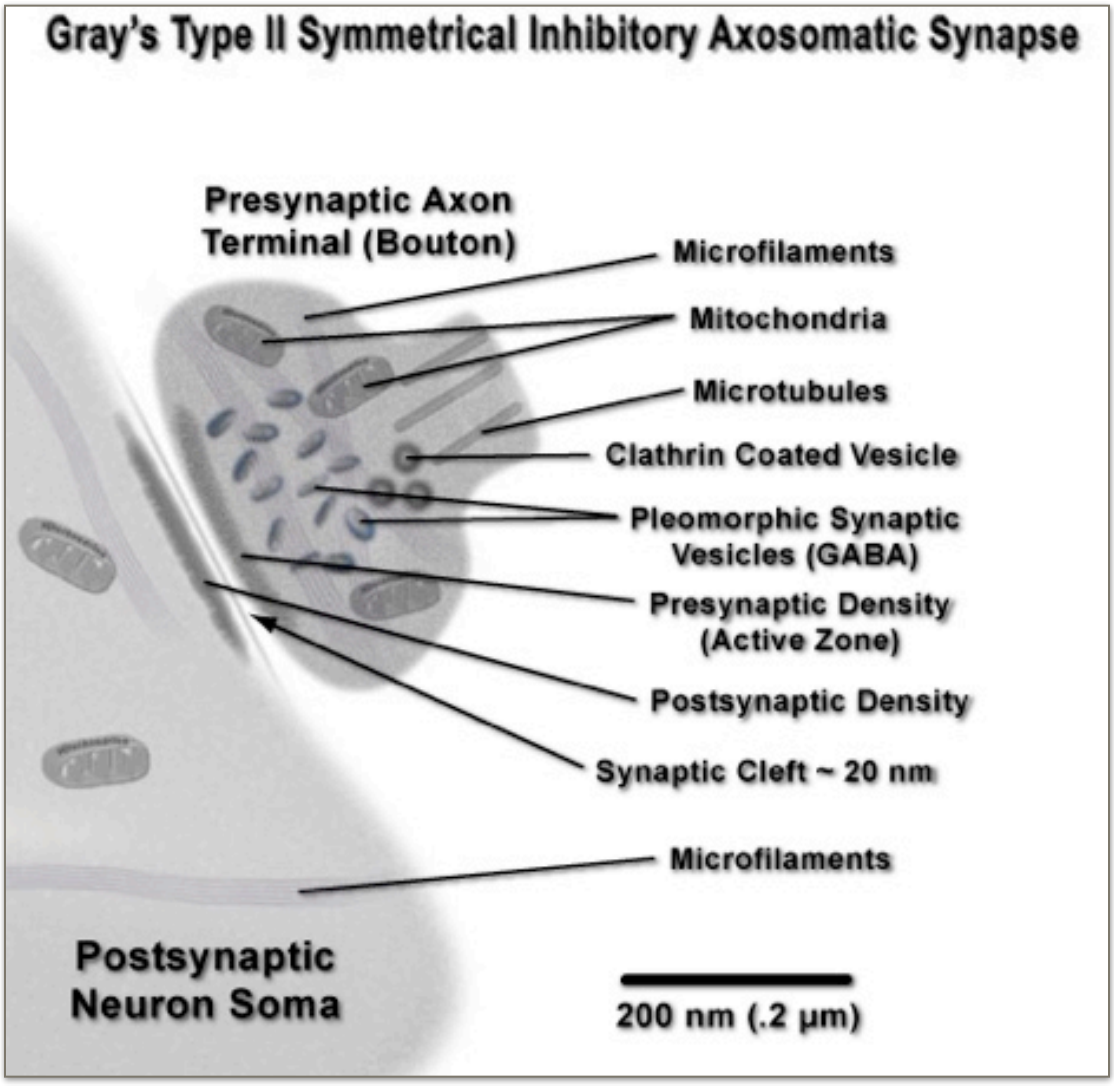

Fig 4-7. Gray's Type II Symmetrical Inhibitory Axosomatic Synapse (gec).

Axo-axonic synapses provide a potential final arbitrator of signal transmission.

Such axo-axonic synapses alter release of neurotransmitter from the postsynaptic axon terminals due to the release of neurotransmitter from the presynaptic axon terminal. The effect could be either excitatory or inhibitory depending upon the neurotransmitter released by the presynaptic axon terminal and/or the ion channel involved in the postsynaptic receptor complex. The unique axo-axonic synapse shown in the Axoaxonic Synapse Gray's Type I synapse on Gray's Type II Axon Terminal-Excitation of an Inhibitory Synapse by Direct Contact figure is an example where the glutamatergic axo-axonic synapse depolarizes an GABAergic axon terminal that, in turn, inhibits a postsynaptic soma by way of its axosomatic inhibitory synapse. Thus, inhibition may occur due to a depolarizing influence of a glutamatergic axo-axonic synapse directly on a GABAergic axon bouton even though the GABAergic neuron did not fire an action potential, e.g., see Szabadics, et.al., 2006. Presynaptic inhibition will be considered in later chapters.

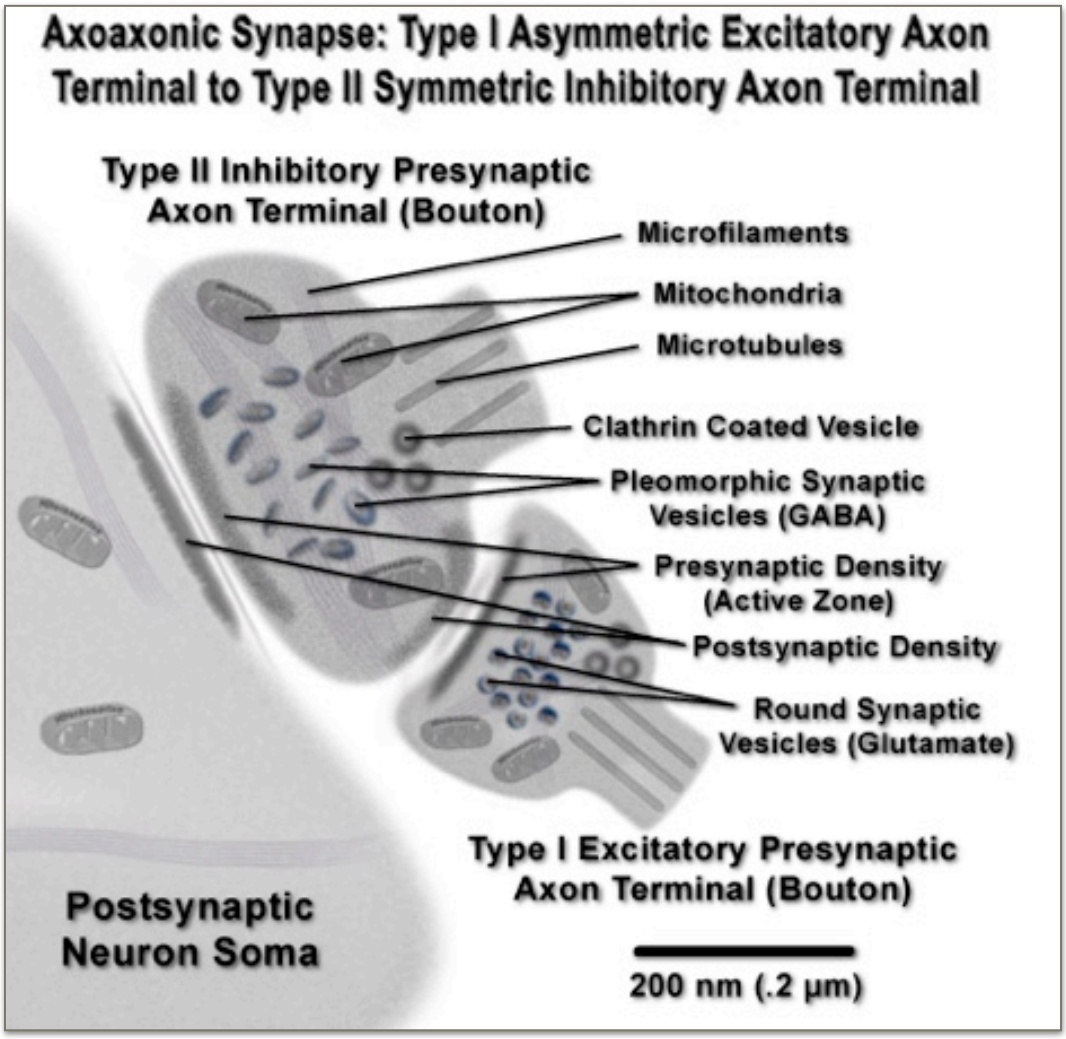

Fig 4-8. Axoaxonic Synapse Gray's Type I synapse on Gray's Type II Axon Terminal-Excitation of an Inhibitory Synapse by Direct Contact (gec).

FAST INCREASED CONDUCTANCE IONOTROPIC SYNAPTIC EVENTS.

The following flash animation shows a simulated sequence of events at a typical fast, ionotropic axospinous excitatory (glutamate) synapse. The EPSP in this example is due to activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptors only. There is no attempt to show actual quantal release events.

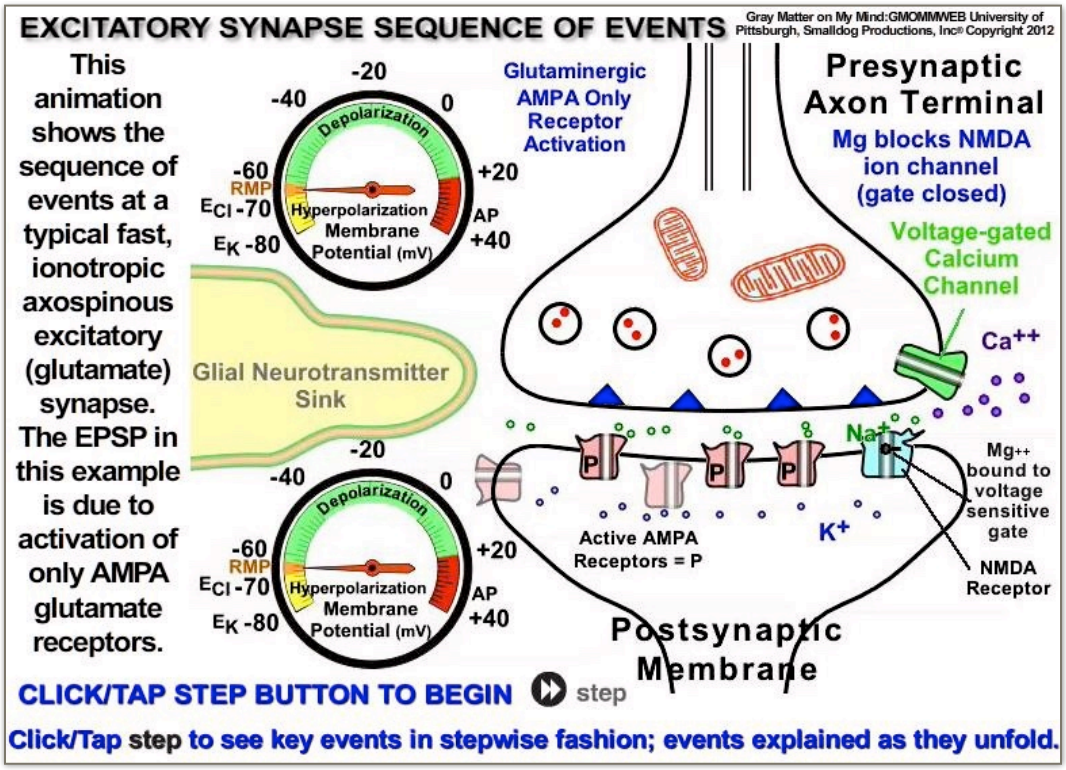

Fig 4-9. Synapse Sequence Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig4-9_Inter-active Media

The Synapse Sequence Interactive Flash Animation allows you to step through the sequence of events from action potential invading presynaptic terminal to re-sequestration of neurotransmitter as the Excitatory PostSynaptic Potential (EPSP) decays. Follow the typical presynaptic and postsynaptic action on a STEP by STEP basis.

- STEP 1: Action Potential Invades and Depolarizes Presynaptic Axon Terminal.
- STEP 2: Voltage-Gated Ca^{++} Channel Opens & Ca^{++} Enters Presynaptic Axon terminal.
- STEP 3: Ca^{++} Activates Release of Neurotransmitter (Glutamate): Vesicles Move to Active Zone Docking Proteins, Fuse With Membrane, Open and Release Glutamate Into Synaptic Cleft. Vesicles then rapidly detach ("Kiss and Run") from membrane.
- STEP 4: Glutamate Binds to Glutamate Receptors (AMPA) in Postsynaptic Membrane; this results in a conformational change so that an Ion Channel Opens; Presynaptic Axon Terminal Repolarizes.

- STEP 5: Postsynaptic Membrane is Depolarized due to Influx of Na^+ Through the Open Ion Channel in the AMPA Receptor Complex. Empty Synaptic Vesicles in the Presynaptic Axon Terminal are coated with a protein (Clathrin) to be recycled. Vesicle Cycling shown here is rapid, termed “Kiss and Run”. Other synapses may use slower detachment vesicle cycling, which I guess should be termed “Stay and Flirt”.
- STEP 6: Membrane Depolarization Produces an Excitatory Postsynaptic Potential (EPSP) that is a graded, local potential lasting ~10-100 msec. The EPSP may decay over distance & time or it may sum with other EPSPs to generate a propagated dendritic potential.
- STEP 7: EPSP Decays and Postsynaptic Membrane Repolarizes; Active Glutamate Reuptake Occurs in Presynaptic Axon Terminal (ATP Required), and Glutamate is Re-Sequestered from the glial (astrocyte) glutamate “sink”.

EPSPs: AMPA & NMDA GLUTAMATE RECEPTORS
AMPA RECEPTOR ONLY ACTIVATION

AMPA receptors produce a small to large EPSP with a time course lasting tens of msec to 100 msec in duration. AMPA receptors are the common “generic” glutamate receptors found in virtually all mature (non-silent) excitatory postsynaptic membranes.

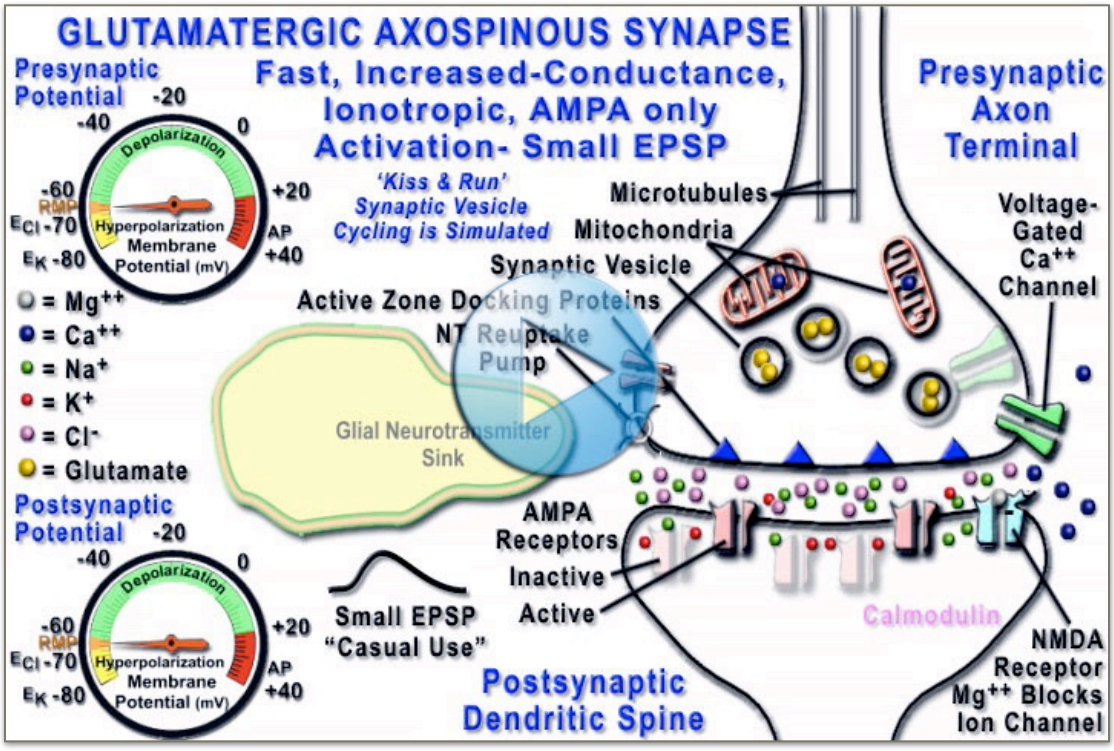

Fig 4-10. AMPA Receptor Only Activation Movie: Small EPSP (gec). The AMPA Receptor Only Activation Movie simulates a typical axospinous synapse where only AMPA glutamate receptors are activated. GO TO: gmomm.pitt.edu *Fig4-10_Video*

The AMPA Receptor Only Activation Movie simulates a typical axospinous synapse where only AMPA glutamate receptors are activated. A N-methyl-d-aspartate (NMDA) glutamate receptor is illustrated in addition to the AMPA receptors. A greater depolarization of the postsynaptic membrane is required to eject the Mg^{++} ions that normally block the NMDA receptor's ion pore. Thus, the NMDA receptor will not be a player unless glutamate binds to the NMDA receptor complex *AND* the postsynaptic membrane is sufficiently depolarized to eject the Mg^{++} (see below).

AMPA + NMDA RECEPTOR DEPOLARIZING INFLUENCES: CALCIUM INFLUX

Ionotropic Phosphorylated "Super" AMPA and the NMDA Glutamate Receptors may be activated together. The postsynaptic membrane must be sufficiently depolarized to eject the Mg^{++} ions that normally block the NMDA receptor's ion pore to allow ions to pass through. Thus, the NMDA receptor is active ONLY if glutamate binds to the NMDA receptor complex AND the postsynaptic membrane is sufficiently depolarized. The NMDA receptor depolarizing potential prolongs the EPSP duration and the open NMDA ion pore allows for influx of both Na^{+} and Ca^{++} ions. Phosphorylated AMPA receptors are typically found in synapses that have a significant history of use. The EPSP will be larger (super AMPA) and often will have a longer duration due to slower time course of NMDA receptor activation.

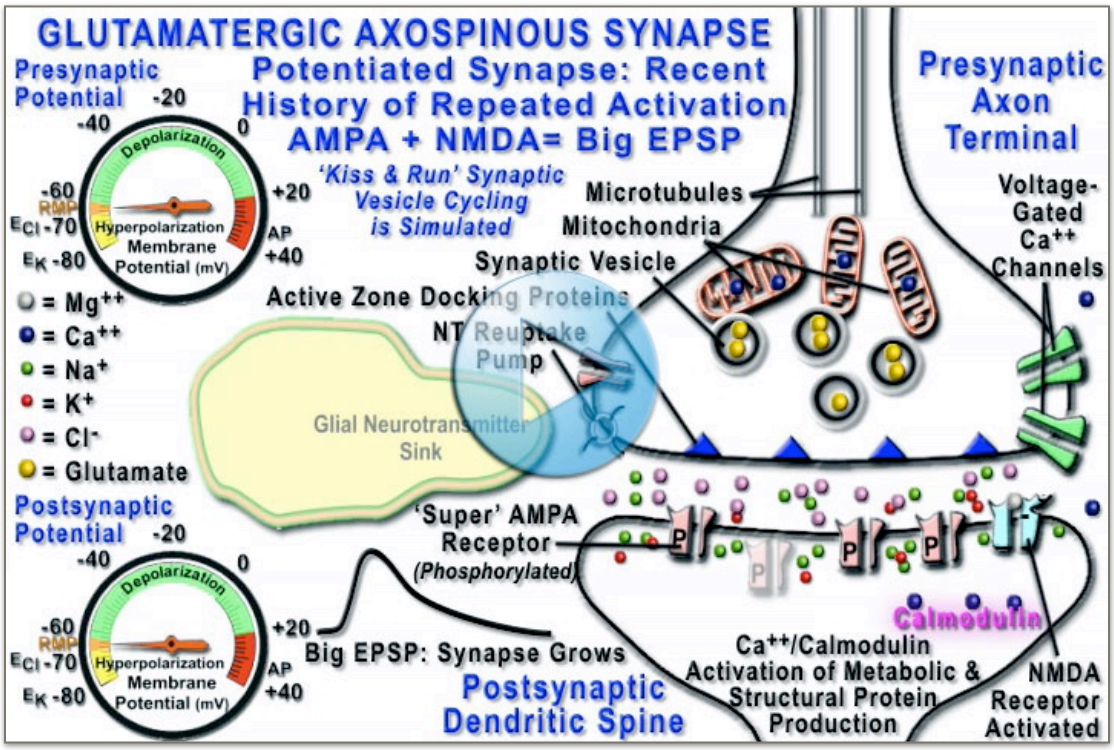

Fig 4-11. AMPA+NMDA Receptor Activation Movie: Big EPSP (gec). GO TO: gmomm. pitt.edu [Fig4-11_Video]

The AMPA+NMDA Receptor Activation Movie: Big EPSP animates the sequence of events. Sodium (Na^+) and Calcium (Ca^{++}) ion influx through the NMDA receptor ion pore provides a longer duration EPSP. Importantly, Ca^{++} is a regulatory signal for second messenger activation of protein production in the postsynaptic dendritic spine.

GABA RECEPTOR ACTIVATION: A CALMING INFLUENCE ON EXCITABLE CELLS

Mature GABA receptors hyperpolarize the cell membrane or shunt depolarizing currents (clamp membrane potential). GABA receptors are responsible for Inhibitory Postsynaptic Potentials (IPSPs). IPSPs suppress neuronal firing. The Axosomatic $GABA^A$ Receptor Activation Movie shows the sequence of events at a typical mature GABAergic ($GABA^A$) Synapse. GABA is released from synaptic vesicles into the synaptic cleft and binds to GABA receptors producing a conformational change in its ion channel so that Cl^- rushes into the postsynaptic cell. The IPSP produces a hyperpolarization and tends to 'clamp' the membrane close to the Cl^- equilibrium potential (-70 mV). Another type of GABA receptor the $GABA^B$ receptor is often found at axo-axonic inhibitory synapses. The hyperpolarizing current is due to an efflux of K^+ ions through the ion pore of the $GABA^B$ receptor. The simulation shows activation of postsynaptic $GABA^A$ receptors.

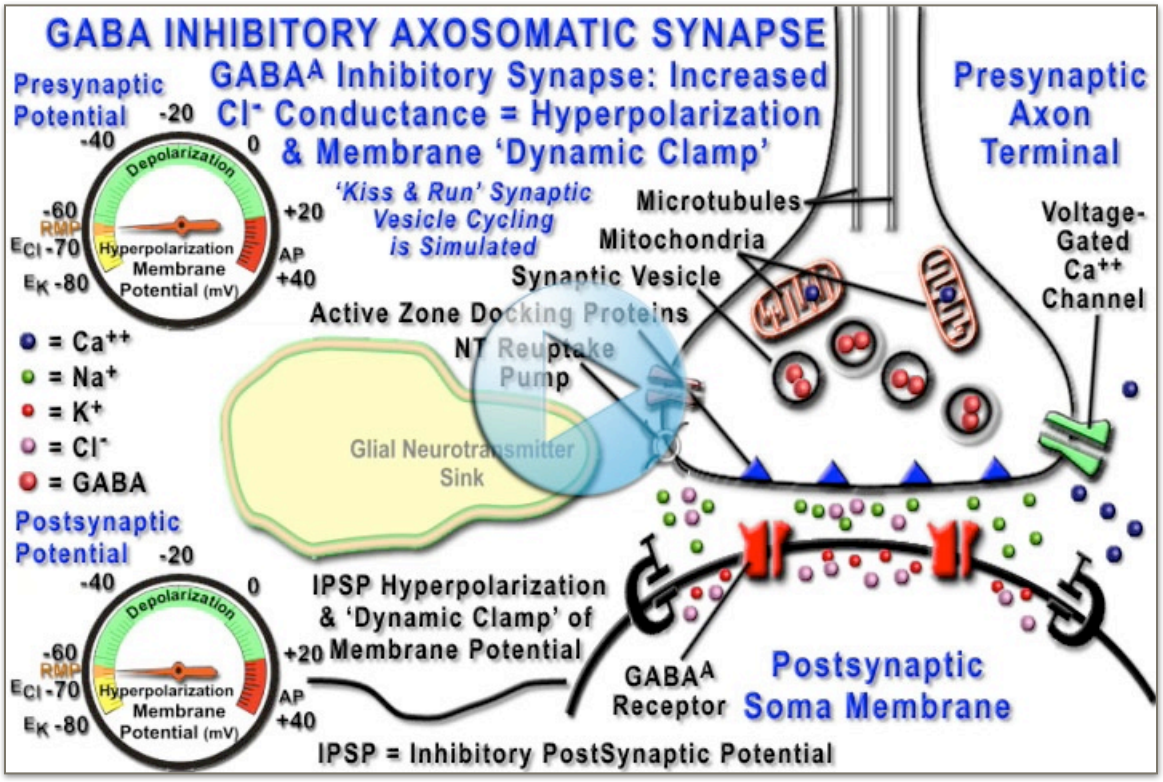

Fig 4-12. Axosomatic $GABA^A$ Receptor Activation: IPSP (gec). GO TO: gmomm.pitt.edu [Fig4-12_Video]

AMPA-NMDA LEARN!

Small mobile spine heads have both AMPA & NMDA receptors that may be activated by Glutamate released by the presynaptic axon terminal (not shown in the animation). If sufficiently depolarized in a repeated fashion, Ca^{++} enters through open ion channels of NMDA receptors and/or through voltage-gated Ca^{++} channels in the postsynaptic membrane. A rise in Intracellular Ca^{++} activates a number of second messenger systems that, in turn, alter membrane-bound and intracellular proteins. The spine head contains dynamic ultrastructural proteins that may change the size and shape of the spine head. In addition, increasing numbers of AMPA receptors may be inserted in the membrane and more membrane-bound AMPA receptors are phosphorylated increasing their efficacy (increased ion transfer). These events lead to a larger spine head, LTP, a larger EPSP and may be correlated with learning at the synaptic level (plasticity). Mobile synaptic spines have been likened to write-enabled data accumulators (RAM memory).

Big Stabilized Spine Heads have large numbers of AMPA receptors but few active NMDA receptors. Internal cytoskeletal 'scaffolding' proteins are stabilized and the large spine seems to be relatively immune to fluctuating levels of Ca^{++} and retains its shape and size over long periods of time. Large stabilized spine heads have been termed “mushroom” spines based on their typical shape. Trans-synaptic adhesion molecules bridging pre- and post-synaptic membranes may stabilize the synapse. It has been suggested that mushroom spines are structural sites for data storage (accumulated memory) that may be write-protected, read-only memory (ROM).; e.g., see Kasai, et.al., 2003; Bourne & Harris, 2007. Estimates suggest that about half of axospinous synapses for a given neuron are mushroom head synapses although this is not a rigid ratio.

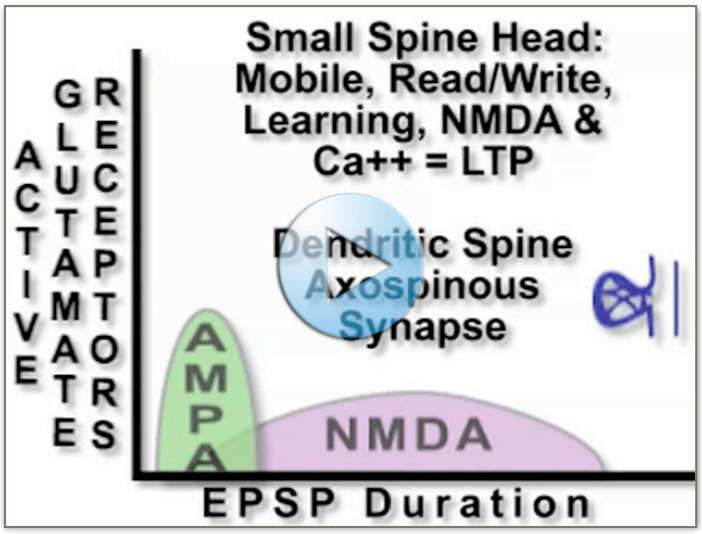

Fig 4-13. AMPA NMDA Learn Movie. Transition from small mobile to large stable dendritic spines. Bridge represents transynaptic proteins, e.g. neurexins, neuroligins & N-cadherin that provide structural stabilization of big mature synapses (gec). GO TO: gmomm.pitt.edu *Fig4-13_Video*

Our ability to retain information as long-term memory may be dependent on the stability of big-headed spines (mushroom or stubby spine heads). NMDA Receptors, LTP, Ca^{++} influx, second messenger cascades, metabotropic glutamate receptors and neurotrophins have all been suggested to be elements that fertilize (grow and/or enrich) mushroom spines. In addition, it may be the presence of a critical mass of trans-

synaptic cell adhesion molecules such as neurexins/neuroligins turns out to be the "band of gold" that forms the molecular basis of long-term relationships between presynaptic and postsynaptic elements within networks that remember!

SMALL MOBILE SPINE: RANDOM ACCESS MEMORY (RAM) "CASUAL USE" SPINE

Three movies below that simulate events as if viewed with increasing microscopic magnification of the synaptic ultrastructure: something that in reality is not technically possible at this time. Excitatory axospinous synapses on small, mobile dendritic spines are typically non-potentiated synapses that have small EPSPs. The simulated sequence of events begins with an Action Potential (AP) depolarizing the axon terminal that opens the voltage-gated Ca^{++} channels. Influx of Ca^{++} activates release of glutamate (Glu) from some of the vesicles into the synaptic cleft. Ca^{++} controls movement of 2 of 4 vesicles to the presynaptic density where the vesicles dock (active zone), fuse with the presynaptic membrane and open into the synaptic cleft. Glu binds to 2 AMPA receptors in the postsynaptic density (PSD) of the dendritic spine causing a deformation of the protein complex and influx of Na^{+} into the spine. NMDA receptors are not sufficiently depolarized to remove the Mg^{++} block of the NMDA ion channel. The resulting small local depolarization (EPSP) excites the spine head. When used infrequently (casual use) the small EPSP must combine with many other EPSPs to depolarize the postsynaptic cell's soma & axon hillock to send a signal (AP) on to other locations. The small, mobile spine may represent volatile RAM data, e.g., see Yuste & Bonhoeffer, 2001; Kasai, et.al., 2003; Bourne & Harris, 2007.

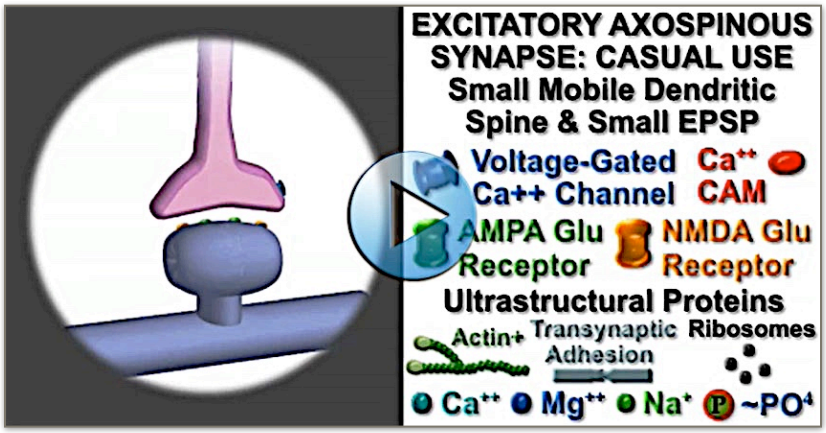

Fig 4-14. Axospinous Synapse-"Casual Use" Movie: AMPA only Small EPSP (gec). GO TO: gmomm.pitt.edu
Fig4-14_Video

SPINE GROWTH: AMPA & NMDA INDUCTION OF LTP-LEARN!

Repeated use of a Glutamatergic (Glu) axospinous synapse will alter the structure and function of the synapse. This animation shows increased depolarization of the postsynaptic membrane when presynaptic Action Potentials maintain a high level of depolarization. The large influx of Ca^{++} moves all 4 vesicles to the presynaptic density where the vesicles dock (active zone), fuse with the presynaptic membrane and releases Glu into the synaptic cleft. Glu binds to AMPA receptors in the postsynaptic density (PSD) of the dendritic spine causing a deformation of the protein complex and

influx of Na^{+} into the spine. NMDA receptors are sufficiently depolarized to remove the Mg^{++} block of the NMDA ion channel so that both Na^{+} & Ca^{++} ions enter the postsynaptic spine. NMDA activation potentiates the postsynaptic spine (Big EPSP). Calcium influx activates: 1.) phosphorylation of AMPA receptors to increase their efficacy, 2.) Calmodulin (CAM) to alter ultrastructural proteins to grow the spine head (Actin + other ultrastructural Proteins) and 3.) insertion of additional AMPA receptors into the PSD. Transforming Small Mobile Dendritic Spines to Large Stable "Mushroom" or "Stubby" Spines is thought to be a structural basis for long-term memory at the synaptic level. Thus, when learning, cell-cell interactions grow to form a big spine head that once stabilized may represent "read only," and "write protected" (ROM) data: remember!, e.g., see Yuste and Bonhoeffer, 2001; Kasai, et.al., 2003; Bourne and Harris, 2007.

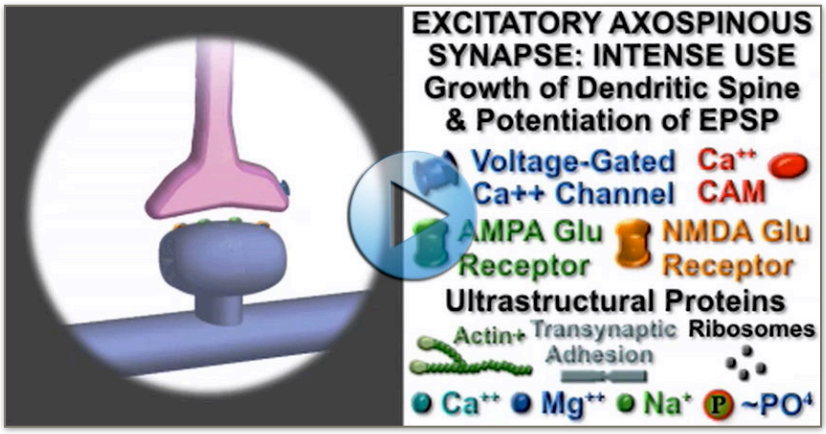

Fig 4-15. Axospinous Synapse-"Intense Use Synapse Grow" Movie: AMPA + NMDA & Big EPSP (gec). GO TO:gmomm.pitt.edu Fig4-15_Video

MUSHROOM SPINE: WRITE-PROTECTED, READ-ONLY MEMORY (ROM)-REMEMBER

Following induction of Long-Term Potentiation (LTP) a Glutamatergic (Glu) axospinous synapse is large and stable. This animation shows increased depolarization of the postsynaptic membrane when presynaptic Action Potentials maintain a high level of depolarization.

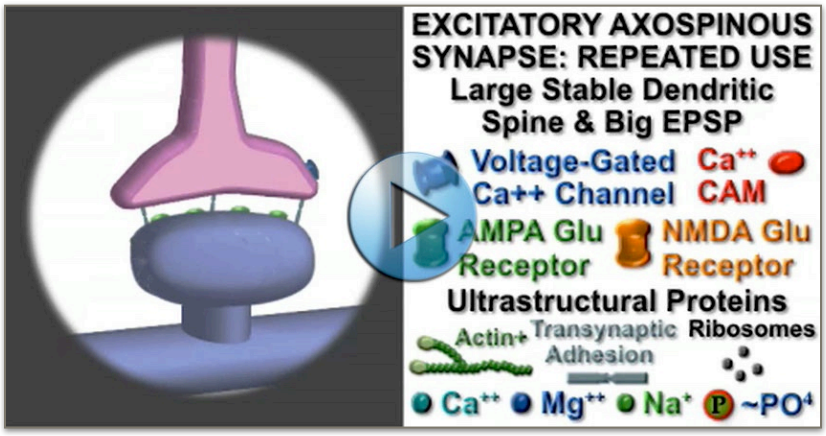

Fig 4-16. Axospinous Synapse-"Big Spine Head" Movie: Many Super AMPA No NMDA=Big EPSP (gec). GO TO: gmomm.pitt.edu Fig4-16_Video

The large influx of Ca^{++} moves all 4 vesicles to the presynaptic density where the vesicles dock (active zone), fuse with the presynaptic membrane and releases Glu into the synaptic cleft. Glu binds to multiple

phosphorylated AMPA receptors in the postsynaptic density (PSD) of the dendritic spine causing a deformation of the protein complex and a large influx of Na^+ into the spine. NMDA receptors are removed from the PSD and no longer provide a source of modulation of the spine. Morphological changes of spine & axon terminal are stabilized by transynaptic adhesion "bridge" proteins linking pre- and post-synaptic elements, see: Yuste & Bonhoeffer, 2001; Kasai, et.al., 2003; Bourne & Harris, 2007.

SPATIO-TEMPORAL SYNAPTIC INTEGRATION

Each neuron is contacted by many other axon terminations from multiple cells. Thousands to hundreds of thousands of synaptic contacts together provide a mechanism for "analog" processing of excitatory and inhibitory influences. If the soma and axon hillock of this postsynaptic cell is depolarized above threshold then the neuron will emit a "digital" signature to other cells if inhibitory inputs do not nullify these excitatory influences. EPSPs are small depolarizing potentials that individually are inadequate to depolarize the CNS neuron's membrane to threshold for generation of an AP; many EPSPs must sum to create an AP. Summation may occur within both a spatial domain and a temporal domain. In reality summation is usually some combination: a spatiotemporal summation of EPSPs arriving at the cell at about the same time. Often the most effective excitatory drive is one where there is a synchronous convergent input from one or more presynaptic sources. Therefore, network properties that tend to synchronize the activity of groups of neurons will enhance the integrative nature of the neurons participating in the neural processing (integrate & fire) and provide additional temporal information (correlated discharge). Axospinous synapses are most often excitatory. Many axospinous postsynaptic membranes include both NMDA and non-NMDA (AMPA or Kainate) Ionotropic Glutamate Receptor Types plus Metabotropic Glutamate Receptors, each of which has a different postsynaptic membrane effect.

Six simulations show different types of spatiotemporal synaptic integration from multiple presynaptic sources to a single postsynaptic pyramidal cell. Most inputs are excitatory but inhibitory inputs provide important modulation of depolarizing inputs. See membrane potential changes within different compartments of the neuron. Five membrane potential meters illustrate membrane potential changes measured by patch microelectrodes at five different locations along the neuron's membrane: 1) distal apical dendrite, 2) mid-apical dendrite, 3) proximal basal dendrite, 4) soma, 5) axon. All simulations are shown in slow motion. The first three movies show different spatio-temporal integration of excitatory inputs only. The last three illustrate the effects of inhibitory inputs to three different locations as GABAergic modulation of the depolarizing inputs. Replay movies several times to attend to all of the events at different locations along the dendrites, at the soma, at the axon hillock and along the axon of the simulated pyramidal cell. Note the back propagated dendritic plateau action potential (BAP) when the axon hillock is depolarized above threshold to initiate an axonal AP. The BAP may or may not invade the distal dendritic tuft arbor.

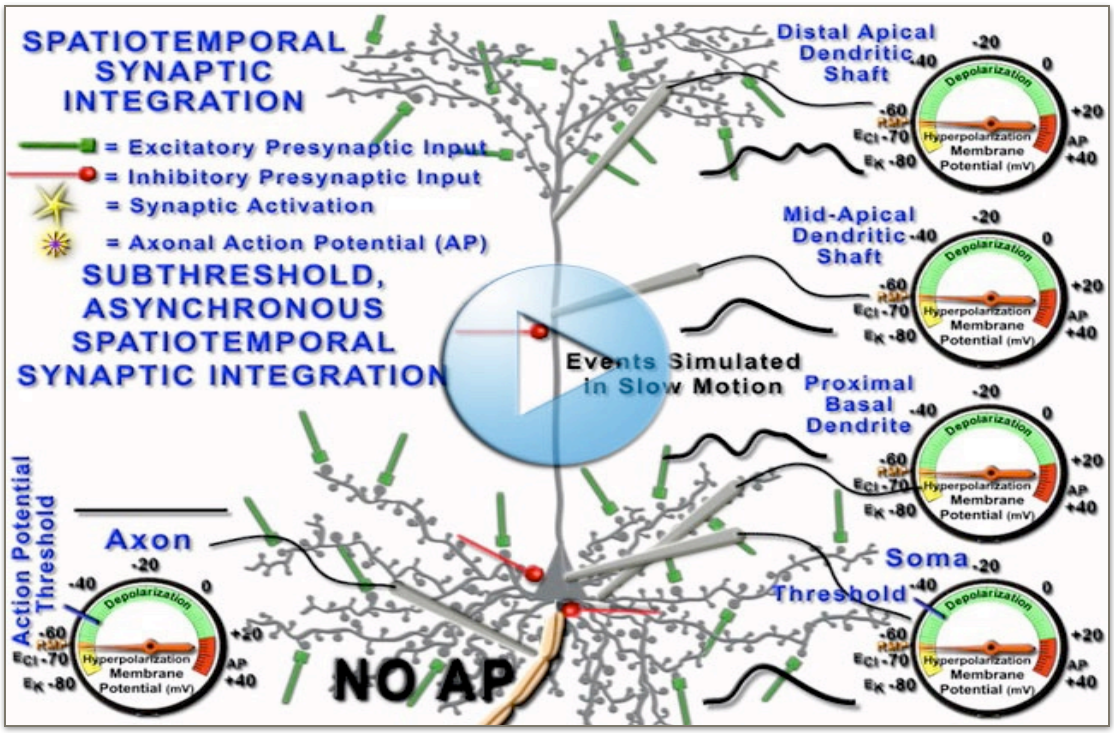

Fig 4-17. Spatiotemporal integration of asynchronous subthreshold EPSP inputs: No AP (gec). GO TO: gmomm.pitt.edu *Fig4-17_Video*

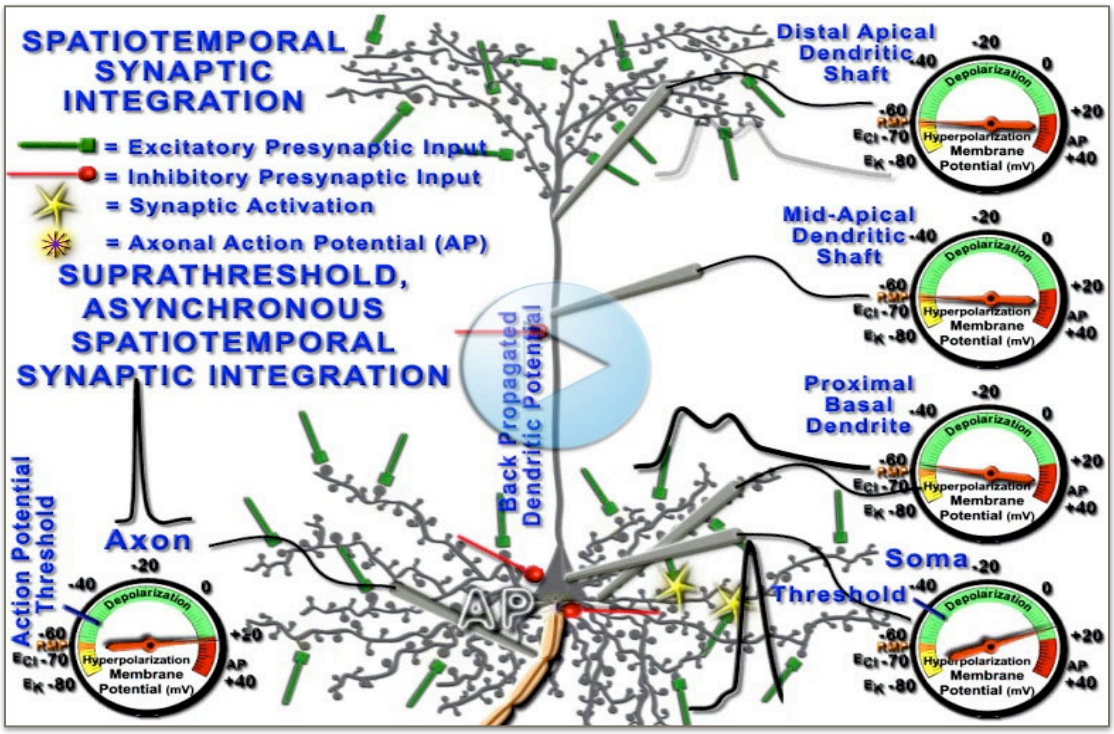

Fig 4-18. "Slow-fuse/ Integrate & Fire" asynchronous supra-threshold EPSP inputs = AP (gec). GO TO: gmomm.pitt.edu *Fig4-18_Video*

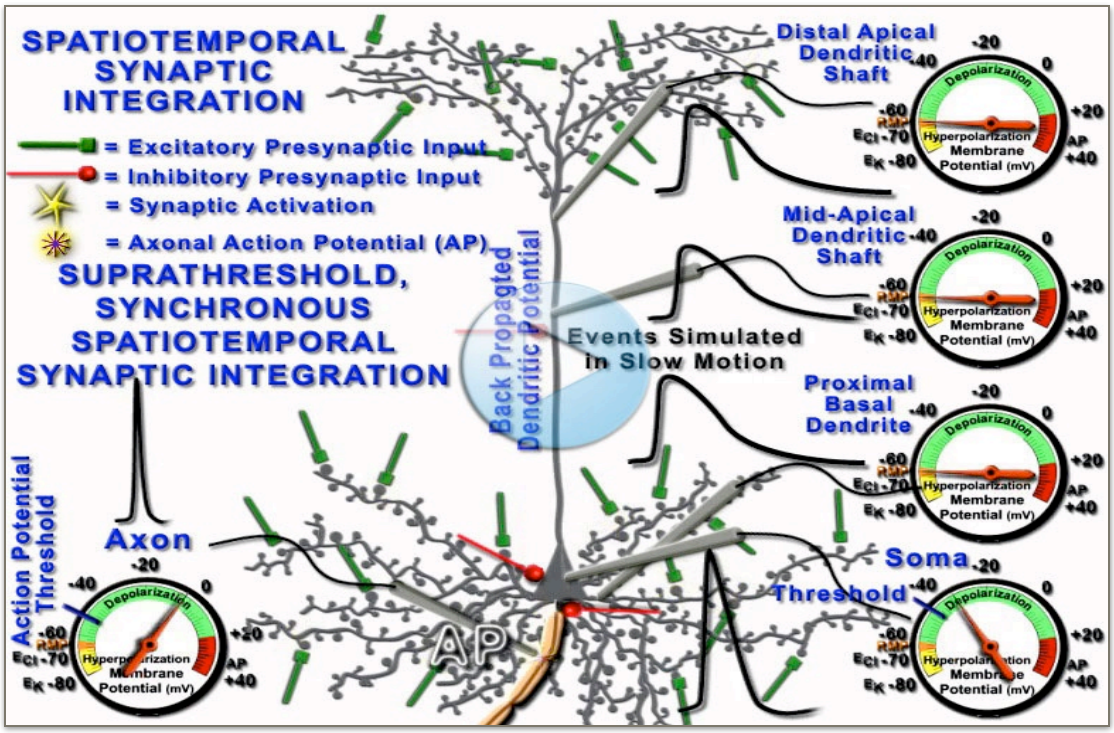

Fig 4-19. "Quick-Fire/ Coincidence Detection" synchronous EPSP inputs= AP (gec). GO TO: gmomm.pitt.edu [Fig4-19_Video]

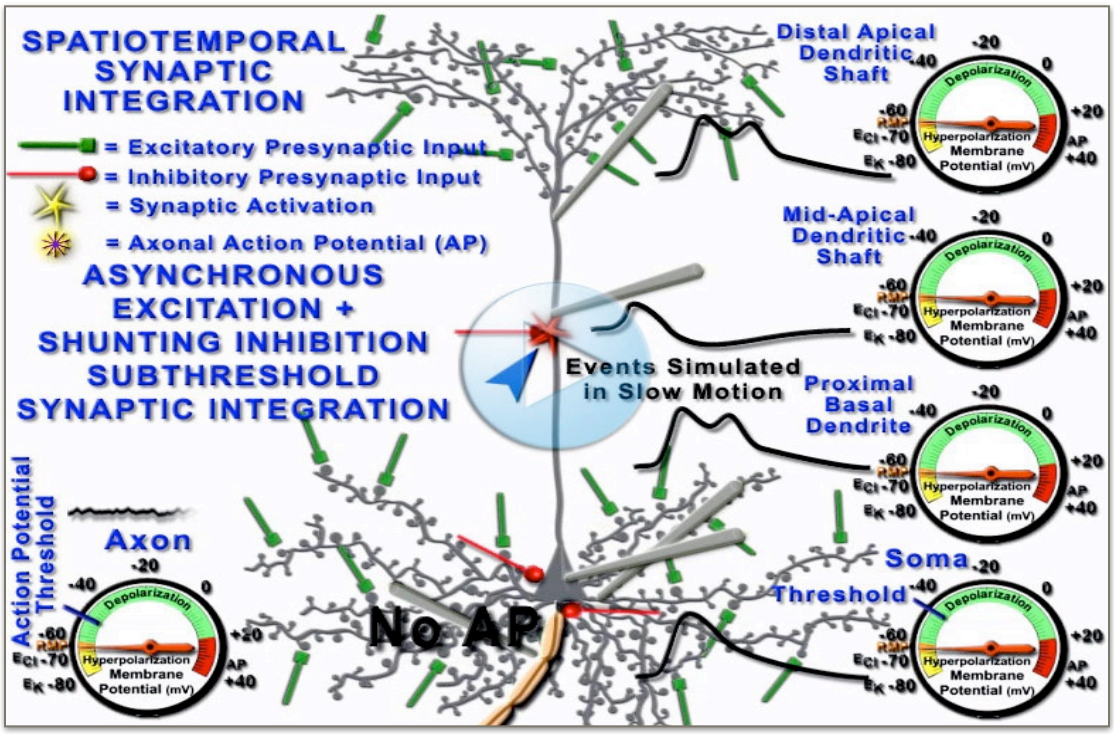

Fig 4-20. GABA Inhibition of Distal Dendrite Depolarization- Shunting Inhibition (gec). GO TO: gmomm.pitt.edu [Fig4-20_Video]

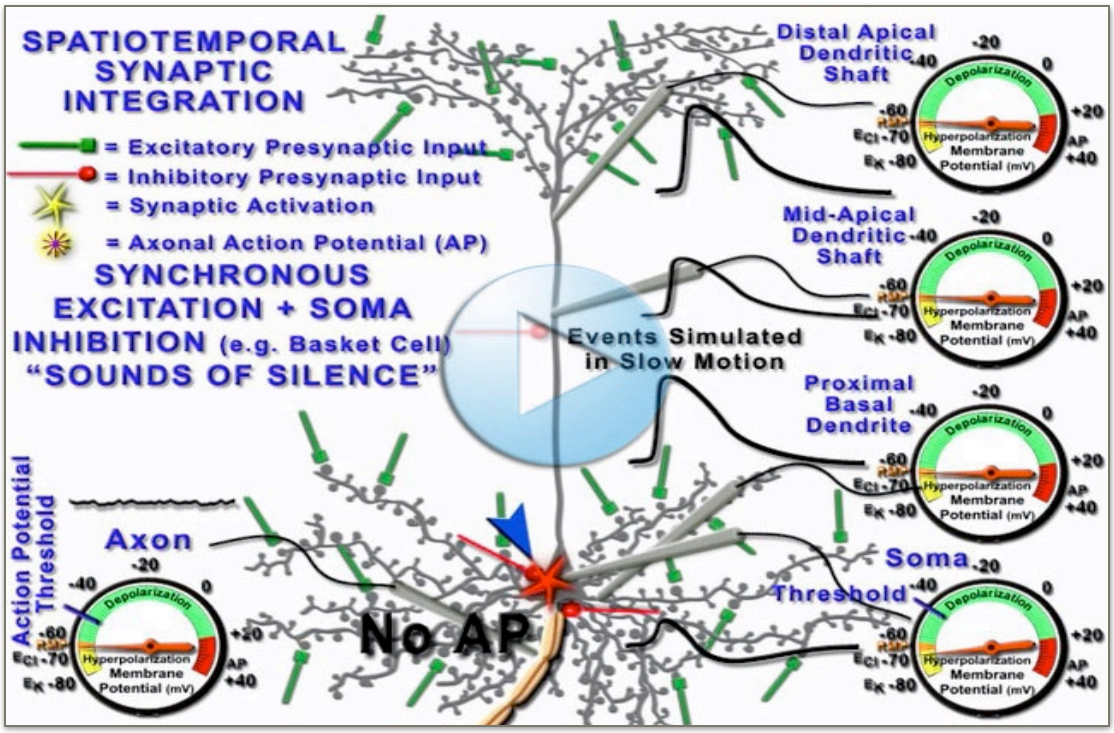

Fig 4-21. Powerful GABA Inhibition of Soma: Sounds of Silence (gec). GO TO: gmomm. pitt.edu [Fig4-21_Video]

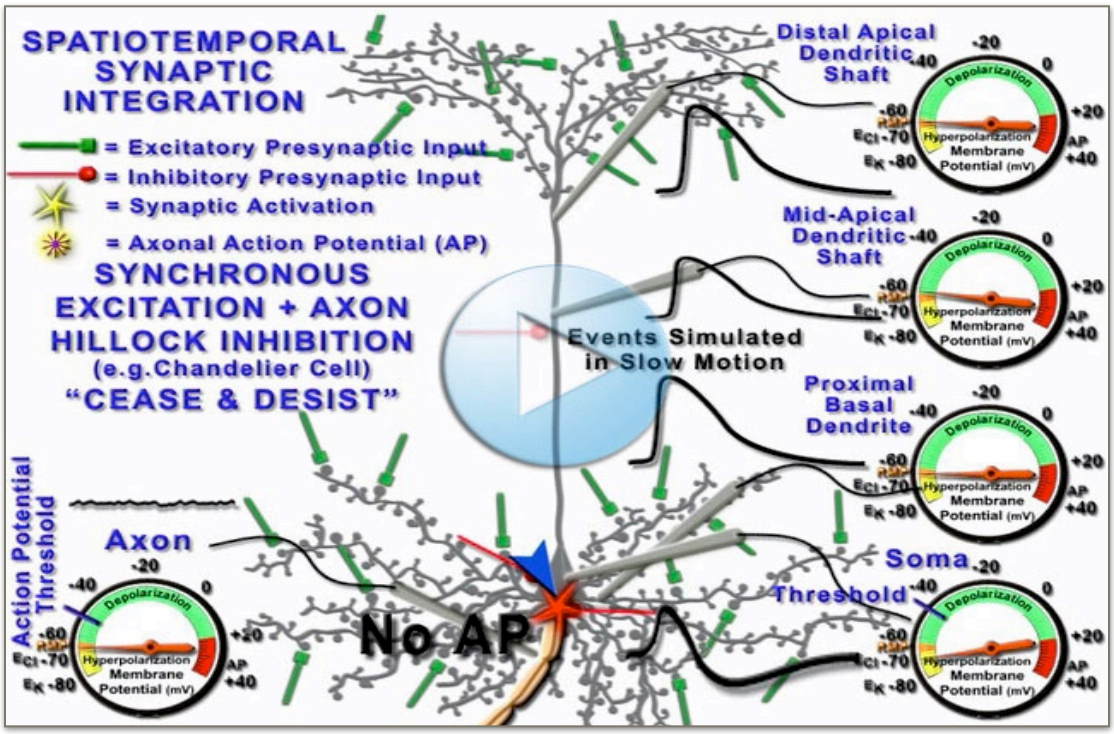

Fig 4-22. GABA Inhibition of Axon Hillock: Chandelier Cell Cease & Desist Order (gec). GO TO: gmomm.pitt.edu [Fig4-22_Video]

GABAergic inhibition of the neuron's soma produced profound inhibition of the cell such that initiation of an action potential is effectively prohibited.

A "Cease and Desist" Order may be issued by a Chandelier Cell's GABAergic axo-axonic synapse on the axon hillock of a Pyramidal Cell: a powerful control mechanism.

GABA INHIBITION KEEPS OUR EXCITABLE BRAINS CIVILIZED

Optical Imaging of voltage-sensitive dyes using an *in-vitro* thalamocortical slice preparation allows one to visualize the global synaptic activity (EPSPs) of many neurons across a prolonged time course. Such global activity cannot be measured with a single microelectrode. Thalamocortical afferents are stimulated to activate the cortical cells. A low concentration (2 μM) of a GABA antagonist bicuculline (BIC) increases the amplitude of the optical signals, while a higher dose (5 μM) of BIC induces a highly abnormal paroxysmal activity that spreads vertically and horizontally by way of excitatory pathways (seizure-like activity); nACSF = normal ionic Artificial Cerebrospinal Fluid that bathes and nourishes the brain slice. BIC is added to the bath. When you play the movie note two waves of spreading excitation after adding 5 μM of BIC to the bath. Such abnormal excitability following a single extrinsic stimulus suggests activation of a reverberating circuit within the cortex unleashed by blocking GABA, see Laaris et.al., 2000. Inhibitory synapses have a key role in controlling levels of neuronal excitability.

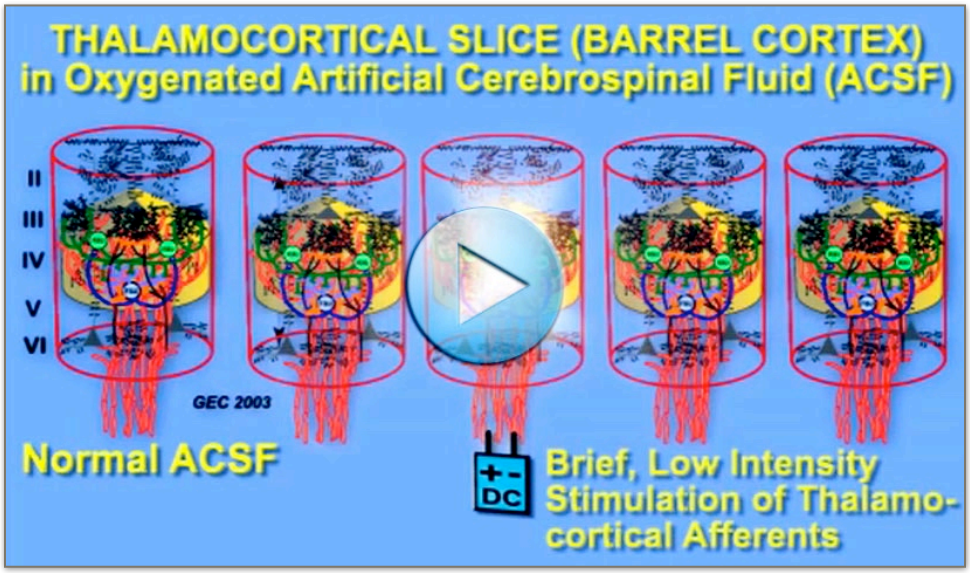

Fig 4-23. GABA reduces spread of maladaptive waves of excitability similar to seizure activity in the intact brain (gec). GO TO: gmomm.pitt.edu *Fig4-23_Video*

Neuronal activity be measured at the cellular, metabolic level. Glucose is the major source of energy for neurons. Radioactively labeled glucose: 2-Deoxyglucose (2DG) can be measured at the level of single cells in the brain. If a rat explores its environment, its brain will "light-up" in those areas that are most metabolically active. One such area is the whisker representation in the somatosensory "barrel" cortex of rodents. Rodents use their whiskers to explore & engage their environment. When 2DG

label is quantified, data show that the most active neurons are GABAergic (inhibitory neurons) in the barrel cortex see: Laaris, et.al., 2000. Although inhibitory neurons represent only a small fraction of the total number of cortical neurons, the few (but typically very active) inhibitory cells provide a necessary control to reduce the total excitatory activity in the brain: a critical factor to prevent circuit overload leading to a "brownout," "blackout" or worse in the brain, e.g., see McCasland & Hibbard, 1997; DeFelipe, 1999; Laaris et.al., 2000; Halder, et.al., 2006.

GABA MAY ENTICE VERY YOUNG NEURONS TO DEVELOP EXCITATORY CONNECTIONS

The prenatal and early postnatal brain is a beehive of activity. Early in prenatal life precocious neural tube and neural crest cells are replicating and some are forming appropriate connections with targets in the periphery or within the developing CNS. Most of these cells will define themselves as either neurons or glial cells while a minority may put off such a decision and remain as neural stem cells in a few regions of the developing brain even into adulthood. Some cells will not match with an appropriate target and undergo naturally occurring cell death (apoptosis). Patterns of cell migration and pathway development continue within the prenatal and early postnatal period. During postnatal development, cells may decide early what they will be when they grow up while others put off this decision until greater experience with the outside world is obtained.

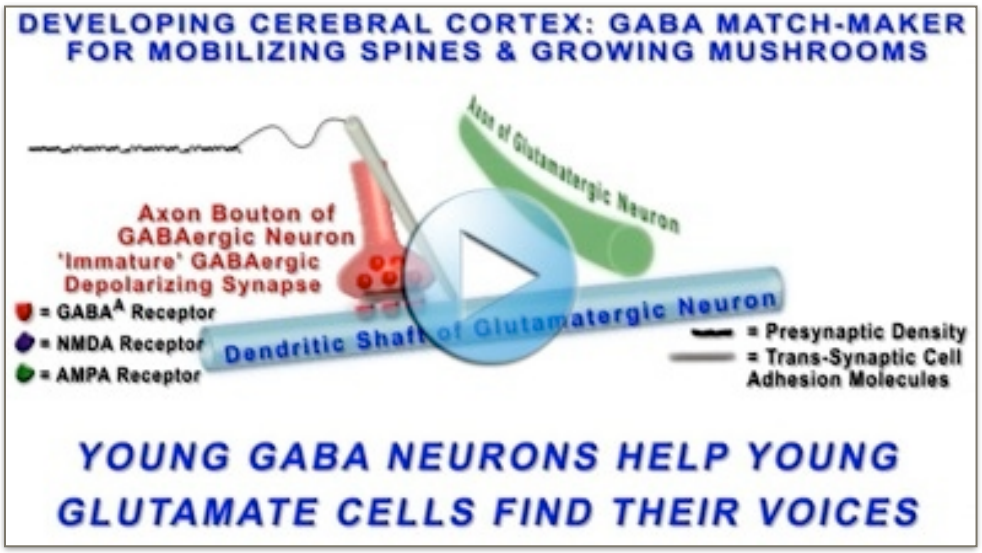

Fig 4-24. GABA Enhances Immature "Silent" Glutamatergic Synapses to find their voices, i.e., develop functional connections (gec). GO TO: gmomm.pitt.edu Fig4-24_Video

Development of synaptic connectivity is intense in the young brain. Many genetic, molecular and activity-dependent cues appear to be important in creating, eliminating or stabilizing synaptic connections. This appears to be a "mutual admiration society" where some level of consensus is reached between the presynaptic and postsynaptic neuron. This "mating" may be dependent upon chemical cues alone or in many cases the match requires some more work as patterns of neural activity (Hebbian). Some of these relationships

do not last and the synapse is eliminated while others go on to a more permanent bond as a secure synaptic "marriage." One of the most common types of synapses in the cerebral cortex is the glutamatergic axospinous synapse (axon bouton to dendritic spine). Most dendritic spines start out as filopodia. If "*Mr. Right*" axon bouton meets the filopodia, trans-synaptic adhesions form, pre-synaptic and post-synaptic densities form and NMDA (but not AMPA) receptors are active. However, such nascent synapses are called "silent synapses" since the NMDA receptor requires not only glutamate binding but depolarization of the post-synaptic membrane to open the ion channel. One mechanism proposed to depolarize the post-synaptic membrane in the immature brain is $GABA^{A}$ receptor activation. Immature neurons are said to have a Cl^{-} gradient that unlike mature neurons supports depolarization not hyperpolarization of the membrane. Increased Ca^{++} conductance by way of NMDA receptors may then activate AMPA receptor insertion so the synapse is no longer silent, see Ben-Ari, 2002; Ganguly, et.al., 2001; Luhmann, et.al., 2014.

Initially, GABA neurons may be the "match-makers" for budding excitatory synapses. Once the postsynaptic GABAergic cell matures the Cl^{-} gradient changes and an inward Cl^{-} conductance produces hyperpolarization. GABA neurons now become the "mature" constraining influence on highly excitable cells (recess is over, time to study).

HEBB, BIOCHEMISTRY, SYNAPSE MORPHOLOGY, ACTIVITY-DEPENDENT SYNAPTIC PLASTICITY

The ability of the brain to operate in a normal fashion depends upon a balanced level of electrical and chemical signaling among many neurons connected within regulated networks. Our brains contain sophisticated chemical laboratories that attempt to maintain a balance of potentially volatile biochemical reactions. Early twentieth century studies showed that communication between neurons requires synapses with chemically-gated receptors. Recent research suggests a more diverse and complicated interaction among neurons utilizing both autocrine and paracrine chemical messengers having both short-term & long-term effects on individual cells and cell assemblies. Inspired by Lorente De No's (1938), drawings of synaptic "knobs", (axonal terminal swellings), D. O. Hebb (1949) hypothesized that repeated use of a synapse will grow the relationship between activity-coupled cells. The concept of a Hebbian synapse has become a springboard for revolutionary research on the synaptic & molecular bases of learning and memory. In-vitro methods to study neurons in culture or in brain slices and in-vivo recordings of whole cell (soma) and dendritic potentials show rapid changes that may potentiate or depress synapses. Neurotrophins provide "permissive" or "instructive" roles in maintaining or growing activity-dependent neuronal relationships. Activity may be specific to synapses and/or to the overall activity of the organism (e.g., exercise may influence certain neurotrophin levels). Growing evidence suggests "neurons that play (fire) together stay (wire) together."; e.g., see Bliss and Lomo, 1973; Bi and Poo, 2001; Greenough, 1988; Hebb, 1949; Shatz, 1990, 1992; Narayanan & Johnston, 2007.

INDUCTION OF LONG TERM POTENTIATION (LTP) AND SYNAPTIC PLASTICITY

Following a brief period of intense activation (kindling), some glutamatergic excitatory synapses display a long-lasting (hours to days) potentiation of subsequent individual EPSPs. This is called long-term potentiation (LTP), e.g., see Bliss & Lomo, 1973; Yuste & Bonhoeffer,2001; Zucker & Regehr, 2002; Dan & Poo, 2004; Malenka & Bear, 2004.

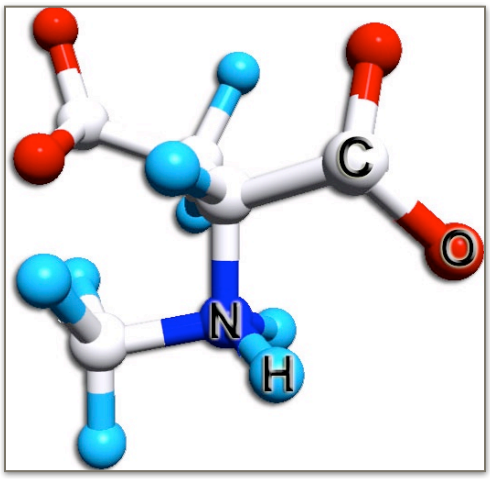

Fig 4-25. Molecular structure of the glutamate agonist N-Methyl-D-Aspartate (NMDA). C= Carbon, H= Hydrogen, N= Nitrogen, O= Oxygen (gec).

LTP is one mechanism to enhance synaptic transmission and may be responsible for structural alterations that strengthen the synapse. These changes occur in the postsynaptic membrane and over time may alter the presynaptic axon terminal as well. There is still debate regarding the mechanism(s) responsible for LTP. One important mechanism involves the special postsynaptic NMDA glutamate receptor.

NMDA receptor protein complexes contain a Mg^{++} ion that normally blocks the ion channel pore. With high, sustained depolarization AND Glutamate or NMDA agonist binding, the voltage-sensitive Mg^{++} gate is opened. This allows the passage of Na^{+}, K^{+}, and Ca^{++} ions. Influx of Ca^{++} results in a cascade of events that alter metabolic and structural proteins in the postsynaptic membrane/cell. Inactive AMPA receptors may be activated (phosphorylated?), and/or inserted into the synaptic membrane. This provides a mechanism for greater depolarization (bigger EPSP) that, in turn, activates the NMDA receptor with resultant Ca^{++} influx. Recent research suggests that within certain regions of dendrites an NMDA plateau “spike” may be generated given a sufficient concentration of activated NMDA receptors. This NMDA plateau depolarization ”propagates” with little or no time- and distance-decay of depolarization typical of AMPA EPSPs: e.g., see Williams, 2004; Williams, et.al., 2007; Rao & Finkbeiner, 2007; Major, et.al., 2013.

EARLY, LATE MORPHOLOGICAL CHANGES FOLLOWING LTP INDUCTION: AXOSPINOUS ULTRASTRUCTURAL ALTERATIONS

Activity/experience dependent plasticity may utilize this mechanism to produce short- and long-term synaptic modifications. The link between high discharge rates of presynaptic elements and enhanced EPSPs is an example of a Hebbian Synapse. Current hypotheses favor this postsynaptic mechanism for LTP, but a presynaptic

mechanism (increased presynaptic Ca^{++} influx & greater Glutamate release) also has been suggested.

Fig 4-26. Axospinous Synapse Ultrastructural Morphing Movie (gec). GO TO: gmomm.pitt.edu *Fig4-26_Video*

Based upon electron microscopic (EM) examination of dentate gyrus pyramidal neurons in the hippocampus of rats there is evidence that an alteration in the physical morphology of the presynaptic and postsynaptic components of axospinous synapses begins within an hour following induction of LTP. The induction of LTP is due to a kindling regime (tetanic stimulation) of the perforant path to the dentate gyrus. The early morphing of the kindled synapse due to LTP induction is followed by further alterations that may include splitting of a single axospinous synapse (one larger axon terminal apposed to two dendritic spines) or a split to two axon terminals apposed to two dendritic spines, e.g. see Weeks, et.al., 1999, 2000, 2001; Yuste & Bonhoeffer, 2001; Bourne & Harris, 2008.

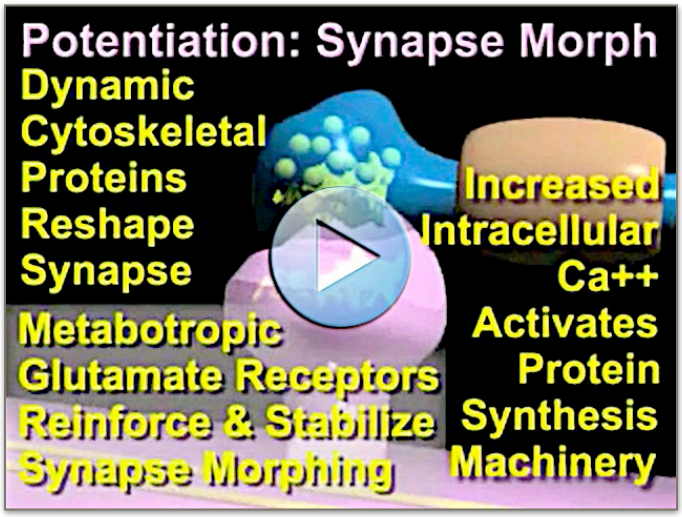

Fig 4-27. LTP Axospinous Morph Movie (gec). GO TO: gmomm.pitt.edu *Fig4-27_Video*

This change occurs within a day following the kindling LTP induction. Several days later the morphology seems to stabilize as a larger stubby or mushroom spine apposed to a large axon terminal. These examples of LTP induced synaptic plasticity suggest that enhancement of synaptic signaling occurs in stages and may reflect the underlying biochemical and ultrastructural protein alterations due to both local synaptic mechanisms and long-range signals associated with nuclear activation of DNA-RNA transcription of new proteins that are transported back to the potentiated synapse, e.g., see Tada & Sheng, 2006; Wake, et.al., 2011. This dynamic morphing at the axospinous synapse due to LTP is illustrated in two movies: LTP Axospinous Morph Movie and the Associative LTP in Motor Cortex Movie. Associative LTP requires coincident inputs from two sources to induce

potentiation of the postsynaptic neuron. This has been shown in the hippocampus and the cerebral neocortex.

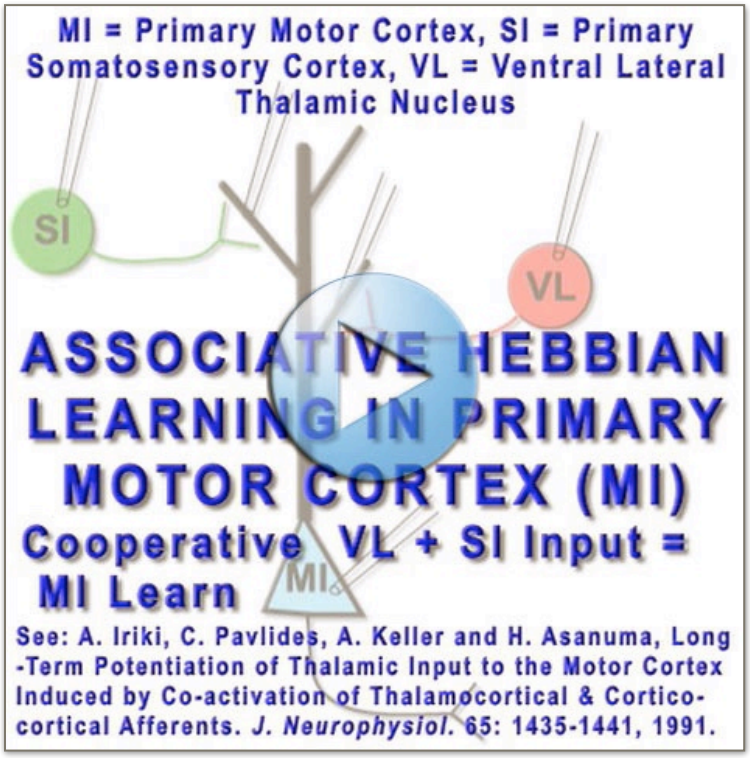

Fig 4-28. Associative LTP in Motor Cortex Movie. Synchronous SI Cortical + VL Thalamic Input induces LTP (gec). GO TO: gmomm.pitt.edu *Fig4-28_Video*

Here LTP in Motor Cortex pyramidal cells is induced only if both cortical SI input is coincident with thalamic input from the VL nucleus. Such LTP occurs in layer 3 but not layer 5 pyramidal neurons, see Iriki, et.al., 1991.

METABOTROPIC RECEPTORS AND SECOND MESSENGER CASCADES

Along with Ionotropic Receptors, many synapses have Metabotropic Receptors. The effects of the neurotransmitter (NT) activates a membrane-bound G-coupled protein. Metabotropic receptor protein complexes do not have an ion channel. Binding of the NT to Metabotropic Receptors results in activation of a second messenger cascade of events that has long lasting effects on the synapse.

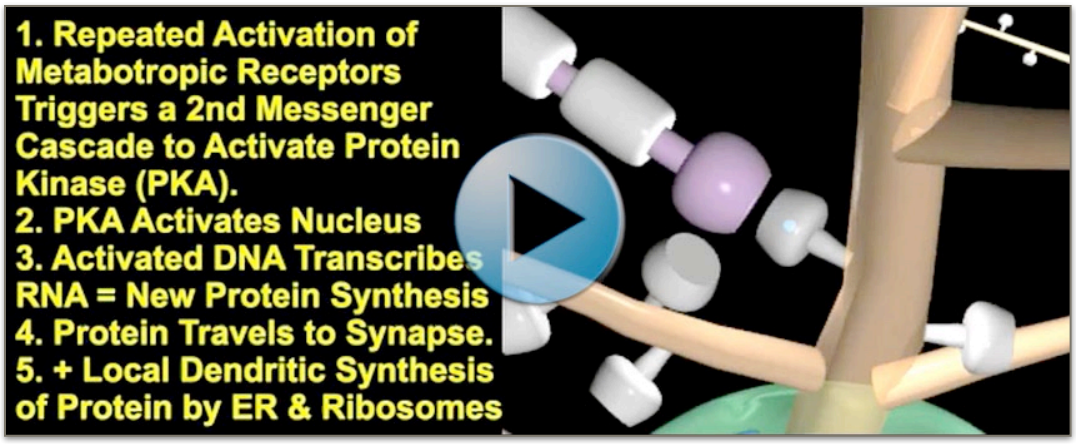

Fig 4-29. Synapse Morphing due to repeated activation. NMDA and Metabotropic Receptors activate 2nd messenger cascades that induce protein production and Synapse grows (gec). GO TO: gmomm.pitt.edu *Fig4-29_Video*

There are a number of neurotransmitters besides Glutamate that may participate including DOPA, ACh, Serotonin (5HT), NOR or Neuroactive Peptides at appropriate synapses. The cascade is typically triggered by the activation of membrane bound cAMP or other regulatory protein that, in turn, activates membrane or cytosol Protein Kinases (PKA). This in turn may activate Endoplasmic Reticulum (ER) & Ribosomes that reside locally in the dendrites resulting in local protein production. If the synapse is repeatedly activated, the PKA may translocate to the Nucleus to Induce DNA to Replicate RNA that will generate new protein in the soma. The protein is transported back to the dendrites & dendritic spines. Some metabotropic receptors indirectly open separate ion channels in the membrane, e.g., efflux of K^+ or influx of Ca^{++}. Typically metabotropic receptor activation has an amplifying effect on many regulatory/metabolic proteins within the postsynaptic cell. Production of new metabolic, regulatory, & structural proteins will then grow the synapse. This is thought to be one important mechanism for learning, memory and maintenance of the health of the postsynaptic cell.

METABOTROPIC RECEPTORS: SECOND MESSENGER CASCADES & PROTEIN PRODUCTION

Most neuroscientists have one of three reactions to biochemistry: 1. "It is my life's work and I love it," 2. "It requires memorization of too many complex names & interactive reactions and it makes me sweat," 3. "It is a process best explained by the life-cycle of single cells not by human brains"; NOTE-options 2 & 3 are not mutually exclusive. Nevertheless, neurons appear to be master cellular biochemists even if they are not typically willing or able to share their vast knowledge with our conscious selves. This biochemistry occurs locally in neurites triggered by regulatory proteins and local RNA, e.g., metabotropic receptor activation of regulatory and structural protein reactions, and most profoundly in the soma where nuclear DNA triggers fantastic cascades of new protein production that influences the health and welfare of the whole cell, e.g., neurotrophic factor influences such as Brain-Derived Neurotrophic Factor (BDNF). Molecular neurobiologists provide new information on a weekly or monthly basis depending on the publication cycle of the journal they choose for our enlightenment. This vast infusion of highly detailed information does not come with an instruction manual. Even if you are willing to read such a step-by-step instruction set, any newly assembled cell would likely be missing some pieces. Until a unifying theory is set forth we must periodically modify our concepts as the genomics and proteomics scientists gather and share more data, e.g., see Deisseroth, et.al., 2003; Abraham, 2008; Cooper & Bear, 2012; Buffington, et.al., 2014.

A “generic” sequence of events is illustrated in the Second Messenger Cascade movie. The actual “players” in the second messenger cascade for each neurotransmitter or neurotrophin have been at least partially revealed by a number of investigators. There are potentially a great many steps involved in this pathway and the chemistry is frequently updated by new data added to the peer-reviewed literature at a staggering

rate. The actual biochemistry involved at particular synapses must be deciphered through reading multiple journal articles and texts.

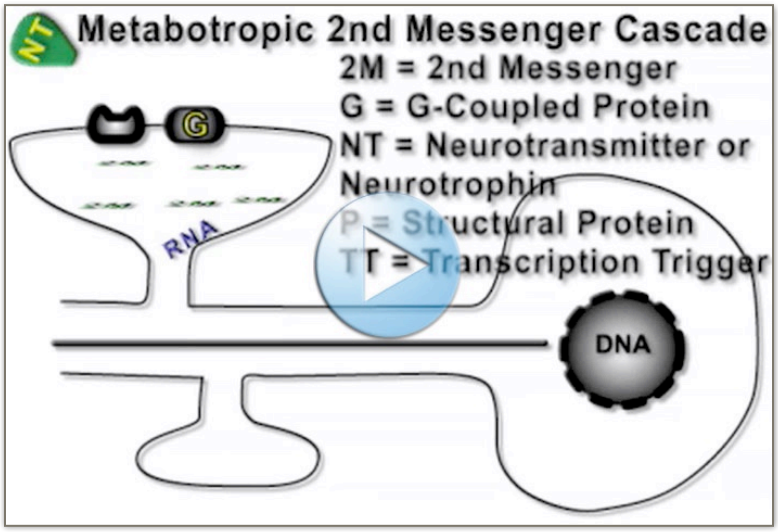

Fig 4-30. Second Messenger Cascade: Local- and Long-Distance Messaging (gec). GO TO: gmomm.pitt.edu Fig4-30 _Video

BACK-PROPAGATED DENDRITIC POTENTIAL: SYNCHRONOUS EPSP SUMMATION "HEBBIAN" SOMA-DENDRITE MESSAGE

Recent studies of neurons with *in-vitro* or *in-vivo* electrophysiological recordings using patch-clamp electrodes allow the investigator to record membrane potentials from multiple locations (e.g. soma and dendrite) in a single neuron. In-vitro studies provide the opportunity to alter the microenvironment of the neuron and its synaptic inputs. These studies have revealed the presence of Voltage-gated Na^+, K^+ & Ca^{++} channels in dendrites. When the soma is depolarized to threshold a spike is initiated at the axon hillock and is propagated down the axon. In addition, there is a back-propagated plateau potential (Na^+ BAP) spread into the dendritic tree.

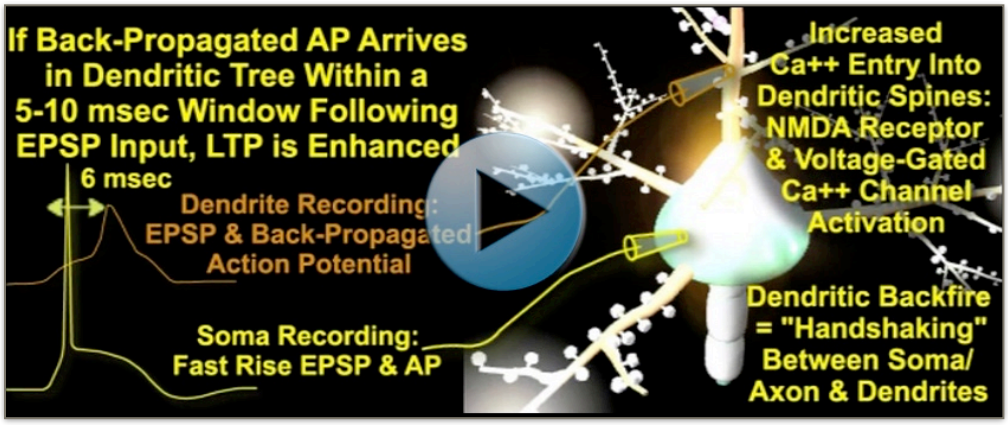

Fig 4-31. Dendritic Backfire Spike Timing-Dependent Potentiation (gec). GO TO: gmomm.pitt.edu Fig4-31 _Video

The back-propagated potential can alter membrane potentials of activated synapses. Depolarization may increase Ca^{++} influx into the postsynaptic membrane by way of voltage-gated Ca^{++} channels and/or NMDA receptors if the BAP invades the dendritic tuft. This "Hebbian" synaptic enhancement: a spike-timing dependent potentiation (STDP) allows the synapse to be strengthened if the back-propagated potential arrives

within a specific time window after the EPSP (time window varies by site, typically it is a 5-10 msec window). Backfired dendritic potentials may not invade the most distal aspects of the dendritic tree if certain dendritic K^+ channels are open. Closing these K^+ channels allows the BAP to invade the dendritic tuft: the dendritic tree may actually be compartmentalized (see below). Play the two Dendritic Backfire movies. The first movie shows STDP. The second shows delayed summation and no STDP.

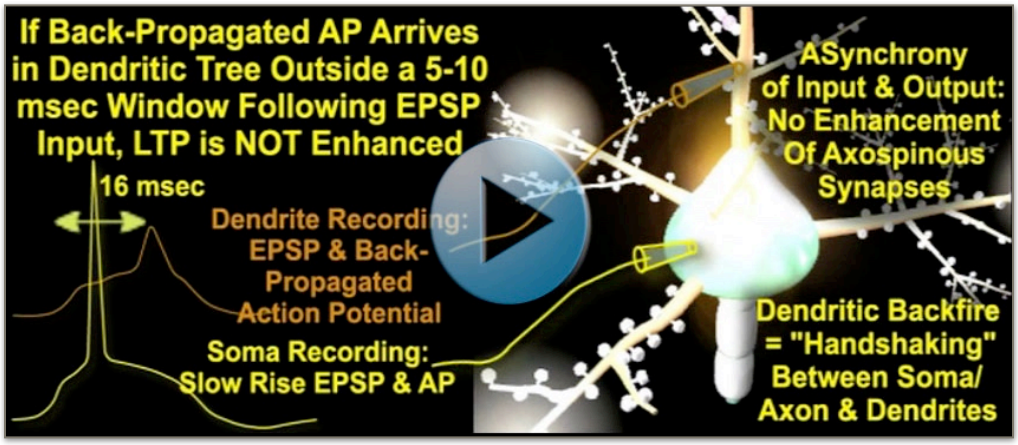

Fig 4-32. Dendritic Backfire-Delayed dendritic potential No Spike Timing-Dependent Potentiation (gec). GO TO: gmomm.pitt.edu Fig4-32

Video

HEBBIAN DENDRITIC PLASTICITY: DENDRITIC PROPAGATED POTENTIALS

The colloquialism "neurons that fire together wire together" (see Shatz, 1992) may not be limited to synaptic mechanisms. Dendritic ion channels may be subject to use-dependent regulation that may alter spatiotemporal integration of depolarizing potentials within different compartments of the dendritic tree. While there is no consensus regarding precise compartments of the dendritic tree, stout proximal portions may be better endowed with ion channels to support propagated dendritic potentials compared to the finer distal dendrites that may propagate depolarizing potentials only if use-dependent activity alters their ionic channel populations. Modern technology allows access and selective activation of these small branches of distal dendrites. This has complicated modeling of “analog” integration of incoming data to a neuron. Many ion channels, synaptic receptors (both ionotropic and metabotropic channels) and neurotrophin receptors contribute to establishing and/or strengthening Hebbian relations between interactive neurons. Different mechanisms may be involved depending upon the cell type and its location, e.g., hippocampus versus cells in various laminar neocortical locations.

The best studied cell type in the cerebral gray is the pyramidal cell. Pyramidal cell basal dendrites are influenced by local cortical circuits, thalamic inputs & brainstem modulatory inputs. The pyramidal apical dendritic tree may be influenced by local and

global connectivity from thalamic & cortical axon terminals in the superficial cortical layers. Enhancing apical dendritic inputs for soma firing may be particularly important for higher level processes such as attention, intention, perception and “non-routine” integration, e.g., learning, memory or novel cognitive processing requiring “new” circuit “wiring.”

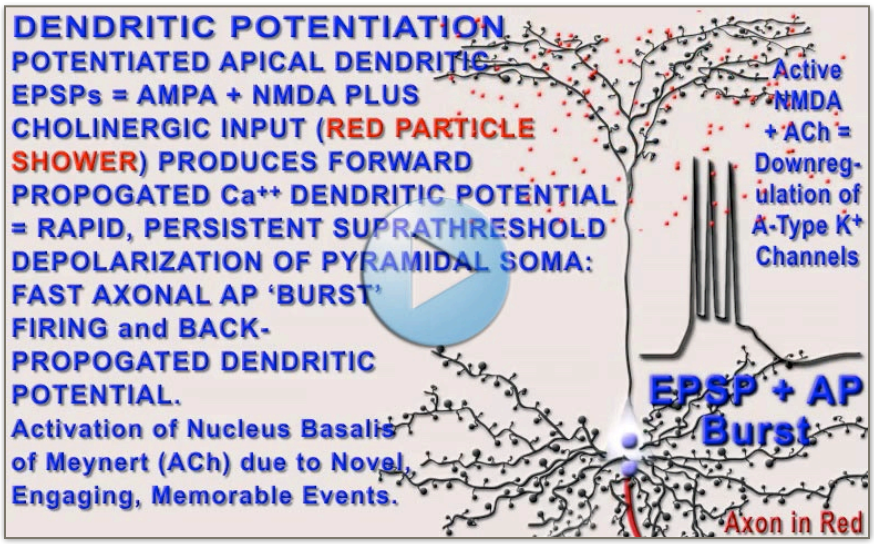

Fig 4-33. Dendritic Potentiation: Acetyl-choline (ACh) + AMPA + NMDA generates Dendritic Potential and Burst Firing of Pyramidal Cell (in-vitro) (gec). GO TO: gmomm.pitt.edu *Fig4-33_Video*

PYRAMIDAL CELL: INTEGRATION OF EXTRINSIC INPUTS TO BASAL DENDRITES AND INTRINSIC INPUTS TO APICAL DENDRITES - COMPARTMENTALIZED COINCIDENCE DETECTION?

Recent research has revealed two possible mechanisms for bringing a layer 5 pyramidal cell to threshold for firing one or more axonal action potentials. Suprathreshold excitatory input from first order core thalamocortical input and intracolumnar inputs (Granular & Supragranular Inputs) to basal dendrites of a layer 5 pyramidal cell produces individual axonal spikes. Within sensory cortex, this "extrinsic" input source relates to "bottom-up" specific sensory drive (Out There Drive).

Alternatively, excitatory inputs to the superficial apical dendrite tufts of the layer 5 pyramidal cell within layers 1 & 2 originates primarily from long-range intracortical or higher order matrix thalamocortical inputs to the superficial cortical layers. These "top-down" inputs may have a powerful influence if A-type K^+ dendritic channels are closed (see Cyan) so a Ca^{++} plateau potential can be initiated and propagated back to the pyramidal soma. Patch-clamp recordings from distal apical dendritic tufts *in-vitro* have revealed long-duration depolarizing plateau potentials (spikes?) due to NMDA channel activation. Neuromodulatory influences, e.g., Acetylcholine, alter the state of dendritic K^+ channels. If many of these K^+ channels are open, the Ca^{++} “spike” is not propagated. The propagated dendritic Ca^{++} "spike" produces a prolonged depolarization of the soma such that a burst of axonal APs is generated (In Here Intrinsic Meets Out There

Extrinsic Influences). This burst firing may be an important code sent to subcortical targets regarding higher level perceptual or conscious intentional processing. The differential effects of inputs to apical versus basal dendrites suggests a compartmentalization of layer 5 pyramidal cells: See Out There Meets In Here Pyramidal Cell Integration Flash File and references listed in Interactive File.

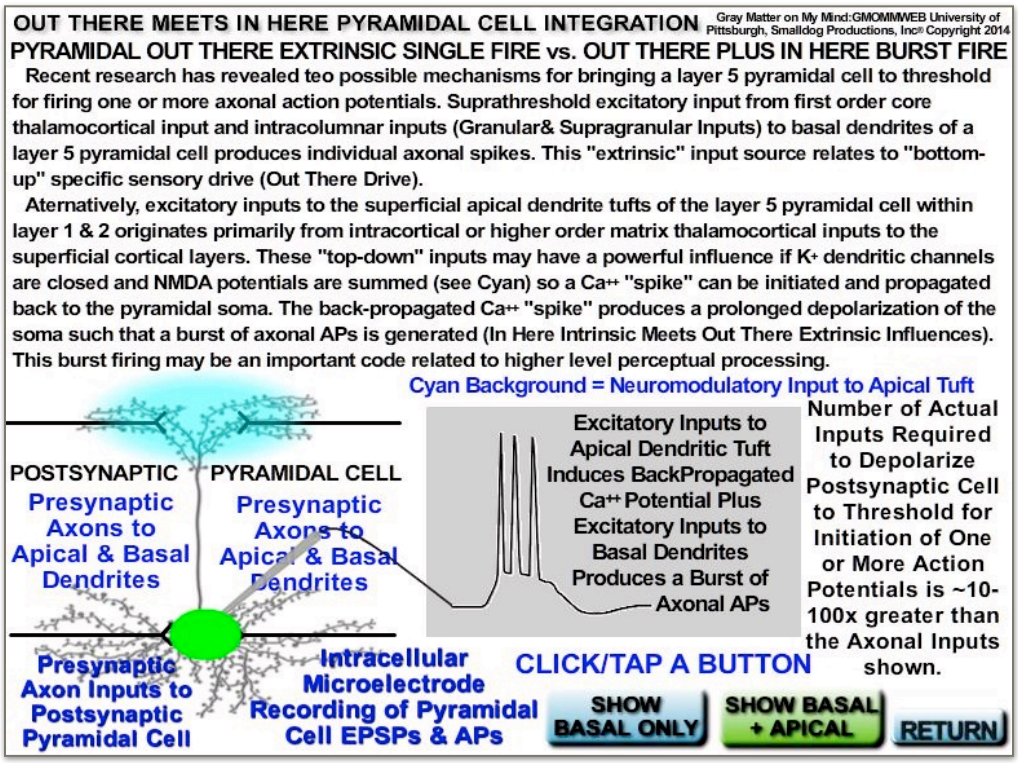

Fig 4-34. Out There Meets In Here Pyramidal Cell Integration Media File (gec). GO TO: gmomm.pitt.edu

Fig4-34_ Interactive Media

NEURAL NETWORKS & CELL ASSEMBLIES

The mammalian nervous system functions only by cooperative interactions among connected neurons. Some of these connections among cells are restricted to a small local cluster of cells (local network). Other neuronal networks are linked by distant connections from one area to another.

CELL ASSEMBLIES: NO NEURON IS AN ISLAND UNTO ITSELF*

A neural network (cell assembly) as a population of cells has greater power and influence than each cell might have as an isolated member of the nervous system: e.g., see Sakurai, 1999; Larkum, 2013; Yoshimura & Callaway, 2005; Yuste, 2015; *See: J. Donne, 1623. Some networks (ensembles) are loose coalitions of cells that have transient binding only if there is one specific pattern of activity. Others have strong, relatively stabilized interconnections to generate more consistent function from time to time (e.g., barrel network in somatosensory cortex [SI] of rats, or segmental motor center interneurons & motoneurons in the ventral horn of the spinal cord). There are

local networks and networks connected over some distance. Networks tend to use nonlinear processes that have some degree of plasticity. Network properties appear to be dependent upon a number of factors: 1.) intrinsic properties of each cell (membrane properties, genetic inheritance, intracellular micro-environment), 2.) types and weighting of intrinsic connections (excitatory and inhibitory), 3.) sources & strength of extrinsic inputs (driving or modulatory inputs, reciprocal connectivity), 4.) past-history (e.g., synaptic potentiation or depression and synapse morphology alterations), and 5.) a critical mass (number of neurons & synapses engaged in the network process).

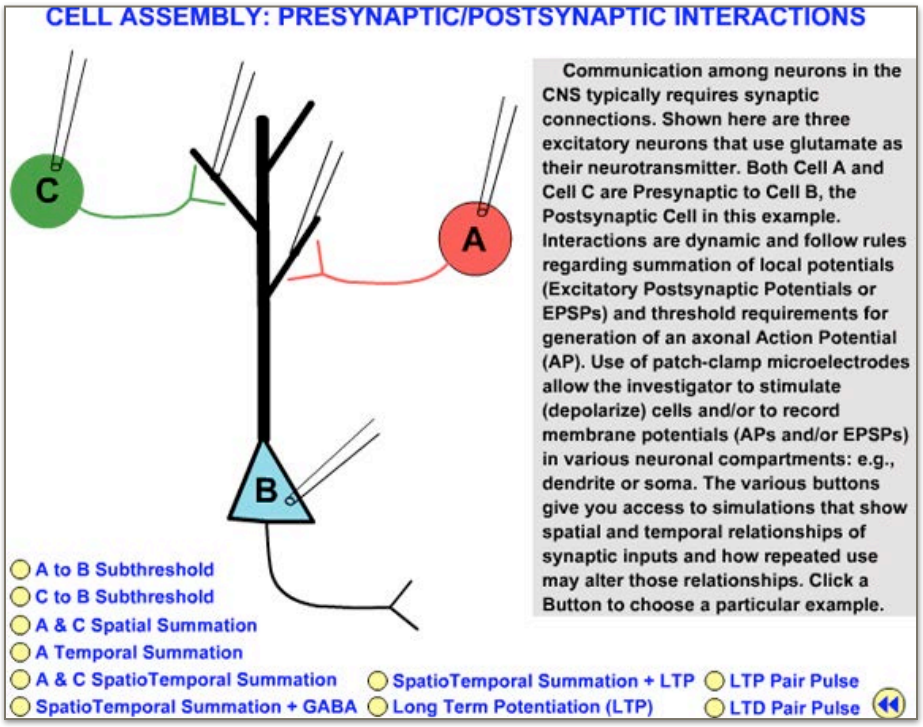

Fig 4-35. Cell Assembly

Many networks develop prenatally or in early postnatal life (e.g., whisker to barrel networks & spinal stepping central pattern generators). These networks are typically subject to environmental influences that fine-tune their function over a lifetime. Other networks may be so transiently coupled that their influence emerges only under “extreme” circumstances such as the oscillatory synchrony of networks (one hypothesized solution to the binding problem for consciousness/ perception/skilled actions).

Networks add excitement to the life of the biological organism in which they live and for the neuroscientist who attempts to do controlled experiments. Networks appear to be subject to statistical probability, dynamic self-organizing interactions and both linear and nonlinear properties; successive iterations rarely result in identical network activity. The roles of subthreshold events (depolarizations & hyperpolarizations) versus supra-threshold neuronal spiking in network processing is an area of intense research.

NETWORKS: NONLINEAR EXCITATORY AND INHIBITORY INFLUENCES - A VIRTUAL WEB EXPERIENCE

Networks typically include both excitatory (E) and inhibitory (I) neurons. The ratio of E to I differs according to the anatomical location of the cells. For example, in sensory

cortex E cells far outnumber I Cells (I Cells = 10-30% of total). The I element in the network below is represented by two electrically coupled Inhibitory Neurons.

Networks are spontaneously active in the awake brain and may be influenced by modulatory drive from local (e.g., intrinsic corticocortical connections) and/or from distant sources, e.g., monoaminergic or cholinergic input from brainstem nuclei to the cerebral cortex (**SPONTANEOUS**).

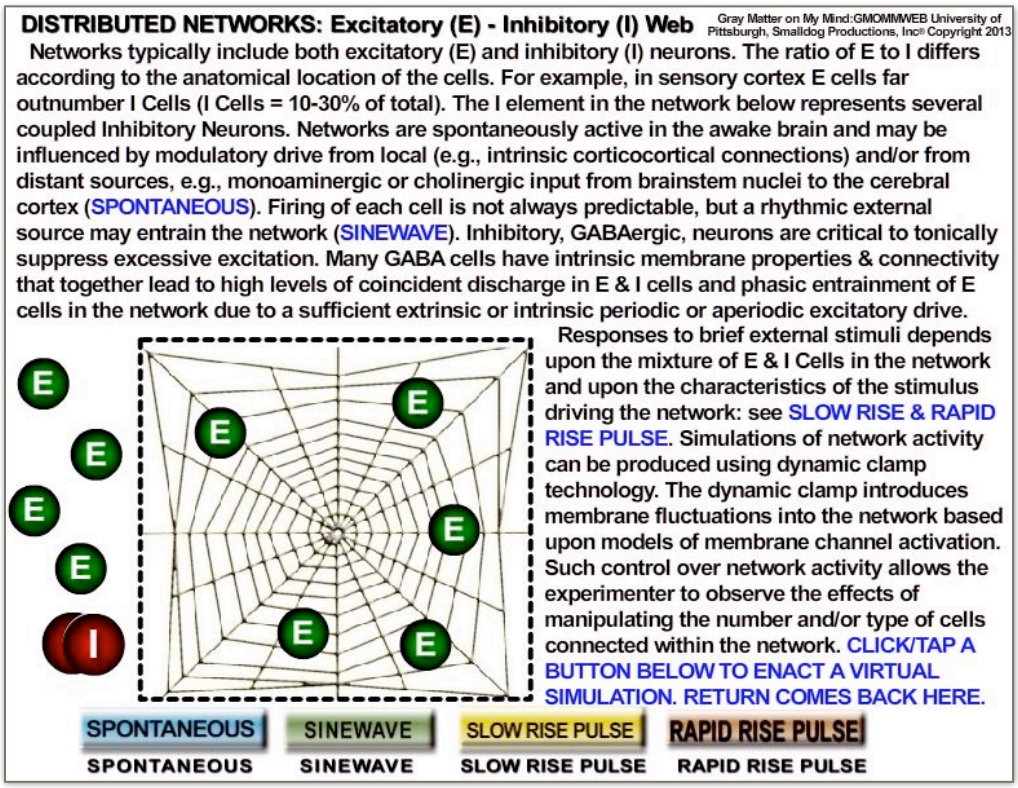

Fig 4-36. Excitatory and Inhibitory Neurons networked to generate neural patterns: E-I Network Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig 4-36 Interactive Media

Firing of each cell is not always predictable, but a rhythmic external source may entrain the network (**SINEWAVE**). Inhibitory, GABAergic, neurons are critical to tonically suppress excessive excitation. Many GABA cells have intrinsic membrane properties & connectivity that together lead to high levels of coincident discharge in E and I cells and phasic entrainment of E cells in the network due to a sufficient extrinsic or intrinsic periodic or aperiodic excitatory drive, e.g., see Tamas,et.al., 2000; Llinas, et.al., 2002. Responses to brief external stimuli depends upon the mixture of E and I Cells in the network and upon the characteristics of the stimulus driving the network: see **SLOW RISE PULSE** and **RAPID RISE PULSE**.

Controlled alterations of network activity can be generated using dynamic clamp technology. The dynamic clamp introduces membrane fluctuations into the network based upon models of membrane channel activation. Such control over network activity allows the experimenter to observe the effects of manipulating the number and/or type of cells connected within the network. Do virtual experiment with Interactive Flash file.

NEURAL NETWORKS-OPENING WINDOWS AND REVOLVING DOORS OF OPPORTUNITY

BRIEF WINDOW OF OPPORTUNITY: STRONG INHIBITION

Granular cerebral cortex (layer IV) is the primary thalamocortical recipient zone for specific afferent input from a core thalamic nucleus. This information is topographically organized and modality specific (e.g., somatotopic, tonotopic or retinotopic). One of the best studied sensory cortices is the barrel cortex of rodents. Barrels contain thousands of densely packed stellate interneurons plus a dense arbor of thalamocortical afferents. While most barrel neurons are excitatory spiny stellate cells, the minority (~10-30%) are inhibitory smooth stellate cells that functionally dominate the response transformation of thalamic input, e.g., see Oberlaender, et.al., 2012.

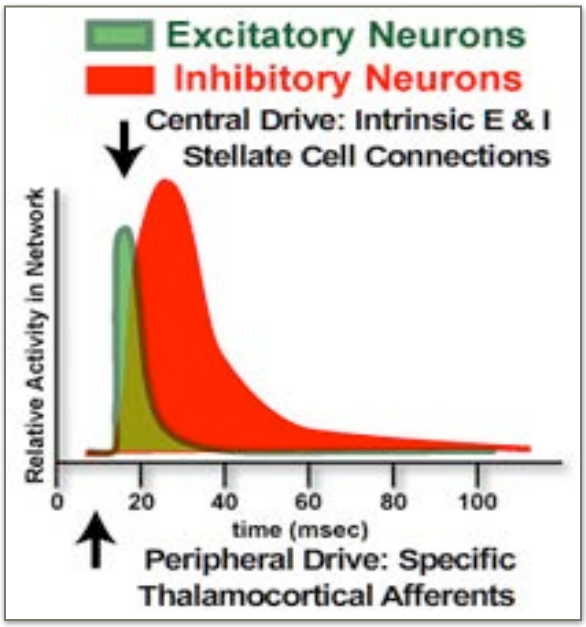

Fig 4-37. A brief window of opportunity for network excitation: the effect of strong "feed-forward" inhibition. Note rapid rise of inhibitory influences (red) that quickly truncates (stops) excitatory influences (green) (gec).

Inhibition within this local network prevents prolonged responses to tactile inputs by rapidly closing the window of excitability set up by thalamic inputs and intrinsic excitatory barrel connections. Only synchronous excitatory drive can briefly overcome the powerful inhibition by smooth stellate barrel neurons, e.g., see Bruno & Simons, 2002; Schoonover, et.al., 2014; Cruikshank, et.al., 2007. Repetitive activation may depress network (I > E) activation to temporally extend the integration window.

Fig 4-38. E-I Network Brief Window of Opportunity Movie (gec). GO TO: gmomm.pitt.edu
Fig4-38_Video

LONG WINDOW OF OPPORTUNITY: WEAKER/DELAYED INHIBITION

Supragranular and Infragranular cortex (layers II/III & V/VI,

respectively) provide the basis for corticocortical (horizontal) communication and corticofugal communication with subcortical brain and spinal cord. This information tends to be more integrated than that of the granular cortex due to both vertical columnar and horizontal corticocortical influences. Pyramidal cells are the major excitatory projection cell type and they are connected to one another and to various types of inhibitory interneurons. Input from the columnar network serves as one source of drive while horizontal central drive integrates information across columns.

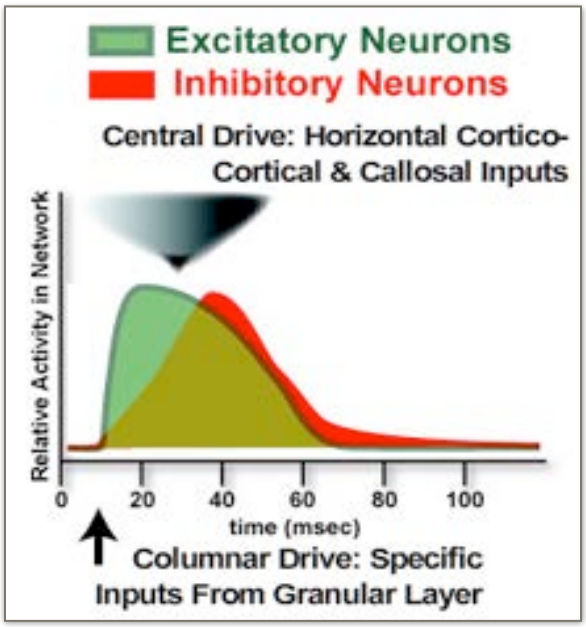

Fig 4-39. An extended window of opportunity for network excitation: the effect of weak "feed-forward" inhibition. Note the delayed rise of inhibitory influences (red) that allows for longer duration of excitatory influences (green) (gec).

In addition, some of these cells are influenced by the corticothalamocortical loop associated with thalamic matrix cells. The window of opportunity for continued excitation remains open longer than in granular cortex and may be altered by either potentiating or depressing synaptic processes (plasticity).

Fig 4-40. E-I Network Prolonged Window of Opportunity Movie (gec). GO TO: gmomm.pitt.edu *Fig4-40_Video*

REVOLVING DOOR: INHIBITORY-EXCITATORY OSCILLATION

Certain excitatory and inhibitory neurons when strongly and reciprocally connected may form an oscillator circuit under certain circumstances. Rhythms may be seen in local networks (Central Pattern Generators or CPGs) or more globally, e.g., rhythms that underlie EEG patterns. Oscillatory behavior may be dependent upon multiple factors: membrane properties of the cells, strength of connections among cells, extrinsic sources of driving or modulatory inputs and history of the cells/network. Frequencies range from < 1 Hz to > 100 Hz in cortical rhythms. One frequency band of interest to

cortical physiologists is the gamma band (40-70 Hz); it has been linked to brain operations such as attention, perception, will, and contemplation. Evidence suggests a fast temporal pairing of excitatory and inhibitory neurons may be critical for these oscillations, e.g., see Hasenstaub, et.al., 2005; Buzsaki, 2006, Buzsaki & Wang, 2012, Salkoff, et.al., 2015, Kim, et.al., 2016.

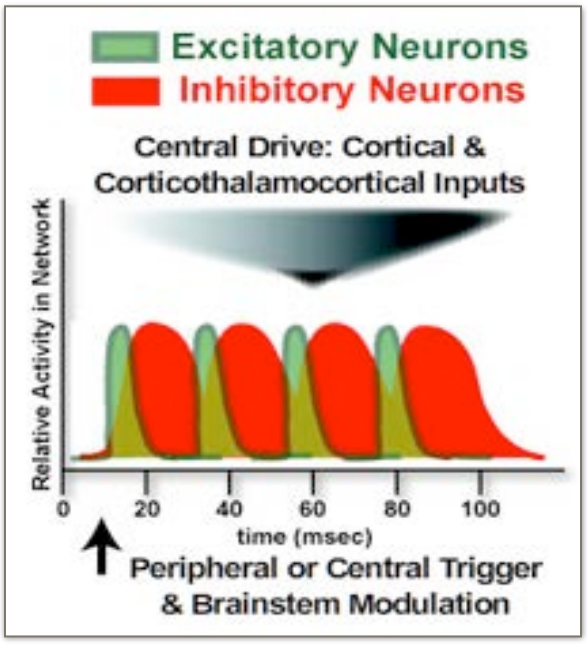

Fig 4-41. Some networks under the right conditions may utilize strong inhibitory connections to induce a periodic excitatory discharge or oscillation in the excitatory (E) cells within a network. Note the periodic rise of inhibitory (I) influences (red) that strongly inhibits excitatory neurons (green) for a short duration. Tonic drive to the network 'energizes' the damped oscillator. E and I cells must have strong interconnections (gec).

Oscillators by their very nature are potential sources of dysfunctional electrical storms so their occurrence, distribution and potency must be tightly controlled. Local circuit GABAergic neurons control excessive excitability and brainstem modulators may have an important role as well. See GABA to Gamma: E-I Periodic Synchrony below.

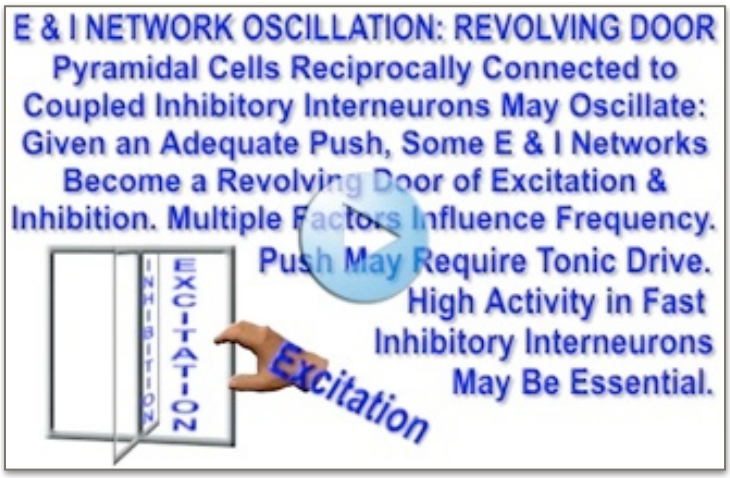

Fig 4-42. E-I Network Revolving Door of Excitability Movie (gec). GO TO: gmomm.pitt.edu
Fig4-42_Video

NETWORK CODES- INTEGRATE & FIRE, COINCIDENCE DETECTION OR PERSISTENT FIRING MODE

Neuroscientists studying the organization of the nervous system are investigating the anatomic and physiologic bases of neuronal interactions. Cooperation amongst a collection of interconnected cells appears to be critical for normal nervous system function. These collections are sometimes referred to as nests, colonies, cell assemblies, centers, blobs, nodes,

columns, etc. Special properties are attributed to the collective that may be either weakly represented by individual neurons or absent in any cell by cell analysis. For example, a population code of some property may emerge when one looks at the group of cells as a whole despite its transparency when examining individual units (cell by cell analysis of firing data). It is concluded that this emergent property is dependent upon a network. Networks may interact in one of several ways, e.g., see Dan & Poo, 2004; Froemke, 2015; Halder, et.al., 2006; Larkum, et.al., 1999; Mauk & Buonomano, 2004; Sakurai, 1999. The "default" mechanism is thought to be an Integrate & Fire coding where an increased rate of firing within a colony determines its output to other colonies of cells. An alternative model suggests that a sparse spike code may provide rapid efficient cell assembly coupling. This Coincidence Detection coding requires a temporal precision (synchrony) of spike discharge within & among colonies of cells. The latter coding may provide a more efficient (sparse but temporally coherent spiking) mechanism to form an internal representation of well-rehearsed processes.

INTEGRATE & FIRE MODE OF INTEGRATION

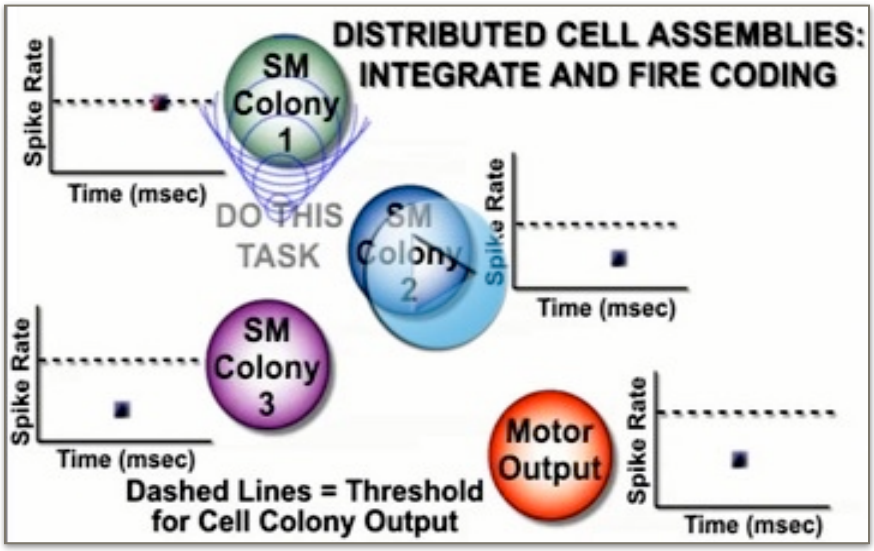

Fig 4-43. Network Integrate & Fire Coding Movie (gec). GO TO: gmomm.pitt.edu
Fig4-43_Video

Integrate and Fire Mode: This movie simulates the Integrate & Fire mode of integration across several cell assemblies. Note Serial Processing across Cell Colonies. Each Colony does not send information to next group of cells until a critical threshold of firing has been reached (piling on impulses according to firing rate of summed inputs); threshold is not time-locked: depolarizing inputs sum in a relatively "simple algebraic" fashion (spatial or spatiotemporal integration). Motor Output (in this simulation) must wait for summed events. This may be a "default" mode of integration when timing is not critical and/or when firing must be sustained for some time, e.g., for sustaining an ongoing feedback assisted sensorimotor sequence. The Integrate & Fire mode also may be the best coding mechanism when a novel coalition of neurons is just forming and the precision of temporal firing in a select group of neurons has yet to be established, e.g., early stages of learning a new task.

COINCIDENCE DETECTION MODE OF INTEGRATION

Coincidence Detection mode of integration occurs when a coalition of neurons is well established. A high precision of temporal firing produces a coherent discharge within a local colony AND across a distributed group of colonies. Coincidence Detection Movie: Note simultaneous broadcast of the Intent (Do This Task) to all Cell Colonies (Limbic Drive?). There is a rapid (time-locked) periodic depolarizing and hyperpolarizing coupling of many cells across all relevant colonies. Note the periodic Large Spike Coherence Index (Spike C Index) at time 0 in simulation. Thus, relatively few impulses are required to bring cells to threshold (Sparse Spike Coding) due to a rapid rise in the summed EPSP input (fast temporal summation). Colonies are transiently "bound" to one another in a synchronous fashion and quickly send their message along to a common location (Motor Output in this simulation).

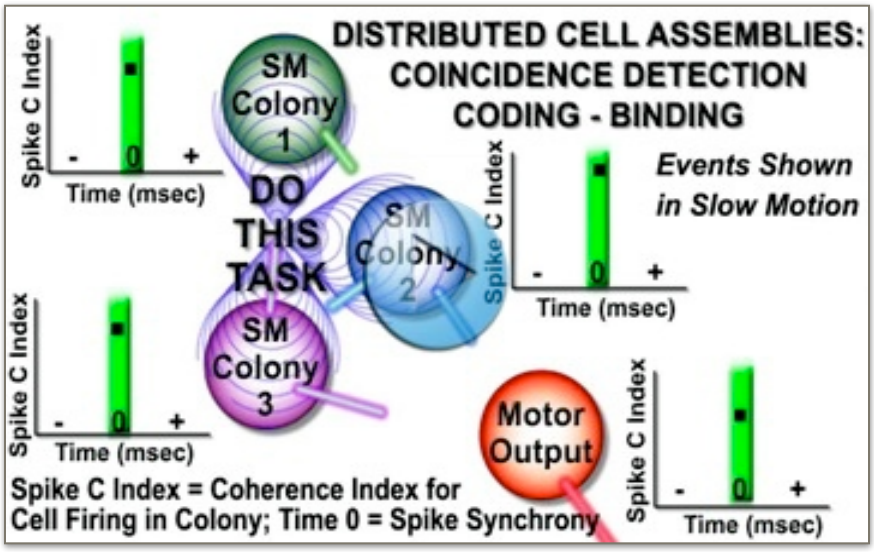

Fig 4-44. Network Coincidence Detection Coding Movie (gec). GO TO: gmomm.pitt.edu
Fig4-44_Video

PERSISTENT FIRING MODE FOR WORKING MEMORY & REENTRANT NETWORK PROCESSING

Some cell assemblies may maintain discharge over a relatively long period of time (seconds to minutes) to keep select information "in mind" for tasks requiring a series of temporally integrated processes. For example, instruction delay tasks may be used to discover the neural components that provide working memory regarding the choice of a response to a delayed instructional cue. Several choices could be required and these data must be kept "on-line" until the cue is given to select the correct response.

Evidence suggests that a cell colony can maintain activity in select neurons by reentrant (feedback) corticocortical and corticothalamocortical connections from the target that received feedforward signals. The reentrant inputs activate elevated firing of neurons over a period of hundreds to thousands of milliseconds in duration. The Network Reentrant, Persistent Activity (Working Memory) Movie illustrates this processing. Note the feedforward and feedback connectivity among cell colonies (SM1, SM2, SM3) and the maintained activity above threshold in these cell groups before there is output by the ensemble of connected colonies (Now Act Colony). Persistent firing may require opening or closing of specific dendritic ion channels to support

propagated dendritic potentials and bursts of axonal action potentials in pyramidal cells. Reentrant network to network connections may activate apical dendritic tufts of pyramidal neurons in a differential fashion to cause this persistent firing mode of integration, e.g., see Larkum, et.al., 1999, 2004; Williams, et.al., 2007; Major, et.al., 2013.

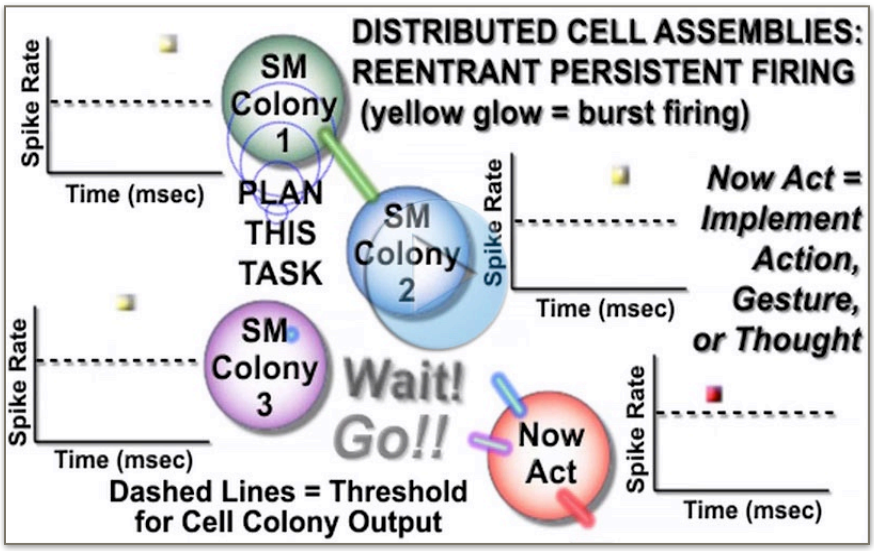

Fig 4-45. Network Reentrant, Persistent Activity (Working Memory) Movie (gec). GO TO: gmomm.pitt.edu [Fig4-45_Video]

The persistent firing mode may require generation of Ca^{++} potentials that propagate from pyramidal cell distal dendrites to the soma to generate potent lasting depolarization of the soma and burst axonal firing. The AP burst may be a code representing inclusion of internal, higher level brain processes to modify ongoing sensorimotor events.

ACTIVITY-DEPENDENT ALTERATIONS IN MYELINATION: CLOSE AND DISTANT CELL INPUT SYNCHRONIZATION

One of the potential impediments to achieving temporal synchrony within neural networks is the different distances of close and distant presynaptic cell inputs to a third cell receiving these inputs.

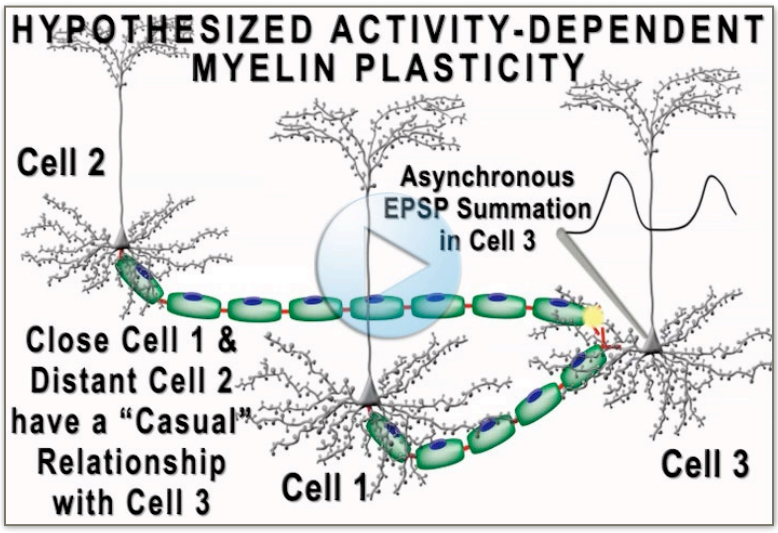

Fig 4-46. Myelin Activity-Dependent Plasticity Movie (gec). GO TO: gmomm.pitt.edu [Fig4-46_Video]

If the speed of AP propagation is the same for both presynaptic cells that fire at the same time then the EPSPs generated by the variable distant inputs will be temporally asynchronous in the third (postsynaptic) cell. One

hypothesized mechanism to increase synchrony of inputs from the close and distant presynaptic cells is a change in myelination so the distant cell's axon has a slightly higher speed of AP transmission to the postsynaptic cell. Such altered myelination would ensure that the AP from close and distant cells arrive at the same time to produce temporal synchrony in EPSPs in the postsynaptic third cell.

This alteration in myelination has been suggested to be an activity-dependent process. Repeated use of the three cells together as a coherent network in this simple model increases the likelihood of a coincidence detection mode of integration (See Myelin Activity-Dependent Plasticity Movie). The changes that must occur within a more realistic multi-neuron network could be quite complicated if AP timing is to be consistent among the many cells, e.g., see Bi & Wang, 2002; Halder, et.al., 2006.

There is some indirect evidence for such activity-dependent changes in myelination but direct evidence for altered myelin thickness, altered inter-nodal distance or altered nodal characteristics has not been obtained yet at the electron-microscopic level. A variety of potential mechanisms have been proposed to induce and maintain altered myelination but none have been confirmed by direct measurements within the human brain: for review see Wake, et.al., 2011; Gibson, et.al., 2014; and Fields, 2005, 2015.

COMPARTMENTALIZED PYRAMIDAL CELL ACTIVATION: SUPERFICIAL APICAL VS. DEEP BASAL DENDRITIC INPUTS

Initial intracellular recording from individual neurons was accomplished by sharp microelectrodes with very fine tips that impaled the cell to gain access to intracellular depolarizing and hyperpolarizing potentials. Methodology initially designed by Bert Sakmann, (see Neher & Sakmann, 1976; Stuart, et.al., 1993; Stuart & Sakmann, 1994) allows the investigator to record intracellular events without entering the cell by patching onto the neuronal membrane with a microelectrode and opening a very small part of the membrane within the lumen of the microelectrode. Such patch electrode recordings may occur at the soma, dendrite or both. This technique allows for simultaneous recordings from different compartments of a neuron to reveal greater details about the form and temporal profile of membrane potential changes at the soma and at distant locations, e.g., basal dendrites or distant apical dendrite of a pyramidal cell. Such recordings *in-vitro* occur by direct visualization of fluorescent-labeled neurons which reveal the soma and dendritic tree of an individual cell. These investigations have shown a critical differential effect of excitatory (depolarizing) and inhibitory (hyperpolarizing) inputs to the proximal basal dendrites and soma of a layer 5 pyramidal neuron versus inputs to the distal apical dendritic arbor of that cell. The deep inputs appear to be related to specific sources of input (modality, and source localization of data) while inputs to the superficial layers (Layer 1 & 2) appear to be related to long-range horizontal cortical axonal inputs coupled to local dendritic and axonal arbors of pyramidal cells and several inhibitory interneurons. Layer 1 also receives widespread thalamocortical inputs from matrix cells within higher-order thalamic nuclei cells. Thus, layer 1 inputs to the apical dendrites of

layer 5 pyramidal cells appear to be related to more integrated information thought to be crucial for the layering of “higher level” perceptual and cognitive processes onto more specific data accessed by basal dendrites of those layer 5 corticofugal pyramidal neurons. An important mechanism for altering pyramidal cell firing seems to be the propagation of Ca^{++} spikes from the distal apical dendritic tree to the pyramidal soma which initiates a burst of axonal spikes. NMDA plateau potentials plus AMPA receptor depolarization in the distal dendritic tufts may provide large depolarizing influences to facilitate activation of the Ca^{++} plateau potentials, see Larkum, et.al., 2004; Larkum, 2013. A-type K^{+} channels in the apical dendritic tree regulate plateau potential generation, see Hoffman, 2013. Some of these K+ channels may be up-regulated or down-regulated by neuromodulators. In addition, GABAergic Martinotti cells which have strong excitatory input from pyramidal cells may limit Ca^{++} spiking, e.g., see Berger, et.al., 2010; Higley, 2014; Silberberg & Markram, 2007. Thus, only a limited number of pyramidal cells will show axonal AP bursting. The Compartmentalized Pyramidal Neuron Activation Movie simulates several of these differential influences as revealed by investigators using patch-recordings of pyramidal cell dendrites and soma and several types of inhibitory interneurons in the intact cerebral cortex or in cortical slices (*in-vitro* recordings) of rodents: see references at end of movie.

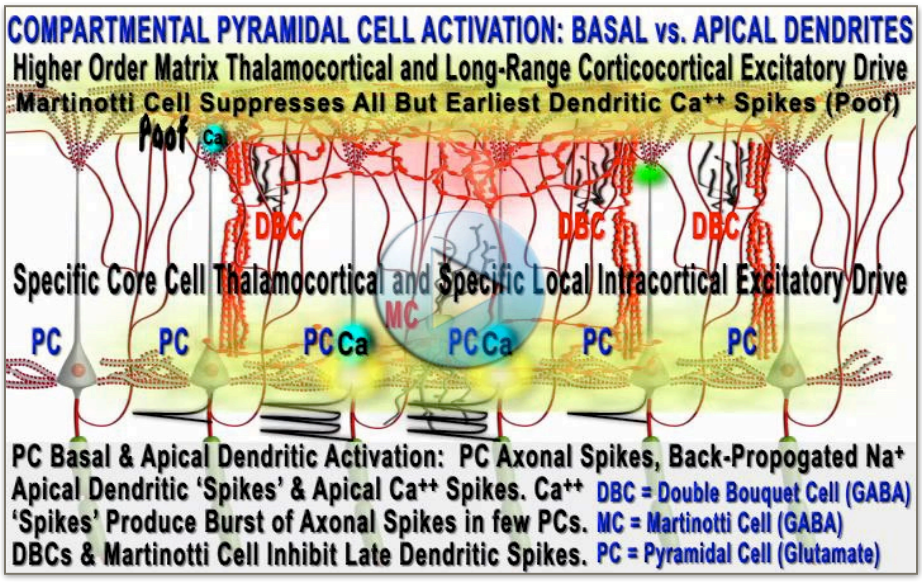

Fig 4-47. Compartmentalized Pyramidal Neuron Activation Movie: Pyramidal Cell Burst Firing. Pyramidal Cell Apical Dendritic Tuft Ca^{++} plateau potential (gec). GO TO: gmomm.pitt.edu
Fig4-47_Video

GABA TO GAMMA: PERIODIC SYNCHRONIZATION OF E-I NETWORKS

Excitatory-Inhibitory (E-I) networks provide the neural basis for the brain to interpret data arising from the peripheral sensory receptors via ascending pathways and for generation of movements via descending pathways from brain to spinal cord to muscles based upon an extrinsic stimulus to act. However, most of our brain’s work is more complex than a simple “bottom-up” drive to sense or a “top-down” drive to move. Perception, attention, volition all require intrinsic network patterns of neural activity to be coded within the brain. Recent mouse studies in awake, behaving animals provide

evidence to suggest that E-I networks are firing in oscillatory patterns of synchronized brain networks, including gamma band (40-70 Hz) periodicity. A pattern of high activation of Parvalbumin-Positive, Fast Spiking (PV-FS) GABAergic Interneurons (Basket cells and Chandelier cells) appears to be highly correlated with the synchrony of pyramidal cell activation such that an ~15-25 ms strong hyperpolarization of the pyramidal cell's soma and axon hillock is followed by a brief window of opportunity for excitatory pyramidal cell firing. This is expressed as a local ~40-70 Hz (gamma band) reciprocal oscillation of E and I cell activity, e.g., see Buzsaki, 2006; Buzsaki & Wang, 2012; Siegle, et.al., 2014; Pritchett, et.al., 2015; Salkoff, et.al., 2015.

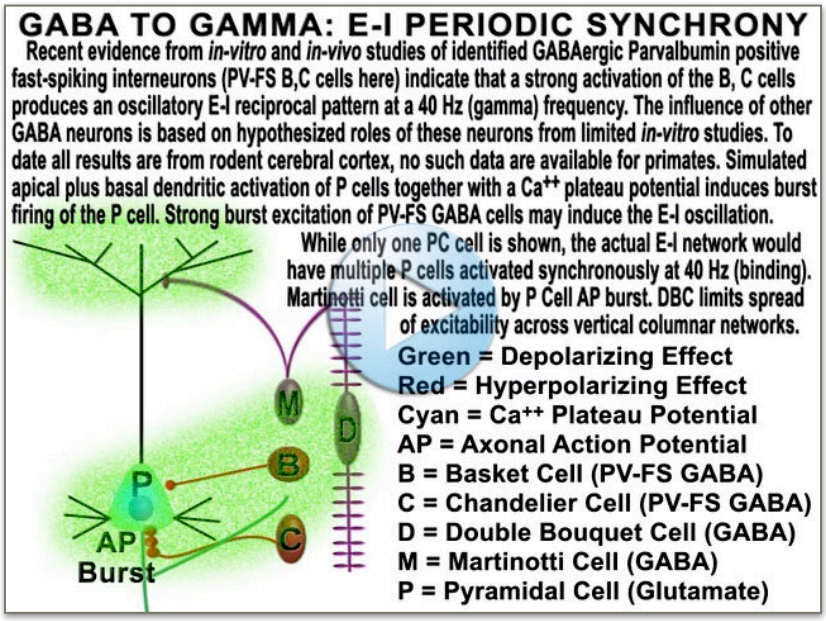

Fig 4-48. GABA to GAMMA : E-I Periodic Synchrony Movie (gec). GO TO: gmomm.pitt.edu
Fig4-48_Video

There is evidence from single cell & population recordings (local field potential recordings) in rodent, monkey and human species showing a correlation between gamma binding oscillations and neural processes of attention, perception and discriminative sensorimotor behavioral choices: see references at end of GABA to GAMMA Movie. The GABA to GAMMA: E-I Periodic Synchrony Movie illustrates the critical role of PV-FS GABAergic interneurons to induce synchronous 40 Hz (gamma) firing of pyramidal cells. Note effects of apical dendrite excitation and generation of Ca^{++} plateau potentials to generate axonal burst Action Potential firing of the pyramidal cell during synchronous oscillatory activation of the simulated E-I network.

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Chapter 5

BRAIN STRUCTURE FUNCTION RELATIONSHIPS

The brain resides within the portion of the skull known as the cranial vault. This chapter of the book relies heavily upon access to flash content by way of your web browser. While individual pages could be reproduced individually such a format would not be the best experience for you since the flash format is an interactive learning environment. Gross neuroanatomy like gross anatomy is a visual and tactile experience. While the virtual brain specimens provided here do not allow you to touch in 3D, the visual experience should be engaging and may entice you to participate in laboratory classes that integrate the visual and tactile experience (hands-on lab). This book is not intended to replace an atlas of skull and brain structures. There are a number of very good neuroanatomy atlases currently in print. Content presented here is a basic introduction to brain and skull morphology. Multiple interactive media files provide access to details of structure-function relationships for external and internal brain morphology.

THE CRANIAL VAULT: PROTECTING YOUR SQUISHY BRAIN TREASURES

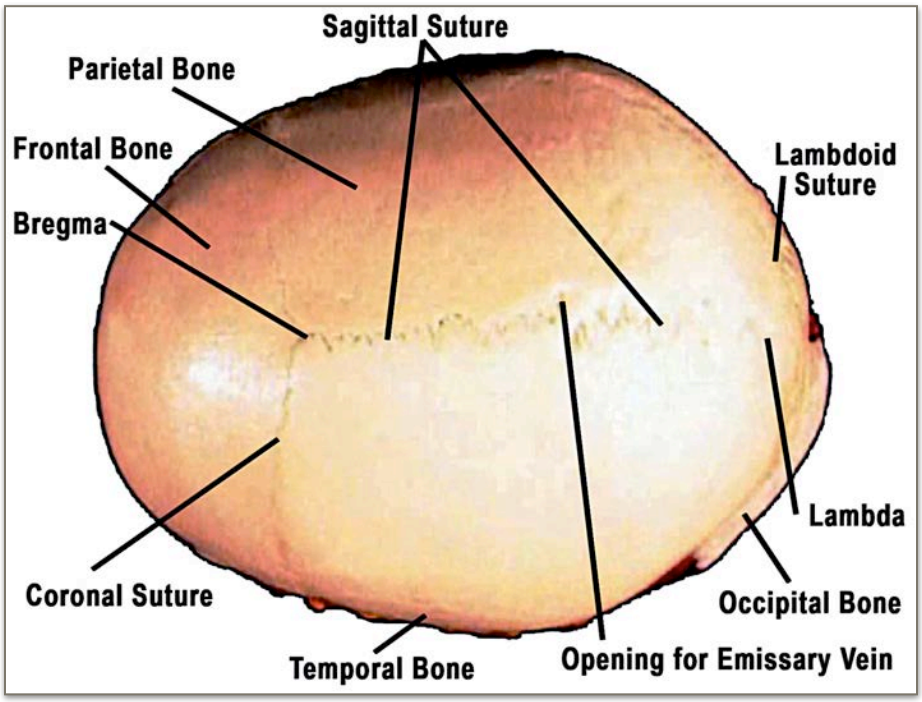


Fig 5-1. Selected Features of the Top of the Skull (gec).

The skull provides a solid bony encasement for the lipid-dense somewhat "squishy" brain (think butter that has been sitting on your table at room temperature for an hour). While this bony encasement provides a potential barrier to prevent or limit severe acute traumatic brain tissue damage, the skull may not prevent functional and ultrastructural damage to brain tissue due to repeated linear or "torsional" blows to the head that may or may not result in concussion

or even self-reported and recognized acute signs and symptoms of “minor” trauma, e.g., see Mez, et.al., 2017.

Additional structural supportive structures include the meninges: dura mater, arachnoid mater and pia mater and the cerebrospinal fluid surrounding the brain and spinal cord. The pia and arachnoid are together referred to as the leptomeninges. The toughest most superficial meningeal layer is the dura. The dura has two layers-an external periosteal layer that is adherent to the inner table of the skull and an inner meningeal layer that becomes folded on itself to form three dural reflections at three locations: the falx cerebri, the falx cerebelli and the tentorium cerebelli. The key features of the skull cap and the interior of the cranial vault are shown above and below. Skull sutures in the infant are open while they become tightly bound as skull growth ceases in late adolescence/adulthood. Bregma, Lambda plus the Coronal and Sagittal Sutures are important landmarks related to neurosurgery and some brain imaging. Emissary veins provide a potential anastomosis between external scalp veins and the superior venous sinus within the cranial vault. The Head-Cranial Vault VR Movie allows you to inspect the skull, face, cervical vertebrae & cranial vault as an Unlabeled or Labeled VR Movie.

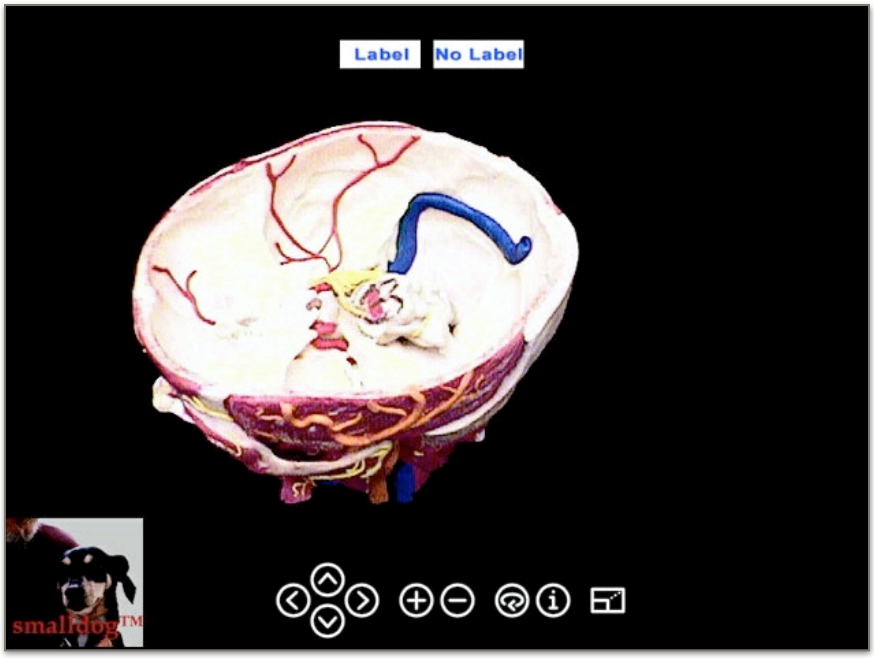


Fig 5-2. Head-Cranial Vault Two State: Unlabeled or Labeled VR Movie. Soft tissues are simulated with clay sculpture (jac) on skull and cervical vertebrae. The Label and No Label Buttons at the top of the movie allow you to shift between labeled or non-labeled images; the default state is unlabeled. The control buttons at the bottom of the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen. (gec, jac, jec). GO TO: gmomm.pitt.edu Fig5-2_VR_MOVIE

The interior of the skull is called the cranial vault where the brain, cranial nerves, blood supply and meninges are found. Three regions are defined: the anterior fossa

where the frontal lobe is found, the middle cranial fossa where the temporal lobe is found and the posterior fossa where the posterior fossa brainstem, cerebellum and cranial nerves exiting the brainstem are found.

A system of venous sinuses is associated with the cranial vault. The venous sinus system is drained by the internal jugular vein. Superficial brain veins drain into the superior and inferior sagittal sinuses and deep brain structures drain into the great vein of Galen that drains into the straight sinus. The straight sinus drains into the confluence of sinuses. At that confluence the transverse sinuses are formed along the attached border of the tentorium cerebelli. The transverse sinuses drain into the sigmoid sinuses that form the beginning of the internal jugular veins. Other smaller sinuses exist at other dural reflection locations. The superior sagittal sinus is formed along the midline where the periosteal and meningeal layers of the dura separate. The two layers of meningeal dura form the falx cerebri that separate the two cerebral hemispheres. The inferior sagittal sinus forms along the free border of the falx cerebri: see figs 5-1 through 5-6.

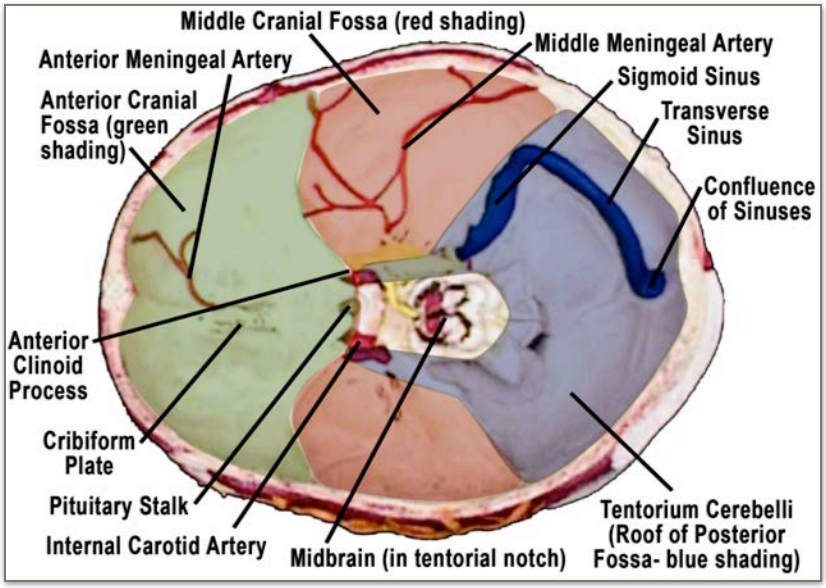


Fig 5-3. Cranial Vault: Anterior, Middle and Posterior Fossa (gec, jac).

The brain and spinal cord are "bathed" in a normally clear, colorless fluid called the cerebrospinal fluid (CSF) manufactured by the choroid plexus found in all four brain ventricles: the right and left lateral ventricles, the midline third ventricle and the fourth ventricle in the posterior fossa.

CSF is continuously produced by the choroid plexus located within each of the four ventricles and flows from the ventricles into the subarachnoid space that surrounds the brain and spinal cord. The exit for intra-ventricular CSF to the extra-ventricular subarachnoid space occurs through three openings in the fourth ventricle: one median aperture (foramen of Magendie) and two lateral openings (right and left foramina of Luschka). This closed system requires an outlet to "drain" the CSF which occurs by way of the arachnoid villi (arachnoid granulations) located primarily in the superior sagittal sinus (see figure 5-4). At this point the CSF is resorbed into the venous blood. The CSF pressure is "regulated" by both the total volume of CSF in the closed system and the "back pressure" due to venous system pressure. Therefore CSF will continue to flow and be resorbed only if the "plumbing" remains patent and the venous pressure does not exceed that of the CSF.

Pathology could block the normal flow by clogging the plumbing which results in continued production of CSF by choroid plexi that have no adequate feedback regulation of production. If the plumbing is clogged there is inadequate flow and resorption. The result is an increased CSF volume/pressure that will enlarge the ventricles and cause brain tissue compression (hydrocephalus).

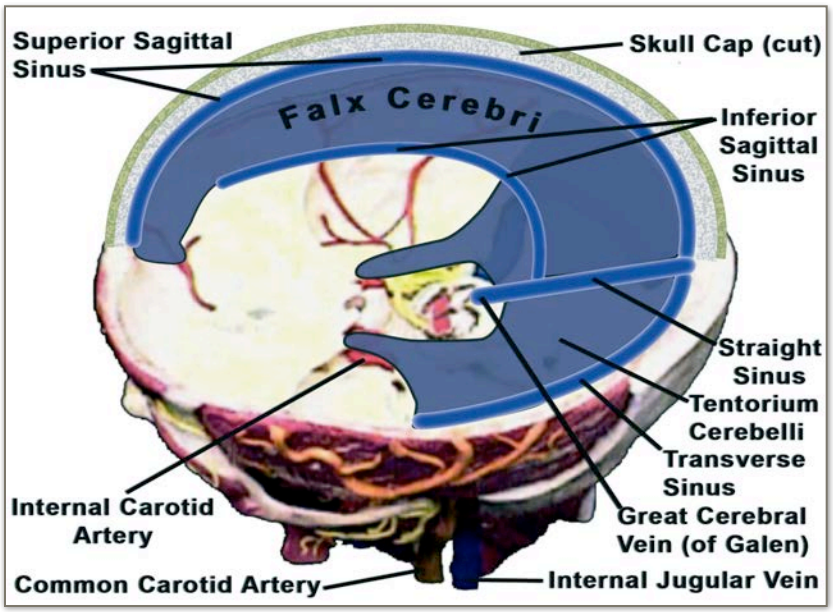


Fig 5-4. Dural Reflections and Major Associated Venous Sinuses (gec, jac).

If the pressure is not relieved the result may be life-threatening particularly when pressure compresses the life-sustaining brainstem. Shunts to drain CSF fluid may be placed as temporary or permanent measures to relieve CSF pressure increases. A temporary or permanent rise in venous pressure will halt CSF resorption since the arachnoid granulations will not 'empty' CSF into the venous sinus unless CSF pressure exceeds that of the venous pressure within the superior sagittal sinus.

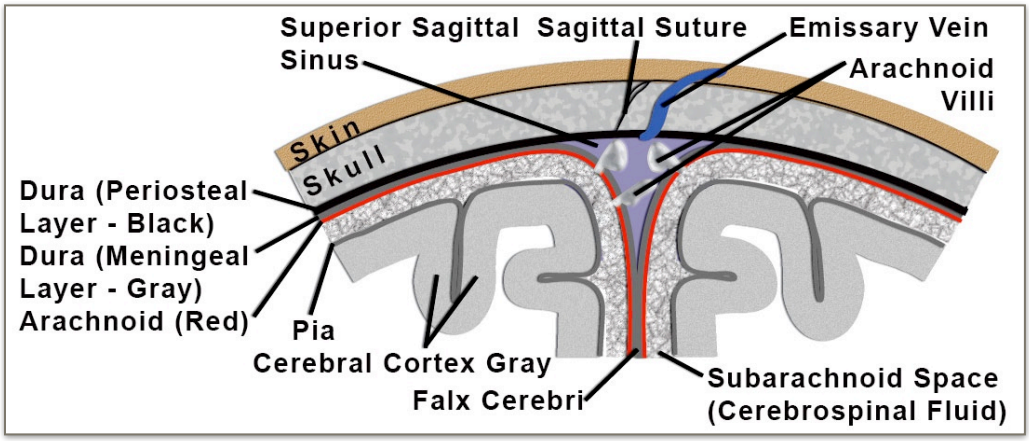


Fig 5-5. Details of the Meninges, Falx Cerebri, Superior Sagittal Sinus, Subarachnoid Space and Arachnoid Villi. Dura plus arachnoid = leptomeninges. (gec). Movie animates formation of the Superior Sagittal Sinus. GO TO: gmomm.pitt.edu Fig5-5_Video

An example is the transient increase in venous pressure caused by a Valsalva maneuver (holding one's breath= closed glottis and "bearing down" with increased abdominal pressure). Such Valsalva effects may occur with heavy resistive exercise or with bowel movements.

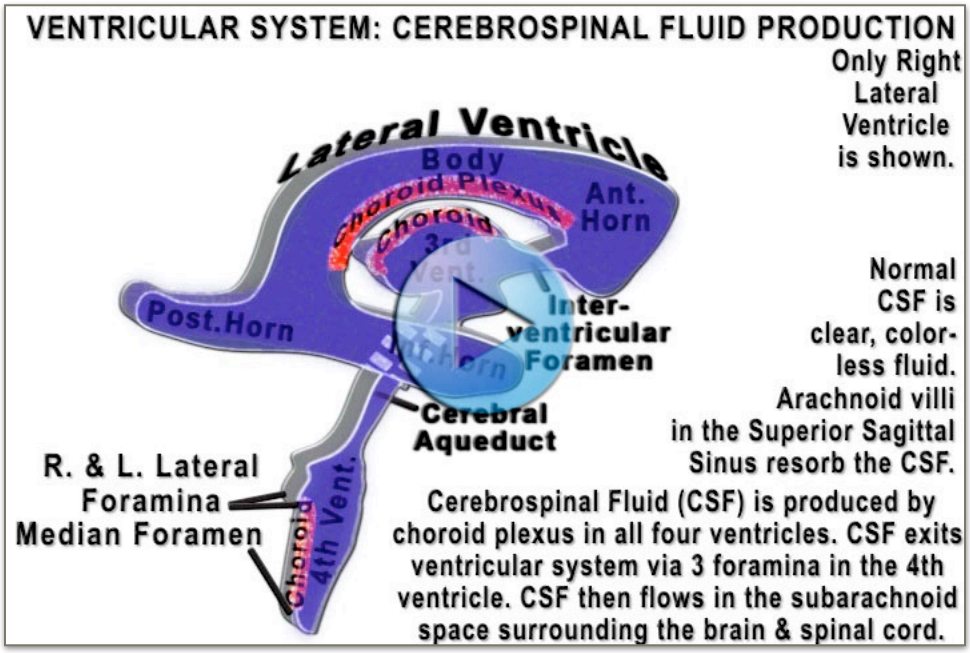


Fig 5-6. Ventricular System-Flow of CSF (gec). GO TO: gmomm.pitt.edu Fig5-6 Video

The Ventricular System-Flow of CSF Animation shows the ventricles, choroid plexi and the flow of CSF from the ventricles into the subarachnoid space within a normal patent CSF System. The animation suggests that the CSF system is being filled with fluid like a bathtub with increasing flow flooding out beyond the confines of the bathtub into the surrounding space (subarachnoid space). In life no drain plug is pulled nor does fluid overflow beyond the closed CSF system unless opened by trauma, pathology or a neurosurgeon.

ARTERIAL BLOOD SUPPLY OF THE BRAIN

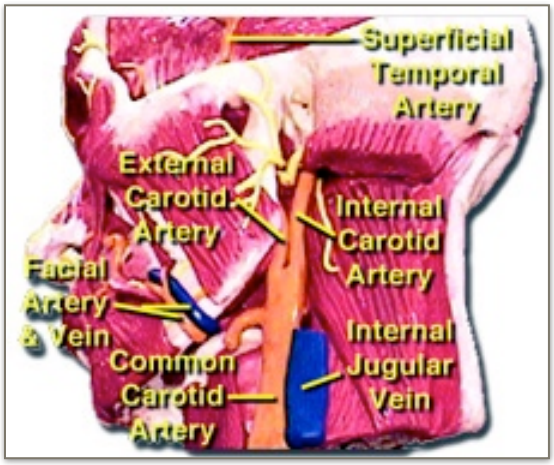


Fig 5-7. Carotid Arteries: Common carotid, External Carotid and Internal Carotid (gec, jac).

The right & left Internal Carotid Arteries (Carotid or Anterior Circulation) and the right and left Vertebral Arteries that join to form the Basilar Artery (Vertebrobasilar or Posterior Circulation). The Internal Carotid Arteries are branches of the Common Carotid Artery in the neck. Together the two internal carotid arteries supply about two-thirds of the brain (most of the supratentorial brain). The Vertebral Arteries most commonly arise from the Subclavian Arteries and travel through the foramina of the

transverse processes of the upper six cervical vertebrae (see figure 5-7).

The vertebrobasilar blood supply accounts for about one-third of intracranial arterial circulation. This posterior arterial circulation supports the posterior fossa contents (brainstem, cranial nerves, cerebellum) and the right & left posterior cerebral artery as the classic terminal arteries of the basilar artery worm their way above the tentorial notch to supply a portion of the posterior and inferior supratentorial brainstem and the entire occipital cortex (right and left).

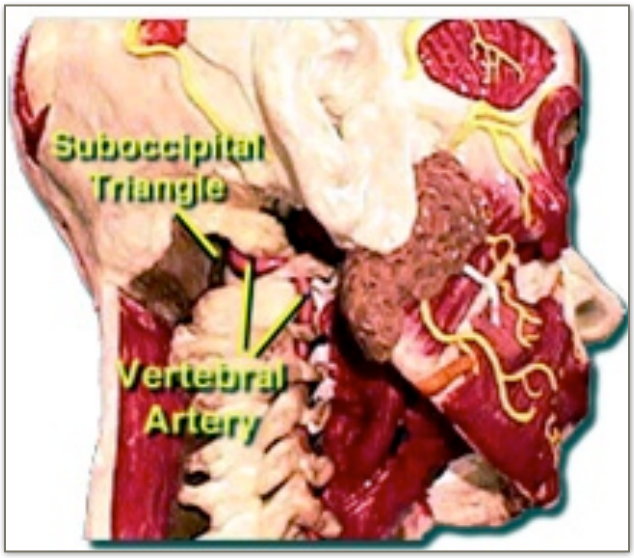


Fig 5-8. Vertebral Artery-Feeder for Vertebrobasilar (Posterior) Circulation of the Brain (gec, jac).

There are several anastomoses that provide for potential alternative blood flow if volume/pressure is reduced in one or more vessels. One potential anastomosis is found in the orbit of the eye where branches of the External Carotid Artery (ECA) may join branches of the Ophthalmic Artery. The Ophthalmic Artery is the first major intracranial branch of the Internal Carotid Artery (ICA). Thus the ECA could provide a "back flow" into the ICA territory if ICA blood flow is compromised in the neck. A second anastomosis is formed by the terminal branches of the major cerebral arterial branches located along the surface of the cerebral cortex.

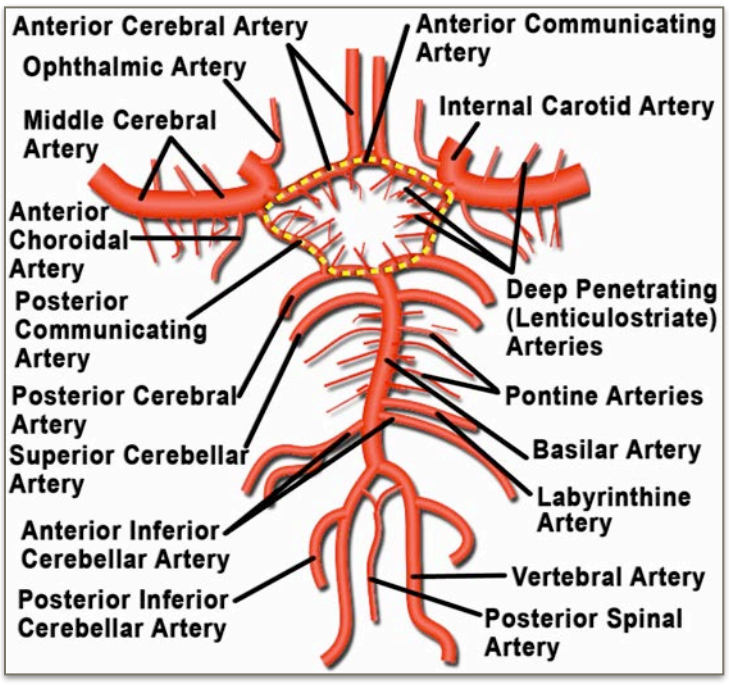


Fig 5-9. Major Arterial Feeders for the Brain: Circle of Willis (yellow dashed line) and Major Arterial Branches (gec).

These superficial cerebral cortical "leptomeningeal" arterial anastomoses provide a potential shunting of blood among these major cerebral arteries. A third anastomosis occurs due to arterial feeders at the base of the brain associated with the circle of Willis. The major arteries involved are the midline anterior communicating artery joining the right and left anterior cerebral artery plus the

right and left posterior communicating arteries that classically join the internal carotid artery and the posterior cerebral artery on each side. The circle of Willis is a potential mechanism to shunt blood between the right and left internal carotid territories by way of the anterior communicating artery and shunting of blood between the anterior and posterior arterial circulation by way of the posterior communicating arteries.

While the brain accounts for less than 3% of the body weight it consumes ~17% of the cardiac output and ~20% of the oxygen available to the entire body. The brain utilizes oxidative (aerobic) metabolism for most of its physiological needs. Thus the arterial blood supply represents a critical supportive element for normal brain function.

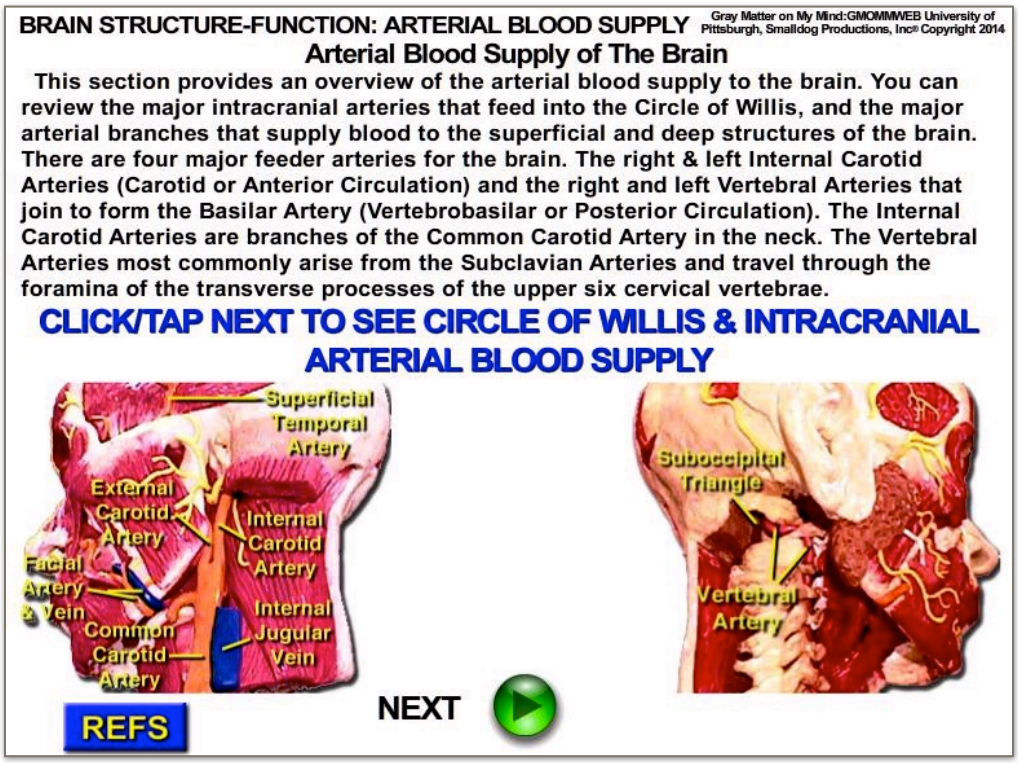


Fig 5-10. Interactive Media file that provides details for arterial blood supply of brain (gec, jac). GO TO: gmomm.pitt.edu *Fig5-10_Interactive Media*

Blood flow in the brain is related primarily to the metabolic demands of the neurons and glia.

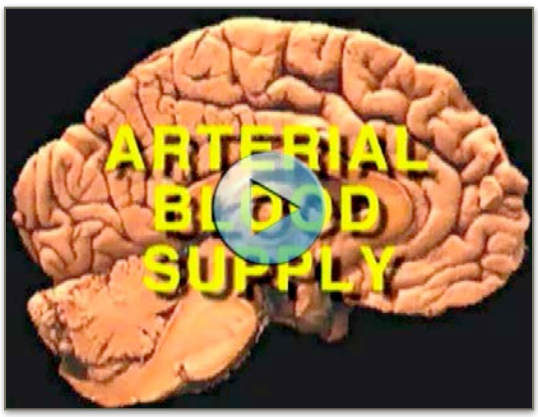


Fig 5-11. Medial Cerebral Arterial Blood Supply Movie (gec). GO TO: gmomm.pitt.edu *Fig5-10_Video*

A measure of regional cerebral blood flow (rCBF) has been utilized to gauge alterations in local rCBF in different brain areas by measuring the BOLD signal with fMRI technology in awake human subjects that perform different behaviors or cognitive tasks while their heads are in the fMRI scanner. This has provided a wealth of

information regarding structure-function relationships for brain activities that would be difficult to replicate using animal models.

Fig 5-12. Lateral Cerebral Arterial Blood Supply Movie (gec). GO TO: gmomm.pitt.edu
Fig5-12_Video

However, one must be guarded in interpreting these findings since the relationship between the BOLD signal and neuronal activity is complex and not a linear measure of cell firing. In addition, the BOLD signal appears to be related to astrocytic activity as well as neuronal activity. The fMRI BOLD signal is discussed in some detail in Chapter 1.

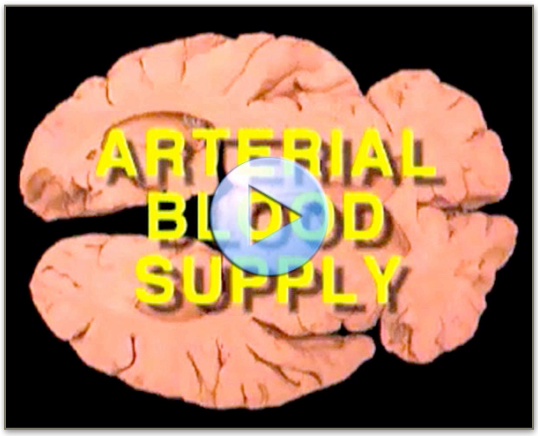


Fig 5-13. Deep Cerebral Arterial Blood Supply Movie (gec). GO TO: gmomm.pitt.edu
Fig5-13_Video

MICROVASCULATURE: BRAIN IS AN ENERGY HOG!

Microvasculature within the gray and white matter provides the constant supply of blood nutrients (e.g., glucose) and transport of blood gases (O^2 & CO^2) required for an organ that has limited capacity for anaerobic metabolism. While slight changes in blood flow follow cardiovascular and respiratory cycles, increased demand by elevated neuronal activity is related directly to more substantial changes in local blood flow. The classic view is that elevated blood flow is directly correlated with increased neuronal firing: a typical supply versus demand relationship. However, recent investigations suggest that elevated cellular activity (neurons and glia) is related in a complex fashion to the demands of increased metabolic requirements and hyperemia (elevated blood flow). In fact, there is no simple one-way pathway among neurons, glia and capillaries. Multiple signals from all of these elements interact and such an interaction may provide a critical contribution to brain function.

The following Cerebral Microvasculature Blood Flow Movie animation shows localized arterial (red) and venous (blue) network within a portion of a cortical column in the cerebral cortex. Yellow spots represent increasing levels of neural activity (subthreshold and suprathreshold synaptic events) within a number of small neuronal networks: note change when thalamic input excites many neurons. Vessel pulsations mimic cyclic cardiovascular and respiratory effects on blood flow. Remember that the

brain surrounded by meninges, cerebrospinal fluid and a bony cranial vault. The brain "floats" within a pressurized closed compartment. Mechanical micropulsations are transmitted through the semisolid brain tissue. Recent direct measurements of localized blood flow suggest that as neuronal activity increases, there is a localized hyperemia.

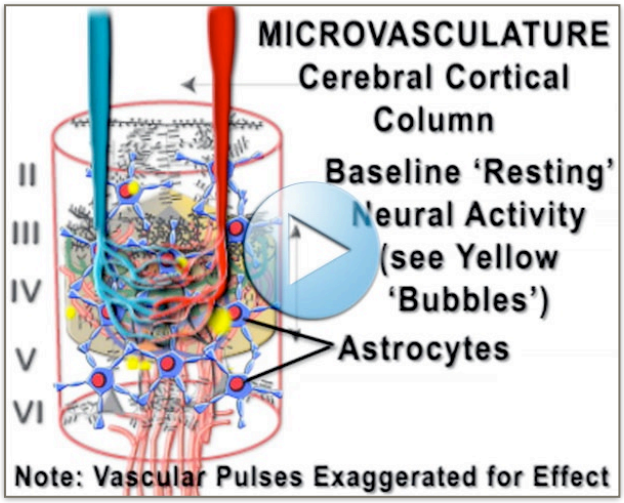


Fig 5-14. Cerebral Microvasculature Blood Flow Movie (gec). GO TO: gmomm.pitt.edu *Fig5-14_Video*

However, the hyperemia appears to be far in excess of actual requirements: i.e., blood supply exceeds metabolic demand. While some might argue that this represents a "safety factor," others have suggested that the excessive hyperemia represents a real signal of altered brain function beyond a simple summation of sub-threshold and supra-threshold synaptic events. Hyperemia is the basic process being measured in a functional Magnetic Resonance Imaging (fMRI) of the brain. Thus the Blood-Oxygen-Level Dependent (BOLD) signal of the fMRI is only an indirect measure of neuronal function. Moreover, the BOLD signal is delayed relative to an initial neural network activation and is evident only with repeated activation within the neural network. If the stimulating event is brief, increases in neural activity may be over before the BOLD signal is recorded. Neurovascular coupling associated with the BOLD signal is being investigated.

BLOOD BRAIN BARRIER: RESTRICTED MOLECULAR ACCESS TO BRAIN PARENCHYMA

A blood brain barrier (BBB) prevents the transportation of many molecules that in the body's circulation would gain access to surrounding tissues from the bloodstream.

The major structural element responsible for this brain parenchyma gated community is the special endothelial cells that form the inner lining of brain blood vessels. These endothelial cells have tight junctions between them and special transporter protein complex channels that limit access. Outside the brain most blood vessel endothelial cells have fenestrated structure whereby spaces exist for free transport or passive transfer of most molecules both large and small. The tight junction endothelial cells are assisted by pericytes and astrocyte end feet which are found surrounding microvasculature arterioles and capillaries see figure below. Brain trauma, brain pathology and perhaps even aging may all cause a partial or more complete breach in the BBB due to biochemical or physical disruption of this neurovascular complex (see references). The influence of Pericytes on neurovascular control of

microvessels is illustrated in the accompanying GMOMM Movie links. Neurotransmitters influence both pericytes and astrocytes associated with cerebral microvessels. Therefore neural activity and blood supply are interrelated in a complex fashion.

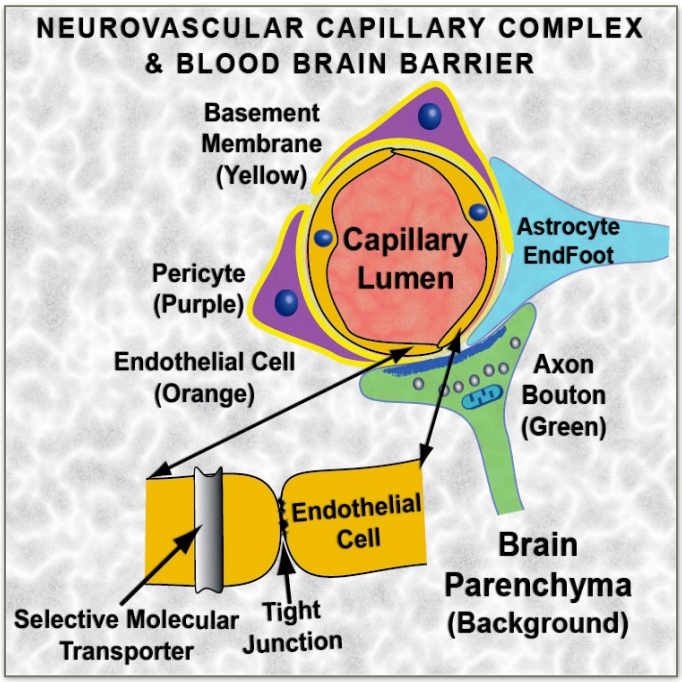


Fig 5-15. Neurovascular Capillary Complex and Blood Brain Barrier (gec). GO TO: gmomm.pitt.edu

Fig 4-15_Video

STRUCTURE/FUNCTION ARE RELATED: "SHADES OF GRAY AND WHITE"

Korbinian Brodmann in the 19th century published a "map" of the cerebral cortex gray matter based upon the cytoarchitectonic differences from one portion of the cortex to another. This map of ~50 separate areas has been used as a "template" for relating structure to function in anatomical, physiological and imaging studies of monkey and human brains. The Brodmann Areas map has been reproduced here as an introduction to structure-function relations "by the numbers." Brodmann's original map, like the living brain is not this colorful. Brodmann Areas (BAs) are used as identifiable landmarks for anatomical & physiological studies in monkeys and for brain imaging studies in humans.

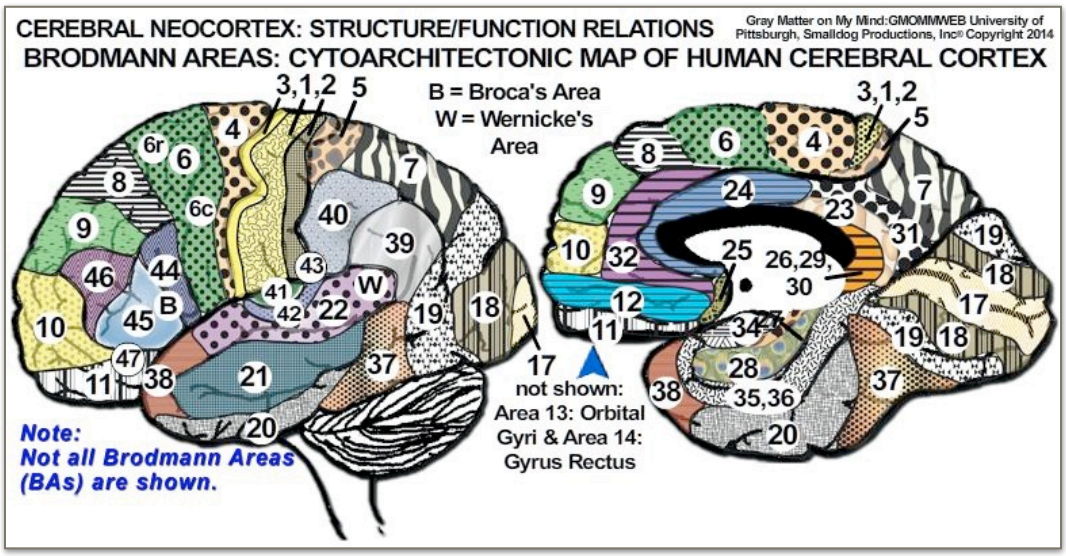


Fig 5-16. Brodmann Areas (BAs) of the Human Cerebral Cortex. Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig5-16_Interactive Media

BRAIN STRUCTURE-FUNCTION RELATIONS: EXTERNAL MORPHOLOGY AND 3D VR MOVIES

The external morphology of the brain is dominated by the gyrations of the cerebral hemispheres with the relatively smaller external structures of the cerebellum and the brainstem filling in the remainder of the brain mass. An interactive VR Movie allows you to see the whole brain from multiple angles as an Unlabeled or Labeled Wholebrain VR Movie, a second virtual reality movie allows you to view a Brain cut in the midsagittal plane from various angles: Unlabeled or Labeled Halfbrain VR Movie.

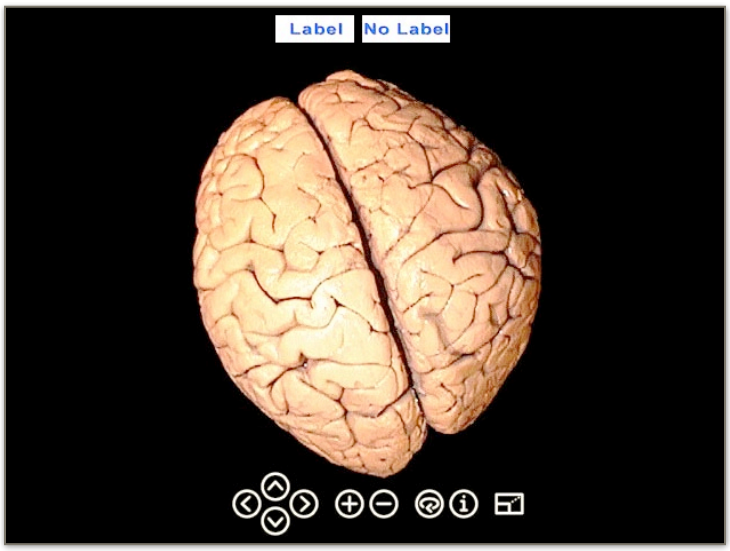


Fig 5-17. Wholebrain Two State: Unlabeled or Labeled VR Movie. The Label and No Label Buttons allow you to shift between labeled or non-labeled images; the default state is unlabeled. The control buttons at the bottom of the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen (gec, jec). GO TO: gmomm.pitt.edu Fig5-17_VR_MOVIE

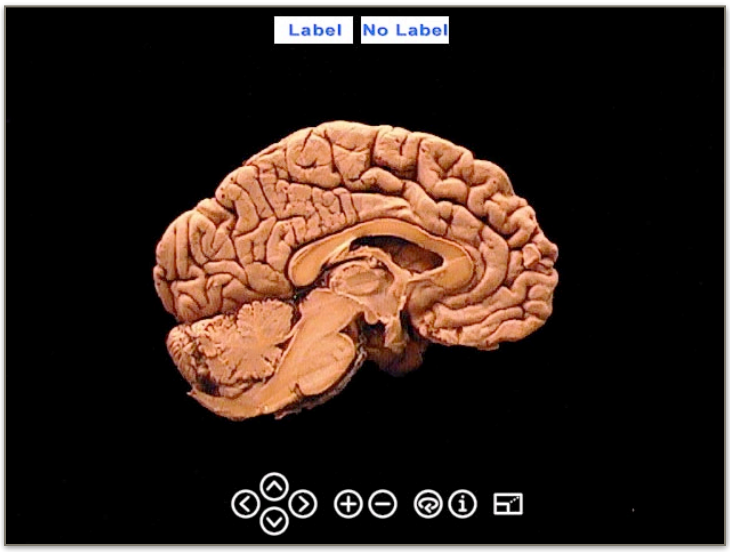


Fig 5-18. Halfbrain Two State: Unlabeled or Labeled VR Movie. The Label and No Label Buttons allow you to shift between labeled or non-labeled images; the default state is unlabeled. The control buttons at the bottom of the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen (gec, jec). GO TO: gmomm.pitt.edu Fig5-18_VR MOVIE

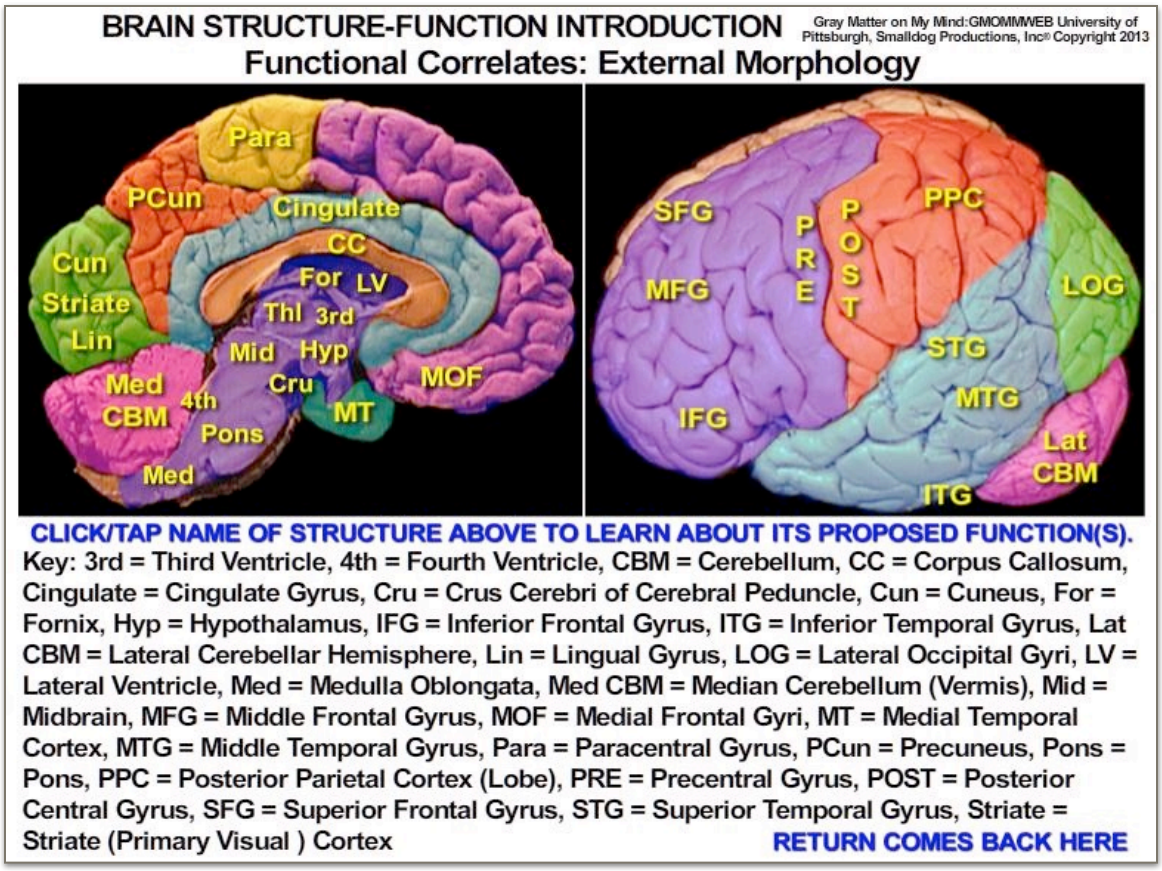


Fig 5-19. External Morphology of the Brain Interactive Media file (gec). The External Morphology of the Brain interactive flash file provides a place by place examination of the most recognizable external structures of the brain. GO TO: gmomm.pitt.edu

Fig5-19_Interactive Media

MIDSAGITTAL VIEW OF BRAIN

Splitting the whole brain in the sagittal plane into a left and a right halfbrain reveals medial cerebral cortical structures, medial cerebellum and both supratentorial and posterior fossa brainstem structures found along the midline of the brain. In addition, the location of the spaces occupied by most of the ventricular system are seen in this midsagittal view. A static reconstruction of the midsagittal view of the left half of the brain is shown in three stages: panel A shows cerebrum alone, panel B adds the cerebellum and brainstem to the cerebrum and panel C adds the ventricular system. The Midsagittal Halfbrain Labeled Movie allows you to build the left halfbrain in the midsagittal view in stages first with no labeling then with labeling added. The static images of panels A, B and C are taken from specific frames of the Midsagittal Halfbrain Labeled Movie.

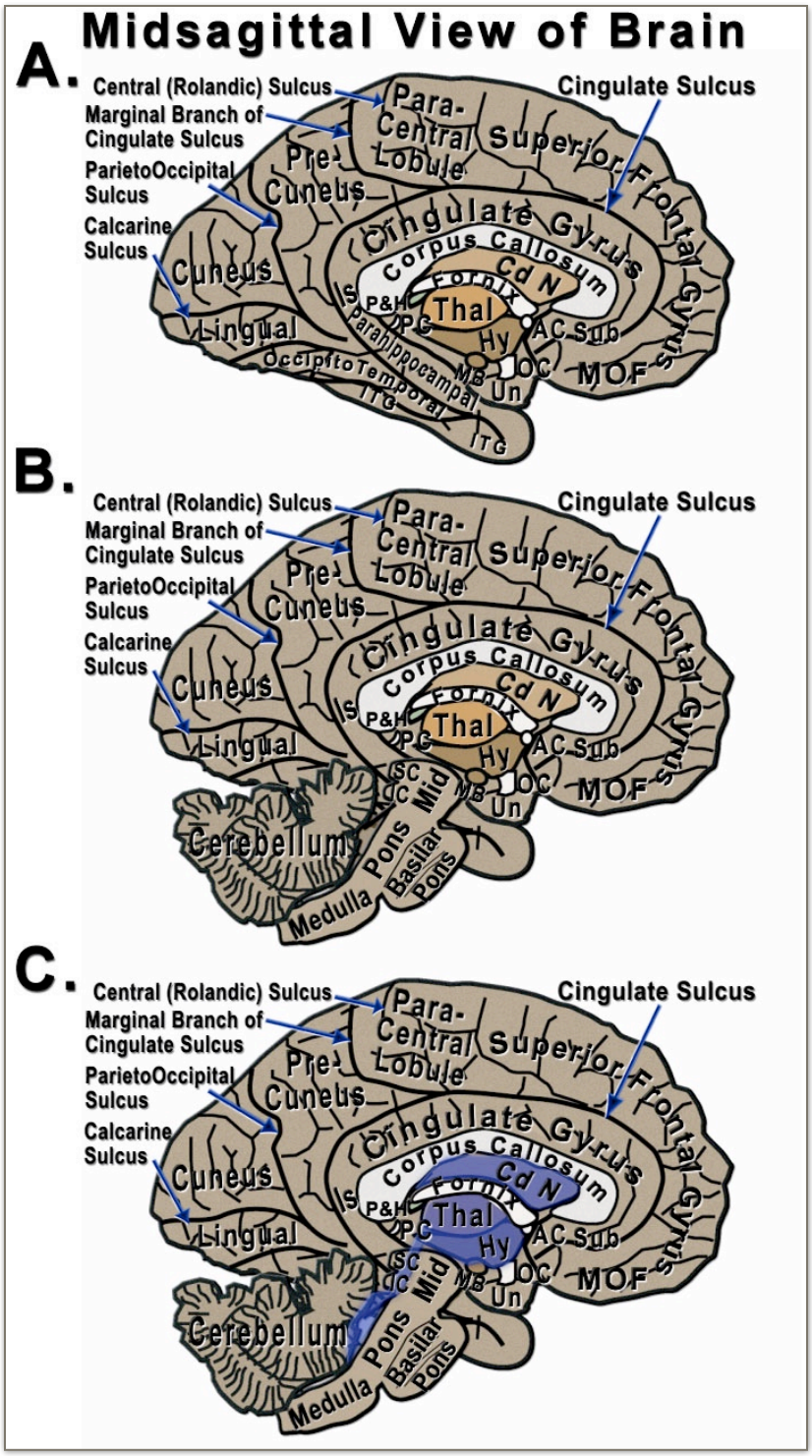


Fig 5-20. Midsagittal View of Left Halfbrain. Panel A: Cerebrum only, B: Cerebrum plus Medial Brainstem and Cerebellum, C: Ventricular System added. KEY: AC = Anterior Commissure, Cd N = Caudate Nucleus, Hy = Hypothalamus, IC = Inferior Colliculus, Is = Isthmus of the Cingulate Gyrus, ITG = Inferior Temporal Gyrus, MB = Mammillary Body, Mid = Midbrain, MOF = Medial Orbitofrontal Cortex, OC = Optic Chiasm, OccipitoTemporal = Occipitotemporal Gyri, Parahippocampal = Parahippocampal Gyrus, PC = Posterior Commissure, P&H = Pineal Gland and Habenula, SC = Superior Colliculus, Sub = Subcallosal Region of Cingulate Gyrus, Thal = Thalamus, Un = Uncus. Midsagittal Halfbrain Labeled Movie (gec). GO TO: gmomm.pitt.edu

Fig5-20_Video

LATERAL VIEW OF BRAIN

The lateral view of the brain shows many of the major frontal, parietal, temporal and occipital lobe areas responsible for our brain's ability to survive and more importantly to succeed. Deep within the lateral (Sylvian) fissure that separates the temporal lobe from frontal and parietal lobes are the insular cortex (insula) and the transverse temporal gyri (of

Heschl). The Lateral Brain Labeled static images and movie illustrate these structures for a brain outline.

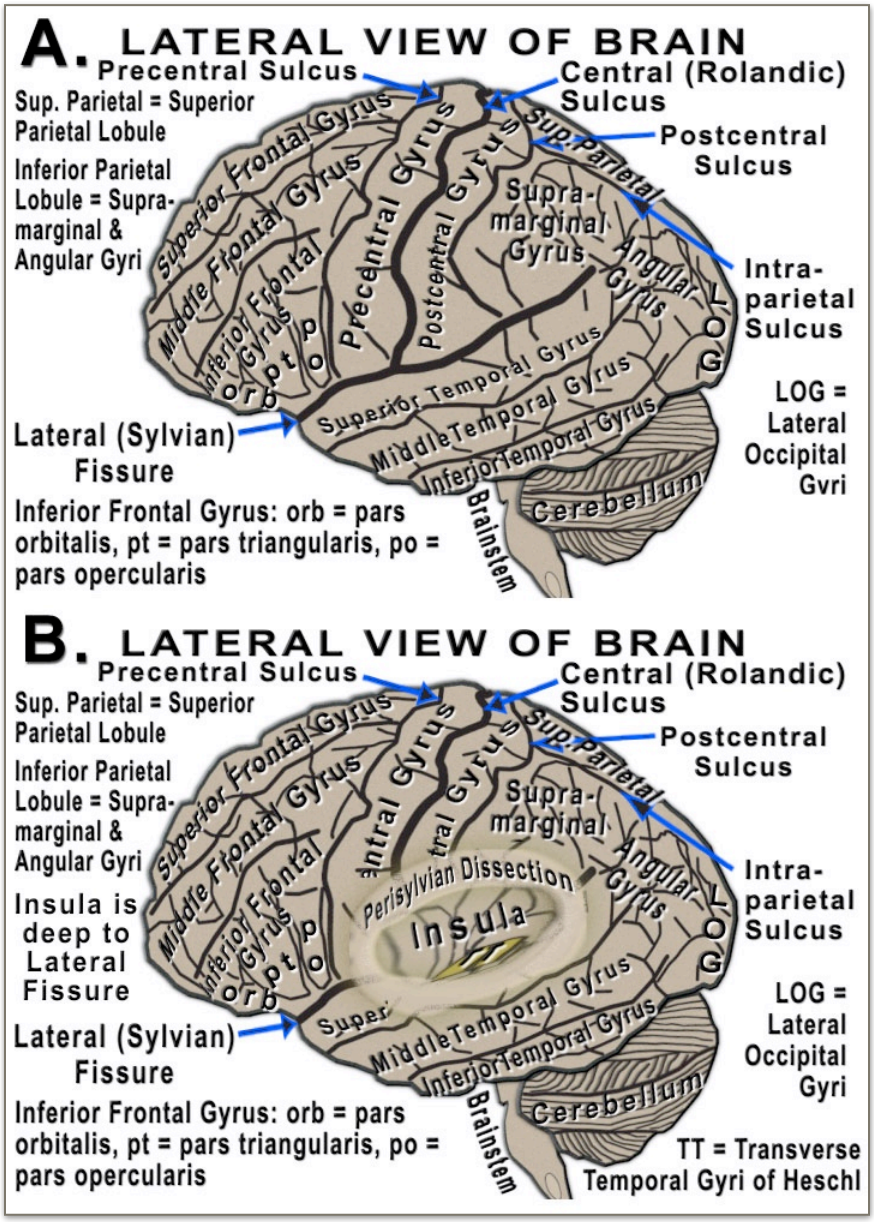


Fig 5-21. Lateral Brain Labeled. Panel A: Surface Structures, B: Surface & Deep structures revealed by dissection of the Perisylvian cortex. These structures are rendered in stages in the Lateral Brain Labeled movie (gec). GO TO: gmomm.pitt.edu
Fig5-21_Video

INFERIOR VIEW OF CEREBRUM

Despite its anatomical location, the inferior cerebrum is not in the basement of brain functions. Orbital gyri in the inferior frontal lobe are considered to be an important limbic cortical area involved in decision making including reward processing. The inferior portion of the occipital lobe is involved in visual processing that leads to conscious perception and visually-derived identification of animate and inanimate objects and persons. Portions of the inferior and medial portions of the temporal lobe are involved in explicit (declarative) memory and learning as well as forming and recalling personal autobiographical events from your past. These functions will be addressed in much greater detail in later chapters. The Inferior View of the Cerebrum figure shows cortical areas involved in these important functions.

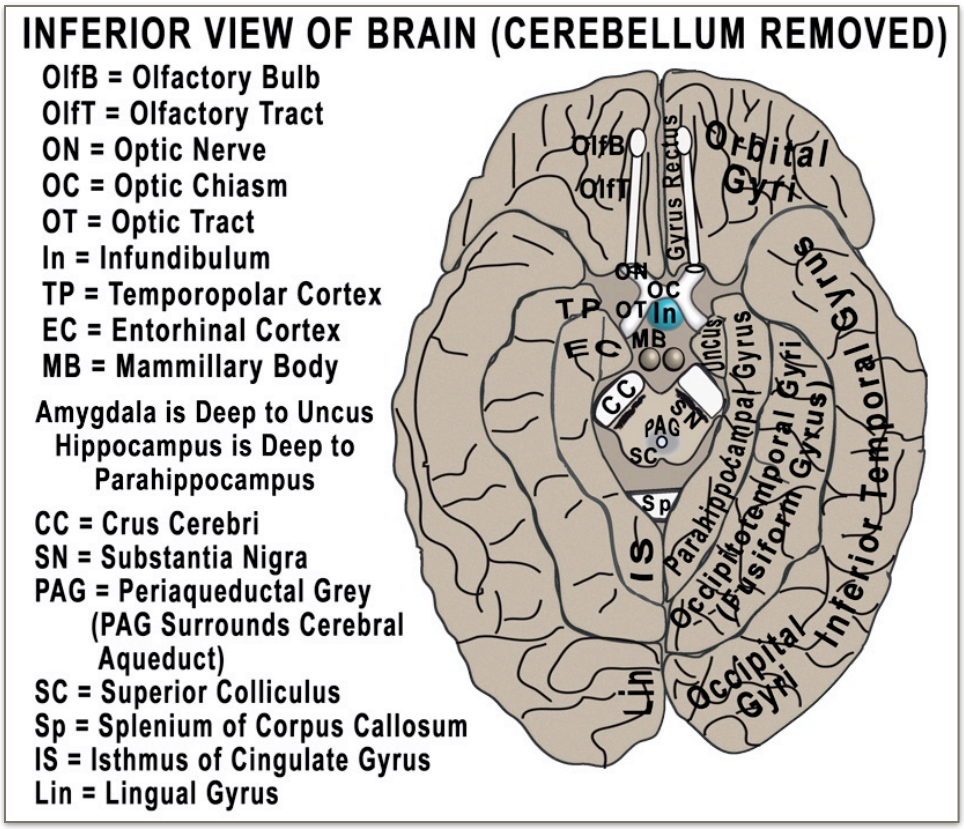


Fig 5-22. Inferior View of Cerebrum: (Posterior Fossa Brainstem and Cerebellum removed). The most rostral aspect of the transected midbrain is labeled along with cortical structures and the Olfactory and Optic Cranial Nerve Structures (gec).

BRAIN

STRUCTURE, FUNCTION: INTERNAL MORPHOLOGY

The internal morphology of the brain is the structural basis of what's inside the gray mantle of the cerebrum.

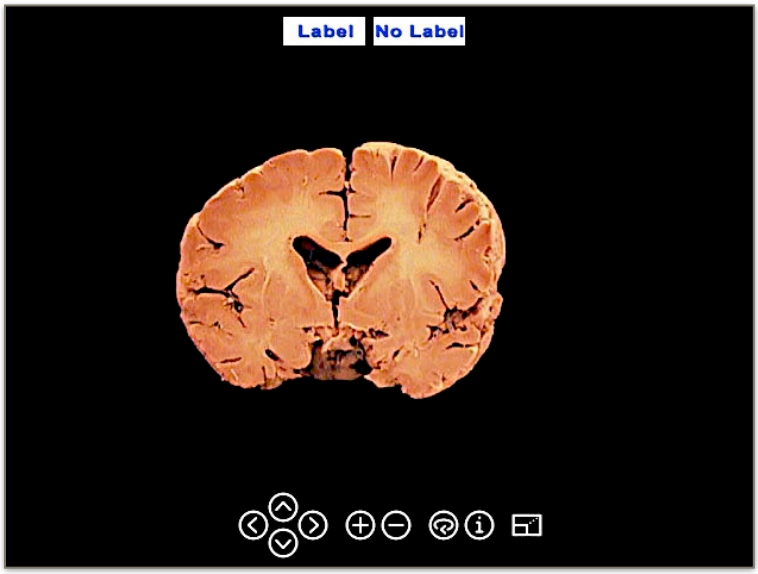


Fig 5-23. Coronal Two State: Unlabeled or Labeled VR Movie. The Label and No Label Buttons allow you to shift between labeled or non-labeled images; the default state is unlabeled. Control buttons at the bottom of the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. Arrow buttons allow you to move in a single direction. Curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen (gec, jec). GO TO: gmomm.pitt.edu Fig5-23_VR_MOVIE

  eISBN-978-0-578-29958-7

The Coronal Two State VR Movies allows you to perform a virtual coronal sectioning of the brain as you alter the view to “cut” the brain (unlabeled or labeled).

The Internal Morphology of the Brain Interactive Flash file allows you to label structures and learn about their basic functions.

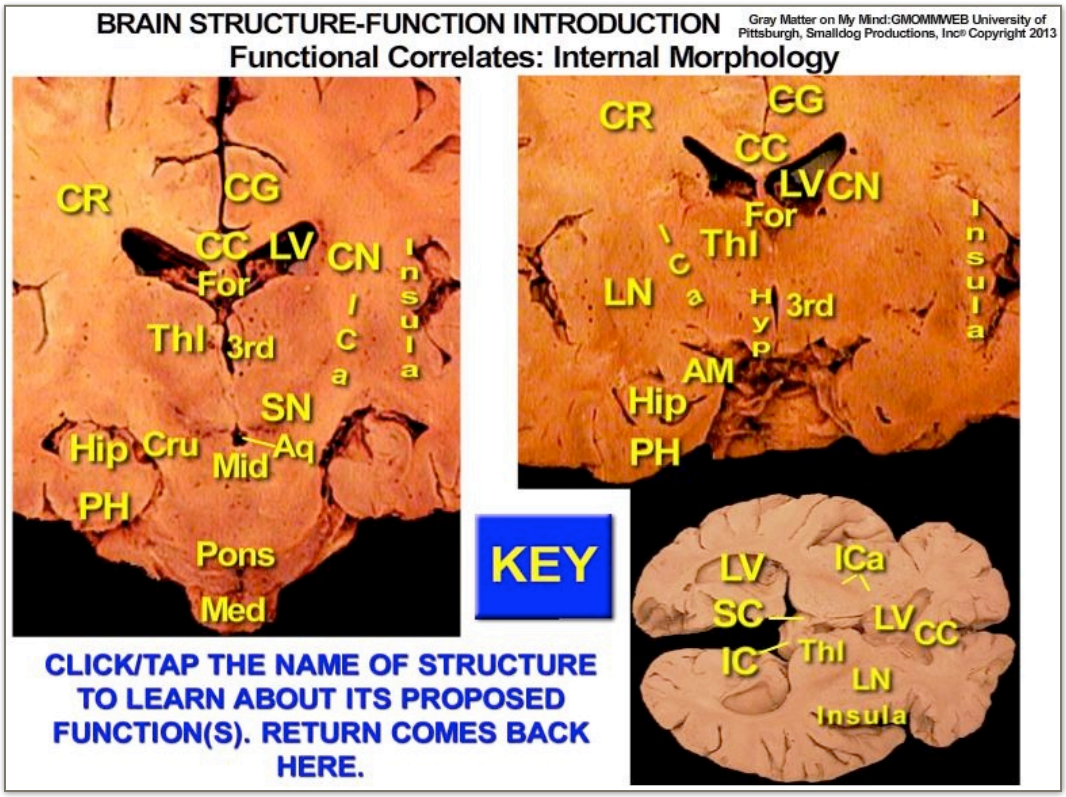


Fig 5-24. Internal Morphology of the Brain Interactive Media file (gec). GO TO: gmomm.pitt.edu

Fig5-24_Interactive Media

The cast of characters presented in the Internal Morphology of the Brain Interactive Flash File includes (see Key Button in Interactive file): 3rd = Third Ventricle, Aq = Cerebral Aqueduct, CC = Corpus Callosum, CG = Cingulate Gyrus, CN = Caudate Nucleus, CR = Corona Radiata, Cru = Crus Cerebri (of Cerebral Peduncle), For = Fornix, Hip = Hippocampus, Hyp = Hypothalamus, IC = Inferior Colliculus, ICa = Internal Capsule, Insula (as itself), LN = Lentiform (Lenticular) Nucleus (Putamen & Globus Pallidus), LV = Lateral Ventricle, Med = Medulla, Mid = Midbrain, PH = Parahippocampal Gyrus, Pons (as itself), SC = Superior Colliculus, SN = Substantia Nigra, Thl = Thalamus.

BRAINSTEM: NEURAL BASIS FOR SURVIVAL & PRIMER FOR SUCCESS

The brainstem includes gray and white matter that together provide neural control of fundamental physiological operations that keep us alive, allow us to recognize internal and external events (at a non-conscious level) and then react in a reflexive or “automatic” fashion to remove us from danger, construct biological rhythms for visceral functions, sleep-wake cycles and fundamental motion and postural patterns.

In addition, the brainstem includes those pathways (tracts) that allow for ascending and descending signals that originate or terminate in levels above or below the brainstem. Not to be outdone the cerebellum connects to the rest of the brain through three cerebellar peduncles. Virtually all neuromodulatory neurons are located in brainstem nuclei.

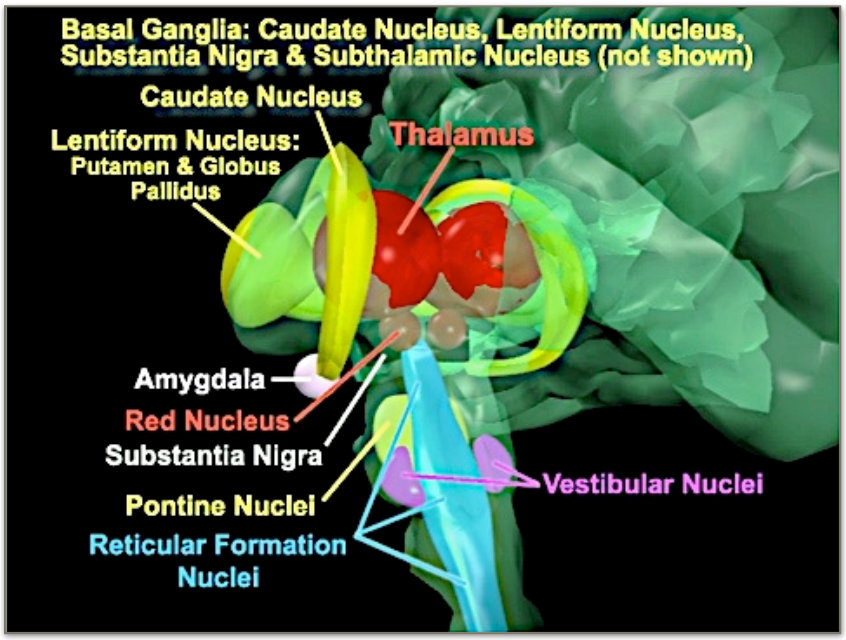


Fig 5-25. Some Major Brainstem Structures associated with Survival & Success (gec).

BRAINSTEM CORONAL AND TRANSVERSE SECTIONS OF DEEP BRAIN

The Supratentorial Coronal Brain Structures Interactive flash file allows you to visualize stained deep structures within Coronal Sections of the Supratentorial Brain.

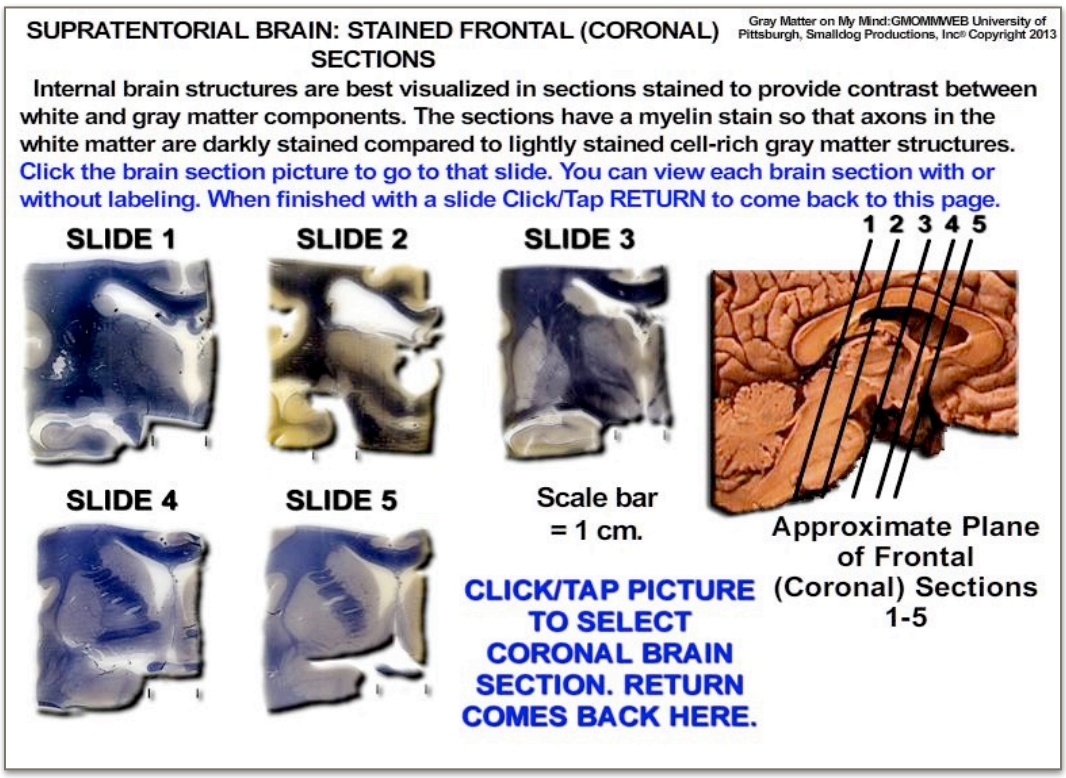
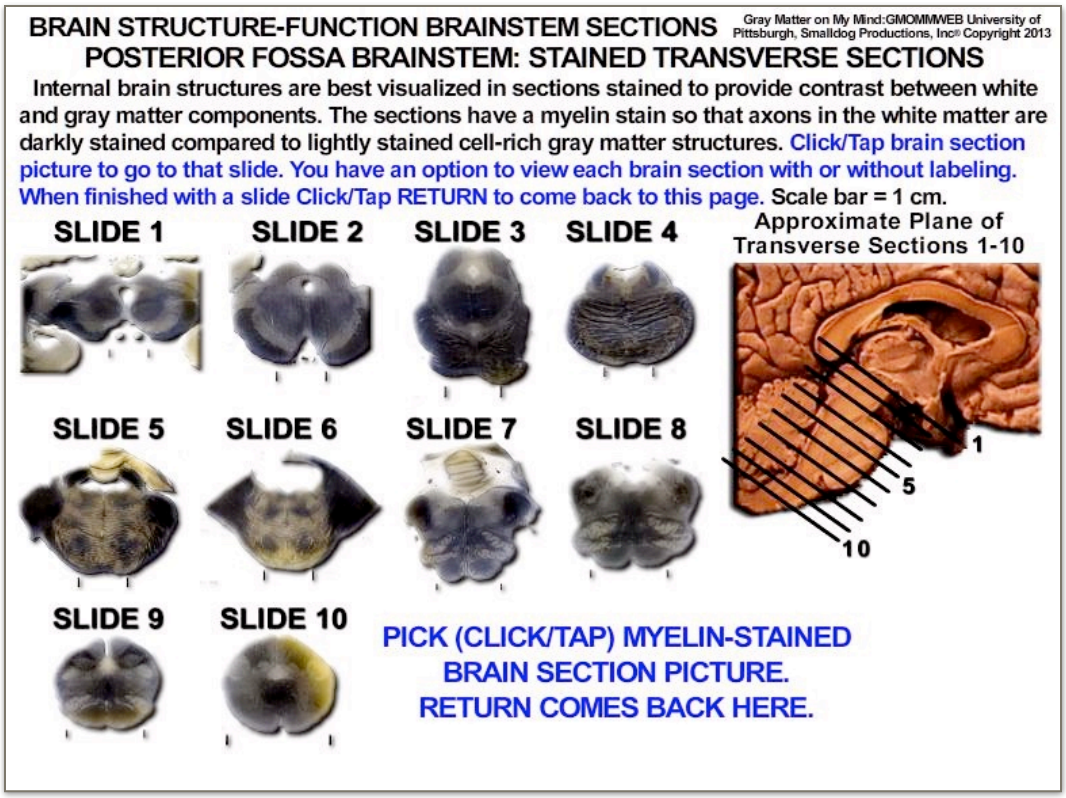


Fig 5-26. Supratentorial Coronal Brain Structures: Interactive Media file (gec). GO TO: gmomm.pitt.edu

[Fig5-26_Interactive Media]

Fig 5-27. Brainstem



Transverse Sections Interactive Media file (gec). GO TO: gmomm.pitt.edu

Fig5-27_Inter-Active Media

The Brainstem Transverse Sections Interactive Flash file shows stained transverse sections through the posterior fossa brainstem. Both flash files provide an unlabeled image and the opportunity to add labels and outlines of the major gray and white matter structures visible in each section.

BRAINSTEM RETICULAR FORMATION NEURO-MODULATORY CENTERS

A major collection of brainstem nuclei known as the reticular formation, is located at all levels of the posterior fossa brainstem: midbrain, pons and medulla. These nuclei have a widespread influence over other structures distributed throughout the brain and spinal cord.

Various nuclei within the reticular formation generate/regulate complex motor patterns, e.g., respiration, locomotion, vocalization, swallowing. Other nuclei influence complex behavior, e.g., sleep/waking cycles, neuroendocrine control, autonomic function, pain modulation. Reticular Formation (RF) Nuclei within the midbrain contain projection neurons which provide one of the sources for input to the thalamus, hypothalamus and cerebral cortex as the ascending arousal system. All ascending tracts originating in the spinal cord that project to the thalamus or to other brainstem locations superior to the midbrain must travel through the posterior fossa brainstem. Some of these ascending axons send collateral axonal branches to nuclei within the brainstem RF and others (spinomesencephalic axons) synapse directly on neurons within the superior colliculus, periaqueductal gray or in the reticular formation

(spinoreticular axons). Likewise, descending axons originating from the cerebral cortex (Corticospinal Tract) may send axonal branches to nuclei in the reticular formation (RF) as the axons travel to their spinal cord destination, or cortex may project directly to the RF (Corticoreticular Projections).

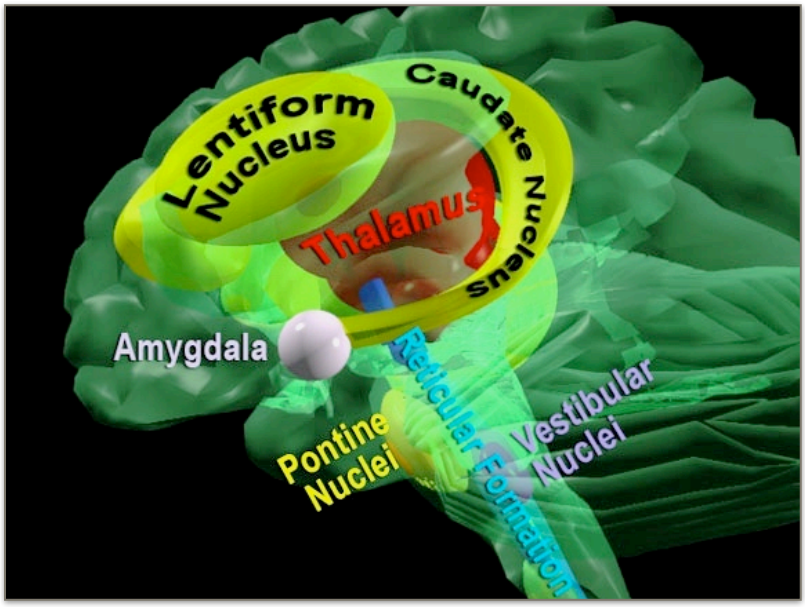


Fig 5-28. Brainstem Reticular Formation and Some Associated Supratentorial and Posterior Fossa Brainstem Structures (gec).

Neuronal ensembles within the reticular formation have been classified according to the neurotransmitter (NT) released by axon terminals of projections from cells in these ensembles. RF projection neurons have a widespread distribution of influence typically to most or all levels of the neuraxis.

Major structures of the Supratentorial and Posterior Fossa Brainstem are labeled in an Interactive Brainstem Labeled VR Movie. The Brainstem Labeled VR Movie has only a single plane of motion.

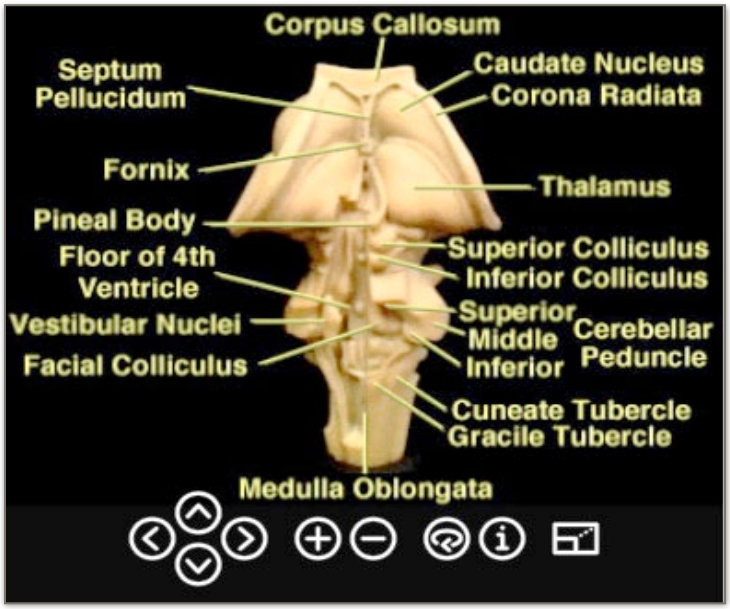


Fig 5-29. Brainstem Labeled VR Movie (gec). The control buttons at the bottom of the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen. (gec). GO TO: gmomm. pitt.edu Fig5-29_VR_MOVIE

BRAINSTEM GLOBAL NEUROMODULATORY CELL GROUPS

Groups of cells in the brainstem are identified according to the neurotransmitter that they release at their axon terminations. Axonal projection patterns of individual neurons provide a diffuse influence on CNS neurons at multiple levels. These 'metastatic' projections provide a neuromodulatory not a driving influence on their targeted neurons. Since the targeted neurons in these various locations will have many different influences on neuronal function such neuromodulatory influences provide a global mechanism to alter "states" within the brain and often within the spinal cord. The conditions that trigger such altered states are often linked to a change in physiological conditions within the body, external stimuli that are perceived as a threat to homeostasis, animate or inanimate objects that trigger a reward response or the alteration of an integrated neural pattern associated with alertness (vigilance), feelings, emotions or a change in affect. All of these conditions would seem to require a global multilevel response not a local network response at a single CNS location.

The neuromodulatory cell groups include those neurons that use amines as neurotransmitters: dopamine, noradrenalin (norepinephrine), serotonin (5-HT) and histamine. The other major neuromodulatory cell groups are cholinergic (Acetylcholine).

SLEEP-WAKE CYCLES: A BIOLOGICAL RHYTHM DEPENDENT ON BRAINSTEM CENTERS

Sleep is one of a number of circadian rhythms controlled by nuclei in the posterior fossa brainstem and forebrain. A normal sleep period consists of a number of stages. Stage 1 non-REM is the transition from wakefulness to sleep a period when our waking consciousness wavers between alertness, drowsiness and immobile retreat from the external stimuli that tend to dominate our waking hours. Stage 4 non-REM represents deep sleep and REM (Rapid Eye Movement) sleep simulates an 'akinetic' awake state according to some measures of brain (EEG) and muscle (EMG) activity Noradrenergic levels are will in stage 4 deep sleep (see below). During REM an electrooculogram measures rapid eye movements (REM) while the EMG of most other somatic muscles is typically silent. Original sleep studies suggested that we dream only during REM, but more recent work suggests that dreaming also may occur during non-REM sleep. The percentage of time spent in deep sleep changes through the lifespan of an individual. As we get older there we spend less time in non-REM stage 3 or 4 sleep (deep sleep), and have more frequent periods of brief (or prolonged) awakenings during the night; REM sleep is relatively preserved with aging in adults. Newborns spend about half of their sleep in REM although REM in infants differs somewhat from adult REM.

Neural centers in the brainstem in cooperation with medial frontal cortex regulate sleep. Sleep spindles and synchronized EEG seen in the cortex during non-REM sleep are thought to be generated by GABA Neurons in the Thalamic Reticular Nucleus and changes in other thalamic nuclei that induces thalamocortical rhythms. REM sleep is regulated by some cells in the rostral raphe Nuclei, the Locus Coeruleus. Some caudal raphe nuclei cells project to the spinal cord to suppress motor activity during REM.

NORADRENERGIC (NOREPINEPHRINE) LOCUS COERULEUS NEURONS

Noradrenalin/norepinephrine (NOR) provides an important neuromodulatory influence on brain and spinal cord to increase overall excitability and may optimize information processing-"I'm going to pump you neurons up!"; and in sleep-wake cycling- "Wake up and smell the coffee!". Most of these cells are located in the locus coeruleus in the dorsal rostral pons. There are relatively few of these NOR neurons but they have a major impact on neuronal excitability in virtually all levels of the CNS. Locus coeruleus NOR neurons like their cousins the dopaminergic cells in the ventral tegmental area and the substantia nigra are pigmented with melanin and would appear dark in the living brain (if you could see them). The locus coeruleus does appear as a small dark spot in fresh sections of an autopsied, unstained brainstem and may be visible as a very small spot in fixed brainstem sections.

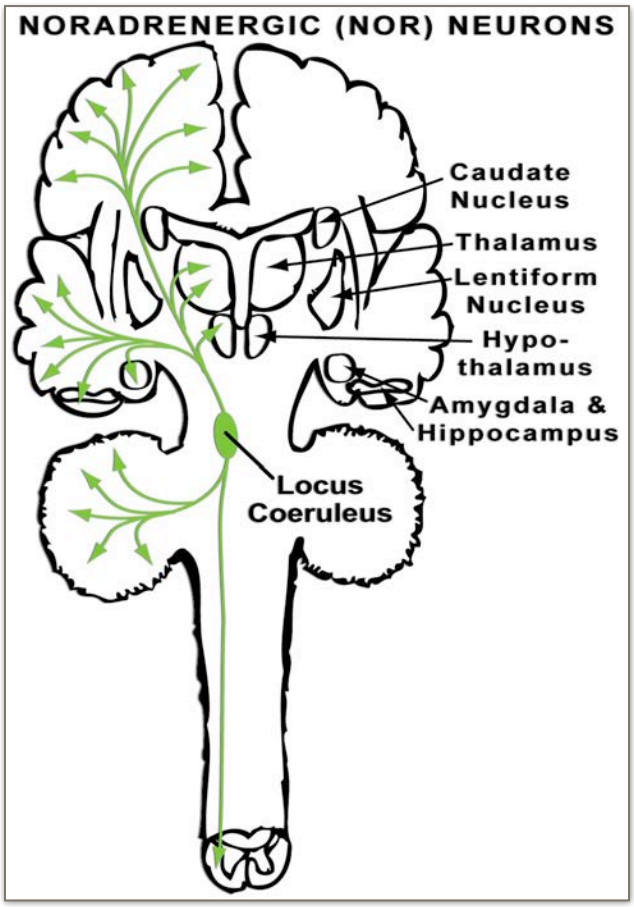


Fig 5-30. Neuromodulatory Noradrenergic Locus Coeruleus cell group in the brainstem (gec).

DOPAMINERGIC (DOPA/DA) SUBSTANTIA NIGRA & VENTRAL TEGMENTAL AREA NEURONS

Dopamine (DOPA or DA) is important in motivating intentions and actions (reward-based); adding limbic "flavor" to our perceptions and actions; and selecting/doing automated behaviors (habits). Melanin pigmented neurons in the substantia nigra pars compacta (SNc) and the nearby ventral tegmental area (VTA) provide the major source of dopamine to the forebrain. SNc projects primarily to the dorsal striatum of the basal ganglia: putamen and caudate nucleus. As will be emphasized in a later chapter loss of the SNc DA cells is a fundamental hallmark of neuropathology in Parkinson Disease. DOPA cells in the VTA project axons to terminate in the ventral striatum of the limbic portion of the basal ganglia and project to the cerebral cortex directly. The frontal lobe receives the highest density of this DA cortical projection.

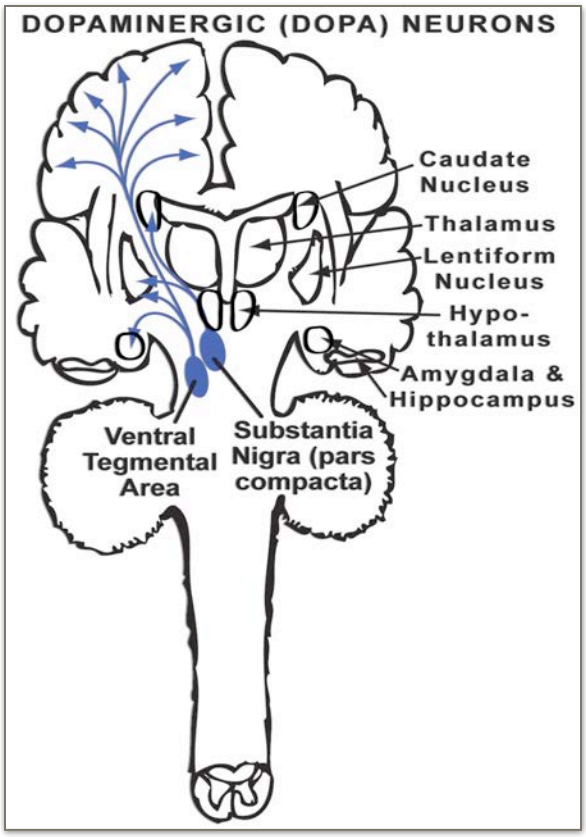


Fig 5-31. Neuromodulatory Dopaminergic centers and their forebrain projections (gec).

SEROTONERGIC (5-HT) ROSTRAL & CAUDAL RAPHE NUCLEI.

Serotonergic (5-HT) neurons are located in a large group of brainstem neurons known as raphe nuclei along the midline. The influences of 5-HT are widespread and may lead to significant changes in brain and spinal network activity. For example, 5-HT is important in pain control ('opiate' pain modulation); activating spinal pattern generators & other motor centers-"Walk on!". Serotonergic neurons are involved in sleep-wake cycles-"Wake up!" and in changes in mood, affect and emotions.

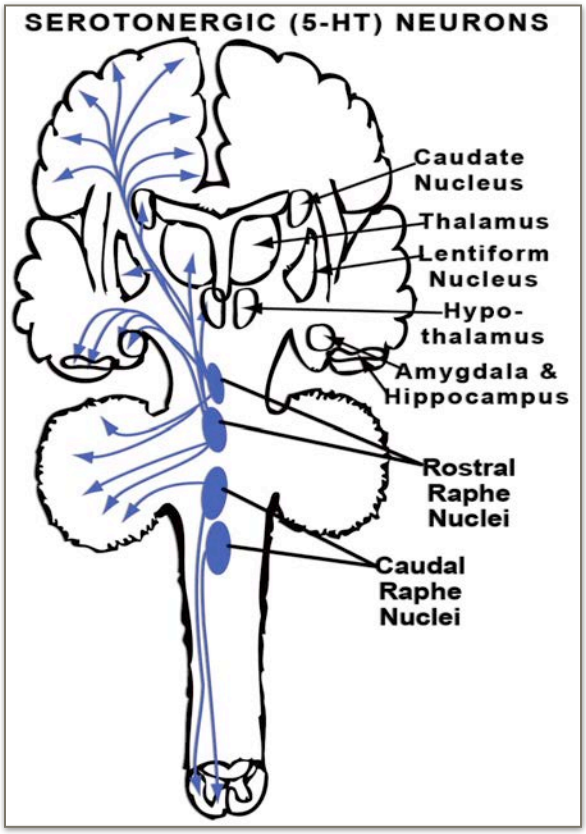


Fig 5-32. Neuromodulatory Serotonergic (5-HT) Raphe brainstem centers (gec).

CHOLINERGIC (ACH) NEURO-MODULATORY BRAINSTEM CENTERS

Acetylcholine (ACh) is important in regulating overall arousal, CNS excitability & setting biorhythms; it may have an important role in learning & memory formation. Cholinergic neurons in the basal forebrain: septal nuclei and nucleus basalis of Meynert) and the posterior fossa brainstem: ponto-mesencephalo-tegmental complex provide the major source of ACh to brainstem and cerebral cortex. Cholinergic receptors may alter voltage-gated channels to alter neuronal responses to synaptic inputs. Loss of ACh neurons in the basal forebrain is one of several identified factors associated with dementia in Alzheimer's Disease. Additionally, cholinergic interneurons provide

a major source of local integration within the striatum: putamen and caudate nucleus.

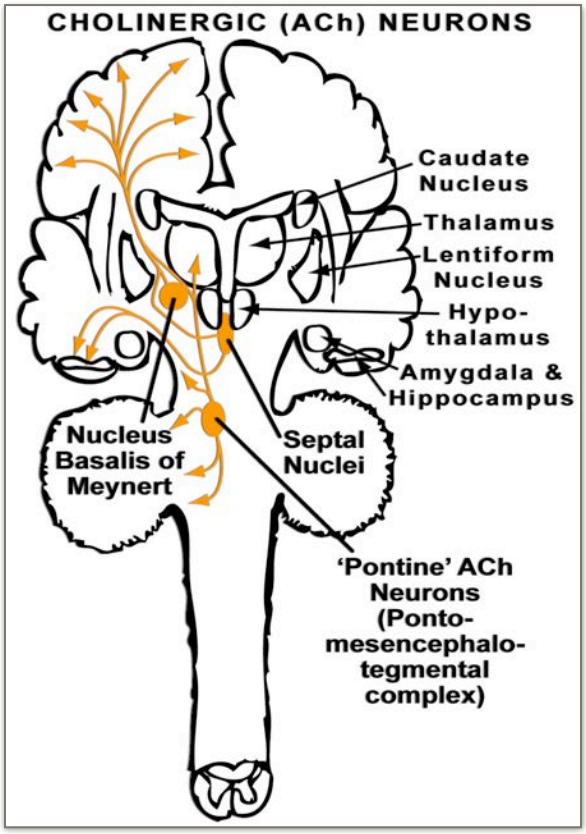


Fig 5-33. Neuromodulatory Cholinergic Centers: Septal Nuclei, Nucleus Basalis of Meynert and Pontine ACh Neurons (gec).

POSTERIOR FOSSA BRAINSTEM: CRANIAL NERVES AND CRANIAL NERVE NUCLEI

All the true cranial nerves (III-XII) exit the brainstem in the posterior fossa. The true cranial nerves are part of Peripheral Nervous System. The cranial nerve nuclei associated with these nerves are located in the posterior fossa brainstem. Cranial nerve I (Olfactory Bulb and Tract) is an adult derivative of a telencephalic out-pouching that lies beneath the olfactory sulcus on the inferior surface of the frontal lobe. The Optic nerves, Optic Chiasm, and Optic Tracts (Cranial Nerve II) are adult derivatives of the diencephalic optic stalk. The optic disk attached to the optic stalk projects to the primordial eye. The embryonic optic disk will become the retina of the eye.

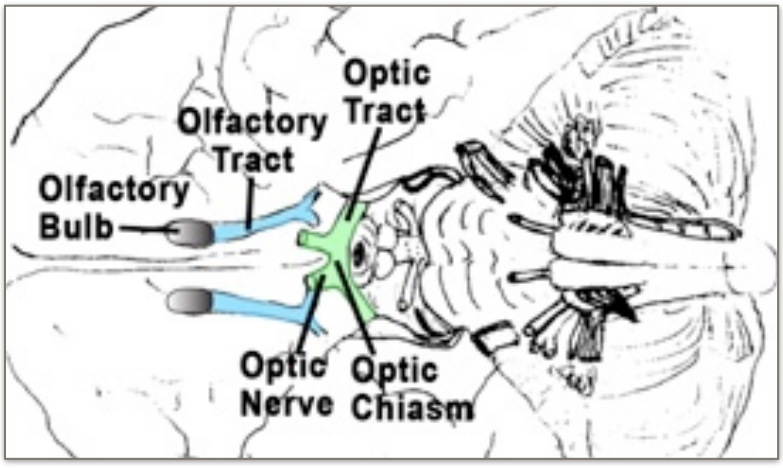


Fig 5-34. Outline of Inferior surface of brain showing Cranial nerve I (Olfactory Bulb & Tract) and Cranial nerve II (Optic Nerve, Optic Chiasm, & Optic Tract) (gec).

The Cranial Nerve Nuclei CNNSpin Two State VR Movie allows you to locate cranial nerve nuclei (unlabeled or labeled) within the posterior fossa brainstem (brainstem rendered transparent in 3D) in different views.

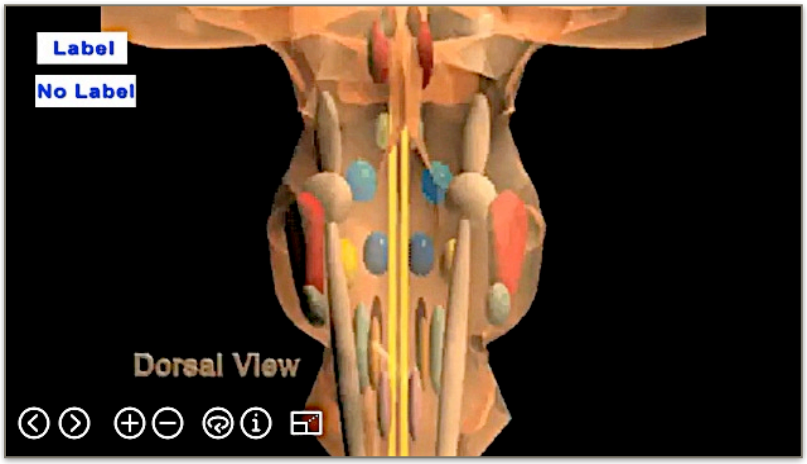


Fig 5-35. CNNSpin Two State: Unlabeled or Labeled VR Movie. The Label and No Label Buttons allow you to shift between labeled or non-labeled images; the default state is unlabeled. The control buttons at the bottom of the VR Movie allow you to zoom-in (+), or zoom-out (-). By dragging the "hand" cursor across the brain you can alter its orientation to see various views. The arrow buttons allow you to move in a single direction. The curved arrow button rotates object automatically. Rectangle-in-rectangle button changes movie to full screen (gec). GO TO: gmomm.pitt.edu *Fig5-35_VR_MOVIE*

The Cranial Nerve Nuclei Structure-Function Relationships interactive flash file identifies cranial nerve nuclei as shown in the CNNSpin Two State VR Movie and allows you to learn the function(s) associated with each cranial nerve nucleus or the Medial Longitudinal Fasciculus (MLF) in the posterior fossa brainstem.

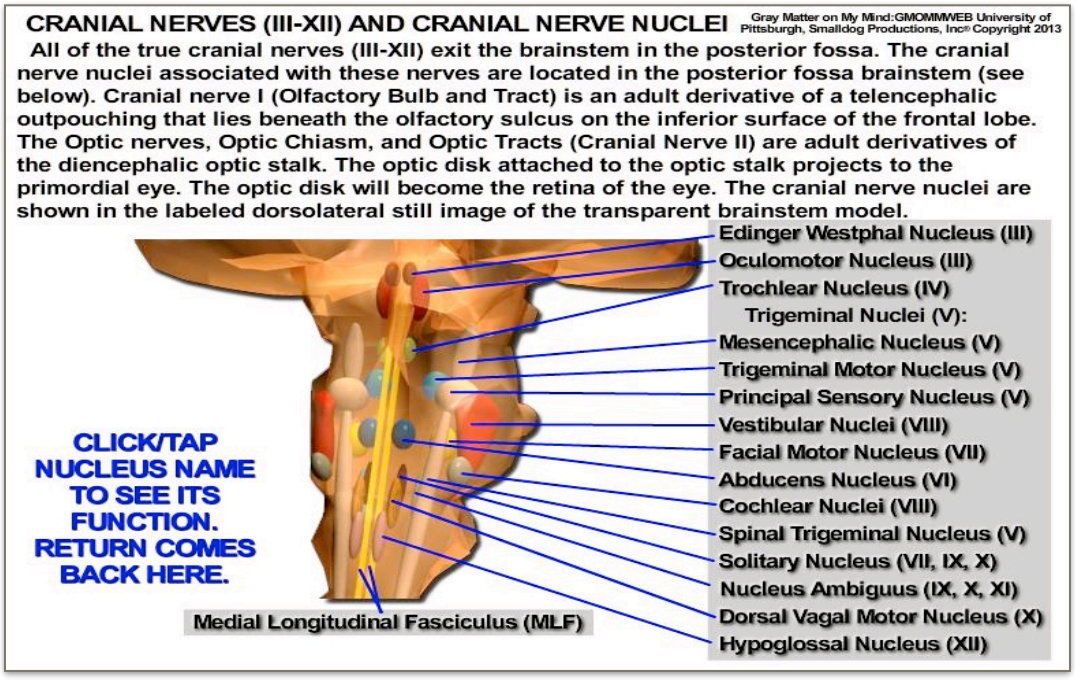


Fig 5-36. Cranial Nerve Nuclei Structure-Function Relationships Interactive Media file (gec). GO TO: gmomm.pitt.edu *Fig5-36_Interactive File*

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Chapter 6

SPINAL CORD STRUCTURE FUNCTION OVERVIEW

The Spinal Cord has gray matter where neurons live and work (communicating and integrating information sent to, and received from the Brain, the Periphery, and other Spinal Cord segments). This circuitry incorporates Relay (Projection) Neurons, Propriospinal Neurons (spinospinal connections) and local Interneurons (excitatory and inhibitory) and Motoneurons to innervate muscle. White matter surrounding the spinal gray provides highways for Action Potential (AP) signals among segments of the Spinal Cord, for AP signals that ascend from the Spinal Cord to the Brain (Ascending Tracts/ Pathways), and for descending AP signals from the Brain to the Spinal Cord (Descending Tracts/Pathways). While neurons are cast in the leading roles on this stage, they could not reach their lofty goals without the support of others. The Supporting Cast includes glia (astrocytes, oligodendrocytes, and microglia), the spinal meninges, cerebrospinal fluid system, pericytes, and the arterial/venous blood supply of the spinal cord.

The adult spinal cord begins at the medulla-spinal cord transition at the foramen magnum and ends as the conus medullaris at the L1-L2 vertebral level. Below the conus, spinal roots continue caudally as the cauda equina. Lumbar and sacral roots of the cauda equina exit at the appropriate lumbar or sacral orthopedic (bony) level. A spinal tap at the L4-5 level is used to measure the pressure and constituents of the CSF. There are 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal segments in the human spinal cord.

Representative labeled pictures of myelin-stained cross-sections at the cervical, thoracic, lumbar and sacral levels are shown below. There are two bulges in the cord. The cervical and lumbar enlargements represent the areas where gray matter expands to accommodate the requirements for innervation of the upper and lower extremities.

This chapter provides a general overview of spinal levels, gray matter, white matter and supportive structures. Later chapters will provide greater detail regarding spinal gray and white subregions associated with sensory, motor and integrative functions.

CERVICAL CORD LEVEL

The cervical cord (C1-C8) provides somatic sensory innervation of the neck, the back of the head, and the upper extremity. The cervical somatic motor innervation includes the deep neck muscles, and the skeletal muscles of the upper extremity including all the muscles that attach the scapula to the thorax except the trapezius and sternocleidomastoid (SCM) muscles. The trapezius and SCM are innervated by the Spinal Accessory Nerve (Cranial Nerve XI). In addition, the upper cervical cord contains motoneurons that innervate the diaphragm by way of the phrenic nerve. Note the large

lateral motor nucleus in the ventral horn gray matter where motoneurons & interneurons that control limb muscles live.

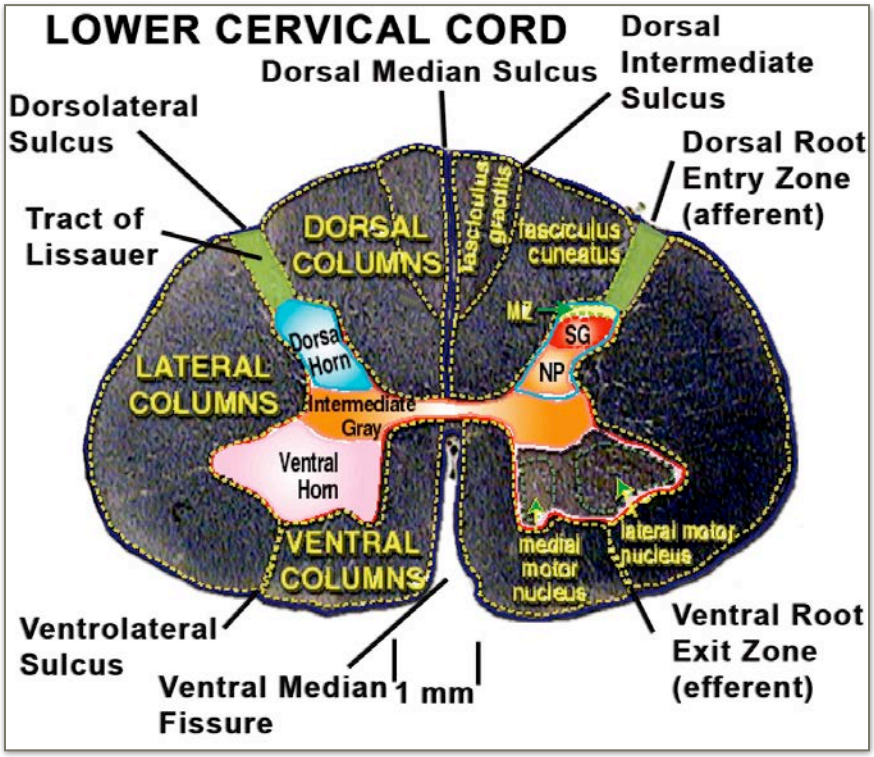

Fig 6-1. Lower Cervical Spinal Cord. Myelin-Stained Section Labeled. MZ = Marginal Zone, SG = Substantia Gelatinosa, NP = Nucleus Proprius (gec).

THORACIC CORD LEVEL

The thoracic cord (T1-T12) provides somatic sensory and motor innervation to the thorax, abdominal wall and the first thoracic segment contributes to the brachial plexus that innervates the upper extremity.

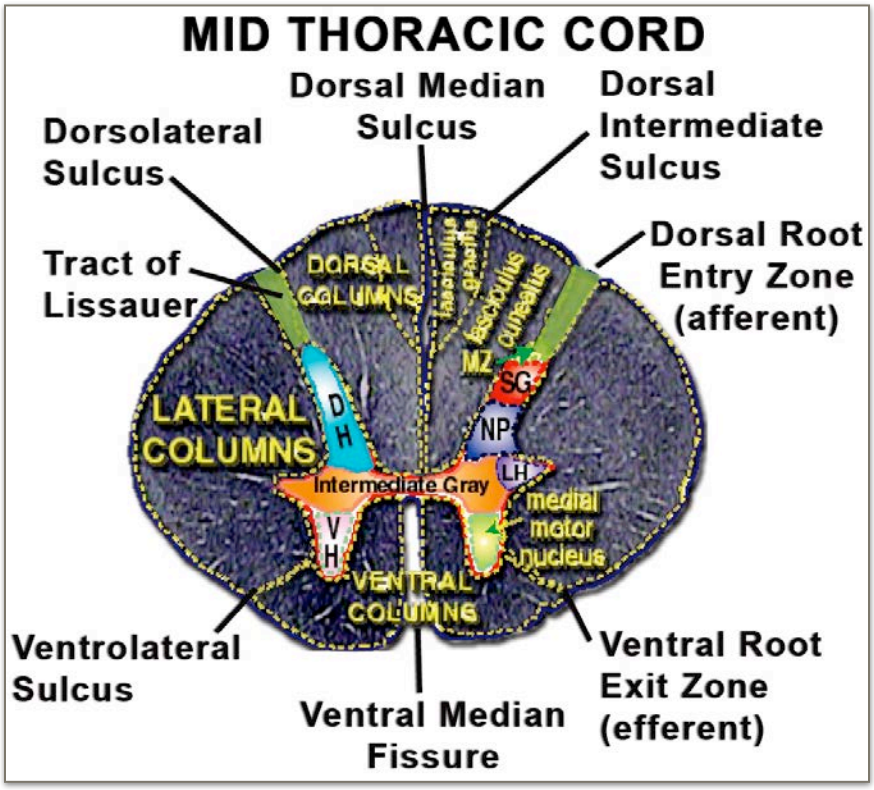

Fig 6-2. Mid Thoracic Cord level. Myelin-Stained Section.DH = Dorsal Horn, LH = Lateral Horn, MZ = Marginal Zone, SG = Substantia Gelatinosa, NP = Nucleus Proprius, VH = Ventral Horn (gec).

The thoracic cord has a narrow ventral horn since there is no lateral motor nucleus below T1; only a medial motor nucleus that provides motor innervation of the intercostal and abdominal muscles and the erector spinae (T2-T12).

The thoracic cord has a pronounced lateral horn which contains preganglionic sympathetic motoneurons that will innervate smooth muscle and glands of the head, neck, thorax, and the upper extremity. In addition, the thoracic viscera receive sympathetic innervation from the motoneurons in the lateral horn of the thoracic cord. The autonomic sympathetic outflow is localized to the thoracic and upper lumbar levels. This sympathetic thoracolumbar outflow extends from C8 to L2-L3. Postganglionic sympathetic motoneurons are located in the paravertebral ganglia (chain ganglia).

LUMBAR CORD LEVEL

The lumbar cord (L1-L5) provides somatic sensory and motor innervation to the lower abdomen/pelvis, the lower back and the lower extremity. The lumbar cord has a large ventral horn to accommodate the medial and lateral motor nuclei. The lumbar segments contribute sensory and motor roots to the lumbosacral plexus that innervates the lower extremity. The upper lumbar cord contains preganglionic sympathetic motoneurons that will innervate smooth muscle and glands of the abdomen, and the lower extremity.

In addition, the abdominal viscera receive sympathetic innervation from the motoneurons in the intermediolateral cell column of the intermediate gray of the lumbar cord. Unlike the thoracic cord, there is no well-defined lateral horn in the lumbar cord. The autonomic sympathetic outflow is localized to the thoracic and upper lumbar levels. This sympathetic thoracolumbar outflow extends from C8 to L2-L3. Postganglionic sympathetic motoneurons are located in the paravertebral ganglia (chain ganglia).

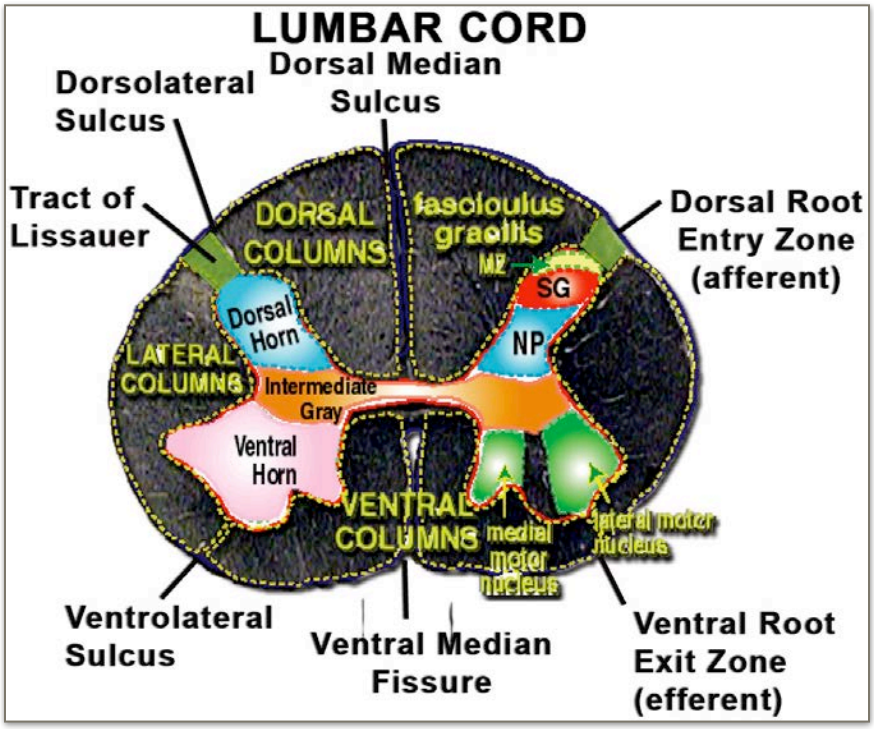

Fig 6-3. Lower Lumbar Cord level. Myelin-Stained Section. MZ = Marginal Zone, SG = Substantia Gelatinosa, NP = Nucleus Proprius (gec).

SACRAL CORD LEVEL

The sacral cord (S1- S5) provides somatic sensory and motor innervation to the "saddle" region of the pelvis, the external genitalia, anus, and the lower extremity. The sacral cord has a relatively large ventral

horn to accommodate the medial and lateral motor nuclei. The sacral segments contribute sensory and motor roots to the lumbosacral plexus that innervates the lower extremity. The sacral cord contains preganglionic parasympathetic motoneurons that will innervate the lower abdominal and the pelvic viscera. The parasympathetic motoneurons are located in the intermediolateral cell column of the intermediate gray of the sacral cord. Unlike the thoracic cord, there is no well-defined lateral horn in the sacral cord. The autonomic parasympathetic outflow is localized to the cranial and sacral levels. This parasympathetic craniosacral outflow includes autonomic efferent axons of sacral roots and cranial nerves III, VII, IX, and X. Postganglionic parasympathetic motoneurons are located in ganglia within or next to the visceral organs in the head, neck, thorax, abdomen, and pelvis or the orbit of the skull.

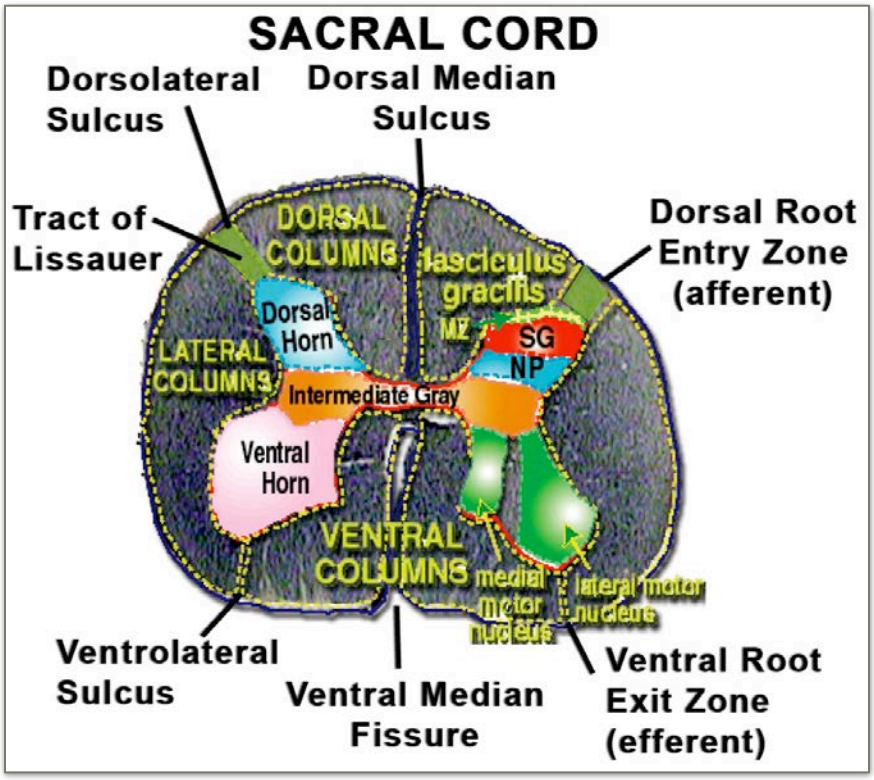

Fig 6-4. Sacral Cord Level. Myelin-Stained Section. MZ = Marginal Zone, SG = Substantia Gelatinosa, NP = Nucleus Proprius (gec).

SPINAL GRAY MATTER OVERVIEW

The Spinal Gray develops from the mantle layer of the neural tube. It is divided in half (both right to left and dorsal to ventral). The dorsal median sulcus and ventral median fissure draw the line right to left. The sulcus limitans (seen as a midline groove in the developing neural tube) divides dorsal from ventral. Dorsal gray is derived from the alar (roof) plate, ventral gray from the basal (floor) plate of the developing neural tube. Dorsal horn neurons are typically associated with sensory function and ventral horn with motor. While this distinction is generally true, normal function may draw no such distinct structural boundaries. For example, gamma motoneurons in the ventral horn modify the sensitivity of the muscle spindle to changes in muscle length and thus modify the sensory signal. The Dorsal Nucleus of Clarke located at the base of the dorsal horn contains projection neurons that send ascending signals about the consequences of movement (proprioception, kinesthesia) to the cerebellum to guide/modulate movement. The gray matter contains local excitatory and

inhibitory interneurons that influence neural networks within one or several segments. Propriospinal (spinospinal) neurons in the gray interconnect spinal segments: within a local region (e.g., short propriospinal neurons at the cervical level) or across regions (long propriospinal neurons interconnecting multiple levels). Projection Neurons in the dorsal and intermediate gray send information from the spinal level to the brain. Alpha Motoneurons in the ventral gray innervate extrafusal skeletal muscle to move our articulated skeleton. Gamma Motoneurons innervate intrafusal muscle in the muscle spindle to alter sensitivity of the proprioceptive endings. Preganglionic Autonomic Motoneurons in the lateral portion of the thoracolumbar Intermediate Gray innervate smooth muscle, and glands by way of a two neuron chain (output to postganglionic sympathetic chain ganglia).

DORSAL HORN OVERVIEW

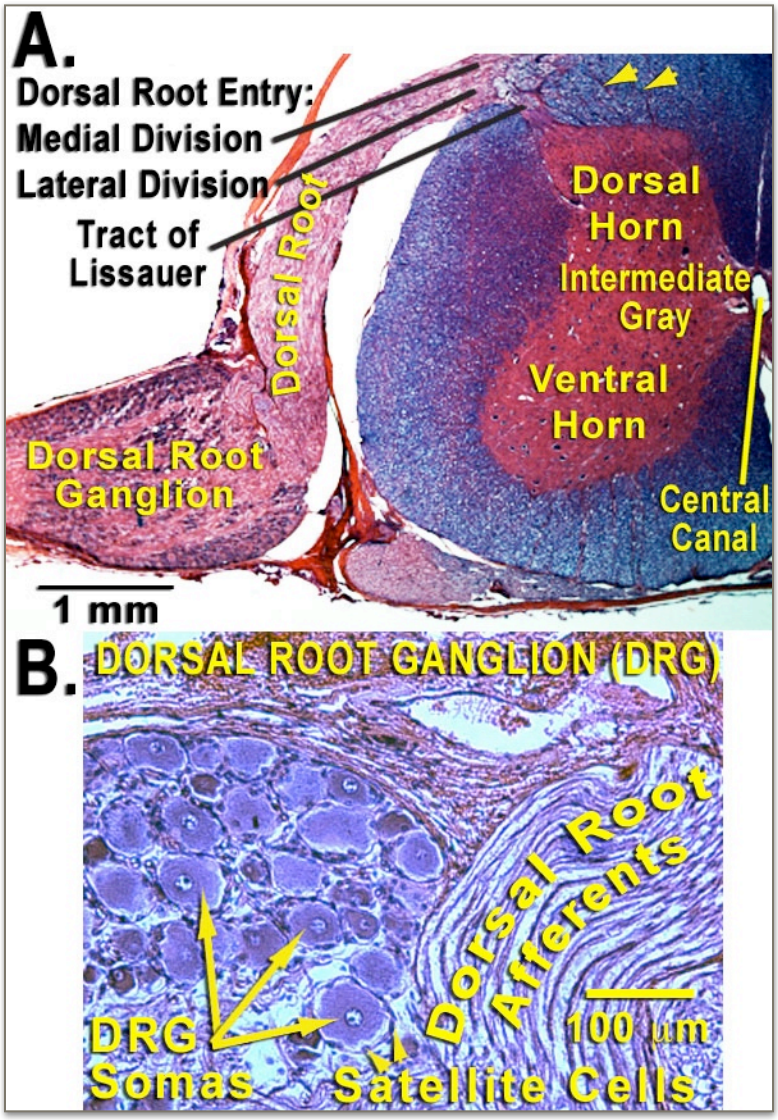

Fig 6-5. Panel A: Dorsal Root Ganglion & Dorsal Root Entry Zone. Arrowheads point to axons in medial division. Panel B: Magnified view of Dorsal Root Ganglion Somas, Afferents & Satellite Cells (gec).

The dorsal horn of the spinal gray matter contains projection neurons whose axons ascend in the dorsal, lateral or ventral funiculus. For example, Spinothalamic Tract Neurons live in the dorsal horn. Local excitatory and inhibitory interneurons modulate the discharge properties of these projection neurons. Both types of neurons are influenced by peripheral afferent input and by descending pathway axons. Small fiber dorsal root afferents in the lateral division enter the Tract of Lissauer, branch, and axons then terminate in the dorsal horn and/or the intermediate gray. Large dorsal root afferents enter the dorsal column in the medial division and branch. Large fiber

branches enter the gray matter to terminate on neurons in the dorsal horn, intermediate gray and some even terminate on neurons in the ventral horn. In addition, many large fibers have ascending axonal projections to the dorsal column nuclei in the medulla. A considerable degree of 'sensory' integration occurs in the dorsal horn which, in turn, influences spinal segmental motor centers. Ascending projections provide the major input for “conscious” discriminative somatic sensation and “feedback” for control of simple to complex behaviors.

INTERMEDIATE GRAY OVERVIEW

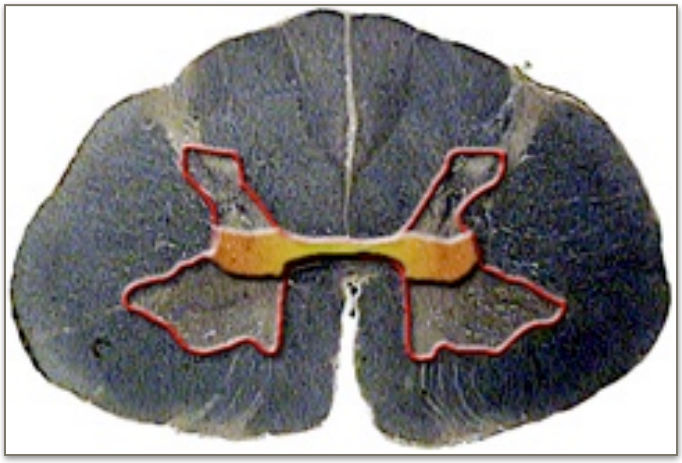

Fig 6-6. Cervical Intermediate Gray Fill (gec).

The intermediate gray contains a class of relay neurons that connect different segments of the spinal cord. Short propriospinal neurons operate within nearby regions, while long propriospinal neurons interconnect segments across many levels of the spinal cord. One set of propriospinal neurons located in the third and fourth cervical segments have a special role in coordination of synergistic actions of the upper extremity (e.g., reaching) and others at lower segments assist in coordination of lower extremity/trunk synergistic activity (e.g., locomotion & postural control). Commissural interneurons located close to the midline connect the right and left sides. Projection neurons that send their axons into the lateral funiculus are located in the thoracic and lumbar levels. Local interneurons at all levels influence ventral horn segmental motor centers. Autonomic preganglionic motoneurons live in the lateral aspect of the intermediate gray (sympathetic at thoracolumbar levels, and parasympathetic at the sacral level). The sympathetic/parasympathetic efferent axons exit the ventral roots to synapse on postganglionic autonomic motoneurons in the periphery.

VENTRAL HORN OVERVIEW

The ventral horn contains alpha motoneurons whose axons exit the by way of the ventral root to innervate a defined set of striated, extrafusal muscle fibers (motor unit). Gamma motoneurons, that coexist with the alpha motoneurons, innervate the specialized muscle fibers (intrafusal muscle) found within the muscle spindles. Interneurons modulate the firing pattern of motoneurons and other interneurons within the ventral horn. Together the ventral horn interneurons and motoneurons form functional units called Segmental Motor Centers (SMCs) that generate and modulate actions in the axial and limb skeletal musculature. SMCs located medially in the Medial Motor Nucleus innervate axial muscles while those in the Lateral Motor Nucleus

innervate limb muscles. These segmental motor centers are the final site for decisions regarding activation or inactivation of motor units used in all forms of motor activity.

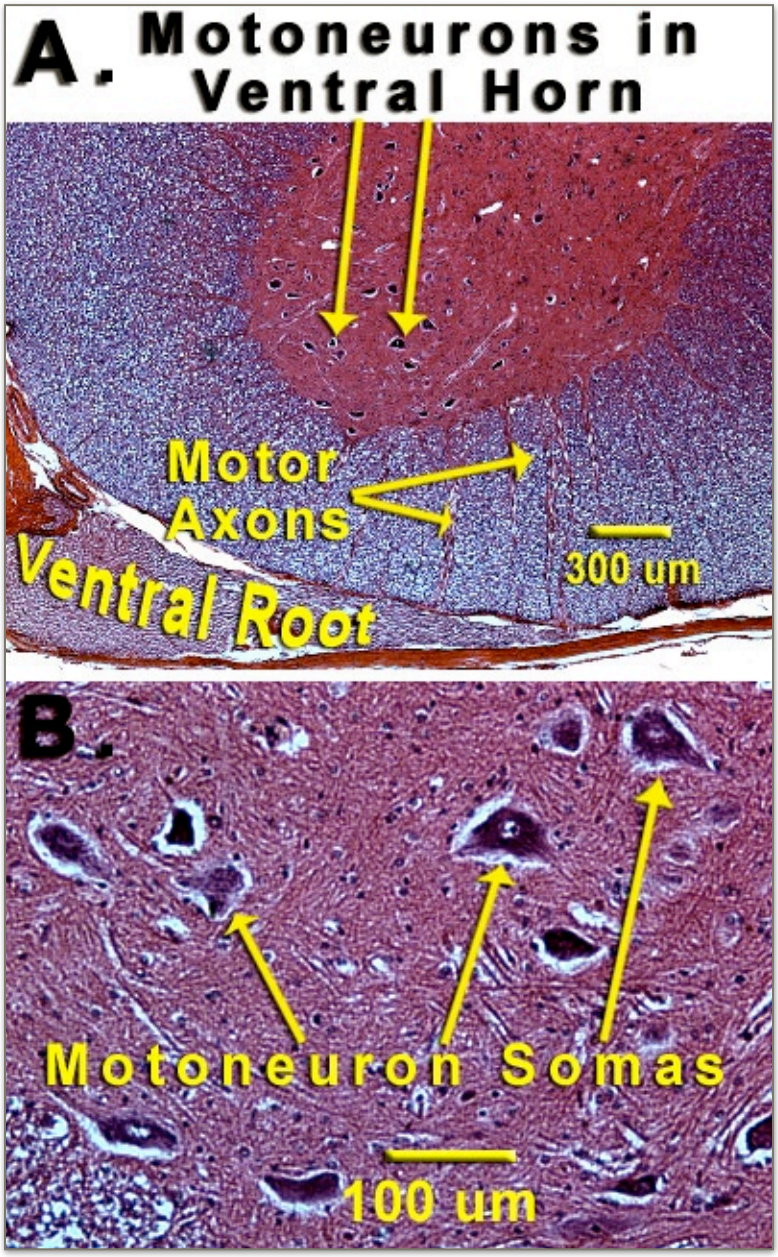

Fig 6-7. Panel A: Ventral Horn, Ventral Roots and Motoneurons. Panel B: Magnified view of ventral horn showing Motoneuron Somas (gec).

VENTRAL HORN MOTOR NUCLEI OVERVIEW

The lateral motor nucleus of the ventral horn is located in the cervical and lumbosacral enlargements where motoneurons innervating the limbs are found. The lateral motor nucleus contains alpha and gamma motoneurons that innervate, respectively, the extrafusal and intrafusal muscle of the ipsilateral limb. The lateral motor nucleus has major interconnections with short propriospinal neurons and to a lesser extent with some long propriospinal neurons.

The medial motor nucleus of the ventral horn is located at all levels of the spinal ventral gray matter. It contains alpha and gamma motoneurons that innervate, respectively, the extrafusal and intrafusal muscle of the ipsilateral axial skeleton (neck, back, thoracic cage, and abdominal muscles). The medial motor nucleus has major connections with the long propriospinal neurons and with commissural interneurons (located close to the midline in the gray matter) that provide distributed, bilateral connectivity over many segments.

Extrafusal muscle (EFM) is the skeletal muscle that is found in the motor units that move the joints. Intrafusal muscle (IFM) is the specialized muscle found within the

muscle spindle capsule. Contraction of the IFM alters the sensitivity of the spindle stretch receptors and thus changes the proprioceptive feedback. For most actions that we perform, both the EFM and the IFM are co-activated (Alpha-Gamma Co-Activation Pattern).

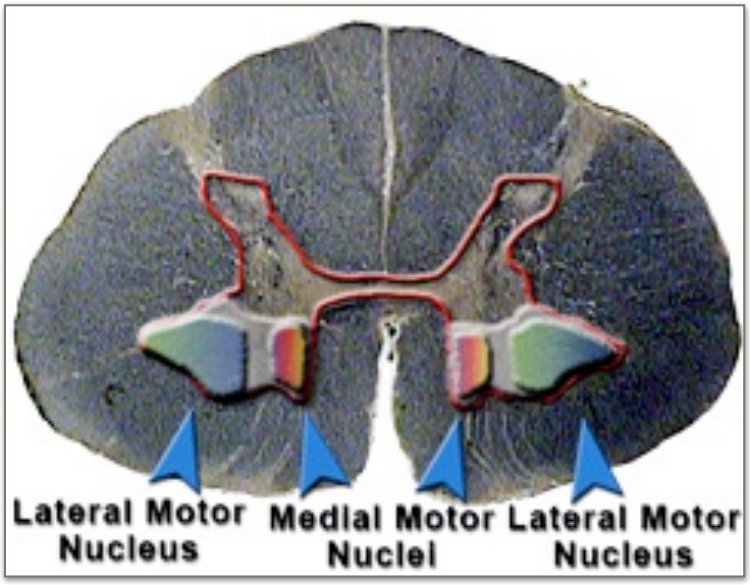

Fig 6-8. Location of the Lateral & Medial Motor Nuclei in the Ventral Horn (gec).

SPINAL WHITE MATTER OVERVIEW

The Spinal White develops from the marginal layer of the neural tube, and surrounds the gray matter. It is divided into three funiculi (columns): dorsal, lateral and ventral (anterior). Axons in the white matter provide continuity between spinal segments (Propriospinal Tract) and between the brain and spinal cord levels of the CNS (ascending and descending tracts). In addition, peripheral (sensory) afferents enter the spinal white at the dorsal root entry zone.

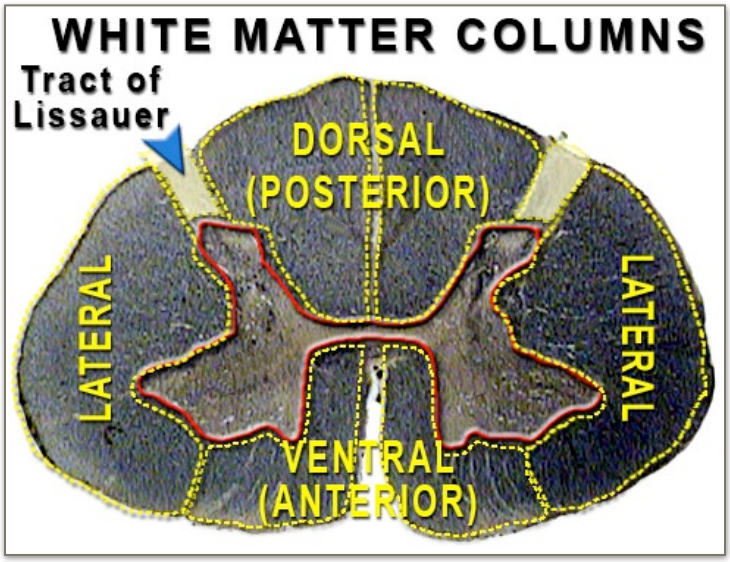

Fig 6-9. Spinal White Matter Columns: Dorsal, Lateral and Ventral Columns (gec).

Dorsal root ganglion cells send central axons into the dorsal funiculus (dorsal column) via the medial division of the dorsal root afferents or into the Tract of Lissauer via the lateral division of the dorsal root afferents. The Tract of Lissauer is located at the juncture of the dorsal and lateral funiculi. Although most tracts extend the full length of the spinal cord there are exceptions, e.g., descending Medial Longitudinal Fasciculus (MLF). The MLF projects to the cervical segments only. The Tract of Lissauer is a special portion of the white matter that contains small dorsal root afferents that travel in this tract after entering the cord at the dorsal root entry zone. These are small axons from the lateral division of the dorsal root

filaments (large fiber dorsal root afferents in the medial division enter the Dorsal Column).

The small fibers in the Tract (Zone) of Lissauer travel up and down the cord over a number of segments to enter the Dorsal Horn Gray at many levels. The small fiber afferents in the Tract of Lissauer have extensive convergent and divergent connections within the dorsal horn and to a lesser extent within the intermediate gray. The small fibers carry information about “crude” touch, pressure, temperature and pain.

LATERAL WHITE COLUMN

The lateral funiculus (column) is located between the dorsolateral sulcus and the ventrolateral sulcus. It contains axons of ascending and descending tracts. The descending tracts include the lateral corticospinal tract (LCST), the rubrospinal tract (RuST), and the dorsolateral funiculus (DLF). The DLF contains descending reticulospinal axons. The descending tracts influence the dorsal horn, the intermediate gray, and the lateral motor nucleus > medial motor nucleus in the ventral horn. Ascending tracts include the dorsal spinocerebellar tract (DSCT), the ventral spinocerebellar tract (VSCT), the spino-olivary tract (SOT), and axons in the anterolateral system (ALS) ascending pathway. The ALS includes spinothalamic tract axons, spinoreticular axons, and spinomesencephalic (spinotectal) tract axons.

DORSAL WHITE COLUMN

The dorsal funiculus (column) is located between the dorsal median sulcus and the dorsolateral sulcus. It contains large myelinated axons originating from dorsal root ganglion cells (medial division of the dorsal root). These medial division axons enter the dorsal column and send a collateral branch to enter the spinal gray and a branch that ascends to the medulla as dorsal column axons. Medial bundle axons that enter the spinal gray synapse on interneurons, projection neurons, and propriospinal neurons that live in the dorsal horn, intermediate gray and to a lesser extent the ventral horn. The presynaptic axons (from the dorsal root ganglion are accompanied by postsynaptic dorsal column axons. The 'postsynaptic' dorsal column axons originate from projection neurons located in the nucleus proprius of the dorsal horn. These postsynaptic dorsal column projection neurons are named Low Threshold Mechanoreceptive (LTM) neurons since they receive monosynaptic excitatory connections from A beta axons that innervate low-threshold tactile mechanoreceptors. These axons represent a significant proportion of the medial division bundle of axons in the dorsal root.

VENTRAL WHITE COLUMN

The ventral funiculus (column) is located between the ventral median fissure and the ventrolateral sulcus. It contains axons of ascending and descending tracts. The ascending tracts include spinothalamic tract axons, spinoreticular axons, and spinomesencephalic (spinotectal) axons. All of these ascending axons are located in the anterolateral system (ALS) which extends into the lateral funiculus. The ALS carries

touch, pressure, pain and temperature information to the brainstem (spinoreticular & spinomesencephalic) and to the thalamus. The descending tracts include reticulospinal, vestibulospinal and tectospinal tract axons from brainstem nuclei and anterior (ventral) corticospinal tract axons that originate from pyramidal tract neurons located in the cerebral cortex. A specialized descending tract called the Medial Longitudinal Fasciculus (MLF) is found in the cervical ventral funiculus only. The descending MLF contains vestibulospinal, reticulospinal and tectospinal axons that are functionally related to brainstem eye movement control nuclei. The descending MLF axons synapse on interneurons and motoneurons that control neck muscles. The descending MLF plus an ascending MLF in the brainstem coordinate eye/head tracking of visual objects.

PROPRIOSPINAL NEURONS AND PROPRIOSPINAL TRACT

The propriospinal tract is an almost continuous band of axons immediately surrounding the gray matter.

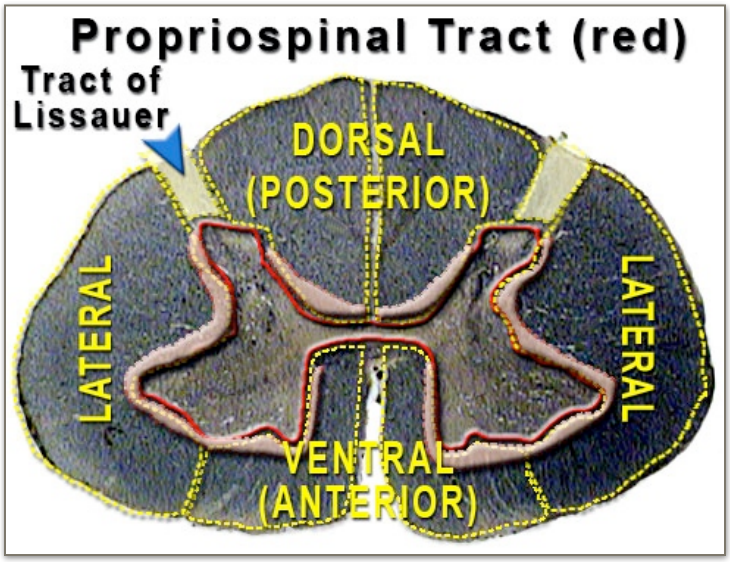

Fig 6-10. Propriospinal Tract surrounding gray matter (gec).

This tract provides a major source of intersegmental connectivity within the spinal cord. Propriospinal Neurons are scattered throughout the intermediate gray. Some cells in the dorsal and ventral horn may also contribute axons to ascend or descend in this tract. A special group of these neurons found at the third and fourth cervical levels are thought to be a major source of intersegmental coordination for upper extremity actions that require synergistic cooperation from many muscles. A similar group of propriospinal neurons in the lumbosacral cord may have a like function for synergistic lower extremity actions. They are influenced by converging inputs from descending pathways, peripheral inputs, and spinal interneurons. Long propriospinal neurons send their axons over many segments at multiple levels of the cord. These long-range connections may be important for 'whole body' integration since bilateral influences are common for these projections (interlimb and limb-trunk coordination). Short propriospinal neurons tend to restrict connectivity unilaterally and within that specific level of the cord (intralimb coordination).

SPINAL ASCENDING TRACTS OVERVIEW

The following interactive flash file presents ascending spinal tracts. Tracts originating from the peripheral afferents or from dorsal horn neurons signal sensory events while

those tracts or portions of tracts that arise from projection neurons in the intermediate gray or from the ventral horn provide integrative information or even signals regarding outgoing motor events. Most of these ascending tracts project to cell stations in the posterior fossa or supratentorial brainstem. Several tracts specifically project to the cerebellum. Many of these tracts will eventually provide detailed information to specific thalamic nuclei which, in turn, project to specific regions of the cerebral cortex.

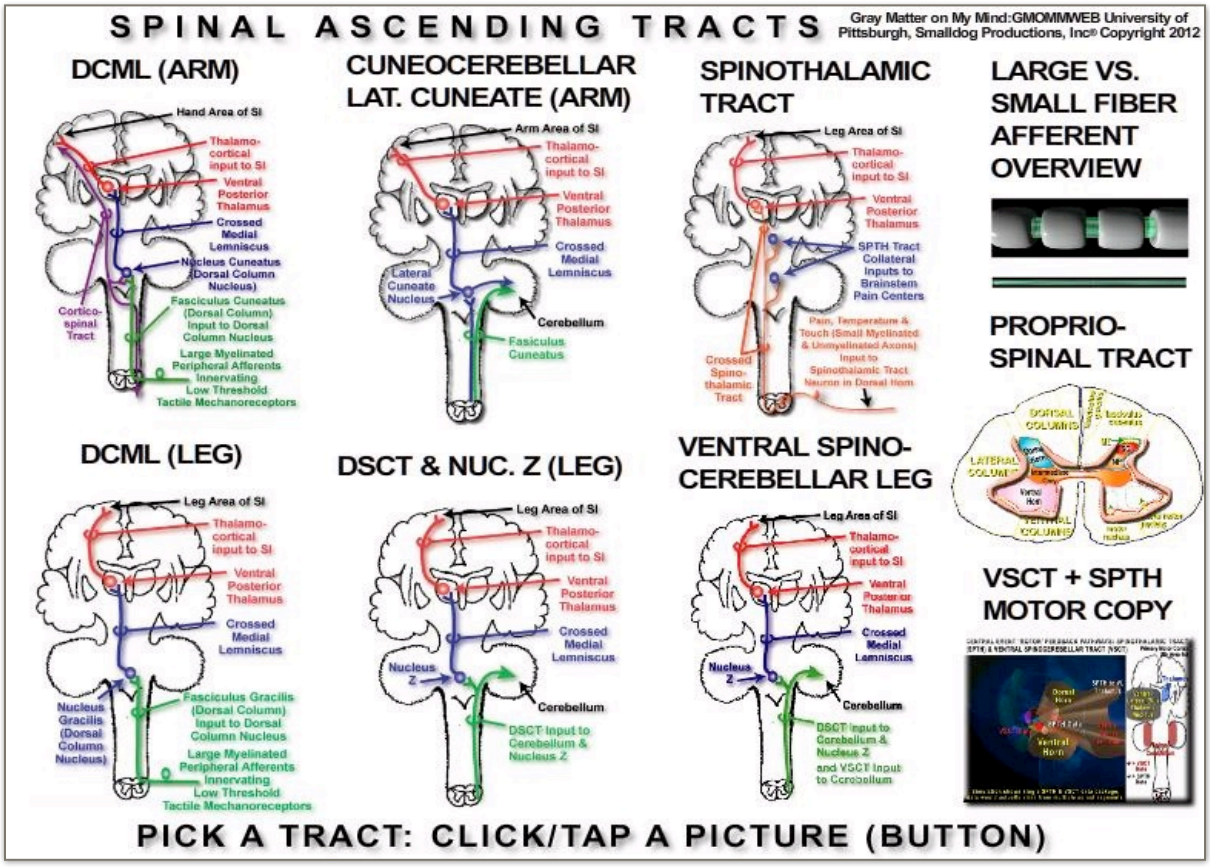

Fig 6-11. Ascending tracts originating from the Periphery and Spinal Gray Matter Projection Neurons: Interactive Media File (gec). GO TO: gmomm.pitt.edu [*Fig16-11_Interactive Media*]

SPINAL MENINGES AND SUBARACHNOID SPACE

Like the brain, the spinal cord is surrounded by three layers of meninges. The inner layer is the pia mater that forms a thin covering over the external surface of the spinal cord. The outer layer is the thicker, and tougher dura mater (see figure). In addition, the dura forms a dural sleeve around the dorsal and ventral roots and the dorsal root ganglion. The dural sleeve joins the epineurium formed around the spinal nerve (not shown). The middle layer, the arachnoid, in life is a thin membrane just beneath the dura. The subarachnoid space is normally filled with cerebrospinal fluid (CSF) that was manufactured by the choroid plexi located in the ventricles of the brain. There is a

continuous turnover of CSF. However, little CSF is resorbed in the spinal canal. The major site of resorption is the arachnoid villi located in the superior sagittal sinus at the top of the cranial vault. Therefore, the subarachnoid space is contiguous throughout the cranial vault and spinal canal. There is a rich plexus of veins surrounding the spinal dura (not shown). These epidural veins receive venous drainage from the veins that surround the spinal cord and the spinal roots (not shown). In anatomical specimens, the arachnoid appears as a thin, translucent film surrounding the cord. The dura is seen as the tough membrane surrounding the spinal cord, the cauda equina, and the roots (dural sleeves). The pia is adherent to the surface of the spinal cord. The next several pages describe the arterial blood supply of the spinal cord.

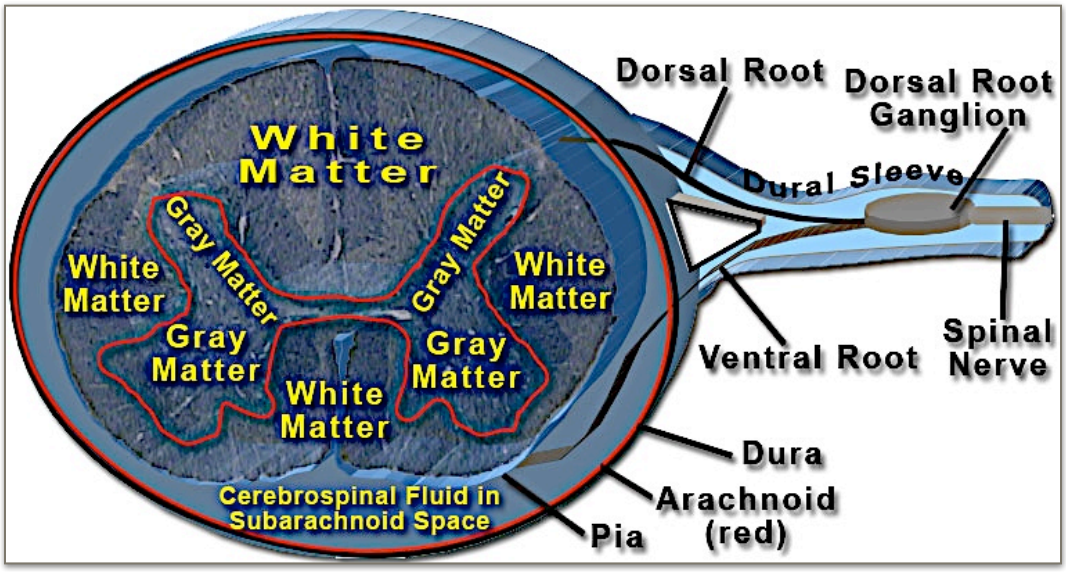

Fig 6-12. Spinal Meninges: Dura, Arachnoid and Pia plus Subarachnoid Space (gec).

SPINAL CORD ARTERIAL BLOOD SUPPLY: POSTERIOR SPINAL ARTERIES

The Posterior Spinal Arteries (PSAs) supply the dorsal columns and most of the dorsal horn gray.

Shown here is the classical right and left PSA in parallel. However, the PSAs have extensive anastomoses between the two sides and rarely have a true symmetric parallel course along the dorsal aspect of the spinal cord. The PSAs receive arterial blood from the Vertebral Arteries in the upper cervical region, and from Posterior Radicular Arteries (PRAs) in the lower spinal cord segments.

There are a variable number of these PRAs (~20-24) along the spinal column; and the distribution is typically not symmetric between the right and left sides of the cord. The PRAs also provide blood supply to the dorsal roots and the dorsal root ganglia. The PRAs are fed by segmental arteries that arise from either the Vertebral Arteries in the neck or from the Thoracic or Abdominal Aorta in the trunk. The PRAs also feed the

Arterial Vasocorona found along the lateral border of the spinal cord. Anastomoses may join the PSA and the Arterial Vasocorona territories of the Spinal Cord. Loss of blood supply to the PSA territory is rare and most often follows direct trauma to the Spinal Cord or follows an interruption of blood flow due to dissections of an aortic aneurysm. Note: the caliber of the arterial branches within the parenchyma of the cord are enlarged for illustrative purposes in these diagrams. In reality, these are small diameter vessels.

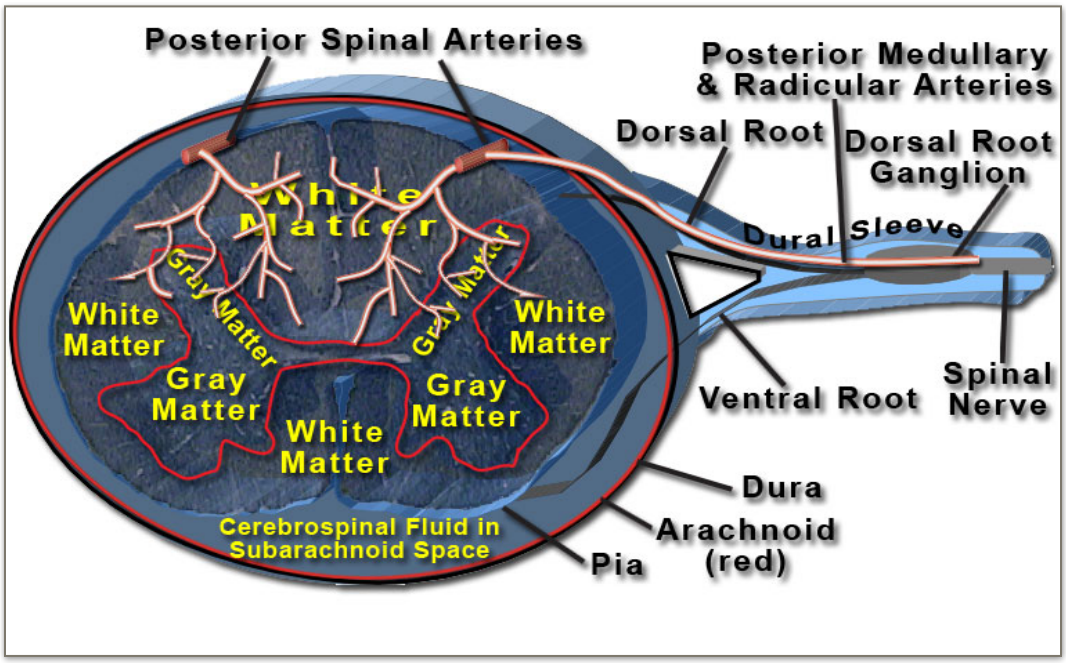

Fig 6-13. Spinal Arterial Blood Supply: Posterior Spinal Arteries (gec).

SPINAL CORD ARTERIAL BLOOD SUPPLY: ARTERIAL VASO CORONA

The Arterial Vasocorona (AVC) supplies the peripheral margins of the lateral white column and the most dorsal aspect of the ventral white column of the right and left spinal cord. The AVC is fed by the Posterior Radicular Arteries (PRAs) and Anterior Radicular Arteries (ARAs). There are a variable number of these PRAs (~ 20-24) and ARAs (~ 8-16) along the spinal column. The distribution of these arteries is typically not symmetric between the right and left sides of the cord.

The PRAs also provide blood supply to the dorsal roots and the dorsal root ganglia. The ARAs provide blood supply to the ventral roots. The PRAs and ARAs are fed by segmental arteries that arise from either the Vertebral Arteries in the neck or from the Thoracic or Abdominal Aorta in the trunk. Anastomoses may join the PSA and the Arterial Vasocorona territories of the Spinal Cord. According to some authorities, the ARA may have anastomoses with branches of the Anterior Spinal Artery. Due to the abundance of arterial feeders, selective loss of blood supply to the AVC territory is rare.

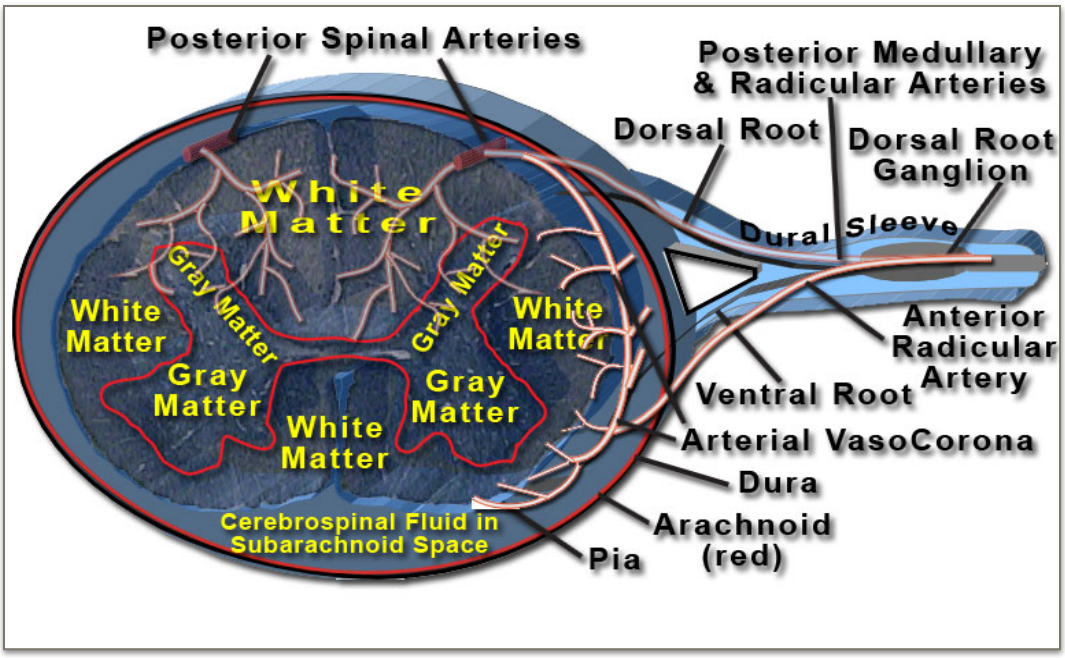

Fig 6-14. Spinal Arterial Blood Supply: Arterial VasoCorona (gec).

SPINAL CORD ARTERIAL BLOOD SUPPLY: ANTERIOR SPINAL ARTERY

The Anterior Spinal Artery (ASA) is a single midline vessel that accounts for about two-thirds of the arterial blood supply of the spinal cord. It supplies the ventral white columns, all but the most peripheral extent of the lateral white columns, the ventral horn, intermediate gray and the base of the dorsal horn gray matter. The ASA is fed by 6-8 medullary arteries that arise from segmental arteries in the neck and trunk. Segmental arteries arise from either the Vertebral Arteries in the neck or from the Thoracic or Abdominal Aorta in the trunk. The largest of these medullary arteries is found in the lumbar cord. This is the Great Medullary Artery of Adamkiewicz. In many individuals, the Artery of Adamkiewicz is the sole supplier of the ASA territory of the lumbosacral cord.

The distribution of these medullary arteries is typically not symmetric between the right and left sides of the cord (left > right). The ASA has a major branch that is located within the ventral sulcus (sulcal artery). The sulcal artery typically gives off branches that favor one side of the cord or the other. Branches of the ASA anastomose with branches of the Arterial Vasocorona. According to some authorities, the ASA may anastomose with branches of the Anterior Radicular Artery. Loss of blood supply to the ASA territory is catastrophic. Complete or incomplete paraplegia may result from a loss of blood supply to the Artery of Adamkiewicz. Discriminative touch sensation is typically spared since the PSAs keep the dorsal column and portions of the dorsal horn perfused.

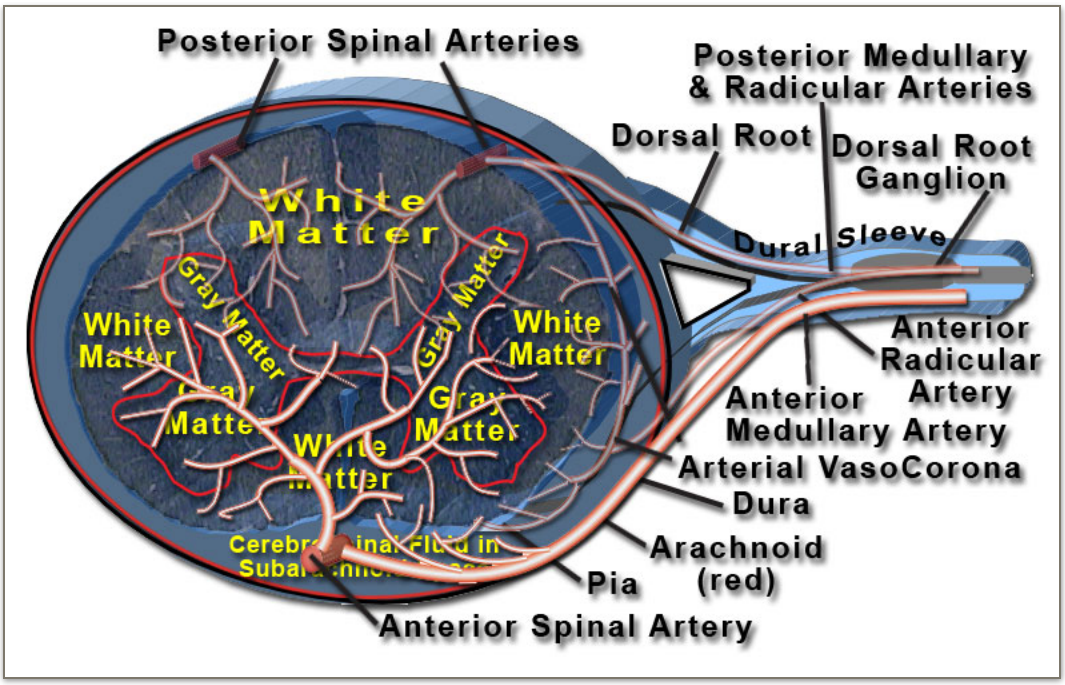

Fig 6-15. Spinal Arterial Blood Supply: Anterior Spinal Artery (gec).

SPINAL ARTERIAL BLOOD SUPPLY DISTRIBUTION AND ANASTOMOSES

Fig 6-16. Spinal Arterial Distribution for Gray & White Matter (gec). GO TO: gmomm.pitt.edu *Fig6-16_Video*

The territorial distribution of the Posterior Spinal Artery (PSA) in red, the Anterior Spinal Artery (ASA) in purple, and the Arterial Vasocorona (AVC) in green is shown diagrammatically. While there is relatively little overlap of these territories deep within the cord, greater anastomoses are found along the peripheral white matter (note the blending of colors where the territories overlap). You are encouraged to remember these relationships between arterial blood supply and gray and white matter structures as you study structure/function of white matter tracts and gray matter neuronal centers.

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Chapter 7

SOMATOSENSATION: PERIPHERAL TACTILE RECEPTORS & ACTIVE TOUCH

> "Action-produced stimulation is *obtained*, not *imposed* - that is, obtained *by* the individual not imposed *on* him. It is intrinsic to the flow of activity, not extrinsic to it; dependent on it, not independent of it." J.J. Gibson, Chapter II, The Obtaining of Stimulation, page 31 In: The Senses Considered as Perceptual Systems. Boston: Houghton Mifflin, 1966.

Although our receptors may be activated passively by stimuli in our environment we, as sentient inquisitive individuals, most often actively obtain data from the world around us. We gather information about our world and we manipulate our immediate environment by coupling somatosensory inputs to our intended motor actions: an integrated somatomotor process. One example, shown here is a young man hammering a nail: a classic example of an integrated somatomotor task requiring precision to pair the hammer head to the head of the nail coupled with sufficient power strokes to nail it. Muscles must be used in a coordinated fashion. The same muscles have multiple roles as agonists, synergists, antagonists to provide both stabilization of the tool in the hand and motion in a particular direction to contact the nail precisely with the hammer. Many somatomotor areas must work together despite little or no conscious attention to details of the actions of motors doing the task. Moreover, success is unlikely with a numb hand.

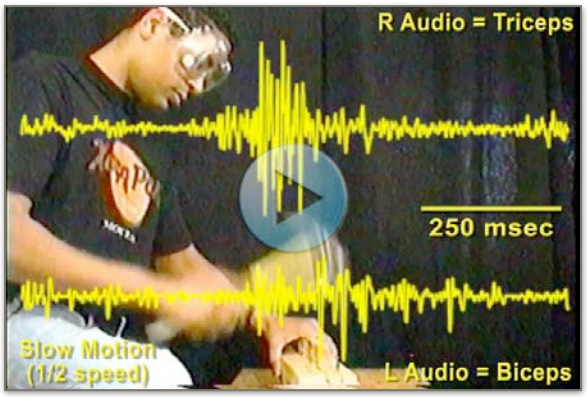


Fig 7-1. Hammering Slow Motion Movie: Look and Listen (jec,gec). GO TO: gmomm. pitt.edu *Fig7-1_Video*

SOMATOSENSATION - LOCATION, LOCATION, LOCATION

Sensory system receptors may be classified according to their somatic (bodily) location.

EXTEROCEPTION

EXTEROCEPTIVE somatic sensation is said to be derived from contact of the exterior of the body and limbs with mechanical, thermal, chemical or noxious stimuli. For somatosensation, these receptors are typically located in the skin or subcutaneous tissues. Other teleoreceptors, e.g., those specialized for vision and audition transduce sensations that originate some distance from the body.

INTEROCEPTION

INTEROCEPTIVE sensation is said to be derived primarily from receptors associated with the viscera, glands and their supporting structures, including blood

vessels. Visceral sensations are often poorly localized but tend to get our attention when the stimuli are of sufficient magnitude to evoke an emotional (visceral) reaction to the events that stimulate our interior. These signals are often related to alterations in our homeostasis and to our overall sense of well-being: PAY ATTENTION!!!

PROPRIOCEPTION

PROPRIOCEPTIVE sensation is said to be due to sensory organs that provide us with information about our position, motion, muscle force/tension and our body schema (body part relationships to one another and to the external world). These receptors are said to include deep somatosensory receptors: skeletal muscle proprioceptors (Muscle Spindle & Golgi Tendon Organ), joint receptors as well as specialized vestibular receptors located in the inner ear (semicircular canals and otolith organs). Some scientists include retinal inputs from the eyes as having a "proprioceptive" function since vision provides important information about our position relative to the horizon and flow of information around our head: as we move ourselves, are moved by external forces or as a portion of our visual world moves around our head (optic flow from linear or circular/angular motion). For our hands, tactile mechanoreceptor inputs often serve as "proprioceptive" input to regulate precision grip force.

Proprioception and its cousin kinesthesia (muscle sense of moving, muscle tension, or muscular effort) utilize sensory data for conscious or unconscious/subconscious perceptions but also provide critical sensorimotor data for precise and coordinated feedforward and/or feedback neural control of posture and movements. Proprioceptors are NOT the "*prima-donna*" sensory organs of the body. Many individuals have only modest awareness of body or muscle activation despite their ability to perform skilled tasks that utilize these data. Actually, those gifted athletes and other skilled performers can achieve grace and precision in their actions with little conscious attention paid to proprioception; they have great difficulty trying to explain how they did the task.

SOMATOSENSORY MODALITIES

Somatosensation refers to sensory modalities associated with receptors in the superficial & deep tissues of the body wall & limbs.

Modalities include:

- 1. Low-Threshold Tactile Mechanoreceptors: Discriminative Touch (high spatial & temporal acuity)
- 2. High-threshold Mechanoreceptors: Ouch
- 3. Thermal Receptors: Warm & Cool
- 4. Proprioceptors: Limb/Body Position, Movement, Force
- 5. Nociceptors: Noxious Mechanical, Thermal, Chemical Stimulants
- 6. Polymodal Receptors: Itch, Hurt, Uncomfortable Feeling

SOMATOSENSORY RECEPTOR TRANSDUCTION

Somatosensory Receptors transduce non-neural energy into Generator Potentials- local graded potentials that depolarize primary afferent axon terminals. Suprathreshold depolarization of these afferent endings generates one or more Action Potentials that propagate back to the spinal cord or brainstem by way of afferent axons.

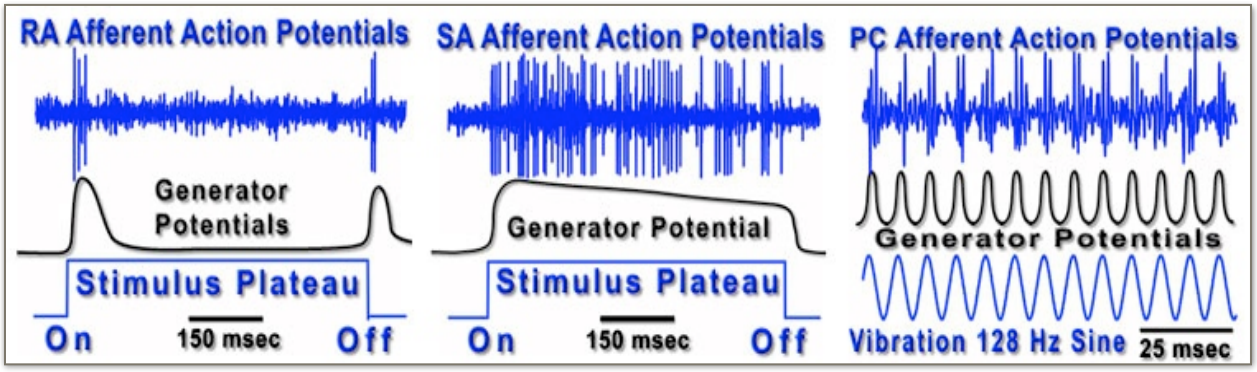


Fig 7-2. Rapidly Adapting (RA) Receptors produce generator potentials during stimulus transients only (On & Off). Slowly Adapting (SA) Receptors produce generator potentials during the stimulus steady state (plateau). Some Rapidly Adapting Receptors such as the Pacinian Corpuscle (PC) respond to rhythmic oscillatory stimuli (vibrations) such that generator potentials are produced during each stimulus cycle (gec).

Somatosensory receptors are classified according to their location (e.g., superficial or deep), type of stimulus that activates them (e.g., mechanical, thermal, chemical, noxious), threshold for activation (e.g., low-threshold versus high-threshold) and according to their adaptation to stimulus properties (e.g., rapidly or slowly adapting). In addition, specialized deep mechanoreceptors in skeletal muscle (muscle spindle and Golgi Tendon Organ) and in synovial joint tissues (joint receptors) are classified as proprioceptors. Proprioceptors provide information about muscle force/tension, muscle stretch, limb/body position & motion.

SPECIALIZED TACTILE MECHANORECEPTOR TRANSDUCTION

Low-Threshold Mechanoreceptors transduce touch, pressure, stretch, vibration and shearing mechanical forces. It is still unclear exactly how this transduction takes place. The specialized tissue associated with the afferent nerve ending has an important role in defining threshold and adaptation to stimuli.

Molecular mechanically-gated and voltage-gated ion channels may differ for various afferent nerve endings, e.g., see Delmas, et.al., 2011 and figure 7-5 video below. One Receptor that has been studied in detail is the Pacinian Corpuscle (PC) also known as the Rapidly Adapting Type II (RAII) tactile receptor. The intact PC has a large myelinated axon that ends in a laminated capsule. The intact PC responds to stimulus transients (ON & OFF) but not to the sustained (plateau) period of indentation.

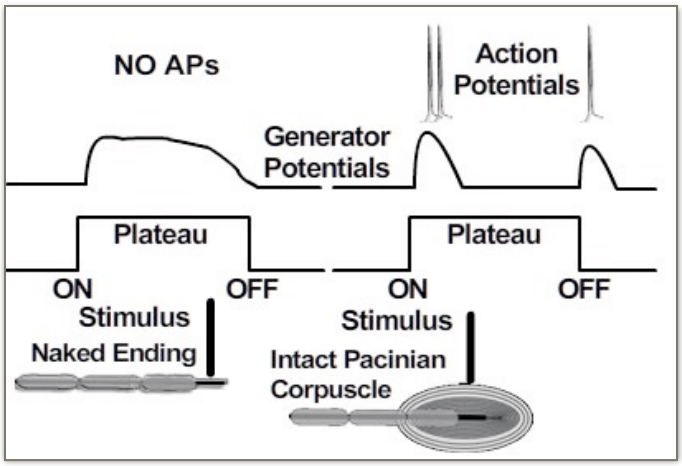


Fig 7-3. Pacinian Corpuscle: Intact and Stripped of its specialized laminated receptor ending (gec).

When the capsule is removed, the naked nerve ending responds to indentation like a slowly adapting receptor: Generator Potential is sustained during the plateau. However, the altered PC can no longer generate Action Potentials (APs), i.e., it is no longer a viable somatosensory receptor (see figure).

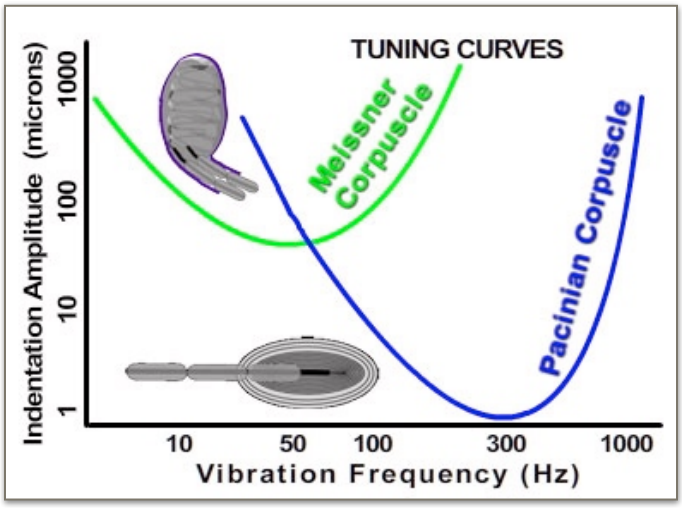


Fig 7-4. The Pacinian Corpuscle (PC) and the Meissner's Corpuscle (MC/RAI) respond to rhythmic oscillatory stimuli. PC tuning curve for higher frequency vibrations (blue) and MC/RAI tuning curve for lower frequency flutter sensation (green) (gec).

Both the RAI Meissner Corpuscle and the RAII (PC) Pacinian Corpuscle respond to periodic stimuli. The Pacinian Corpuscle responds to higher frequencies leading to vibration sensation. The Meissner Corpuscle responds best to lower frequencies known as a flutter sensation. Each has a typical tuning curve that reflects the receptor's response related to a sinewave's amplitude and its periodicity (see figure).

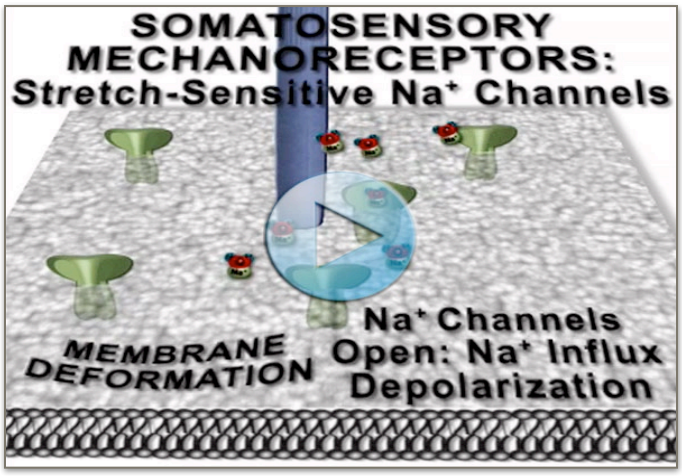


Fig 7-5. Somatosensory Mechanoreceptor Membrane Stretch-Sensitive Sodium (Na^+) Channels Movie (gec). GO TO: gmomm.pitt.edu
Fig7-5_Video

LOW-THRESHOLD TACTILE MECHANORECEPTORS IN THE HUMAN GLABROUS HAND: RA, SA & PC

Low threshold somatosensory receptors transduce mechanical energy into local generator potentials. Generator potentials that exceed threshold generate one or more action potentials that form the basic code for all sensations. Within the glabrous (non-hairy) skin of the hand, four major low threshold tactile mechanoreceptor types have been identified. Two are rapidly adapting (RA), and the others are slowly adapting (SA).

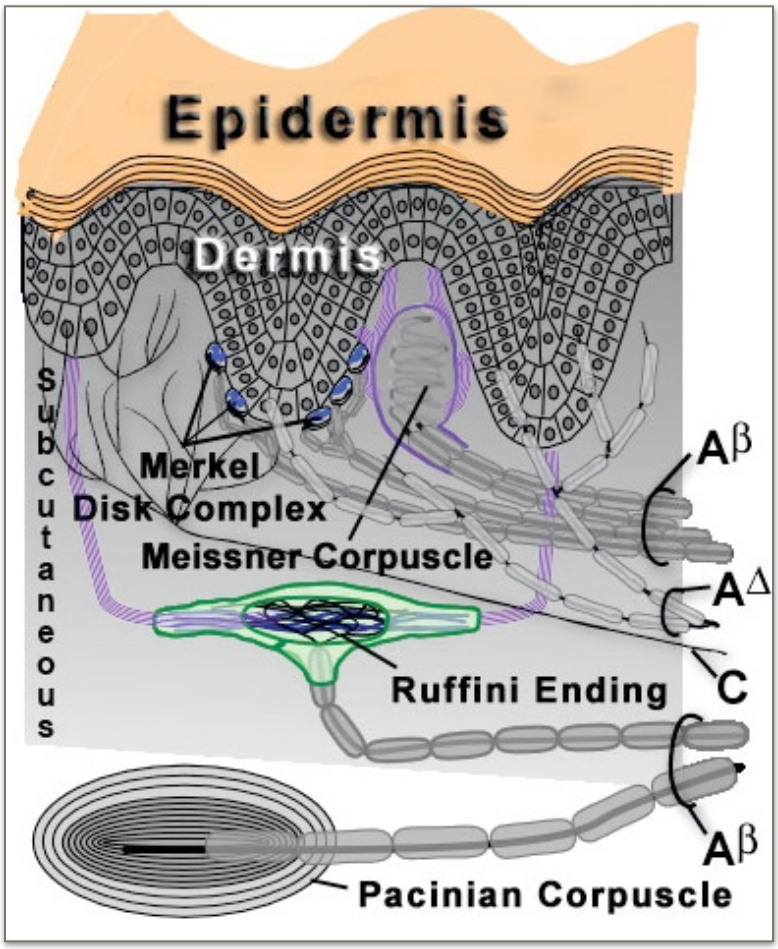


Fig 7-6. Glabrous skin Myelinated "A" Afferents innervate specialized tactile mechanoreceptors & Unmyelinated "C" Cutaneous Afferents innervate free nerve endings (gec).

The physical properties of the skin, e.g., compliance, have a direct impact upon the sensory images that are formed by tactile receptors and the data encoded by the central somatosensory system, e.g., see Morley & Goodwin, 1987; Phillips & Johnson, 1981; Vega-Bermudez & Johnson, 2004.

Human studies employ a technique (microelectroneurography) to record Action Potentials from a single peripheral afferent while identifying its cutaneous receptive field with tactile stimuli. The RA Type I (RAI) afferents identified in human studies are thought to innervate Meissner Corpuscles. The RA II or PC is thought to be an afferent innervating the Pacinian Corpuscle located deep in the dermis or subcutaneous tissue. The SA Type I (SAI) afferent is thought to be associated with the Merkel Disc Complex (multiple Merkel Discs innervated by a single afferent). Recent studies show Merkel cells incorporate a mechanically activated ion channel (MA) thought to be Piezo2. This MA Piezo2 channel may generate Ca^{++} Action Potentials (APs) as a transduction process; these depolarizations initiate Na^{+} APs in a Beta afferent axon, e.g., see Maricich, et.al., 2009, 2012; Coste, et.al., 2010 & Ikeda, et.al., 2014. SA Type II (SAII) may be a deep Ruffini Ending anchored to the dermis by tonofilaments but recent studies question this relationship. Seminal studies conducted by Vallbo, Johansson & others used microelectroneurography to characterize RAI, SAI, SAII, and PC afferents of the Median

or Ulnar Nerve in the human hand, e.g. see: Darian-Smith, 1984; Edin, et.al., 1995; Essick & Edin, 1995; Hagbarth, 2002; Johansson & Flanagan, 1978; Johansson & Vallbo, 1983; Johansson & Westling, 1987; Johnson, et.al., 2000; Johnson & Hsiao, 1992; LaMotte & Srinivasan, 1987a,b; LaMotte & Whitehouse, 1986; Phillips, et.al., 1990, 1992; Sathian, 1989; Vallbo & Hagbarth, 1968; Vallbo & Johansson, 1979.

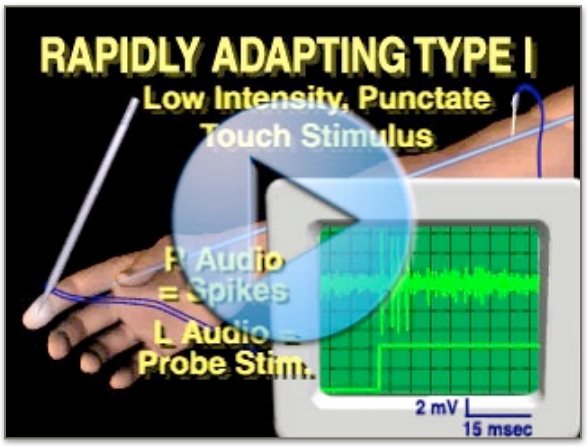
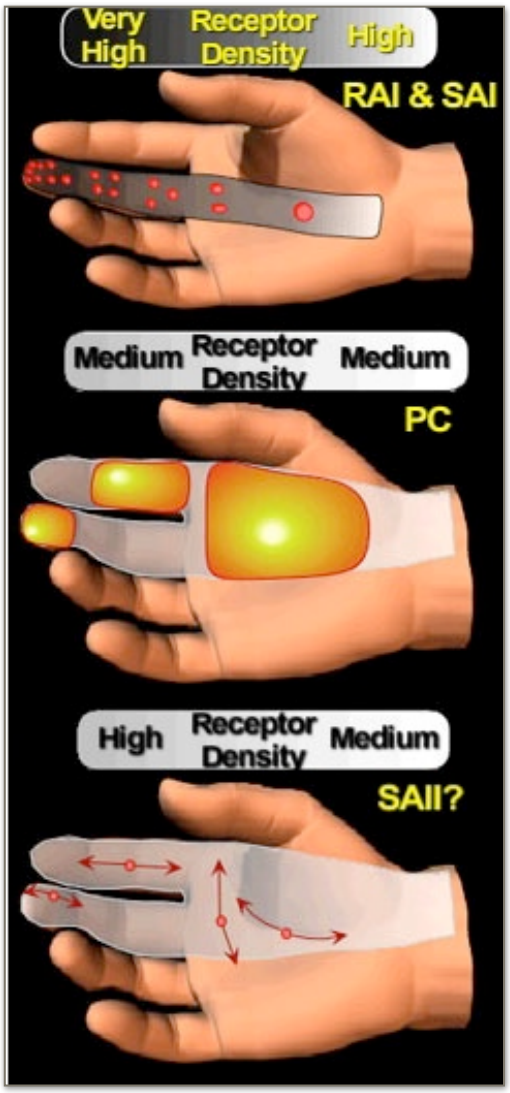


Fig 7-7 (left). RAI Microelectroneurography Movie (gec). GO TO: gmomm.pitt.edu *Fig7-7_Video*

Fig 7-8 (right).



Receptive Field Characteristics of Low-Threshold Tactile Mechanoreceptors in the glabrous skin of the human hand (gec).

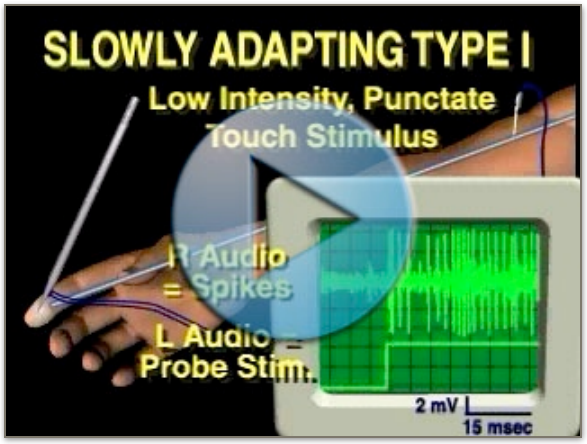


Fig 7-9. SAI Microelectroneurography Movie (gec). GO TO: gmomm.pitt.edu *Fig7-9_Video*

RAI and SAI afferents have small receptive fields with discrete, well-defined borders. Receptive Field (RF) = area of skin that when stimulated with an appropriate tactile input evokes a reliable response from the recorded neuron. As shown in the figure, RFs (red circles) are smallest and most numerous distally. A high density of these receptors with discrete RFs on the fingertips allows for high acuity touch sensations to distinguish small differences in surface

features/textures of an object. The PC afferent has a large receptive field with an optimal point surrounded by a “less sensitive” zone. Most PCs respond best to a vibration (or micro-vibration) of the skin. As shown in the figure, RFs (white spot with sunset surround) are relatively evenly distributed from fingertip to palm. PCs are poorly suited to provide discrete, punctate tactile information, but provide critical information about microvibrations resulting from manipulating tools, utensils, or fine textures. The SAII afferent has a relatively large receptive field with directional preferences; recent evidence suggests that this information may be provided by populations of SAI receptors. Most SAIIs respond best to a 'shearing' deformation of the skin. As shown in the diagram, RFs (red circles plus arrows) are relatively evenly distributed from fingertip to palm. SAIIs are poorly suited to provide discrete tactile information, but provide critical information about motion between an object and the skin when handling tools, utensils, or other objects that can be picked up or grasped. In addition, SAIIs may provide information about the shape of the hand whether holding an object or not.

Fig 7-10 (left). PC 128 Hz Tuning Fork Microelectroneurography Movie (gec). GO TO: gmomm.pitt.edu [Fig7-10_Video]

Fig 7-11 (right). PC 256 Hz Tuning Fork Microelectroneurography Movie (gec). GO TO: gmomm.pitt.edu [Fig7-11_Video]

MERKEL & MEISSNER RECEPTOR BIOAMPLIFICATION

There are two low-threshold tactile mechanoreceptors in the glabrous skin of the human hand that provide high spatiotemporal acuity: the RAI and SAI. Both the RAI and SAI have a built-in biological amplifier. The SAI afferent axon branches to innervate several (2-10) Merkel Disks (Merkel Disk Complex). Thus the SAI afferent Action Potential (AP) discharges are generated by multiple generator potentials that sum to produce a higher rate of APs. Two or more RAI afferents innervate a single Meissner Corpuscle. Therefore, each Meissner Corpuscle generator potential doubles the AP signal sent to the nervous system (2 RAI afferents).

The SAI and RAI afferents innervate a high density of Merkel Disk and Meissner Corpuscle receptors in our fingertips. Taken together with the biological amplification by these receptors one can appreciate how these receptors allow us to focus on details of palpated objects during discriminative active touch. On the other hand, the SAII and PC afferents provide less precise localization of stimulus location. Each SAII and PC (RAII) afferent innervates a single receptor-Ruffini Ending & Pacinian Corpuscle respectively.

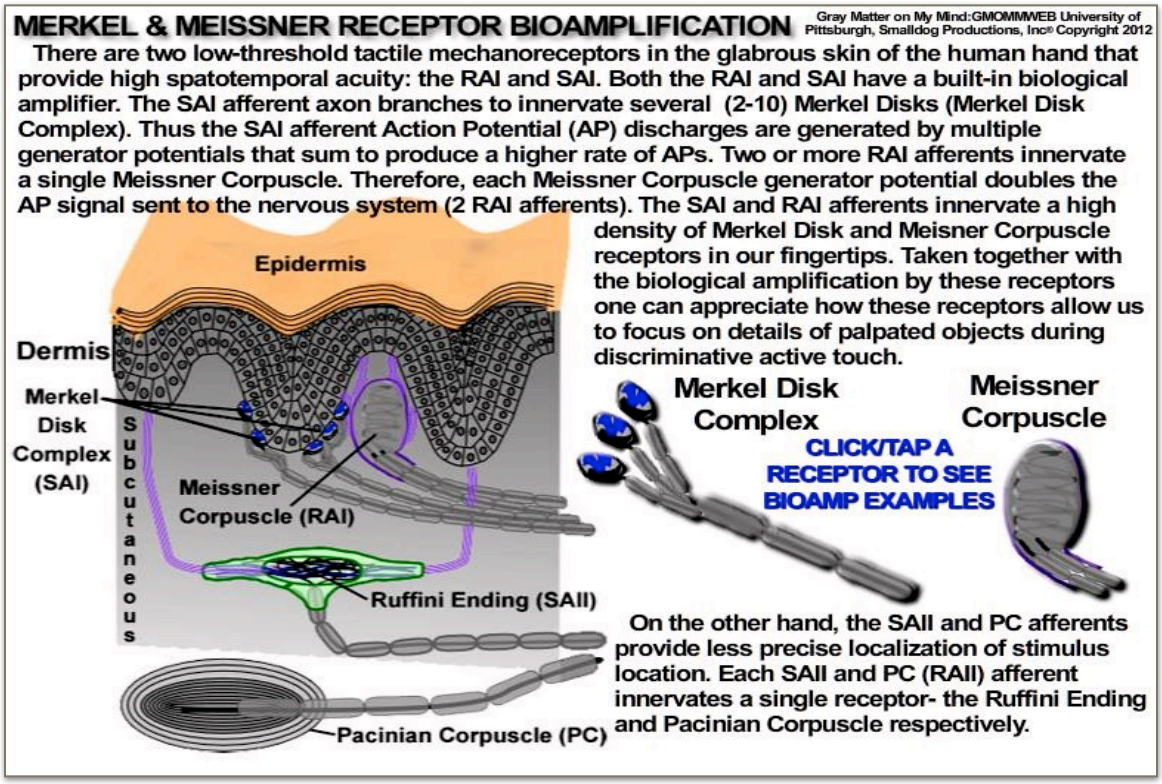


Fig 7-12. Merkel Disk Complex and Meissner Corpuscle as Bioamplifiers Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig7-12_Interactive Media*

The SAI afferent axon branches to innervate several (2-10) Merkel Disks (Merkel Disk Complex). Thus the SAI afferent Action Potential (AP) discharges are generated by multiple generator potentials that sum to produce a higher rate of APs. NOTE: ONE AXON (MAIN AXON) CARRIES “SUMMED” INFORMATION FROM THREE RECEPTORS. ACTION POTENTIALS PROVIDE INFORMATION ABOUT STIMULUS ONSET & STEADY-STATE (PLATEAU) FOR THIS SIMULATION.

Two or more RAI afferents innervate a single Meissner Corpuscle. Therefore, each Meissner Corpuscle generator potential doubles the AP signal sent to the nervous system (2 RAI afferents). NOTE: TWO AXONS CARRY “PARALLEL” CHANNELS OF INFORMATION FROM ONE RECEPTOR. ONLY ”ON” & “OFF” STIMULUS TRANSIENTS ARE TRANSDUCED BY THIS RAPIDLY ADAPTING RECEPTOR.

DISCRIMINATIVE ACTIVE TOUCH: SOMATOMOTOR INTEGRATION

The psychophysical and behavioral characteristics of active touch have been investigated extensively in human and subhuman primates and other species. Electrophysiological recordings of peripheral afferents, identified as innervating specialized, low-threshold, tactile mechanoreceptors in a number of species, have provided important clues how the periphery might encode touch information. However, less is known about details regarding the central representation of active touch in the mammalian somatosensory system. Active touch is the process by which we acquire tactile information by engaging our environment; we actively seek this information, it is not simply applied to our somatosensory receptors. Such sensorimotor integration provides a mechanism to enhance the tactile experience. A recent monkey study suggests that cutaneous and proprioceptive inputs from the digits are integrated in portions of the Primary Somatosensory Cortex: e.g., see, Kim, et.al., 2015.

USING ACTIVE TOUCH:

- **1. We obtain information from our immediate environment about object characteristics (e.g., texture, form, firmness, temperature).**
- **2. We obtain information to assist us in manipulation of objects/tools, and to control actions & postures (i.e., to interact with our environment).**
- **3. We utilize active touch to communicate by artistic, social, emotional, linguistic, or behavioral gestures (including intimate gestures of feeling for one another).**
- **4. We use our sensory and motor systems together. Sensory input provides both feedforward and feedback information for active touch; the engaged motor system modulates both the gain and timing of sensory inputs.**

Fig 7-13. Sculptor at work. Photo Reproduced with kind permission of Artist, Jason A. Carvell, MFA, Photograph by Rebekah Ruppe, RN.

STEREOGNOSIS: HAPTIC "SEEING" WITH OUR HANDS.

Identifying objects by touch is known as stereognosis; this active tactile discrimination is also called haptic sensation, for review see Lederman & Klatzky, 2009. For the Stereognosis Movies the subject reaches his hand through a screen to find a requested object (no visual clues). He explores the objects with his fingertips, sometimes manipulating them

between his fingers. Finding the dime amongst other coins and other distractor items is a high level perceptual task (see Stereognosis Movie I). Stereognosis depends upon excellent tactile acuity and the ability to identify/match objects, store information in memory, and then pick up the correct item. Texture, shape, and previous tactile experience with the items is important for the person to be able to name the object by touch. Note that one strategy used is to group objects (quarter and nickel) at a specific location. For an individual who has a lesion of the ascending Dorsal Column Medial Lemniscal Pathway or Parietal Cortex this task will be difficult or impossible to perform. Likewise, reading Braille would be similarly affected by such somatosensory system dysfunction. The ability to perform dextrous manipulation of objects in the hand requires not only high spatiotemporal tactile sensory signals but motor control providing individual finger movements with fine force control. Humans have a motor control system including motor cortex monosynaptic corticomotoneuronal activation spinal motoneurons innervating distal muscles. The motor system is optimized for fractionated finger motions and fine force control of glabrous skin interaction with objects.

Fig 7-14. Stereognosis Movie I:Small Object Identification (gec, jec). GO TO: gmomm.pitt.edu Fig7-14_Video

Identifying large objects requires a subject to use the hand to form a sampling surface to match the object's shape. SA receptors may be critical to provide information about the shape of the hand to somatomotor areas. For example, when identifying a baseball the subject feels the seams of the ball (SAI) & manipulates the object before selecting it from the distractor items of similar shape. Likewise, he feels the “fuzz” of a tennis ball with his fingertips. Fine texture detection requires RAI & PC receptors.

Fig 7-15. Stereognosis Movie II: Large Object Identification (gec, jec). GO TO: gmomm.pitt.edu Fig7-15_Video

Sanding by hand requires manual dexterity in the application of the correct amount of force to move the sandpaper across the surface of the wood, while maintaining contact of the fingers with the sandpaper and sandpaper on the wood. Different grades of sandpaper are used at different stages of the

process. You can feel the changes in texture of the sandpaper from coarse to superfine grades. Determining the roughness of the wood surface requires you to palpate the surface especially as the sanding progresses. This discriminative touch incorporates a repetitive sampling of the surface as the fingers are moved across the wood. He prepares the surface (blows off dust) and his fingers (wipes them "clean") before palpating the wood. While vision certainly helps you perform the task it cannot provide the best information about the actual smoothness of the textured surface, discriminative tactile input is needed.

Fig 7-16. Texture-Sanding Movie (gec, jec). GO TO: gmomm.pitt.edu Fig7-16_Video

Hand tools provide an extension to our capability to manipulate the environment doing ordinary and sometimes quite extraordinary tasks: See Using Tools Movie). A skilled craftsman "feels" the work through the tool as an extension of his or her hand. Although torque is generated at a distance from the skin's surface it is transposed to the body through active touch.

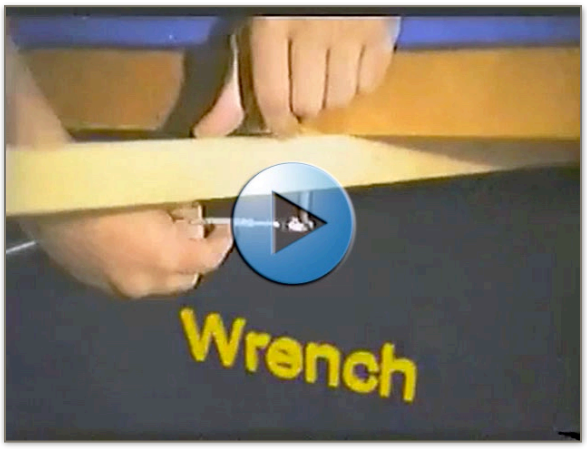


Fig 7-17. Using Tools Movie (gec, jec). GO TO: gmomm.pitt.edu Fig7-17_Video

Notice how the fingers are used to determine the orientation of the sides of the head of the bolt as the wrench is put into place. The hand then grasps the handle to provide leverage to generate adequate torque to turn the bolt. The position of the working surface precludes use of visual information to assist in the task. Use of a screwdriver requires the individual to seat the tip of the screwdriver into the slot(s) of the screw. The fingers may locate the position and orientation of the screw but the hand must be positioned back on the handle to generate torque. The individual must experience appropriate seating of the screwdriver tip in the screw slot(s) at a distance. The tool becomes an extension of our body. Pacinian Corpuscles may be CRITICAL for the TELESCOPING of our tactile sensations. Cerebral cortical areas including portions of the frontal, intraparietal cortex and the medial precuneus have been implicated in the process of embodiment of a tool as an extension of the arm & hand for specific manipulations of the immediate environment to accomplish a goal with the tool (see references).

Skill comes with experience; a skilled craftsman typically acts with little conscious effort applied to anything other than the goal of the task. Novices, on the other hand, may have to concentrate on several aspects of the task at once. Efficiency will drop when this “intimate” fitting of tool to hand is disrupted due to use of gloves, or sensory dysfunction of the hand. Muscle afferents contribute to our control of torque.

FUNCTIONAL CONTRIBUTIONS OF RA, SA AND PC AFFERENTS TO ACTIVE TOUCH.

RAI and SAI afferents have small receptive fields with discrete, well-defined borders. Receptive Field (RF) = area of skin that when stimulated with an appropriate tactile input evokes a reliable response from the recorded neuron. A high density of these receptors with discrete RFs on the fingertips allows for high acuity touch sensations to distinguish small differences in surface features/textures of an object. The PC afferent has a large receptive field with an optimal point surrounded by a “less sensitive” zone. Most PCs respond best to a vibration (or micro-vibration) of the skin. PC RFs are relatively evenly distributed from fingertip to palm. PCs are poorly suited to provide discrete, punctate tactile information, but provide critical information about micro-vibrations resulting from manipulating tools, utensils, or fine textures.

The SAI afferent innervates Merkel Disc Complexes. It is the one receptor that best responds to the form/shape of a palpated object. The SAI provides high resolution spatial “images” of an object's surface features. Research suggests that the SAI afferent action potential discharge profile produces a morphometric code of the spatiotemporal details of an object, e.g. identification of raised letters or dot patterns (Braille). Braille includes letters formed by a raised dot pattern. A high density of Merkel Disc Complexes in the fingertips and SAI afferents innervating them are critical to read Braille.

SAI Afferents provide precise spatiotemporal action potential profiles of a palpated object: a “morphometric” code of shape & form.

The RAI afferent innervates the Meissner Corpuscle. It is the one receptor that best responds to fine surface texture of a palpated object. The RAI along with other low-threshold tactile mechanoreceptors detects surface contact. Research suggests that the RAI afferent is the one best receptor to detect a very small defect (blemish) on an otherwise smooth surface, e.g., a dust particle on an otherwise smooth varnished finish. Action potential (AP) discharge from RAI afferents is a 'sparse spike' code of microgeometric surface defects.

The PC afferent innervates the Pacinian Corpuscle. It is the one receptor that best responds to microvibrations when contacting or manipulating an object. There is evidence that the PC afferent responds to palpating very fine surface textures, e.g., the frosting on a glass slide and projecting a tool's action (microvibrations) back into one's hand. PCs respond with bursts of Action Potentials (APs) to very low amplitude (microns), high frequency (~100-500 Hz) microvibrations. The Pacinian Corpuscle does

not provide a good source of touch localization since microvibrations tend to spread throughout cutaneous, subcutaneous tissues including bone. In this regard, PCs are found in the periosteum of long bones. PCs may be critical receptors to provide necessary information to grasp and manipulate tools. The solid handle of a hand tool actually amplifies vibrations felt by the worker firmly gripping the tool.

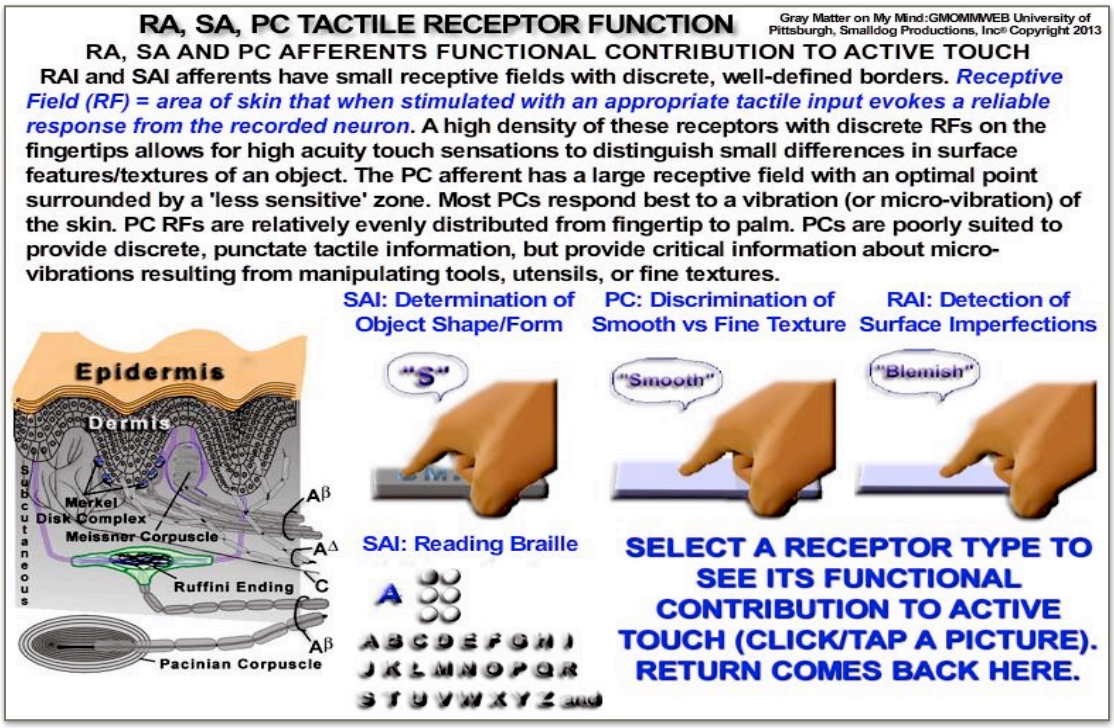


Fig 7-18. SAI, RAI and PC Specialized Functional Characteristics Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig7-18_Interactive Media*

GET A GRIP! RAPID AUTOMATIC ADJUSTMENTS TO PERTURBATIONS-NO TIME TO WASTE.

Precision pinch grip is a very human volitional action that one would expect to be under tight conscious control: "willed" action-perception cycle. However, a series of experiments by a number of investigators have shown that this task utilizes tactile input in a precise, but typically subconscious way to make minor adjustments to "get a grip", e.g. see Augurelle, et.al., 2003; Ballermann, et.al., 2013; Iriki, et.al., 1996; Johansson & Flanagan, 2009; Johansson & Westling, 1987; Monzee, et.al., 2003, Schwarz, 2016; Srinivasan, et.al.,1990, Westling & Johansson, 1984, 1987.

Low-threshold tactile mechanoreceptors in the fingertips appear to be critically involved and the Meissner Corpuscle (RAI) seems to be most sensitive to minute subconscious perturbations. Local anesthesia of the digits causes a large compensatory increase in grip force beyond that used when skin is innervated; microslips and macroslips are common for numb fingers especially when gripping a slippery surface.

For this task, waiting for a conscious reaction is too slow despite the high level of distal muscle control required for precision grip. GRIP-SLIP MOVIE illustrates the sequence of events during a microslip (slow motion) when the nervous system is intact. Deficits occur if there is any peripheral afferent and/or efferent impulse delay or any central processing delay. "Dropping things" or "clumsy hands" is a common complaint for many individuals seen by therapists.

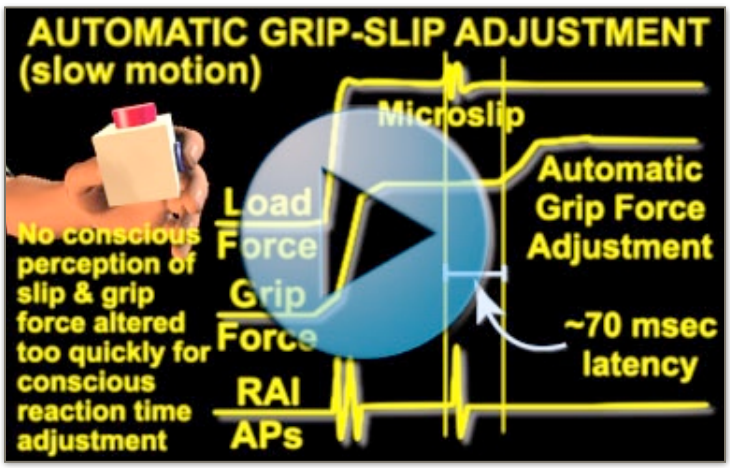


Fig 7-19. Grip-Slip Movie (gec). GO TO: gmomm.pitt.edu _Fig7-19 _Video

TOUCH LOCALIZATION: SALTATORY TACTILE ILLUSION - THE CUTANEOUS RABBIT.

Touch localization is excellent in our fingertips where RAI and SAI receptors are very dense and have very small receptive fields. More proximal forearm and arm have a less dense population of low threshold tactile mechanoreceptors and their receptive field sizes are larger. The central nervous system's representation of the glabrous surface of the fingers is magnified while that for more proximal skin is less detailed. The spatial and temporal localization of tactile inputs from the forearm and arm are less precise and tactile illusions can be demonstrated here. Spatial and temporal features may be perceived by a human subject as motion across the skin when no such actual touch inputs are physically present.

Fig 7-20. Cutaneous Rabbit Movie (gec). GO TO: gmomm.pitt.edu Fig7-20_Video

One such illusion is the cutaneous rabbit originally demonstrated by Geldard and Sherrick, 1972. A simulation of the spatial and temporal features of repetitive tactile inputs on the forearm is

simulated in the Cutaneous Rabbit Movie. This cutaneous rabbit illusion can be produced elsewhere on the body surface except for the fingers and portions of the face where the receptive fields are small and RA & SA receptor density is high. Although the exact mechanism for this illusion has yet to be elucidated, it is likely to be a central neural phenomenon since anesthetizing the skin where "illusory" rabbits are felt does not eliminate the hopping rabbit perception at the insensate skin locations. Moreover, your brain is not a blank slate upon which each sensory experience is written anew. Prior experiences influence what you feel in a Bayesian sense such that perceptions are influenced by both external sensory data and probabilistic intrinsic "expectations", e.g. see Blankenburg, et.al., 2006; Geldard and Sherrick, 1972, 1983; Goldreich and Tong, 2015.

CRITICAL PATHWAYS FOR DISCRIMINATIVE ACTIVE TOUCH

The two tracts that are critical for discriminative active touch are the Ascending Dorsal Column Medial Lemniscal (DCML) Pathway and the Descending Lateral Corticospinal Tract (LCST). Other tracts participate including the Ascending Crossed Spinothalamic Tracts, the Corticobulbar Tract that projects from the Parietal Cortex to the Dorsal Column Nuclei, the Rubrospinal Tract and other descending tracts. However, without the DCML, discriminating a small from a large paper clip or reading Braille would be difficult or impossible. The DCML is the one tract that provides the necessary spatial and temporal detail of actively touched objects to allow sensations of form & texture to be perceived as recognizable entities.

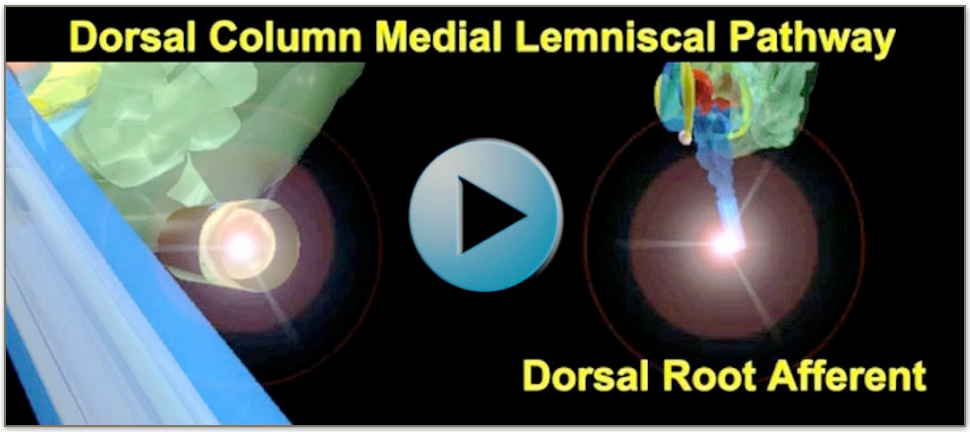


Fig 7-21. DCML Pathway from Dorsal Root to Dorsal Column to Dorsal Column Nucleus to Medial Lemniscus to VPL Thalamus to SI Cortex (gec). GO TO: gmomm. pitt.edu
Fig7-21_Video

The Descending LCST provides the necessary fine motor control of our digits to move the tactile array across the object in a manner that optimizes the tactile information. The LCST collateral axons to Dorsal Column Nuclei and a Corticobulbar projection to the Dorsal Column Nuclei plus Corticospinal Tract projection to the Dorsal Horn act to gate information flow & adjust the traffic patterns during the "rush-hour" crush of impulses as we scan objects with our somatosensory periphery.

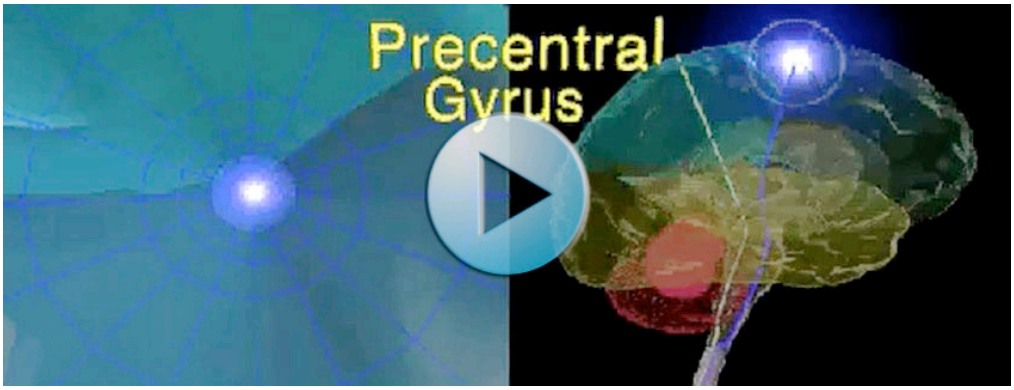


Fig 7-22. LCST Pathway from Layer V Pyramidal Tract Neurons in Cerebral Cortex to Spinal Gray (gec, dh). GO TO: gmomm. pitt.eduFig7-22_Video

RELATIONSHIPS OF AFFERENT FIBER SIZES, ASCENDING PATHWAYS AND SOMATOSENSORY MODALITIES.

Somatosensory modalities have a defined relationship to the size of the afferent innervating the peripheral receptor and to the ascending pathway that carries information about the modality to the brain.

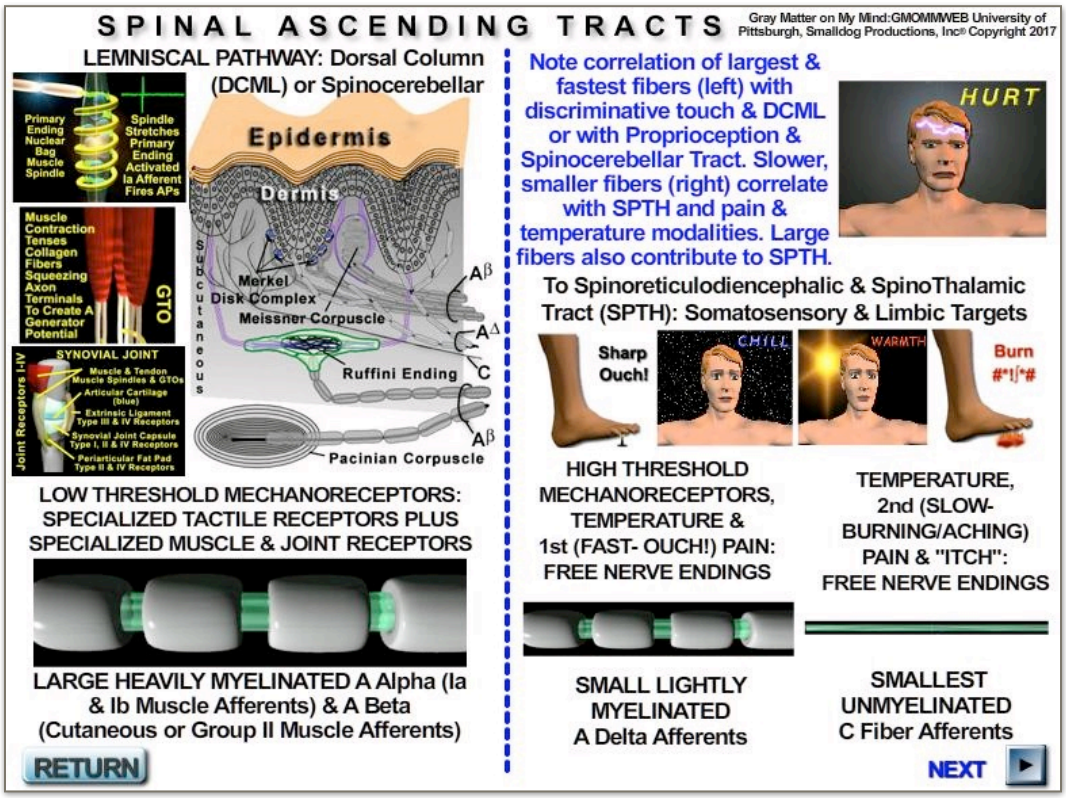


Fig 7-23. Somato-sensory Modalities-Afferent Fiber Size and Ascending Pathways (gec). Interactive Media file shows ascending tracts correlated with somato-sensory modalities. GO TO: gmomm.pitt.edu Fig7-23_Interactive Media

FREE NERVE ENDINGS: TRANSDUCTION OF PAIN, TEMPERATURE, ITCH AND HIGH THRESHOLD "TOUCH"

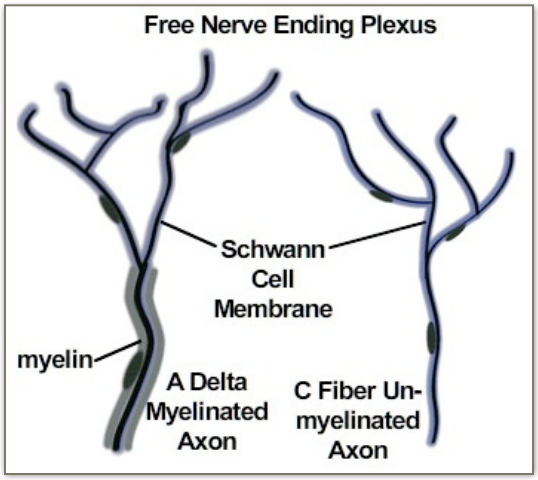


Fig 7-24. Nociceptors Innervated by Myelinated A Delta and Unmyelinated C Afferents (gec).

Free nerve endings of A Delta and C fiber afferent axons typically terminate in a plexus. Although the endings have similar morphology seen at the light microscopic level, these endings may have a variety of differences in the intracellular details of organelles including vesicles that contain neurotransmitters (typically neuropeptides). Many endings have receptors that bind neurotransmitters and chemicals released from the nerve endings or the tissue in which they are embedded. For pain receptors these chemicals may include: K^+ ions, lactic acid, prostaglandins, bradykinin, substance P, serotonin (5-HT), histamine, Calcitonin Gene-Related Peptide (CGRP) and other biochemical agents released from inflamed or injured cells or from blood vessels and nerve endings in these tissues.

Fig 7-25. Warm-Cool-Hurt Movie. Small fiber input associated with feelings (gec). GO TO: gmomm.pitt.edu Fig7-25_Video

Most C fiber free nerve endings in humans are thought to be polymodal receptors that respond to noxious mechanical, thermal or chemical stimuli. Receptors innervated by A Delta axons are said to be responsive to high intensity thermal or mechanical stimuli. Many Non-Narcotic Analgesics work by blocking the action of noxious chemicals in the periphery. Narcotics have their main effect on central pain-modulating mechanisms.

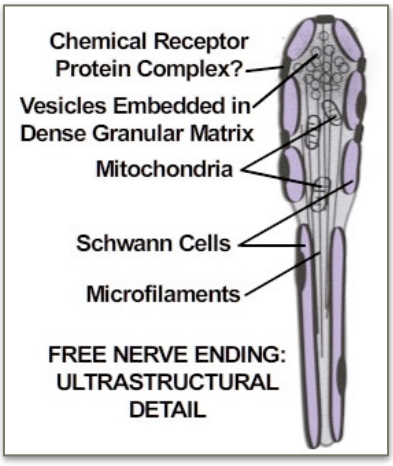


Fig 7-26. Ultrastructural Details of Nociceptor (gec).

VIBRISSAL TACTILE DISCRIMINATION: RATS WHISK TO PALPATE OBJECTS

Rats have 30-35 mobile mystacial vibrissae (whiskers) on each side of the face. The whiskers are arranged in rows A-E in the dorsal-ventral axis and arcs 1-4+ in the caudal-rostral axis. Rats use their whiskers to actively explore their immediate environment. Rats move their

vibrissae as an array to rhythmically whisk objects at rates of ~6-12 whisks/sec. Rats trained to discriminate textures with their vibrissae have fine motor control of these tactile arrays and can discriminate surface differences at a level comparable to humans using their fingertips. These vibrissae emerge from a sinus follicle where hundreds of slowly and rapidly adapting mechanoreceptors surround the hair in a well-developed tactile organ complex. The blood sinus is under autonomic control (sympathetic efferents) that adjusts the turgor of the follicle complex. The peripheral processes of an individual myelinated trigeminal axon in the infraorbital nerve innervates mechanoreceptors in only one follicle; the central processes synapse on neurons in the brainstem trigeminal nuclear complex. The precise somatotopy of this projection provides the basis for the distinct topographic representation of whiskers from the trigeminal nucleus to the Ventral Posterior Medial Thalamus to Primary Somatosensory Cortex.

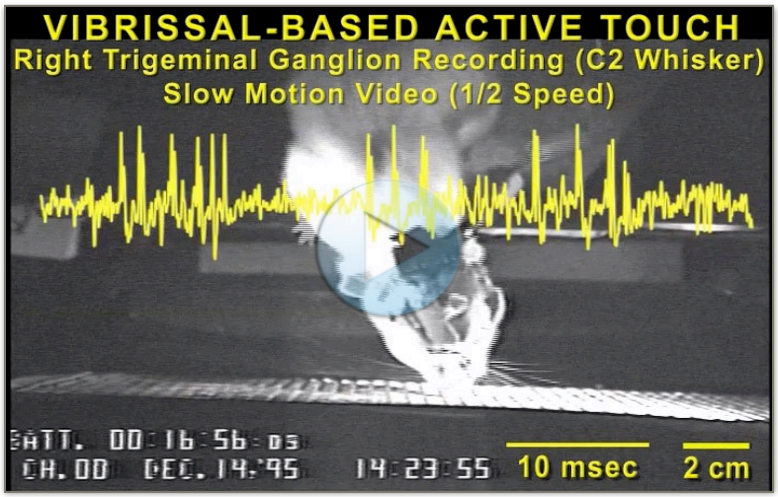


Fig 7-27. Trigeminal Afferent Recording During Vibrissal Active Touch Movie (gec). Unpublished data: Kelly, Carvell, Simons, Dept. Neurobiology, University of Pittsburgh School of Medicine, 2016. GO TO: gmomm.pitt.edu
Fig7-27_Video

(LARGE MOVIE-BE PATIENT.) Trigeminal afferents innervating whisker follicles have high levels of discharge as the whisker contacts a surface and the whisker is bent. For one behavioral study rats were trained to search for a probe that will be pushed through an opening in a 0.25 inch mesh screen at some random time and location. Upon contact with the probe a reward tone is activated and the animal receives a food reward. Animals whisk ~20-40 sec per trial, 30-40 trials per day. During one session microelectrode recordings were made from the right trigeminal ganglion. Action potentials of several individual trigeminal afferents innervating whisker follicles are shown: note rhythmic trigeminal afferent discharge as the animal actively whisks and touches the screen surface.

ACTIVE TOUCH: VIBRISSAL-BASED TEXTURE DISCRIMINATION IN THE RAT.

Blindfolded rats placed on an elevated platform are trained to stretch across a gap to palpate discriminanda attached to the front of choice platforms with their outstretched vibrissae. The animal indicates its choice by jumping to one of these platforms; if correct the animal receives a food reward. The reward discriminandum is matched to another

having a different surface texture. Reward and non-reward discriminanda are randomly interchanged between the two choice platforms (see Behavioral Apparatus for Discriminative Active Touch Task figure).

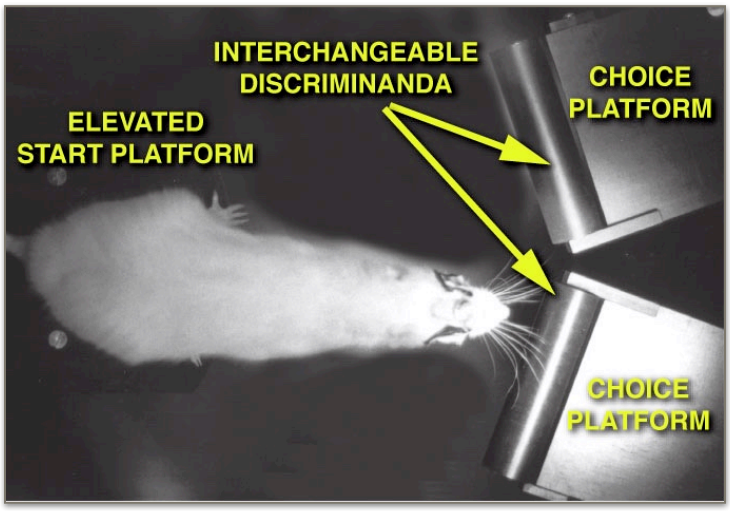


Fig 7-28. Behavioral Apparatus for Discriminative Active Touch Task. Blindfolded Rat Stretches across a gap to Palpate the Surface Texture of a Discriminandum with Protracted Whiskers (gec).

Rats are capable of reliably distinguishing differences as little as 50 to 60 μm after training. There are characteristic motor patterns that distinguish good from poor performers, and whisking biometrics differ for a rough versus smooth (R-S) "detection" and a rough versus rough (R-R) discrimination of differences in the spatial frequencies of relatively widely-spaced gratings. The latter but not the former task requires multiwhisker inputs: see Carvell & Simons, 1990, 1995.

Fig 7-29. Whisking Movie 1: Wide Angle View of Vibrissal-Based Discriminative Touch Task (gec). GO TO: gmomm.pitt.edu

Fig7-29_Video

Two movies show the rat performing the tactile discriminative task. Whisking Movie 1 is a wide-angle view and Whisking Movie 2 shows a close-up of whisker-discriminandum interactions as a rat palpates the discriminanda surfaces. Close Up View of task shows that as the animal palpates a textured surface its whiskers bend, indicating the high level of flexibility of these tactile organs. Animals learn the (R-S) but not the (R-R) task with whiskers regrown in adulthood after a month of trimming as infants; motor patterns are abnormal in those animals that fail to learn the rough versus rough task: see Carvell & Simons, 1996.

Rats who have whiskers chronically trimmed as adults have no such difficulty learning either task with regrown vibrissae: an example of age- and activity-dependent neural plasticity see Carvell & Simons, 1996.

Fig 7-30. Whisking Movie 2: Close Up View Vibrissa-Based Discriminative Touch Task (gec). GO TO: gmomm.pitt.edu
Fig7-30_Video

SENSORIMOTOR CONTROL OF VIBRISSAL SWEEPS: RAT WHISKING & SURFACE TEXTURE PALPATION.

Rats use two sets of facial muscles to control the relative position (set-point) of the whisker array and to control the amplitude & velocity of whisking sweeps. Motor patterns differ according to the animal's level of performance and according to the task at hand. Animals actively generate forward (protraction) motion that is immediately followed by retraction of the vibrissa largely due to the passive elastic recoil of mystacial pad structures. Thus, the animals appear to be repeatedly engaging the object, and resetting the tactile array between samples.

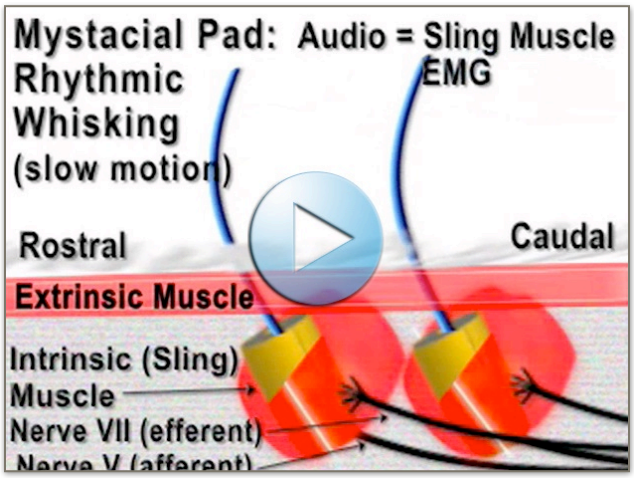


Fig 7-31. Follicle-Rock Movie. Whisker mechanics and EMG (gec). GO TO: gmomm.pitt.edu *Fig7-31_Video*

Motor and Sensory Systems appear to be linked in this process. The frequency of whisking increases by 1-2 Hertz (Hz) at the transition between whisking the air, during the approach, and actual surface contact by whiskers as the discriminandum is actively palpated.

Velocities and amplitudes (angular excursions) of whisking sweeps used by rats are similar to digit biometrics used by humans as they move their fingertips across tactile gratings to discriminate texture differences (although our scanning rate is slower than that of trained rats whisking at ~ 6-8 Hz) see Carvell & Simons, 1990, 1995, 1996; Carvell et.al., 1991 .

Intrinsic (sling) muscles that tilt the vibrissae forward are contain primarily fast twitch muscle fibers. These fast twitch muscles rapidly sweep the whiskers as shown in the Intrinsic Sling Muscle EMG Movie (whisking shown in slow-motion).

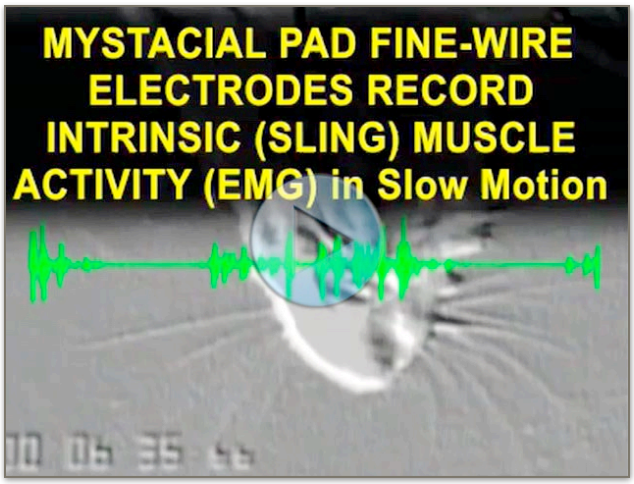


Fig 7-32. Mystacial Pad Intrinsic (Sling) Muscle Whisking Electromyography (EMG) Movie (gec). GO TO: gmomm.pitt.edu *Fig7-32_Video*

The Normal Volitional Versus Fictive Whisking Movie shows that patterned electrical stimulation of the facial nerve can artificially move the whiskers although these fictive whisking motions do not faithfully replicate the smooth contractions produced by volitional recruitment of facial motoneurons (compare normal volitional whisking vs. induced fictive whisking).

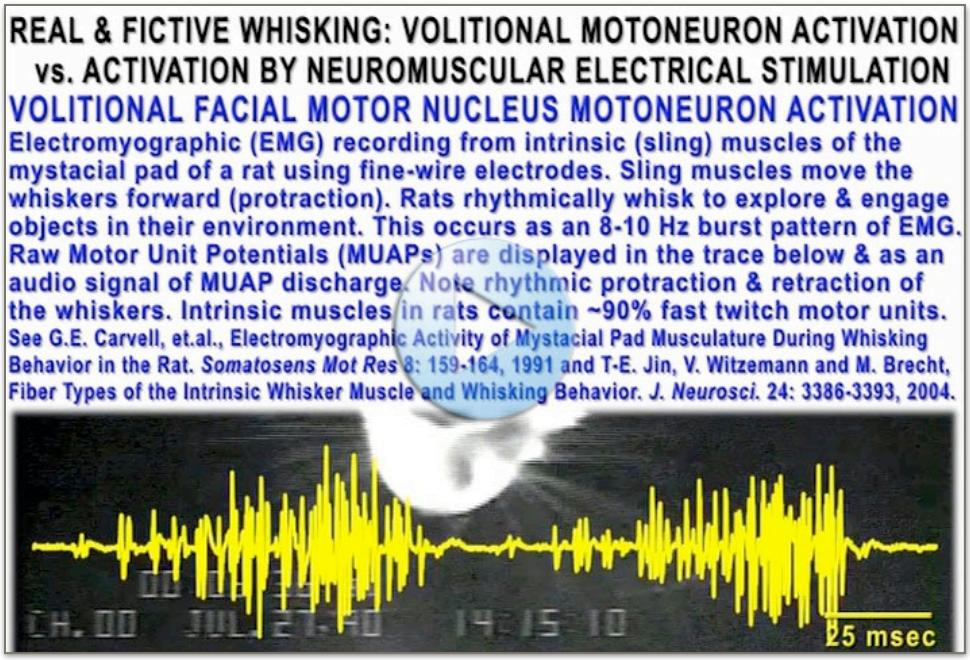


Fig 7-33. Normal Volitional Versus Induced Fictive Whisking Movie (gec). GO TO: gmomm.pitt.edu *Fig7-33_Video*

Whisker-object surface interactions can be measured using video-graphic recording plus measure-ment of forces generated by whisker-surface contact. The Behaving Rat Bimorph Contact movie illustrates one trial of many by a rat trained to whisk against a sensitive piezoelectric bimorph force sensor. The rat received a water reward if a minimal threshold was exceeded for the whisker contact force. The bimorph sensor signal was acquired using an Analog to Digital (AD) converter running at a 40 KHz sampling rate. The signal was amplified x 1000 and filtered at a 0.9-3 KHz bandwidth. Video-graphic data were collected simultaneously with a CCD camera sampling at 100 Hz (100 frames/sec) using a 1 msec electronic shutter triggered at the beginning of each frame. The movie replays the trial at 20 frames/sec to slow down the rapid sequence of events. The bimorph's mechanical properties produce an oscillatory signal (ringing) defined by the

sensor itself; in this case beam mounting of the piezo caused ringing at 3.6 KHz frequency.

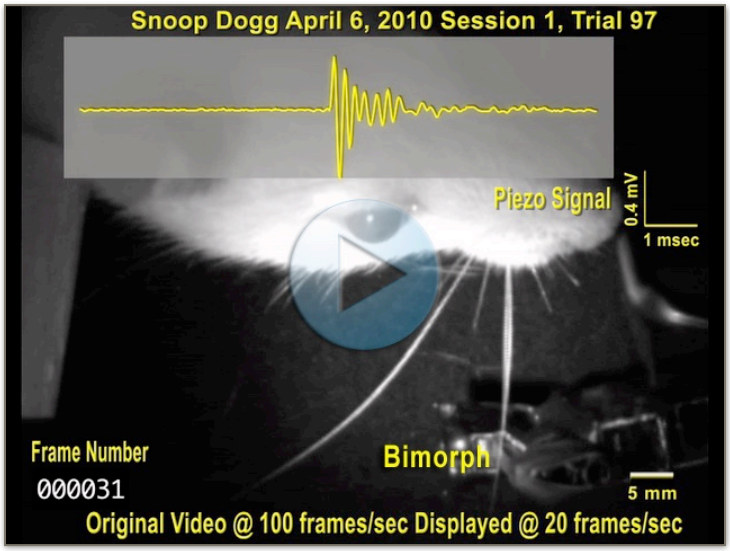


Fig 7-34. Behaving Rat Bimorph Contact Movie (gec). Unpublished movie: G.E. Carvell, D.J. Simons and T. Prigg, Dept. Neurobiology, University of Pittsburgh School of Medicine, 2017. GO TO: gmomm. pitt.edu *Fig7-34_Video*

Details of the components for the construction of the bimorph force sensor used for the behavioral task demonstrated in the movie above is shown in the Bimorph Force Transducer Photograph.

Fig 7-35. Bimorph Force Transducer Photograph (gec). Unpublished photo: G.E. Carvell, D.J. Simons, Dept. Neurobiology, University of Pittsburgh School of Medicine, 2017.

The mobile mystacial vibrissae (whiskers) have a curved, tapered cone architecture. As such, the diameter decreases along its length. This produces a non-linear velocity sensitivity for initial contact forces related to both the velocity of the motion and the surface area (diameter) of the whisker hair. Vibrissal length and thickness differs across the array of whiskers on each side of the rat's face: see Schwarz, 2016; Carvell and Simons, 2017. The relationship of length at contact, and the velocity at contact of one whisker from one animal doing the task shown in the movie above is presented in the Behaving Rat Bimorph Task Biometrics figure. Data points from 513 trials for nine sessions over 18 days are included in the figure. Note distribution of velocities and initial peak signal (bimorph) amplitudes (mV) at differing lengths at point of contact. Length was measured from surface of the face. The median velocity for this task is comparable to that found for rats performing the gap-jumping texture discrimination task (see Table 1, p. 2645 in Carvell and Simons, 1990).

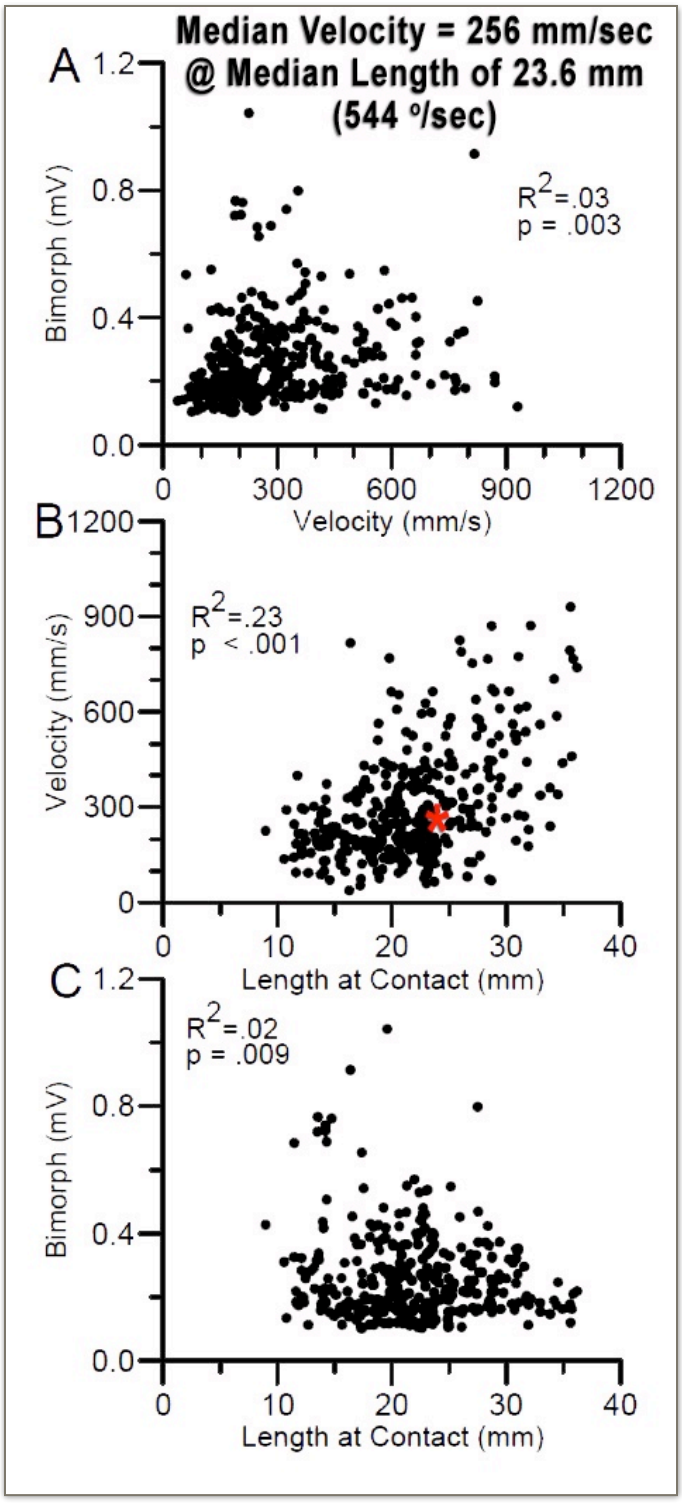


Fig 7-36. Behaving Rat Bimorph Task Biometrics (gec) Unpublished data points: G.E. Carvell, D.J. Simons, Dept. Neurobiology, University of Pittsburgh School of Medicine, 2017.

CLINICAL TESTING OF SENSORY DEFICITS. CLINICAL ELECTROPHYSIOLOGY: NORMAL AND ABNORMAL SENSORY NERVE CONDUCTION

Antidromic Sensory Nerve Conduction Studies record responses from digital nerves or superficial cutaneous nerves. Stimuli are delivered at several locations along the course of the nerve. Brief (0.1 msec monophasic DC pulses) but strong (supramaximal intensity) stimuli are used. Responses are simulated digital oscilloscope traces in these animations. A ground electrode is placed over non-contractile tissue (not shown). The example shown here is antidromic sensory nerve conduction for the Median Nerve. Ring recording electrodes are placed around the proximal and middle phalanges of the index finger. Proximal and distal stimuli & stimulation sites are the same as for median motor nerve conduction. Sensory compound action potentials are small (microvolt range) and high amplifier gain is required. If peripheral nerve disease is present the signal to noise ratio may require waveform averaging to reveal tiny signals buried in the noise (note calibration scale).

Unlike motor nerve conduction where muscle fibers act like bioamplifiers that magnify the motor axon's signal (large compound muscle action potential), sensory

waveforms are small (small compound axon action potential). Summation of all A myelinated sensory axons produces amplitudes in the 20-45 microvolt range (compared to mV ranges for motor potentials). Normal distal latencies for the median nerve should be less than 3.5 msec and conduction velocity should be > 60 M/sec for young adults. Actual normal values vary according to age. Distal & proximal stimulation site waveforms should have similar shape and area. However, waveform area due to proximal site stimulation is temporally dispersed compared to distal site (smaller amplitude, longer duration).

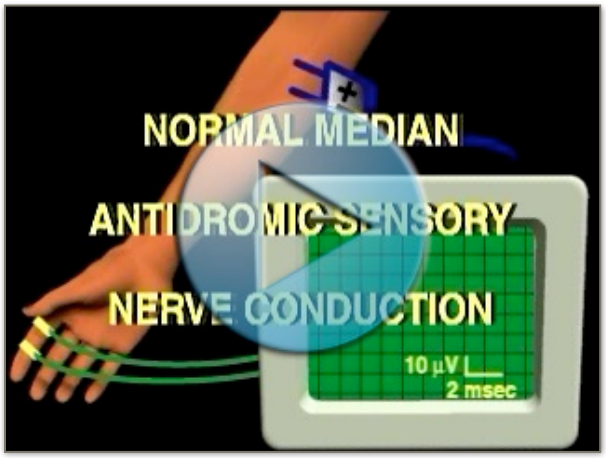


Fig 7-37. Normal Clinical Sensory Nerve Conduction Testing Movie: No Reduction or Slowing of the Compound Action Potential Waveform (gec). GO TO: gmomm.pitt.edu *Fig7-37_Video*

Nerve conduction slowing may result from an acute ischemia (physiological conduction block), demyelination, or as a result of regeneration (conduction in immature axons with reduced diameter and immature myelination). Conduction time is longer than normal and the compound action potential waveforms tend to be temporally dispersed (less uniformity in conduction times of involved axons). Peripheral neuropathies that disrupt the integrity of large diameter axons often show slowed nerve conduction in distal segments of upper and lower extremity peripheral nerves. Both sensory and motor axons are commonly involved. If the neuropathy is restricted to small fibers, Nerve Conduction Velocity (NCV) should be normal, i.e., large fast axons have normal conduction.

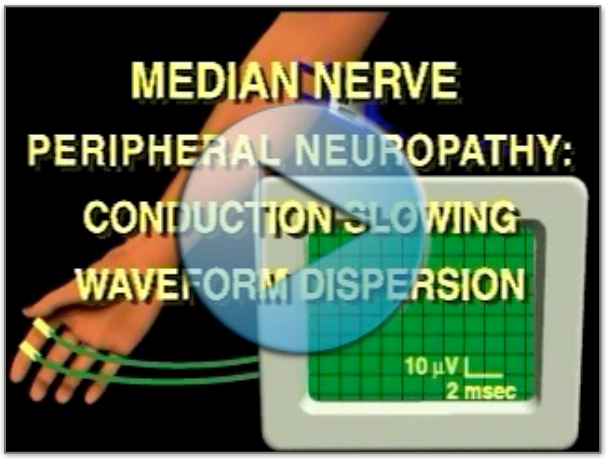


Fig 7-38. Clinical Sensory Nerve Conduction Movie: Peripheral Demyelination Conduction Slowing (gec). GO TO: gmomm.pitt.edu *Fig7-38_Video*

Nerve conduction block can result from axonal degeneration, severe demyelination, or a transient physiologic conduction block due to nerve compression (neuropraxia). If all fibers are involved no evoked waveforms will result from nerve stimulation anywhere proximal to the lesion. If partial conduction block occurs, the waveforms have reduced amplitude but conduction time within normal limits (surviving uninjured axons

conduct at normal velocity). Partial conduction block or reduced velocity in regenerating axons may be found with a partial (first, second or third degree) nerve injury or with certain peripheral neuropathies. Waveforms may have shortened durations or greater temporal dispersion; summed waveform areas may be reduced if damaged axons fail to conduct action potentials. Play Sensory Nerve Conduction Block Movie.

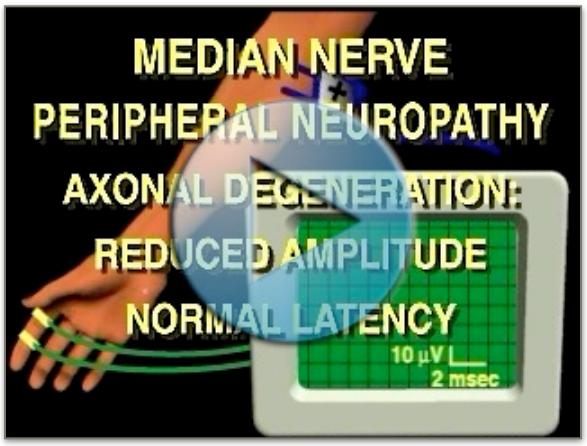


Fig 7-39. Axonal Degeneration Nerve Conduction Block Movie (gec). GO TO: gmomm.pitt.edu [Fig7-39_Video]

PERIPHERAL PRESSURE NEUROPATHY: IMPAIRED REPETITIVE IMPULSE TRANSMISSION-ALTERED TEMPORAL CODE

Pressure on a nerve produces a demyelination of large myelinated axons with little effect on unmyelinated fibers. This causes a conduction delay through the involved portion of the nerve. The effect is seen not only as a reduced conduction velocity but as a reduction in the ability to faithfully conduct impulses in rapid bursts. High frequency bursts of APs are seen in proprioceptive afferents and afferents innervating low-threshold tactile mechanoreceptors. An example of reduced temporal fidelity in coding is illustrated in the figure below. A localized pressure neuropathy was present at the distal thigh between the location of stimulating site at the proximal sciatic nerve and recording site at the distal tibial nerve. Compound action potentials (CAPs) evoked by trains of ten stimuli delivered at 200 Hz (panels A & D), 300 Hz (panels B & E) 400 Hz (panels C & F), 500 Hz (panels G & J), 600 Hz (panels H & K) and 700 Hz (panels I & L) were recorded (photographs of ten consecutive oscilloscope traces in upper traces for each of the six train frequencies). Recordings were done several weeks post-pressure. Lower traces in each photograph shows the times of each of the ten stimuli in the train. Data illustrate the decrement in transmission for the experimental versus the control tibial nerve. Note the reduced amplitude and temporal dispersion of responses in the burst for the experimental nerve which is most evident as frequency of stimulation increases. For the highest frequencies, conduction delay and reduction in amplitude for later CAPs in the train are substantially greater for experimental compared to the control tibial nerve.

These nerve conduction changes may be due to temporal delays and/or conduction failure at the lesion site in pressurized axons. As the frequency of stimulation increases there is a greater likelihood for encroachment upon the safety factor for normal transmission of some axon APs for intact nerve and many more axon APs in the lesioned tibial nerve. A relative depolarized state following the first CAP in the higher frequency trains (500-700 Hz) particularly in the experimental nerve suggests that some

Na^+ channels are not closing and/or there is a failure of the Na^+-K^+ Pump to restore the internal Na^+ concentration to the resting membrane state, i.e., more axons become refractory with these high frequency trains. Pressurized axons may be in various states of demyelination and remyelination in this post-lesion recovery state. Consequences of a pressure neuropathy on temporal coding is greater for sensory than for motor function.

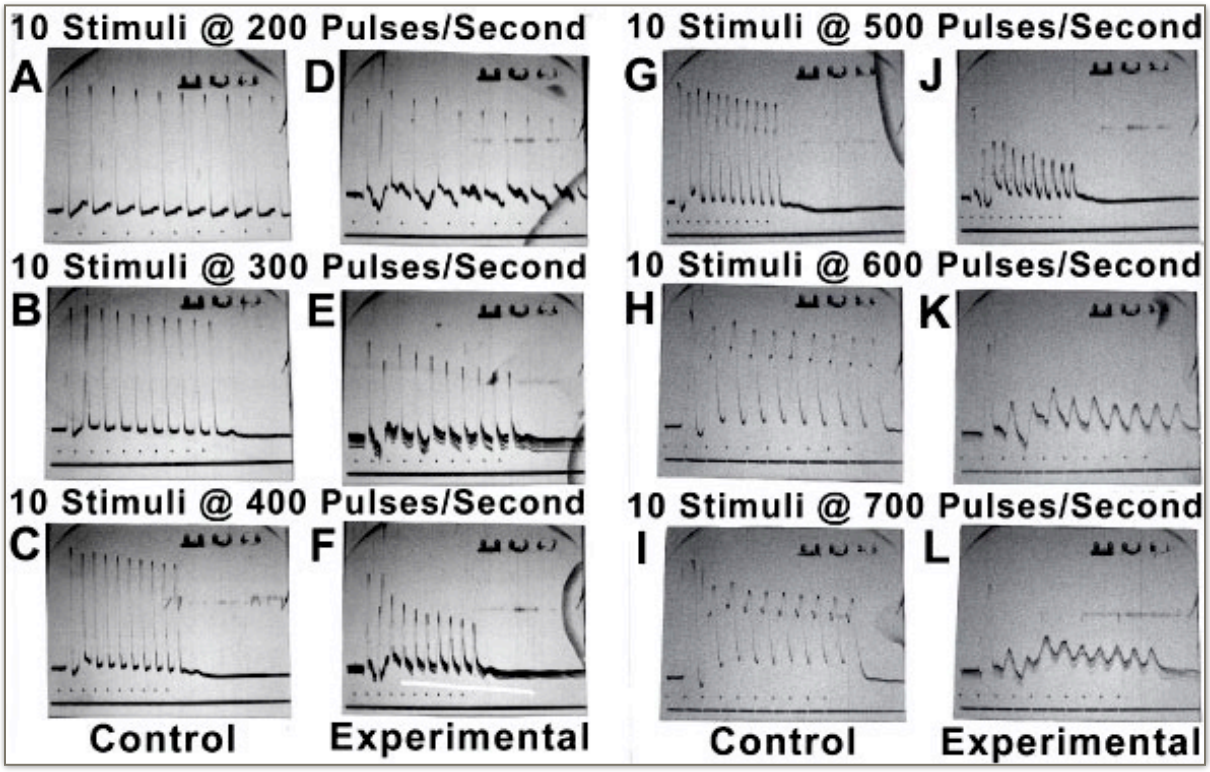


Fig 7-40. Effects of Local Pressure Neuropathy on Repetitive Conduction of Compound Action Potentials (CAPs). Panels A,B,C,G,H,I = Control Tibial Nerve CAPs (top traces) Panels D,E,F,J,K,L = Experimental Tibial Nerve CAPs (top traces). Lower traces in all panels = stimulus timing of the ten stimuli of the train. Each photograph shows ten consecutive traces for each of the stimulus trains. G.E. Carvell and W.D. Letbetter, unpublished data (gec).

Motoneurons do not typically generate AP frequencies above ~50 Hz. Unless there is conduction failure in motor axons, muscles should be well innervated even if there is motor axonal conduction delay. However, muscle proprioceptor afferents plus discrete touch and vibration sense afferents routinely discharge bursts of APs at frequencies up to or greater than 500 Hz. Thus some deep and superficial sensations may be distorted. Small myelinated and unmyelinated axons are little affected or unaffected in a pressure neuropathy: crude touch, pain and temperature sensations should be spared.

RECOVERY OF NERVE CONDUCTION AND DISCRETE ACTIVE TOUCH FOLLOWING PERIPHERAL NERVE LESIONS

Discrete active touch has been best studied in the hands of primates (monkeys and humans). These studies have been accomplished primarily for an intact peripheral somatosensory and motor innervation of the fingers. Following peripheral nerve injury (PNI) the the alterations in quality of discrete active touch is dependent upon the type and extent of the PNI. Crush of a nerve, where epineurium, perineurium and endoneurium remain fundamentally intact, is associated most often with full recovery of sensorimotor function. As the lesion disrupts not only peripheral axons but also the supportive structural components of the nerve, functional recovery is most often incomplete at best. A complete nerve transection if followed by end-to-end microsurgical repair typically shows good to very good functional recovery. If the injury is more extensive and surgical repair is not possible, the chance for full recovery is zero while the extent of partial recovery with complete nerve transection without surgical repair varies by species and across individuals, e.g. younger vs. older persons. If the nerve is not completely transected and both epineurium and perineurium are incompletely disrupted, the likelihood of better recovery rises: e.g., see Haymaker & Woodhall, 1953; Lee & Wolfe, 2000; Seddon, 1943; Sunderland, 1952a,b.

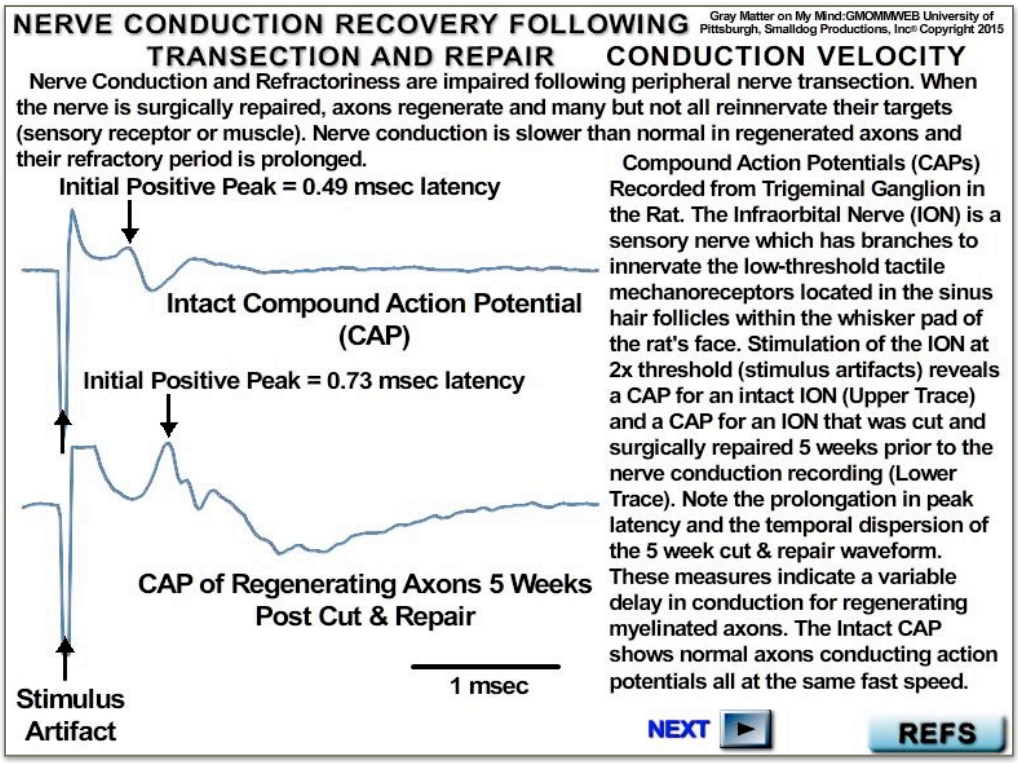


Fig 7-41. Rat ION Nerve Conduction Recovery Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig7-41_ Interactive Media

The Rat ION Nerve Conduction Recovery Interactive Flash File shows recovery of nerve conduction for trigeminal afferents in rats who had complete nerve transection followed by end to end microsurgical repair of the infraorbital nerve (division of trigeminal nerve innervating low-threshold tactile mechanoreceptors in mystacial pad vibrissal follicles); see also Xiao, et.al., 2016.

Clinical testing of recovery of sensory function typically provides a gross status report for reinnervation of cutaneous receptors but does not provide a fine-scale assessment of function for specific slowly adapting (SA) or rapidly adapting (RA) low-threshold tactile mechanoreceptors. Likewise, sensory nerve conduction studies provide information about whole nerve conduction but not details regarding electrophysiology of individual axons. Relatively few studies have attempted to provide a more fine-scaled assessment of cutaneous reinnervation of specific low-threshold mechanoreceptors in rats, cats, monkeys and humans (see references). One clinical system to grade recovery is the Medical Research Council Grading System for Nerve Recovery: see Lee & Wolfe, 2000; see also Xiao et.al., 2016.

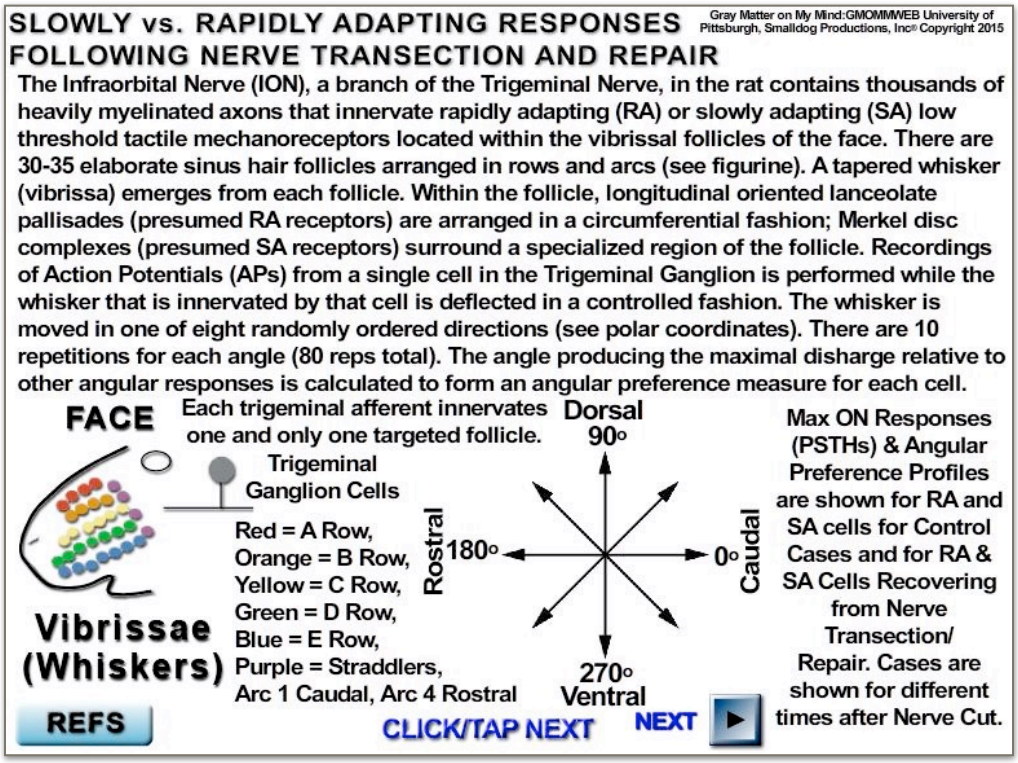


Fig 7-42. Rat ION RA-SA Reinnervation Interactive Media File (gec). GO TO: gmomm.pitt.edu [*Fig7-42_ Interactive Media*]

The rat trigeminal sensory innervation of the vibrissal hair follicles embedded in the mystacial pad of the face by the Infraorbital nerve (ION) division of the trigeminal nerve offers a model that can investigate the fine-scale reinnervation pattern of specific low-threshold SA and RA receptor afferents following complete nerve transection and microsurgical repair. These RA and SA afferents innervate low-threshold tactile mechanoreceptors required for vibrissal-based discriminative active touch (see Vibrissal Tactile Discrimination above & Rat ION RA-SA Reinnervation Interactive Flash File; see also Xiao et.al., 2016). Recent evidence suggests that RA and SA Trigeminal Afferents provide separate codes of information regarding amplitude and velocity profiles of whisker deflections that match psychophysical performance on a vibrissal-based tactile detection task in rats, e.g., see Stuttgen, et.al., 2006.

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Chapter 8

SOMATOSENSATION: PROPRIOCEPTION & KINESTHESIA

We gather information about and manipulate our immediate environment by coupling somatosensory inputs with our intended motor actions: an integrated somatomotor process. Often this information generated by receptors located in skeletal muscle or synovial joints is utilized in the background, outside of our conscious attention and perception. In addition, central motor centers may contribute not only signals that activate skeletal muscles but also may provide corollary discharges as part of a forward model for motor control and perceptual processing. Comparison of sensory data to predicted signals may provide important cues regarding effort expended, the level of precision of our actions and a sense of agency, e.g., see McClosky, 1981; Scott, 2004; Crapse and Sommer, 2008; and Proske and Gandevia, 2009, 2012 for reviews.

PROPRIOCEPTIVE sensation is said to be due to sensory organs that provide us with information about our position, motion, muscle force/tension and our body schema (body part relationships to one another and to the external world). These receptors are said to include deep somatosensory receptors: skeletal muscle proprioceptors (Muscle Spindle & Golgi Tendon Organ), joint receptors as well as specialized vestibular *receptors* located in the inner ear (semicircular canals and otolith organs). Some scientists include retinal inputs from the eyes as having a "proprioceptive" function since vision provides important information about our position relative to the horizon and flow of information around our head. Visual proprioceptive cues occur as we move ourselves, as we are moved by external forces or as a portion of our visual world moves around our head (optic flow from linear or circular/angular motion). For our hands in particular, tactile mechanoreceptor inputs often "serve" as proprioceptive input to regulate precision grip force and finger movements. Indeed, a recent study in awake monkeys shows an integration of information from classic proprioceptive and cutaneous inputs from the digits in the primary somatosensory cortex: see, Kim, et.al., 2015.

Proprioception and its cousin kinesthesia (muscular sense of moving, muscle tension, or muscular effort) utilize sensory data for conscious or unconscious/ subconscious perceptions but also provide critical sensorimotor data used in precise & coordinated feedforward and/or feedback neural control of posture and movements. Proprioceptors are NOT the "*prima-donna*" sensory organs of the body. Compared to touch, we have a relatively poor understanding of the CNS mechanisms that encode or decode this information. Although there is good evidence that proprioception is represented in the somatomotor system at all levels, details regarding these maps of muscle/joint bodily sense is very limited. In addition, many individuals have only modest awareness of body motion or muscle activation despite their ability to perform skilled tasks that use these data. Interestingly, gifted athletes and other skilled performers can achieve grace and precision in their actions with little conscious attention paid to

proprioception. Indeed experts have great difficulty explicitly explaining the biometric features of the task and exactly how they engaged their musculature to perform at such a high level. An example that clearly shows a difference in the neural mechanisms required for procedural implicit learning/memory vs. factual (semantic) and autobiographical explicit learning/memory is the case of H.M. H.M. had a profound explicit amnesia following bilateral anterior medial temporal lobe resection while retaining the capability of learning new procedural (motor) tasks, e.g., see Corkin, 2013.

Traditional somatosensory proprioceptors include specialized, encapsulated joint and muscle receptors that provide us with information about our movements, positions, and torque generated by our appendicular and axial musculoskeletal system. Articular (joint) receptors are found in the joint capsule (fibrous layer), ligaments (extrinsic and intrinsic), and periarticular fat pads associated with synovial joints of the axial and appendicular skeleton. At one time joint receptors were thought to have the key, if not exclusive, role of informing us about limb, neck or back position. Muscle Proprioceptors include the Muscle Spindle and the Golgi Tendon Organ (GTO). Muscle receptors are thought to be important in kinesthesia: a sense of force/tension and sense of muscular effort. The Spindle is a stretch receptor that provides information about actual muscle length (static) and the rate of change of muscle length (dynamic); this translates into signals regarding limb position and changes in position. The GTO provides information about active force/tension as a muscle contracts. Both proprioceptors are highly sensitive receptor organs. Not all feedback originates from peripheral receptors. Central signals concerning ongoing actions originates from neural structures generating motor output. This corollary discharge or efferent copy of events is shared among many CNS neural centers and may act as a feedforward sensory prediction signal.

GOLGI TENDON ORGAN: FORCE/TENSION TRANSDUCER AT SKELETAL MUSCULOTENDINOUS JUNCTIONS

Fig 8-1. Golgi Tendon Organ (GTO) Receptor Ending Squeeze Movie (gec). GO TO: gmomm.pitt.edu [Fig8-1_Video]

The Golgi Tendon Organ (GTO) is an encapsulated sensory organ located at the junction between muscle fibers and the collagenous tendon. This is an ideal location to detect active force/tension generated by contracting muscle fibers. When the muscle contracts the GTO receptor endings entwined in braided collagen fibers at the musculotendinous junction are squeezed. This produces generator potentials that provide both a dynamic and static firing of the Ib afferent that innervates the GTO; a

signal of rate of change of force/tension and a signal of sustained force/tension. The GTO is responsive to the small forces produced by single motor unit activation up to maximal force production. The animation illustrates the compression of multiple GTO afferent endings within a single GTO. This animation has the capsule removed and receptor endings simplified. The actual morphology of the GTO is quite similar to that of the cutaneous Ruffini ending. The afferent axon that innervates the GTO receptor endings is the Group Ib heavily myelinated, rapid conducting axon.

MUSCLE SPINDLE: POSITION AND MOTION SENSE FROM SKELETAL MUSCLE

The muscle spindle lies in parallel with the working skeletal muscle fibers (Extrafusal Muscle or EFM). Thus, as the muscle shortens or lengthens the muscle spindle capsule does so as well (see Muscle Fibers and Muscle Spindle Capsule Mechanics Movie). The muscle spindle receptor endings are activated by stretch (elongation of the portion of the spindle where the receptor endings are located).

Fig 8-2. Muscle Fibers and Muscle Spindle Capsule Mechanics Movie (gec). GO TO: gmomm.pitt.edu
Fig8-2_Video

The typical mammalian Muscle Spindle contains three elements: the Nuclear Bag 1 (NB^1), the Nuclear Bag 2 (NB^2) and the Nuclear Chain (NC). All three have a Primary Ending innervated by a branch of the single Ia afferent axon that enters each spindle capsule. The NB^2 and the NC have Secondary Endings innervated by Group II afferents. The number and type of elements differs across muscles. For example, there is some evidence to suggest that spindles in the deep neck muscles lack NB^1 elements, and facial muscles lack any spindles whatsoever.

Each NB & NC element contains a central, non-contractile equatorial region where the sensory endings are located, and two contractile polar regions where intrafusal muscle (IFM) is located. Gamma efferent axons innervate the intrafusal muscle fibers. The gamma motor axons are smaller than the alpha axons that innervate the extrafusal muscle fibers (EFM) that comprise the motor units that do the work of the muscle.

Gamma dynamic axons innervate the IFM of the NB^1, and gamma static efferents innervate the IFM of the NB^2 and NC. The purpose of the IFM and gamma innervation is to maintain sensitivity of the spindle receptors as the muscle contracts. Gamma dynamic innervation increases the dynamic sensitivity of the primary ending of the NB^1.

Activation of Gamma Static axons will increase the static sensitivity of the primary and secondary endings of the NB^2 and NC.

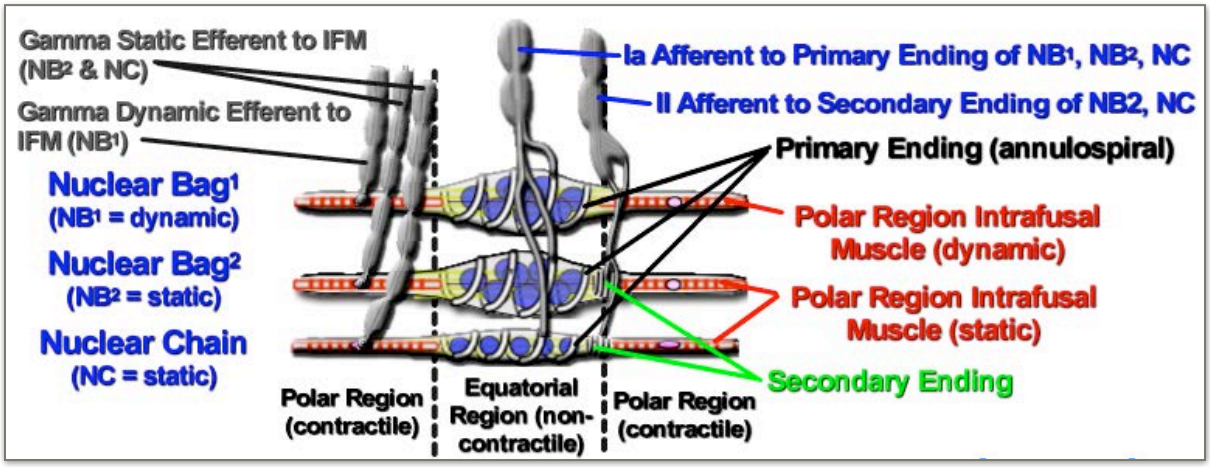


Fig 8-3. Nuclear Bag and Nuclear Chain Elements of the Muscle Spindle (gec). Build Elements Interactive Media file. GO TO: gmomm.pitt.edu *Fig8-3_Interactive Media*

The muscle spindle is a stretch receptor. When the spindle or whole muscle is lengthened the muscle spindle will be activated. The other way to stretch the spindle receptor ending is to elongate the central (non-contractile) portion of the spindle due to contraction of the intrafusal muscle (IFM) located at the two poles of the spindle organ. The Muscle Spindle Activation Movie shows muscle spindle activation.

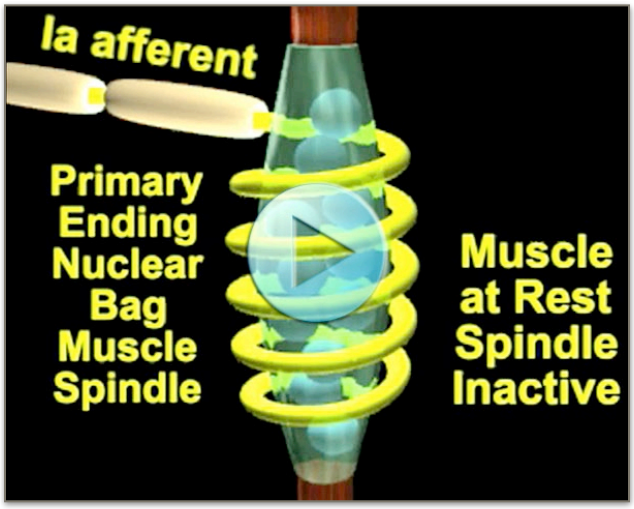


Fig 8-4. Muscle Spindle Activation Movie. Look and Listen (gec). GO TO: gmomm.pitt.edu *Fig8-4_Video*

Stretch of the Nuclear Bag Element of the muscle spindle is illustrated (note collection of nuclei in central equatorial non-contractile region of the muscle spindle). Stretch of the Primary Ending in the central region of the spindle creates generator potentials that depolarize the Ia afferent: see & hear action potentials generated at the nodes of Ranvier of the Ia afferent innervating the receptor as the primary ending coil is “unwound”.

Normally our motor system activates both alpha and gamma motoneurons for most contractions (alpha-gamma co-activation). Alpha motoneurons innervate the muscle fibers of a motor unit (Extrafusal Muscle or EFM). Gamma motoneurons innervate the

muscle fibers within the muscle spindle (Intrafusal Muscle or IFM). Since concentric loaded contractions produce a shortening of the EFM, the spindle capsule also shortens; with no gamma activation of IFM, receptor endings go slack and cease depolarization. If the IFM contracts, the non-contractile equatorial region will be stretched and the primary and secondary spindle endings will continue to be activated even as the whole muscle shortens (see animations).

Fig 8-5. Muscle Spindle Intrafusal Muscle Activation Animation. Watch the change in position of the vertical yellow lines when the muscle shortens and IFM does not contract or does contract (gec). GO TO: gmomm.pitt.edu *Fig8-5_Video*

However, gamma drive may be inadequate to fully maintain spindle sensitivity during very rapid concentric contractions. Even if the spindle endings cannot keep up with rapidly progressing events, they may be activated if a perturbation suddenly interferes with the progression of the contraction. Increasing the gamma dynamic drive increases the sensitivity to rapidly changing muscle lengths (coding the rate of change of muscle length/limb position). Increasing the static sensitivity due to increased static gamma discharge enhances spindle sensitivity to code the actual muscle length (position cue).

Intrafusal muscle (IFM) is a special type of muscle found only within the capsule of the muscle spindle. This distinguishes it from the striated extrafusal muscle (EFM) innervated by Alpha Motoneurons that form the motor units of the muscle. IFM is innervated by gamma motoneurons that live alongside Alpha Motoneurons in the Motor Nucleus of the Ventral Horn of the Spinal Cord. These Gamma Motoneurons are known as Fusimotor Neurons due to their innervation of Intrafusal Muscle. Dynamic and Static IFM have different contractile properties. Dynamic IFM is like amphibian slow muscle where no twitch is seen; only a slow contraction much like that of smooth muscle fibers. This provides a hysteresis (creep property) that is thought to give the dynamic spindle fiber its ability to signal length transient information. Static IFM has a twitch property characteristic of other striated muscle and is associated with fibers that give 'true' static length information. The contractile portions of the IFM are located at the polar regions of the spindle fibers, while the central, equatorial zone is non-contractile. This provides a

mechanism to elongate the central zone where the stretch-sensitive primary & secondary spindle endings are located.

Fig 8-6. Alpha-Gamma CoActivation Animation Movie. Watch the afferent & efferent activation when the muscle is stretched or when the muscle contracts-without (left) & with (right) gamma motor action (gec). GO TO: gmomm.pitt.edu [Fig8-6_Video]

MUSCLE CONTRACTIONS AND PROPRIOCEPTIVE FEEDBACK SIGNALS

When we contract our muscles there is a flood of impulses traveling to the muscle from alpha & gamma motor axons and from the muscle back to the spinal cord (Group Ia afferents from primary endings of muscle spindle elements, Group Ib afferents arising from the GTO receptors, and Group II afferents from secondary endings of the muscle spindle elements). The Muscle Proprioceptor Activation Movie shows the relationship of muscle afferent and muscle activity during different types of movements. The Primary (Ia afferent) and Secondary (II afferent) Endings of the Muscle Spindle and the Golgi Tendon Organ (Ib afferent) have relatively little activity during passive motion. By contrast, when the muscle is loaded the alpha and gamma motoneurons are very active as are the muscle proprioceptors (colored impulses entering & exiting the muscle). Note the increase in Ia & II afferent discharge when muscle lengthens, and increase in GTO firing as the muscle generates force. Group Ia from the primary endings provides dynamic and static information about muscle length. II afferents from secondary endings of the spindle provides only static muscle length information. When a sudden perturbation transiently halts the progression of a loaded contraction, The Ia bursts while the II afferent becomes silent during the quick stretch. Records show firing rates (instantaneous frequency) of the axons or motor unit potentials over the course of the motion (Muscle EMG = Audio). This movie provides one example of the sensorimotor links that exist when we move. Proprioceptors are active when the muscle is active and the gamma system is quiet until gamma motoneurons are coactivated with alpha motoneurons i.e., when the muscle is contracting. Note that only the Ia afferent provides

a clear signal of a sudden perturbation during a loaded muscle contraction due to the dynamic primary ending of the Nuclear Bag[1] muscle spindle receptor.

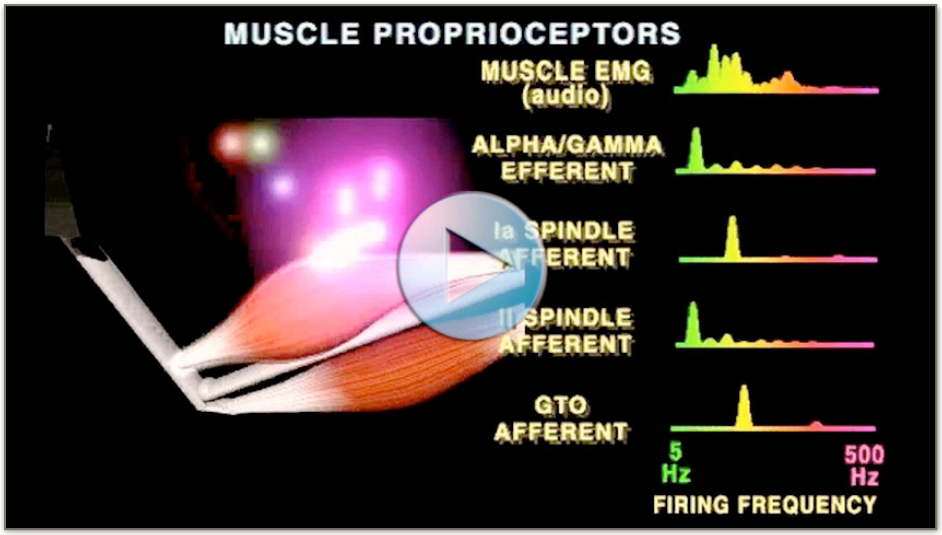


Fig 8-7. Muscle Proprioceptor Activation Movie. Look and Listen (gec). GO TO: gmomm.pitt.edu *Fig8-7_Video*

ARTICULAR (SYNOVIAL JOINT) RECEPTORS: MOST INFORMATIVE AT EXTREMES OF RANGE

Articular (joint) receptors are found in the joint capsule (fibrous layer), ligaments (extrinsic and intrinsic), and periarticular fat pads associated with synovial joints of the axial and appendicular skeleton. At one time joint receptors were thought to have the key, if not exclusive, role of informing us about limb, neck or back position.

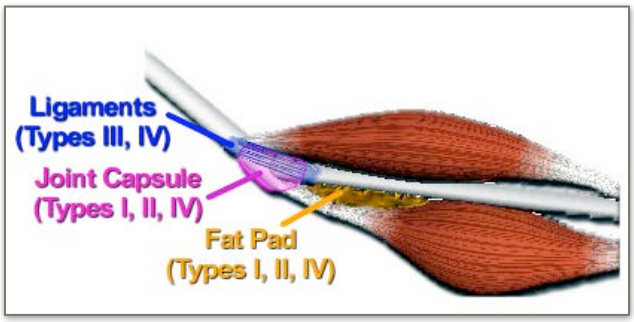
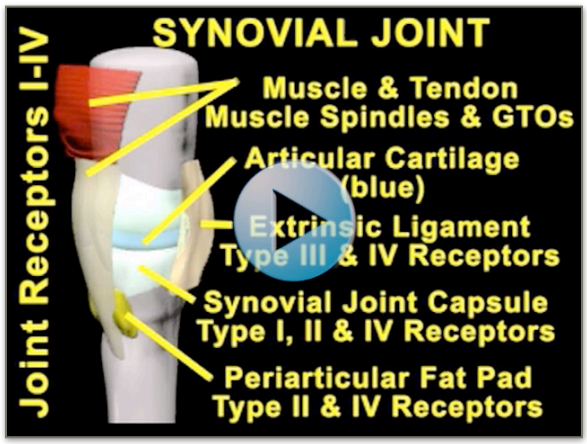


Fig 8-8. Summary of Joint Receptor Locations (gec).

Muscle receptors were once thought to have a minor role in conscious 'joint' position sense. Several lines of evidence now cast doubt on such notions regarding “conscious” proprioception.

Fig 8-9. Summary of Joint Receptor Locations & Functions (gec). GO TO: gmomm.pitt.edu *Fig8-9_Video*

There has never been much doubt about the inclusion of specialized muscle receptors for “unconscious” proprioception, e.g., muscle length and tension input to the spinal cord, brainstem and cerebellum from Muscle Spindle & Golgi Tendon Organ activation.



	Receptor Morphology	Location	Physiological Properties	Function (B. Wyke)*
Type I	Receptors Resemble Ruffini endings	Located in Fibrous but not Synovial Layer of Joint Capsule	Low-threshold, Slowly Adapting Response to Static (Position) Dynamic (Joint Motion) Stretch of Capsule within limited range for each receptor (poor at mid range)	Information about Static Joint Position and Motion- 'Angular' Velocity for Ends of Range > Mid Range
Type II	Receptors Resemble Pacinian or Paciniform Corpuscles	Located in Fibrous but not Synovial Layer of Joint Capsule & Fat Pads	Low-threshold, Rapidly Adapting Response to Dynamic, Rapid Joint Motion) of Capsule (Stretching of Joint Capsule or Deformation of Fat Pad)	Information about Joint Acceleration (but not Joint Deceleration)
Type III	Receptors Resemble Golgi Tendon Organs	Located in Extrinsic & Intrinsic Ligaments	High-threshold, Slowly Adapting Response to Stress on Joint Ligaments ?	Role is Uncertain but may Provide Information About Stress on Ligaments
Type IV	Plexi of Un-encapsulated Fine Free Nerve Endings	Located in Fibrous Capsule, Subsynovium, Ligaments & Fat Pads	High-threshold, Non-Adapting Response to Damage or Irritation of Tissues Due to Intrinsic or Extrinsic Factors: Noxious Mechanical, Chemical or Thermal Energies)	Thought to be Pain Receptors. They also Provide a Rich Source of Flexion Reflex Afferent (FRA) Input to Spinal Reflex Circuitry

Fig 8-10. Articular Receptor Morphology and Physiological Characteristics: Types I-IV.

According to recent evidence articular receptors do not have equivalent sensitivity to joint rotation throughout the full range of motion. The most comprehensive data have been obtained from the knee.

Receptors responsive to dynamic and static joint position are best activated at the ends of the joint range with little to “say” about the middle of the range. Yet we do not lose position sense acuity in the middle of the range. This has been explained by the contribution of muscle receptors to our position sense across the full range of motion. Our knowledge about joint receptors is somewhat limited by the relatively modest bank of information from a few researchers who have worked on joint receptors. Joint Receptors are Classified into Four Types (I-IV). The table describes the four joint receptor types according to B. Wyke’s classification: see: B. D. Wyke, The Neurology of Joints. Arris and Gale Lecture. Ann. Roy. Coll. Surg. Engl. 41: 25-50 (1967).

MUSCLE RECEPTOR ACTIVATION: A WINDOW INTO SPINAL MOTOR EXCITABILITY

MONOSYNAPTIC STRETCH REFLEX OR DEEP TENDON REFLEX: SPINDLE SENSITIVITY TO QUICK STRETCH

The monosynaptic stretch reflex or deep tendon reflex (DTR) is the simplest spinal reflex. The stimulus is a brief, rapid, small amplitude stretch of a muscle (such as tapping the muscle tendon). The receptor most responsive to this stimulus is the primary ending of the nuclear bag1 spindle ending.

Fig 8-11. Monosynaptic Deep Tendon Reflex (DTR) reflex pathway movie (gec). GO TO: gmomm. pitt.edu Fig8-11 _Video

The afferent pathway is the spindle’s Ia afferent that enters the spinal cord to synapse directly on the alpha motoneurons that innervate the homonymous muscle. The efferent pathway is the alpha motor axons that innervate the slow twitch (not fast twitch) motor units located within the muscle that was stimulated (homonymous muscle). The response is a brief muscle twitch of slow twitch motor units in the homonymous muscle. Inputs from the Ia afferents spread to other alpha motoneurons innervating synergistic agonist muscles but these excitatory inputs are typically subthreshold. Although not readily apparent, antagonist motoneurons are reciprocally inhibited. Despite the relative simplicity of the DTR, the effect of Ia input is modulated by descending pathways, spinal circuits, and other peripheral afferent input. Thus, even the monosynaptic reflex loop is modified by state- & task-dependent central processes in the intact sensorimotor system.

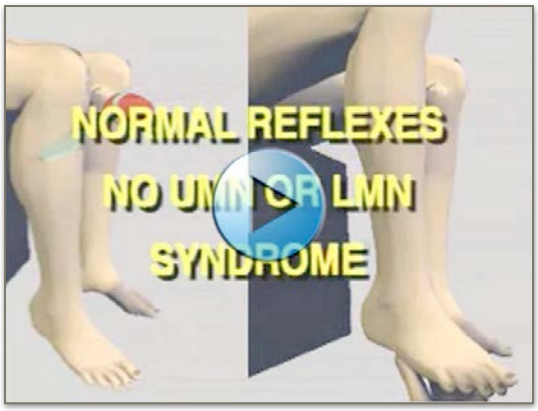


Fig 8-12. Knee Jerk, Ankle Jerk (DTR) Testing for an intact subject (gec, jec). GO TO: gmomm. pitt.edu *Fig8-12_Video*

The DTR is a useful clinical test to rule-out lower motor neuron (LMN) or upper neuron (UMN) disease when accompanied by other clinical tests in the screening exam.

A subject who has weakness due to a peripheral motor pathology (a lower motor neuron or LMN pathology) shows a hypoactive knee and ankle jerk response to tendon taps. A subject who has an UMN lesion typically shows a velocity-dependent hyperactive stretch reflex. This suggests that normally subthreshold Ia inputs now have suprathreshold effects in UMN lesions.

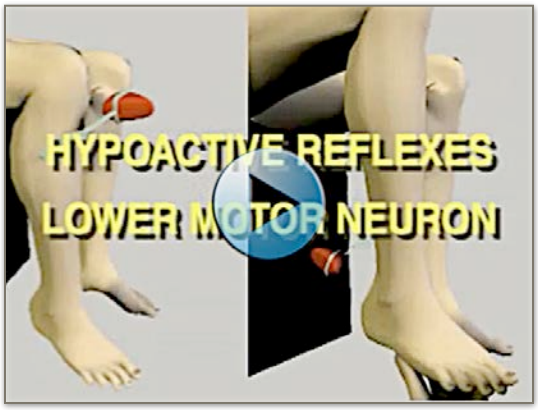


Fig 8-13. Hypoactive (reduced) Knee Jerk, Ankle Jerk in subject with LMN (Peripheral Motor) Disorder (gec, jec). GO TO: gmomm.pitt. edu *Fig8-13_Video*

Play the three movies that show normal DTR testing, lower motor neuron syndrome DTR testing and upper motor neuron syndrome DTR testing. Patellar Tendon (Knee Jerk) and Achilles Tendon (Ankle Jerk) tendon reflexes are illustrated.

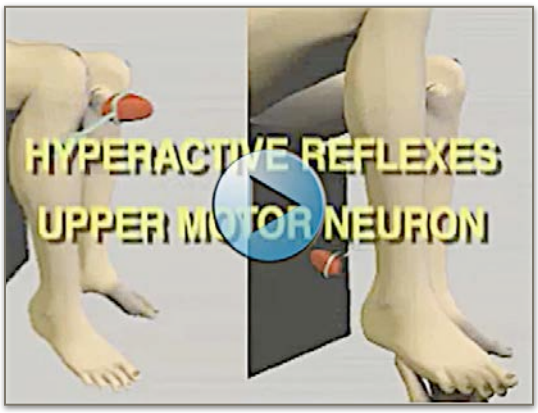


Fig 8-14. Hyperactive Knee Jerk, Ankle Jerk in subject with UMN (Central Motor) Disorder (gec, jec). GO TO: gmomm.pitt.edu *Fig8-14_Video*

T-REFLEX AND H-REFLEX MONOSYNAPTIC REFLEX ARCS ARE WINDOWS INTO CNS EXCITABILITY

Ia afferents have the lowest threshold to electrical stimulation for all peripheral axons. Ia afferents in the Tibial nerve activated at the lowest stimulus intensity evokes a monosynaptic reflex (Hoffmann or H-Reflex). As stimulus intensity is increased, slightly higher threshold A Alpha Motor Axons are activated to produce a direct activation of Soleus Motor Units (M-Wave). The very short latency M-Wave is followed in time by the H-Reflex due to stimulation of Ia afferents that

evoke a monosynaptic reflex response of the Soleus Alpha Motoneurons. Eventually, as stimulus intensity is increased, a maximal H-Reflex response occurs as more Motoneurons are brought to threshold. At maximal stimulation, all Alpha Motor axons are directly activated (Maximal M-Wave) in the peripheral nerve stimulated and the H-Reflex disappears.

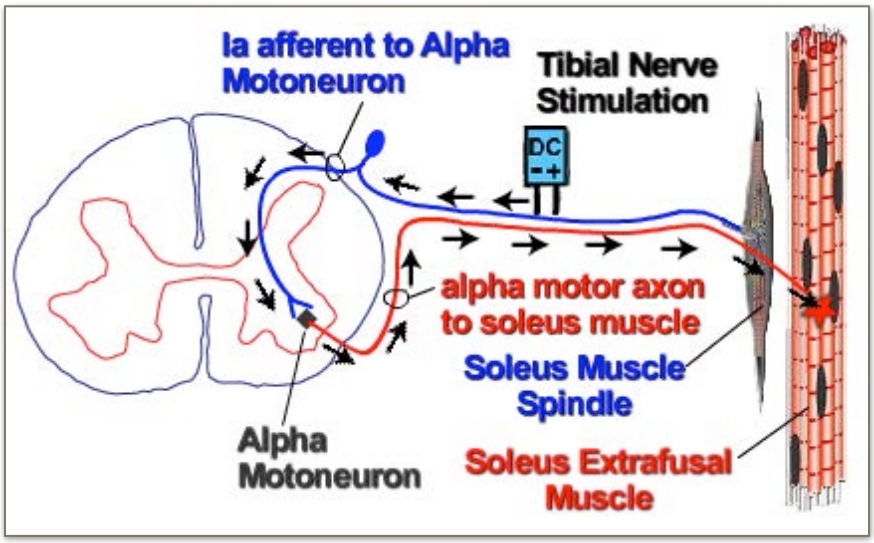


Fig 8-15. Monosynaptic Reflex Arc: H-Reflex Activation from Ia afferent to Alpha Motoneuron to Soleus Muscle (gec).

Loss of the H-Reflex is thought to be due to collision of Action Potentials (APs) in the Slow Twitch Alpha Motor Axons that are traveling orthodromically (from the spinal cord) with those APs traveling antidromically (towards the spinal cord). The T-Reflex (Tendon Reflex) & H-Reflex are short latency, monosynaptic spinal reflexes. Both reflexes utilize Ia Afferents as the afferent limb of the reflex and Alpha Motoneurons (AMNs) in the Homonymous Motoneuron Pool for the efferent limb.

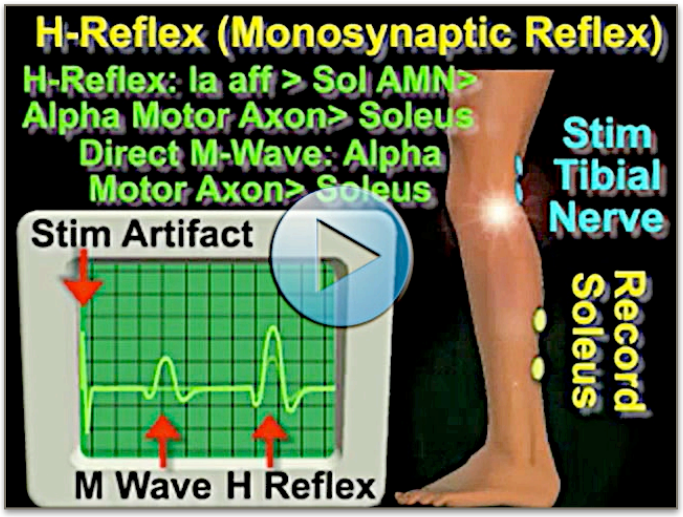


Fig 8-16. H-Reflex Technique Movie: M-Wave and H-Reflex Waveforms (gec). GO TO: gmomm.pitt.edu [*Fig8-16_Video*]

There is a single synapse: Ia to AMN. Both reflexes evoke a brief twitch contraction of a few slow twitch motor units in the homonymous agonist muscle. Shown here is the Achilles T Reflex and H Reflex. The stimulus for the T Reflex for the triceps surae muscles is a tap of the Achilles' Tendon with a reflex hammer. The H Reflex stimulus is a brief DC Pulse delivered to Ia afferents of the Tibial Nerve in the popliteal fossa. The responsive muscle is the soleus in both cases. These simple reflexes are subject to central modulating influences from spinal circuits and descending pathways.

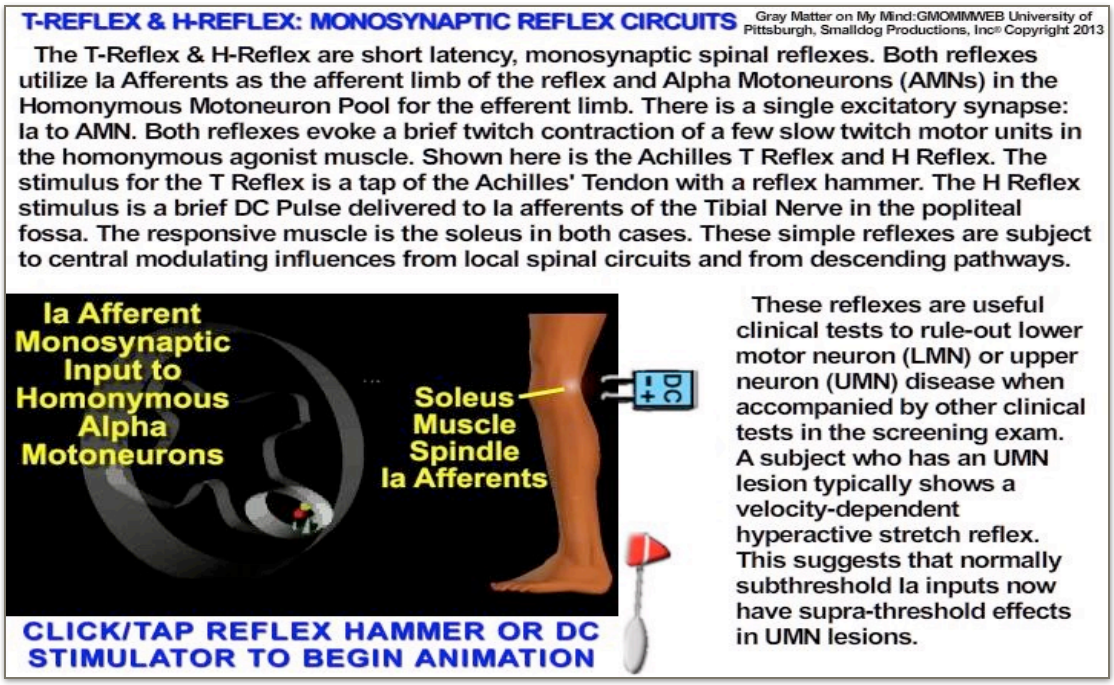


Fig 8-17. T-Reflex Vs. H-Reflex: Monosynaptic Spinal Reflex Pathway Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig8-17_Interactive Media*

SPINAL MOTOR EXCITABILITY: DESCENDING FACILITATION & RECIPROCAL INHIBITION

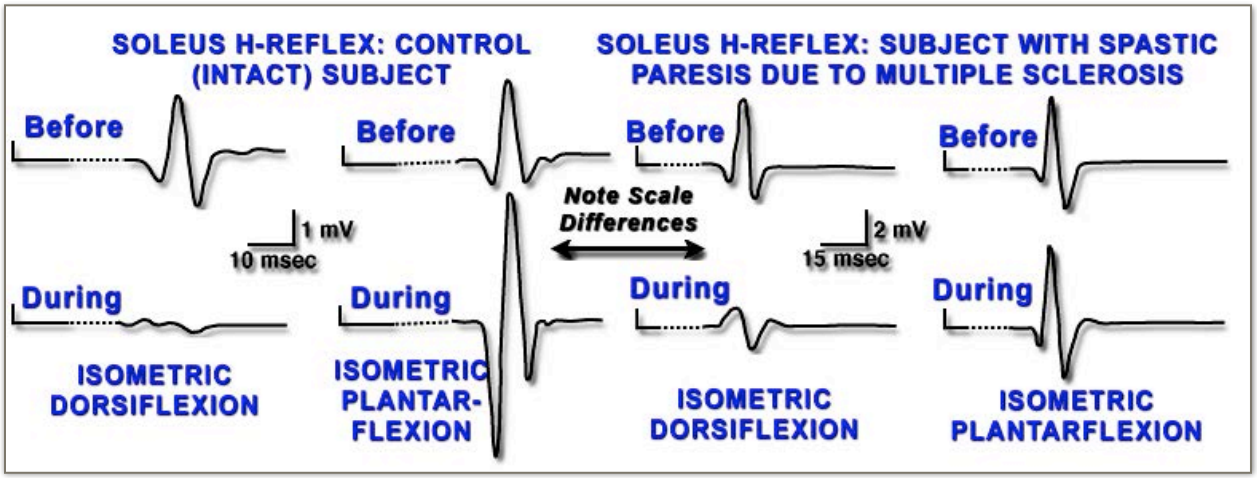


Fig 8-18. Normal versus Abnormal H-Reflex. Note the inhibited H-Reflex in the intact subject when slightly contracting the antagonist dorsiflexors and the facilitated H-Reflex in the intact subject when slightly contracting the agonist plantarflexors. Facilitation is much reduced and Reciprocal Inhibition is inadequate for high level motor control in the patient with an UMN disorder and spastic paresis of the involved limb. Retraced from CRO (Oscilloscope) Recordings. M-Wave not shown (gec).

The advantage of the H-reflex compared to the T-Reflex (Tendon Reflex) is control of the stimulus magnitude and the ability to elicit a reflex while the individual moves. The stimulus magnitude of the tendon reflex is not quantifiable when tapping a tendon with a reflex hammer. The H-reflex provides a noninvasive method of dynamically testing spinal segmental motor center excitability in human subjects performing motor acts.

SPINAL MOTONEURONS KEEP ON TRUCKIN' EVEN ON AN IMAGINARY TRIP

Motoneuron excitability in humans can be indirectly measured using H-Reflex testing while a subject performs a task. Recently, investigators have demonstrated a direct correlation of the H-Reflex with the force (and level of EMG) required for a task. This modulation of the H-Reflex does not require the actual output of force but merely the intent to act. The H-Reflex increases if a person pushes a foot pedal harder OR if the person just imagines the required level of force required for the task without actually performing the action. This suggests that the SMC motoneurons receive descending control signals related to both intentions and actual actions. The former signals appear to provide specific sub-threshold inputs to SMC neurons that also participate in the actual movement when stronger descending signals bring SMC alpha motoneurons to threshold. The actual location(s) of control that switches from sub-threshold to supra-threshold activation of Motoneurons has not yet been determined but is likely to involve both cortical and spinal components. In addition, descending pathway signals to gamma motoneurons from brainstem motor centers and from corticomotoneuronal pyramidal tract neurons in Area 3a will alter the gain of the stretch reflex circuitry for imagined and actual actions. Keep On Truckin' Movie shows a simulation of how this finding might relate to a daily task for many adults: driving. First part shows actual action. The second part shows observation of scenario without actual movement. EMG & H-Reflex of the Right Soleus Muscle and Brake Pedal Force are measured.

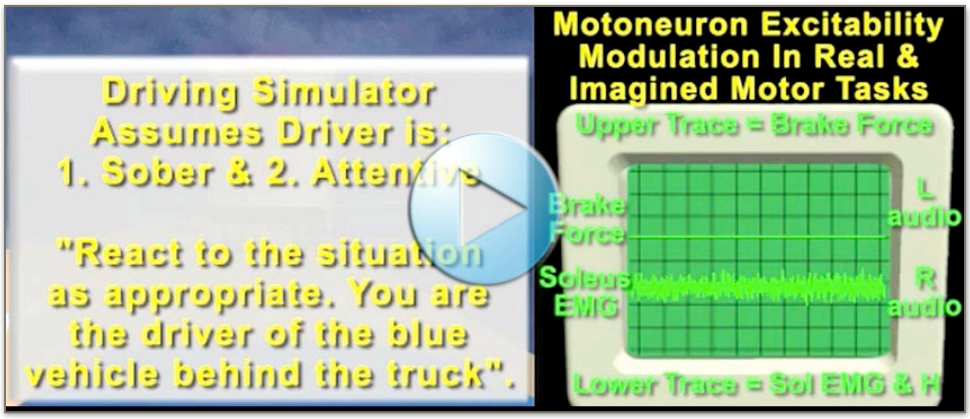


Fig 8-19. Keep On Truckin' Movie: Altered Spinal Segmental Motor Center Excitability even on an Imaginary Trip (gec). GO TO: gmomm.pitt.edu *Fig8-19_Video*

SPINDLES ON A TIGHT ROPE: MUSCLE AFFERENTS & EFFERENTS TO THE RESCUE.

Alpha-Gamma Coactivation has been generally accepted as the typical mechanism utilized for muscle recruitment. However, there is no consensus regarding the nature of the relationship: fixed or flexible? Direct evidence regarding gamma motor activity in behaving subjects is lacking. Inferences from measures of spindle afferents and EMG in a limited number of studies suggest that gamma motor activity may be subject to conditions of the behavioral task. Spindle input and gamma output may rise when conditions require vigilance, precision in limb placement and rapid corrections to external perturbations of the moving limb for a challenging, novel task. Compared to normal overground gait, cats had marked increases in spindle afferent input and presumed gamma output when learning to walk on an elevated narrow beam or horizontal ladder. Both were difficult tasks: cats showed missteps, increased sway and hesitant progression. Ia afferents are very responsive to external perturbations. With practice one would expect fewer errors, faster movements and less need for afferent feedback as skill improves. Nevertheless, when needed, rapid adjustments to unexpected perturbations occur in skilled subjects if spindle afferents & efferents are intact. Recent evidence suggests that monosynaptic corticomotoneuronal control of Gamma Motoneurons may come from Area 3a of Somatosensory Cortex in primates.

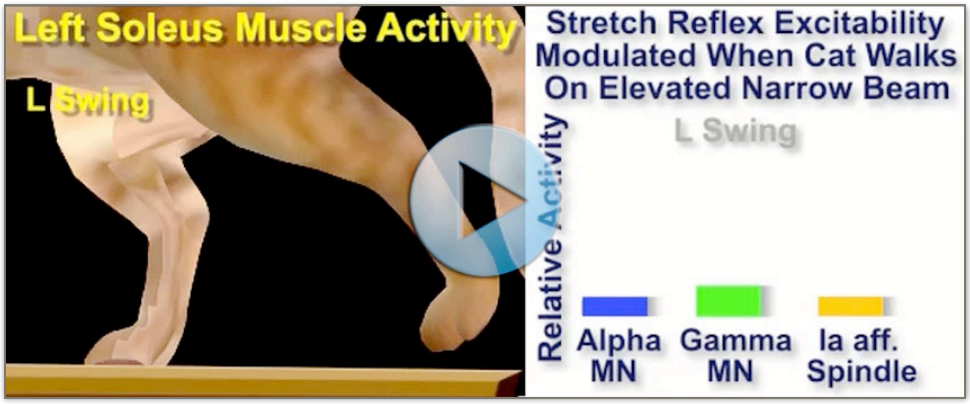


Fig 8-20. Cat Beam Walking: High Information Requirements for Precise Paw Placement (gec). GO TO: gmomm.pitt.edu
Fig8-20_Video

MATHEMATICS: NO SWEAT SOLUTION TO GAIN (INTRAFUSAL) MUSCLE TONE?

Alpha-Gamma Coactivation ensures that both Extrafusal (EFM) and Intrafusal (IFM) Muscle fibers will contribute to motor control for most of our movements. However, there are some instances where a flexible linkage may contribute to subthreshold events within Segmental Motor Centers. Thus Gamma motoneuron (GMN) activity may differ according to the requirements for proprioceptive information in novel, difficult tasks requiring attention, vigilance and rapid responses to, or preparation for, impending perturbations. Although increased spindle afferent input may not bring Alpha Motoneurons (AMNs) to threshold, subthreshold facilitation may provide a mechanism for future recruitment of some AMNs & active suppression of others.

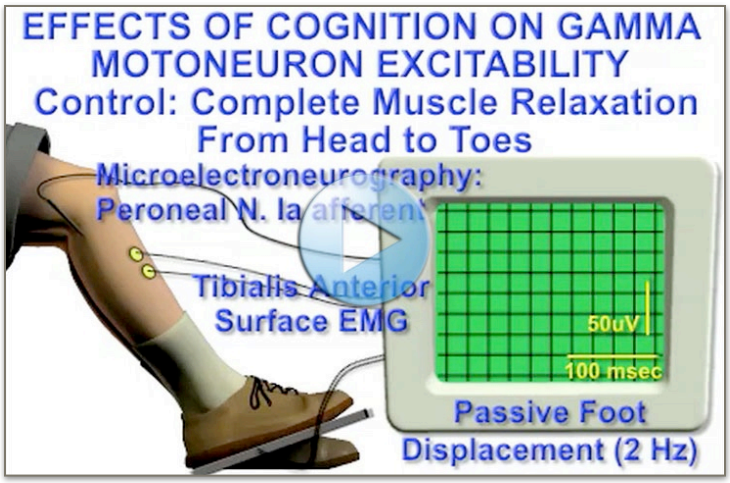


Fig 8-21. Mathematical Solution to Enhance (Intrafusal) Muscle Tone (gec). GO TO: gmomm.pitt.edu *Fig8-21_Video*

Although there is conflicting evidence regarding GMN activation independent of AMN firing, some animal & human studies suggest that IFM "tone" may be increased due to central mechanisms associated with arousal, attention, cognition & "mental" rather than physical effort is expended by the individual. Don't expect such mental effort to transform you into a hulk; physical effort is required to build muscle mass at least in primates. Watch the movie "Effects of Cognition on Gamma Motoneuron Excitability" and you "do the math."

ASCENDING PROPRIOCEPTION PATHWAYS: DORSAL NUCLEUS OF CLARKE, DORSAL SPINOCEREBELLAR TRACT & CUNEOCEREBELLAR TRACT

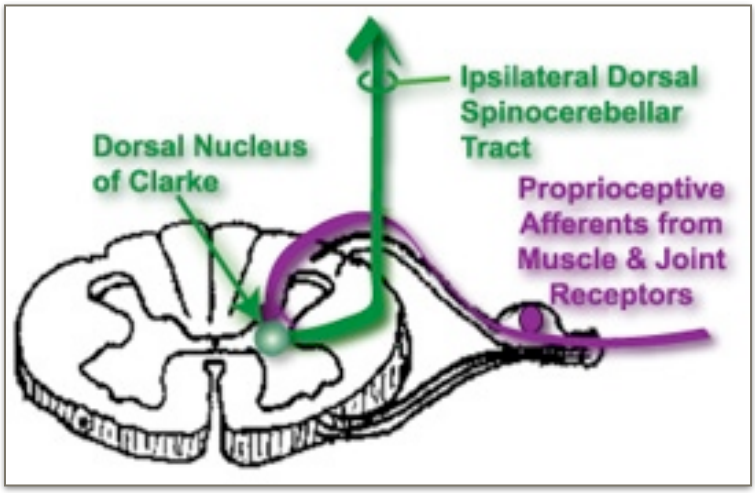


Fig 8-22. Proprioception: Dorsal Nucleus of Clarke and Dorsal Spinocerebellar Tract (gec).

The Dorsal Spinocerebellar Tract (DSCT) provides the major pathway for proprioception & peripheral feedback for ongoing sensorimotor events of the trunk & leg. The DSCT originates primarily from projection neurons located in the ipsilateral Dorsal Nucleus of Clarke (DNC). This column of cells extends from the first thoracic to the lumbar segments of the cord in the medial aspect of the intermediate gray.

Large myelinated A fiber peripheral afferents from Muscle spindle, Golgi tendon organ, joint receptor and some tactile mechanoreceptor peripheral afferents synapse on DNC cells. These large myelinated peripheral axons provide rapid information flow into the CNS. DNC cells are influenced by descending pathways as well. Axons in the DSCT ascend to synapse on deep cerebellar nucleus cells and Granule cells in the Cerebellar cortex.

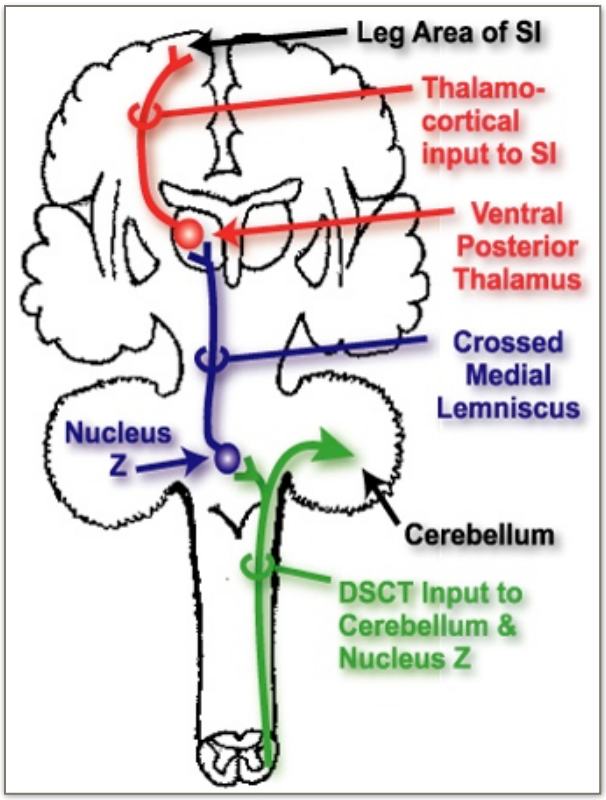


Fig 8-23. Dorsal SpinoCerebellar Tract (DSCT) Proprioceptive Pathway. Note pathway to cerebellum and to thalamus (gec). See Interactive Media file for all Ascending Tracts. GO TO: gmomm.pitt.edu

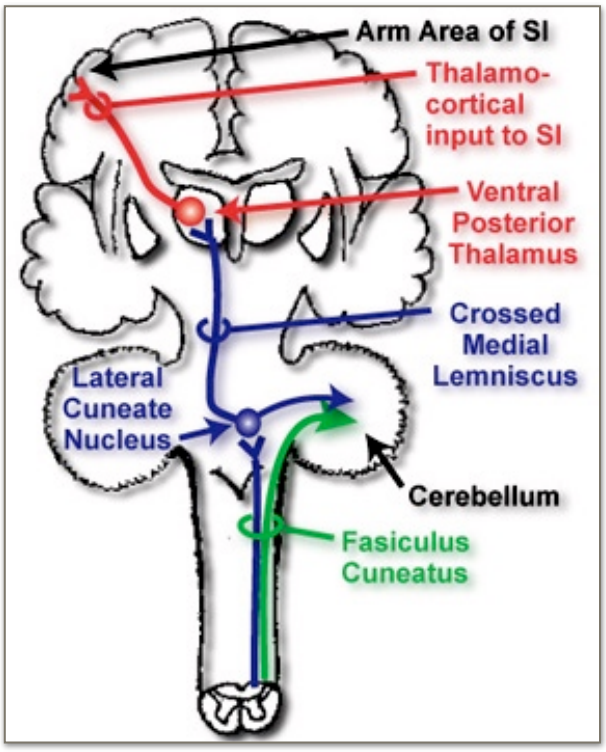
Fig8-23_Interactive Media

Axons also synapse on a medullary nucleus (Nucleus Z) located rostral to the dorsal column nuclei. Projection neurons in nucleus Z send their axons into the crossed medial lemniscus to synapse on neurons in the Ventral Posterior Nuclei (VPL) thalamus. VPL thalamocortical axons project to the Sensorimotor Cortex. The Cuneocerebellar Tract is a subset of axons traveling in the fasciculus cuneatus that project to the cerebellum and eventually to the thalamus as the upper extremity, neck, and upper trunk equivalent of the DSCT.

Fig 8-24. CuneoCerebellar and CuneoLemniscal Tracts: Upper Extremity Proprioceptive DCML Analog for the Lower Extremity/Trunk Proprioceptive DSCT (gec). GO TO: gmomm.pitt.edu

Fig8-24_Interactive Media

Dorsal root ganglion cells innervating proprioceptors & certain tactile mechano-receptors from the upper extremity and the neck project their central axon to the ipsilateral Lateral (External) Cuneate Nucleus in the medulla. Projection neurons in the Lateral Cuneate Nucleus send their axons to the Cerebellum and to the Contralateral Ventral Posterior (VPL) Thalamic Nucleus via the Medial Lemniscus. VPL projects to the Sensorimotor Cortex.



VENTRAL SPINOCEREBELLAR TRACT & "VENTRAL" SPINOTHALAMIC TRACT 3D MOVIE

The Ventral Spinocerebellar Tract (VSCT) provides an "efferent" copy of ongoing motor events from the lower trunk and lower extremity to the cerebellum. There are a number of neurons in the intermediate and ventral gray that project their axons into the contralateral > ipsilateral VSCT. These neurons are influenced by afferent proprioceptive and tactile inputs and by collaterals from propriospinal neurons and interneurons in the segmental motor centers of the ventral horn. Many of the crossed axons cross back in the brainstem (i.e., its effect is as a bilateral pathway). This pathway is active during ongoing motor output and will remain active even if peripheral afferent input is removed. This crossed tract sends axons by way of the superior cerebellar peduncle to portions of both ipsi- and contralateral cerebellar cortex and deep cerebellar nuclei. An equivalent pathway for the upper trunk, neck, and upper extremity is found in the cuneocerebellar tract.

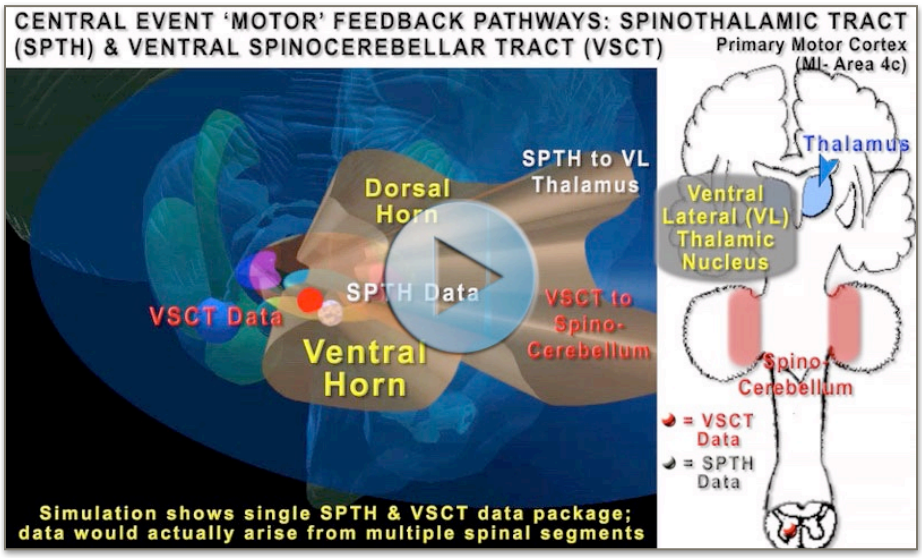


Fig 8-25. VSCT and "Ventral" SPTH Central Event Feedback Pathways in 3D (gec). GO TO: gmomm.pitt.edu [Fig8-25_Video]

The Spinothalamic Tract (SPTH) is implicated in conducting pain, temperature and some touch information to the brain. SPTH arises from Spinothalamic Tract Neurons located in the spinal gray. While most SPTH cells are located in the dorsal horn, some SPTH neurons are residents of the intermediate gray and even portions of ventral horn gray. Ventral SPTH neurons (beneath the dorsal horn) are likely to relay information regarding integrative functions and information about what is going out of the spinal cord to effectors rather than data about sensory inputs. SPTH thalamocortical targets are multiple and not restricted to primary sensory areas. Both limbic and non-limbic areas are influenced by SPTH including Insula and Cingulate Motor Areas in primates, see Dum, et.al., 2009. Some SPTH neurons project to the Ventral Lateral (VL) and Ventral Posterior Inferior (VPI) thalamic nuclei which projects to the Frontal and Parietal Cortices. SPTH projects also to other thalamic nuclei associated with sensory, motor and limbic functions. Therefore, sensory, motor or integrated signals may not belong to any one tract or network.

LONG LOOP AUTOMATIC RESPONSES TO PERTURBATION: FUNCTIONAL STRETCH REFLEX

A prolonged perturbation of a limb typically evokes not only a short latency spinal stretch reflex response but also long loop muscle responses. Long loop responses are not seen with a brief quick stretch such as a tendon tap. The long loop responses are thought to be due to long latency circuits utilizing brainstem centers and transcortical pathway including motor cortex. The long loop response is known also as a functional stretch reflex (FSR), although cutaneous receptors as well as muscle proprioceptors may contribute to the long loop response. The automatic FSR can be suppressed by "volitional", intentional "yield" to the perturbation. Predictive information such as visual cues may allow the subject to non-consciously preload the limb to stiffen it and reduce the extent of limb displacement when the external load is actually applied. Prevolitional automatic responses to perturbation have been called M1-M2-M3 responses. The M1 response is said to be the short latency spinal stretch response. The M2 and later M3 responses are thought to involve supraspinal pathways. The M2 may use spinal and brainstem centers as well as a possible transcortical loop. The M3 response is thought to be an even longer latency transcortical response (ascending input to somatosensory cortex and output from motor cortex).

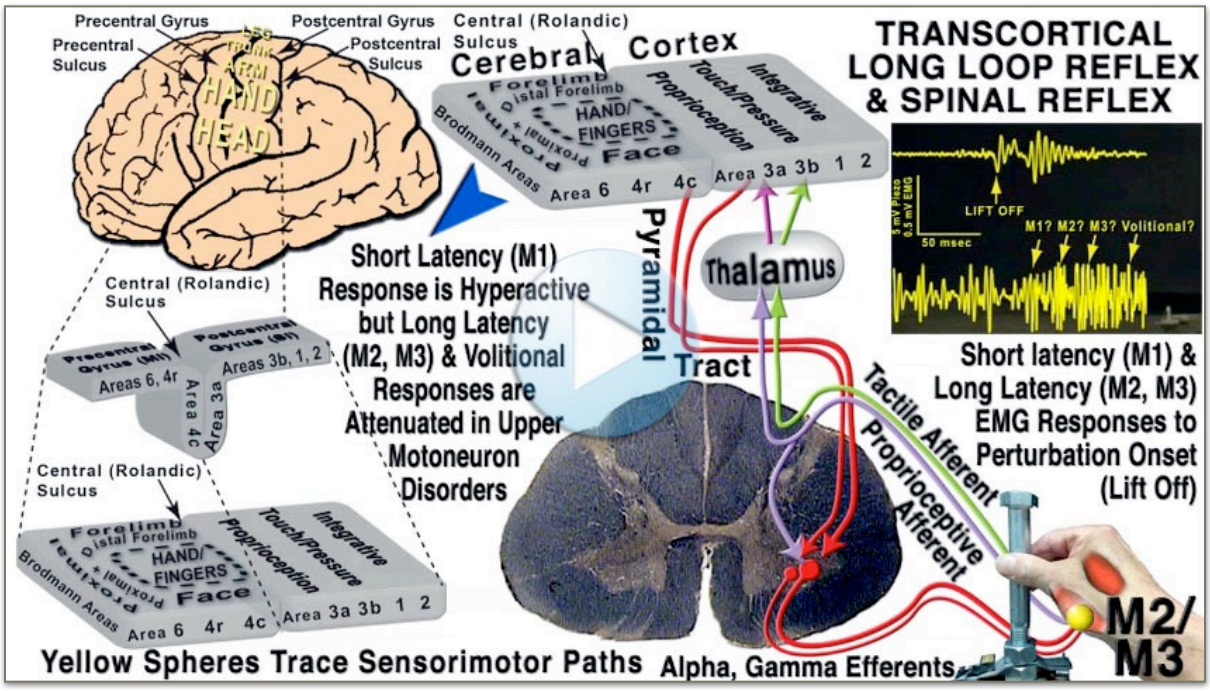


Fig 8-26. Transcortical and Spinal Circuitry for M1, M2, M3 Automatic Adjustments to Movement Perturbation(gec). GO TO: gmomm.pitt.edu Fig8-26_Video

Typically there is a delay between each of the responses (M1, M2 and M3) although in some instances the M2 and M3 responses may merge at least for upper extremity

responses. While the exact circuitry for the long loop responses is unknown, an Upper Motor Neuron (UMN) lesion due to a lesion of the sensorimotor cortex or the internal capsule results in altered responses to perturbations. The hemiparetic limb muscles show an exaggerated M1 response (hyperactive stretch reflex) but NO or much attenuated M2, M3 and later volitional responses. If the nervous system is intact "volitional" EMG activity follows (blends with) the M3 response.

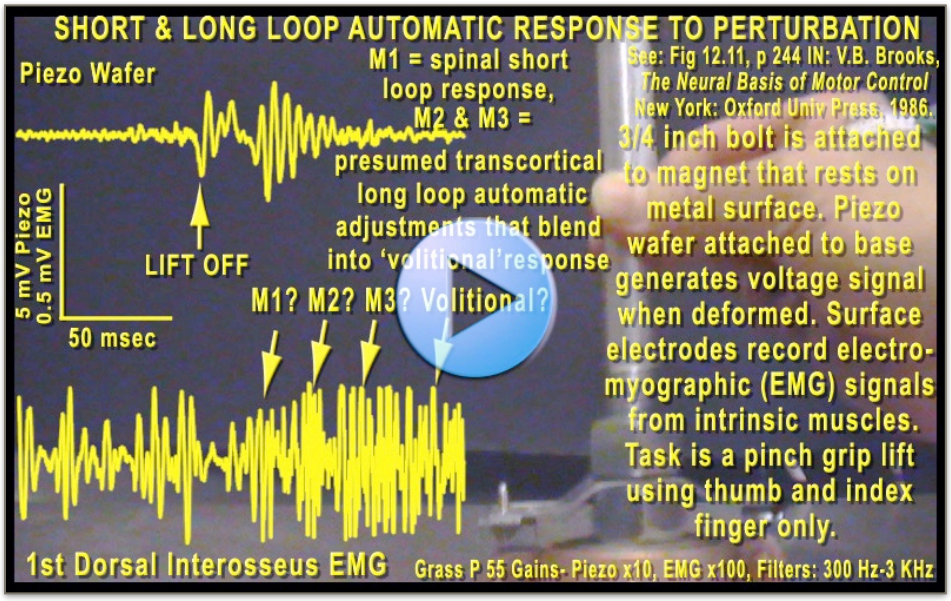


Fig 8-27. Perturbation of Pinch Force: M1, M2, M3 Automatic Adjustments Movie (gec). GO TO: gmomm.pitt.edu Fig8-27 _Video

Volitional responses to stimuli as tested by Reaction Time (RT) experiments show latencies of ~150-250 msec for simple RT while any uncertainty due to complex RT protocols delay response onsets up to 300 msec or later. An example of these three automatic responses to perturbation is shown in the *Perturbation of Pinch Force: M1, M2, M3 Automatic Adjustments Movie (gec).* The subject is pinching & tugging on a bolt attached to a strong magnet resting on a metal surface. When the magnet suddenly "lets go" by sufficient force the short loop and long loop responses are added to the background EMG recorded from the first dorsal interosseus muscle (surface electrodes).

CLINICAL PROPRIOCEPTIVE TESTING: PASSIVE & ACTIVE POSITION SENSE & ROMBERG AND "FINGER-TO-NOSE" ATAXIA SCREENING

Position sense may be tested passively by moving the subject's body part with vision removed or by active matching tasks. Active matching is typically done by moving one limb into a specific posture and asking the subject to match that position actively with the contralateral limb with vision removed. Aging may alter proprioception especially if there is sarcopenia and loss of or functional denervation of muscle receptors: the primary endings of muscle spindles (dynamic sensitivity) may be at greatest risk, e.g., see Miwa, et.al., 1995: Kim, et.al., 2007; Desaki and Nishida, 2010.

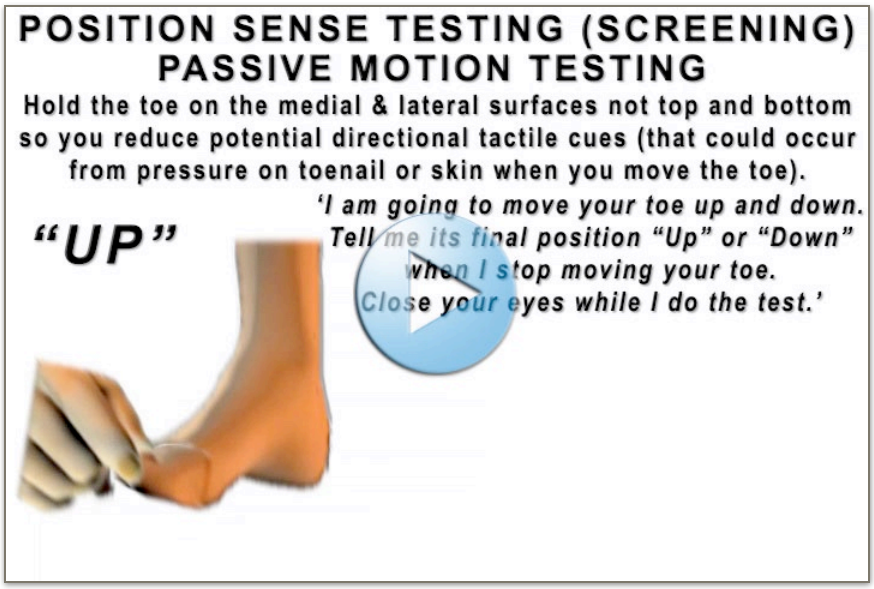


Fig 8-28. Passive Position Sense and Active Matching Testing of Proprioception (gec). GO TO: gmomm.pitt.edu
Fig8-28 Video

The subject must have adequate strength to perform the active matching test; do a manual muscle test before this proprioceptive test. Both tests require an alert, cooperative subject who is capable of understanding and following your directions. Test accuracy depends on many factors that limit this to a general screening test (compare sides). Nevertheless, conscious (which you are testing for passive motion) position sense and conscious/non-conscious active matching proprioception both require large myelinated afferents and one of two ascending tracts to be functioning; the Dorsal Spinocerebellar Tract (DSCT) for leg & trunk or the Dorsal Column Medial Lemniscal (DCML) Tract for arm & neck.

The Romberg Test is a simple test of static balance (station). The subject stands with feet together: first with eyes open and then with eyes closed. A positive Romberg test is one where the subject must step to regain balance with eyes closed but not with eyes open. It is a test for sensory ataxia.

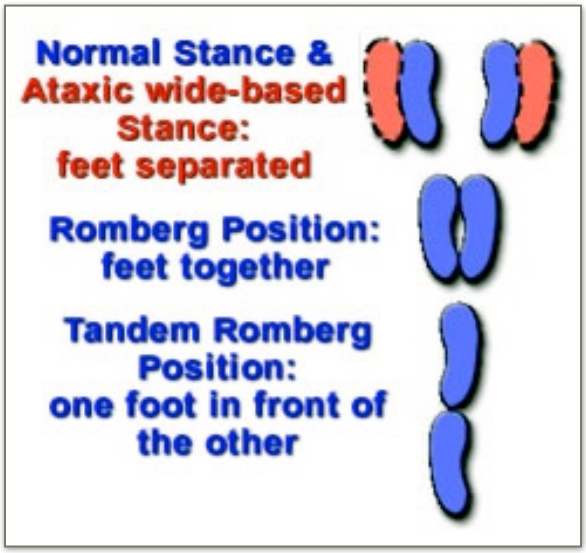


Fig 8-29. Footprints for Various Stance Conditions: Romberg Testing for Intact and Ataxic Subjects and Normal versus Ataxic Stance Profiles (gec).

Individuals who have sensory medial lemniscal and/or spinocerebellar long tract signs, and proprioceptive deficits of the lower extremities typically have a positive Romberg and sensory ataxia. An increase in sway with the eyes closed condition is not a positive finding. Placing the person in a Tandem Romberg position increases the challenge and may reveal more subtle sensory ataxic deficits. If the individual cannot get into the feet together stance (eyes open) without losing her balance, she has a negative Romberg but a positive test

for balance deficits (sway) likely due to a central sensorimotor postural disorder such as is found with cerebellar or central vestibular disease. Without visual and somatic cues, the vestibular system cannot readily detect or compensate for the small slow drifts in the center of mass that lead to the postural imbalance when eyes are closed. Proprioceptive deficits may lead to an abnormal wide-based gait and an inability to maintain a constant postural position of arms or even trunk such that the limbs may "wander" or the whole body may sway when the individual holds the arms outstretched for more than a few seconds with eyes closed.

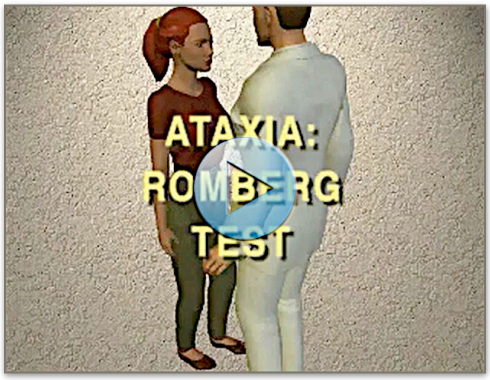


Fig 8-30. Romberg Test Movie: Intact versus Positive Romberg (Sensory Ataxia) (gec, jec). GO TO: gmomm.pitt.edu Fig8-30_Video

These movies show Romberg Testing (Standard Standing Romberg Stance) and Sensory Ataxia Testing using the "Finger-to-Nose" Test. The "Finger-to-Nose" Test is used most often to screen for cerebellar ataxia.

Fig 8-31. Sensory Ataxia Movie: Intact versus Proprioceptive Deficit Results for Finger-to-Nose Test (gec, jec). GO TO: gmomm.pitt.edu Fig8-31_Video

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Chapter 9

SOMATOSENSATION: PAIN & TEMPERATURE

Pain is not a primary sensation but is really an unpleasant experience that includes an emotional, autonomic and even a somatic motor component. It is a complex phenomenon that we do not like: it hurts! Chronic pain may lead to profound alterations in behavior and in the person's outlook on life itself.

PAIN IS AN UNPLEASANT EXPERIENCE NOT A PRIMARY SENSATION

Pain is:

> • "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Subcommittee on Taxonomy of International Association for Study of Pain, Pain 6: 250, 1979.
>
> • "That sensory experience evoked by stimuli that injure or threaten to destroy tissue, defined introspectively by every man as that which hurts." V.B. Mountcastle, Medical Physiology Vol. 1 Chapter 13, p 391, St. Louis: Mosby, 1980.

BRAIN INTERPRETATIONS OF AFFECTIVE QUALITY OF SOMATOSENSORY INPUTS

Somatosensory inputs often result in an affective overlay to the specific primary sense interpreted by the brain, e.g., see Craig 2002, 2003, 2009; Craig et.al., 2000; Dum et.al., 2009; Sewards & Sewards, 2002. A recent set of experiments shows how the quality of a stimulus can activate different portions of the brain. Intact adult subjects rated the relative affective quality of different textures. Subjects chose velvet as most pleasant compared to other samples and coarse sandpaper and a punctate metal tip as unpleasant (painful). The flat end of a wooden dowel was rated as neutral. Brain imaging (fMRI) revealed similarities and differences in activation of somatosensory and limbic cortical areas when each stimulus was moved across the surface of the subject's palm. The basic findings are simulated below (see: Rolls, et.al., 2003).

"NEUTRAL" AFFECT: Motion of flat-tip wooden dowel on the palm activates Contralateral Primary Somatosensory Hand Area (SI) and bilaterally activates the Second Somatosensory Cortex (SII) in the Parietal operculum.

"PLEASANT" AFFECT: Motion of velvet-tipped dowel on the palm activates the Hand Area of the Primary Somatosensory Cortex (SI) and to a lesser extent the Second Somatosensory Area (SII) in the Parietal Operculum (within the lateral sulcus). Velvet also activates limbic areas including portions of the Anterior Cingulate Cortex, Orbitofrontal Cortex and in some subjects the Amygdala.

"UNPLEASANT" AFFECT: The metal-tipped probe stimulus produced little activation of SI but intense activation was seen in Deep Parietal Opercular Cortex (Parietal Ventral = Area PV) and in Anterior & Posterior Portions of the Insula (areas known to respond to pain). Limbic Areas were activated, including a portion of the Cingulate Cortex and Orbitofrontal Cortex. In addition, this stimulus activated the Periaqueductal Gray (PAG) surrounding the Midbrain Cerebral Aqueduct. Interestingly, portions of the basal ganglia and some motor cortical areas were active as well (not shown). see: Rolls, et.al., 2003.

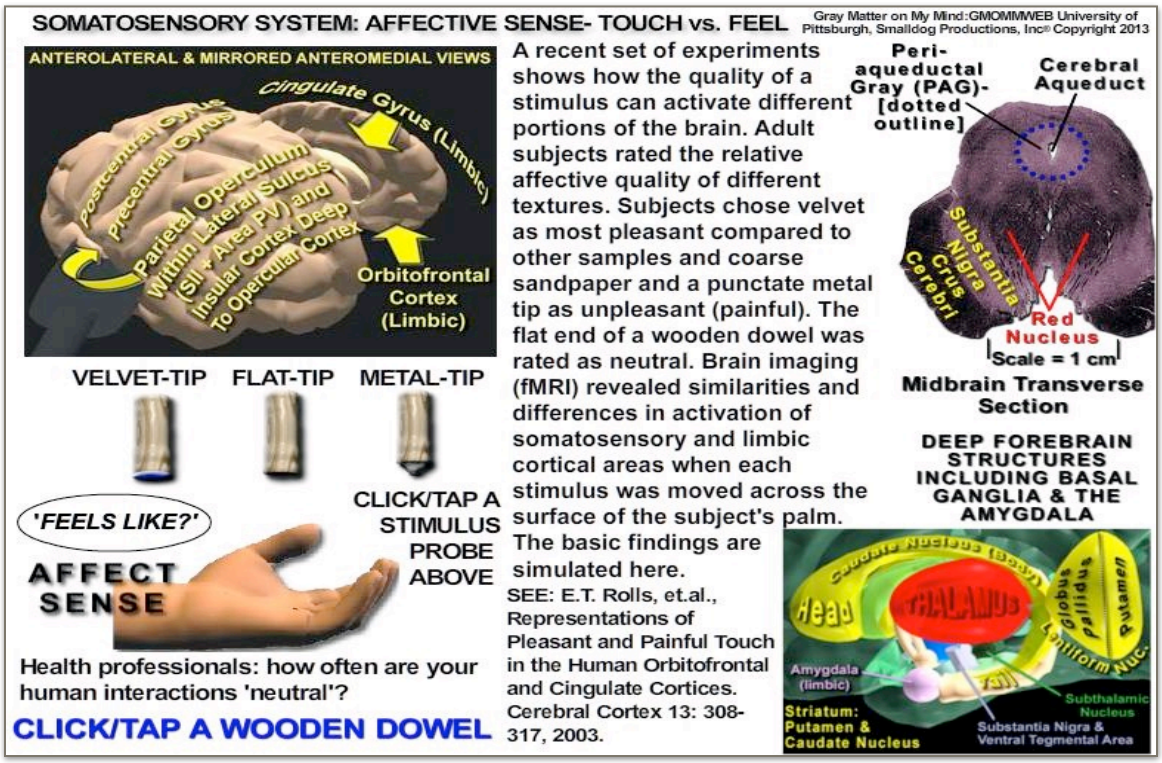

Fig 9-1. Affect Sense: fMRI Brain Imaging of Qualitative Sensory Experience Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig9-1_Interactive Media]

FREE NERVE ENDINGS: TRANSDUCTION OF PAIN, TEMPERATURE, ITCH & HIGH THRESHOLD "CONTACT"

Free nerve endings of A Delta and C fiber afferent axons typically terminate in a plexus. Although the endings have similar morphology seen at the light microscopic level, these endings may have a variety of differences in the intracellular details of organelles including vesicles that contain neurotransmitters (typically neuropeptides). Many endings have membrane receptors that bind neurotransmitters and chemicals released from the nerve endings or the tissue in which they are embedded (see below). Most free nerve endings of C fibers in humans are thought to be polymodal receptors that respond to noxious mechanical, thermal or chemical stimuli (slow pain) others are

associated with itch. Membrane receptors innervated by A Delta axons are said to be responsive to high intensity thermal or mechanical stimuli (fast pain).

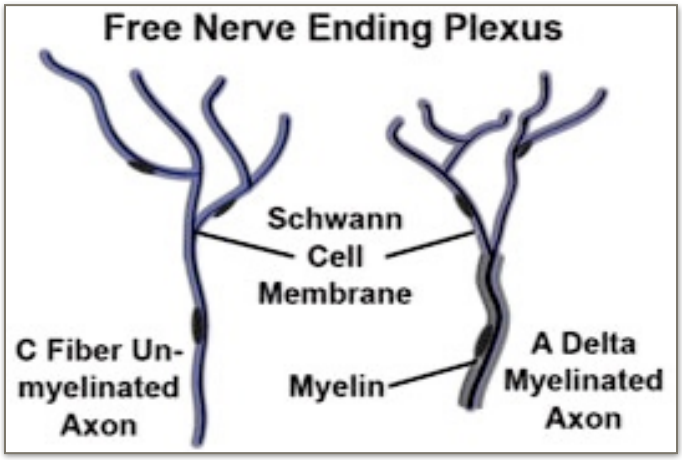

Fig 9-2. A Delta and C Axons Innervating Nociceptors (gec).

Injury & Inflammation of tissue causes multiple chemical reactions due to release of noxious ions or proteins from damaged cells, the blood and due to the release of Substance P from activated pain fiber terminals. Thus noxious stimuli trigger a "positive-feedback" reaction in the damaged tissue triggering "non-adapting" pain ending generator potentials (continuous pain transmission).

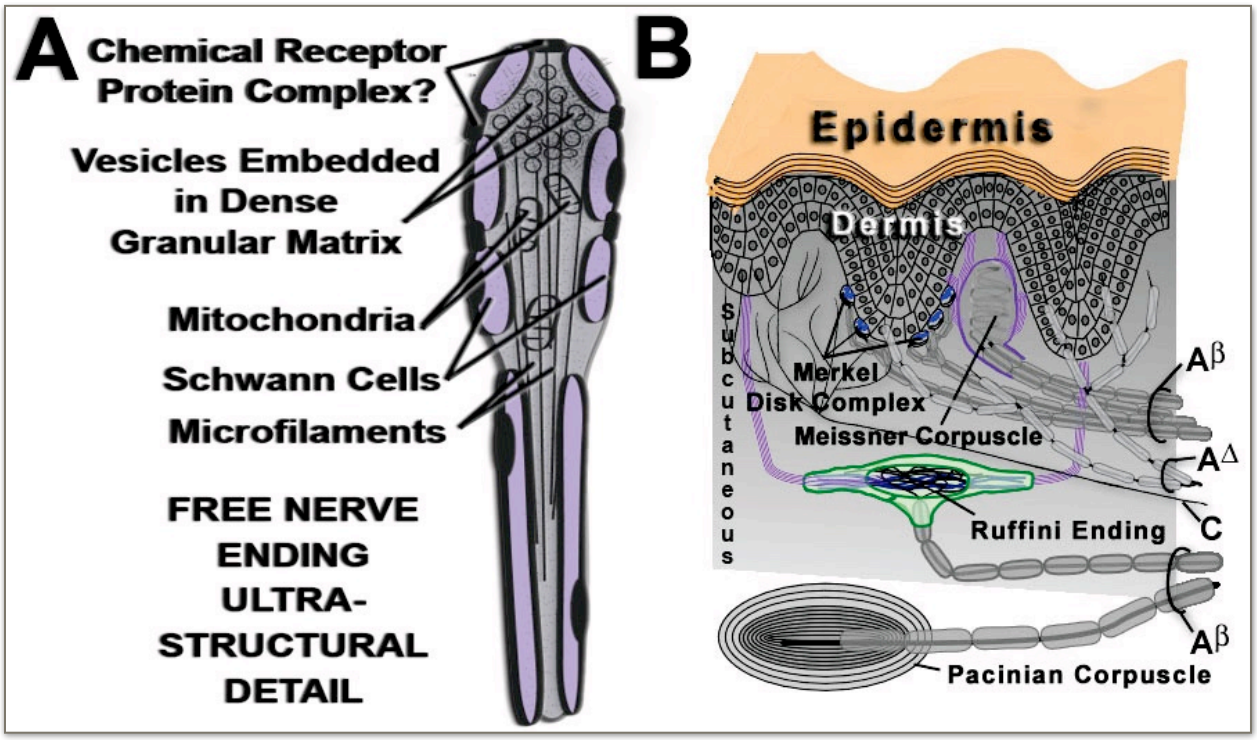

Fig 9-3. Nociceptor Morphology: Panel A shows ultrastructure of unencapsulated "free" nerve ending. A Delta & C fibers innervate Pain Endings in the skin (panel B) (gec).

Pain receptors respond to a "noxious alphabet soup" of chemicals that include: K^+ ions, lactic acid, prostaglandins (Pg), bradykinin (Br), substance P (SP), serotonin (5-HT), histamine (Hi), Calcitonin Gene-Related Peptide (CGRP), Cyclooxygenase-2 (COX-2) and other biochemical agents released from inflamed/injured cells or from blood vessels and nerve endings in these tissues. Many Non-Narcotic Analgesics work

by blocking the action of noxious chemicals in the periphery. Narcotics have their main effect on central pain-modulating mechanisms. Play Hurt Soup Movie.

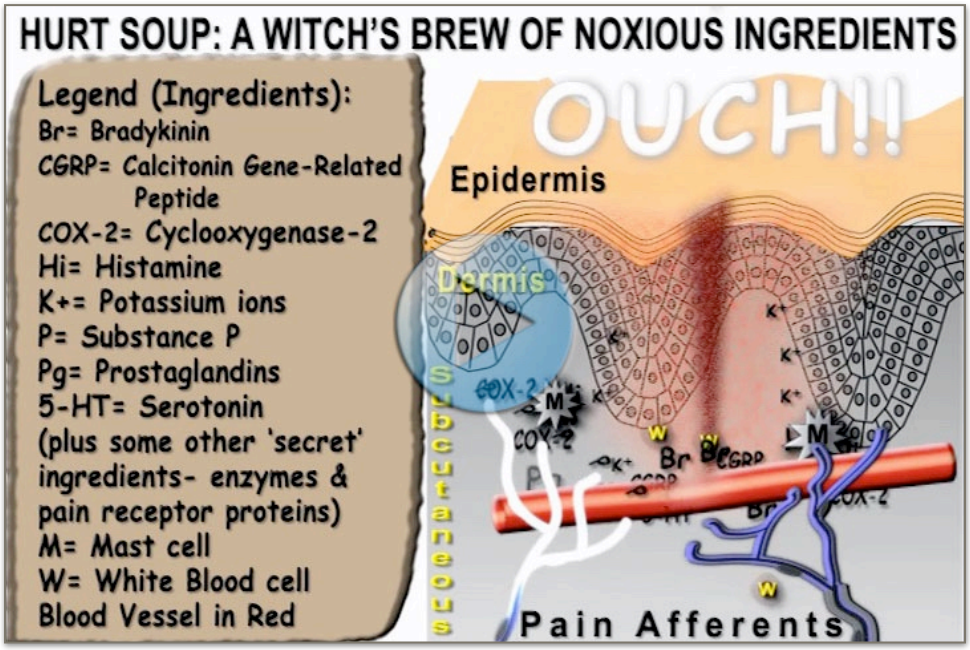

Fig 9-4. Hurt Soup Movie. A Witch's Brew of Noxious Ingredients (gec). GO TO: gmomm.pitt.edu Fig9-4 _Video

DORSAL HORN NEURONS: TOUCH, PAIN & TEMPERATURE

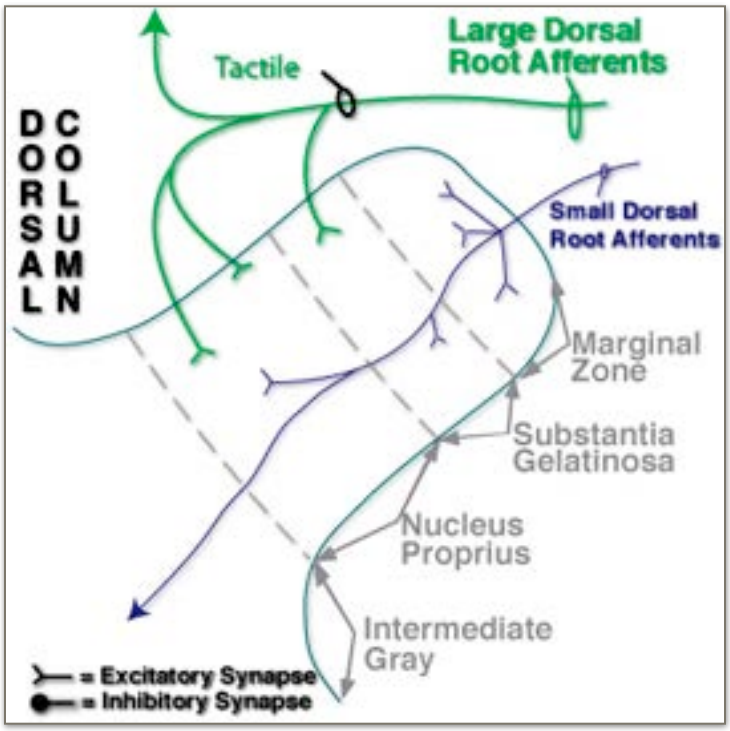

Fig 9-5. Dorsal Horn Outline: Marginal Zone, Substantia Gelatinosa and Nucleus Proprius (gec).

Small dorsal root afferents are lightly myelinated A Delta and unmyelinated C fibers. They enter the spinal cord as a bundle of axons in the lateral division of the dorsal roots. Large Dorsal Root are A Alpha (Group I proprioceptive) and A Beta Cutaneous (discriminative low-threshold tactile mechano-receptors) plus Group II proprioceptive afferents. They enter in the medial division.

The Dorsal Horn processes and relays somatosensory information that provides us with knowledge of our environment and the objects that we contact within our world. Different portions of

the Dorsal Horn receive Large and/or Small Dorsal Root Afferent input. This is our link to peripheral sensory events detected by somatic and visceral receptors. Like other areas in the nervous system, a network of interneurons and projection neurons integrates and "filters" this information before passing it along to other networks. Presented at once this circuitry can be overwhelming. Therefore, we will introduce you to the circuitry in stages.

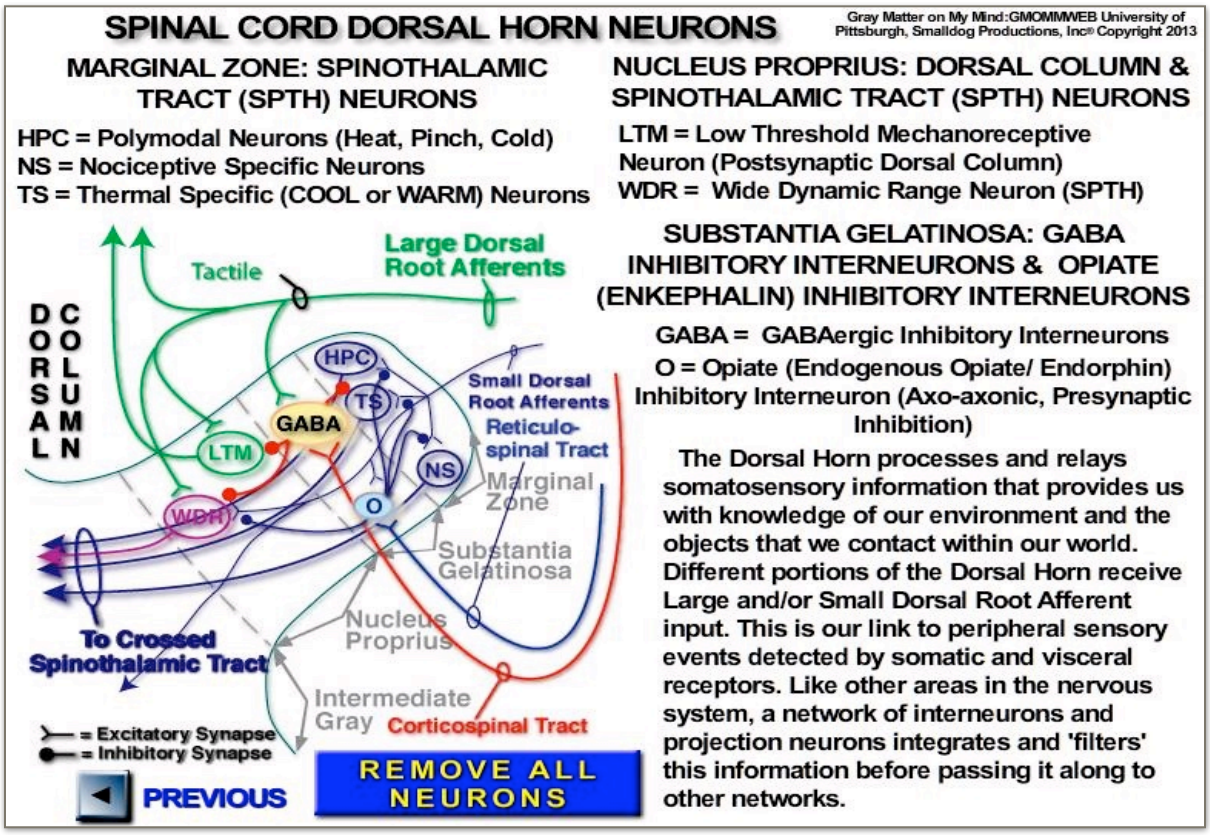

Fig 9-6. Dorsal Horn Neurons: Interactive Flash File allows you to add dorsal horn neurons in stages. All neurons are displayed in this figure from the Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig9-6_Interactive Media]

MARGINAL ZONE: SPINOTHALAMIC TRACT (SPTH) NEURONS

The Marginal Zone is a relatively thin "cap" on the dorsal horn that contains projection neurons (~half of all Spinothalamic Tract Neurons) that receive input from small dorsal root afferents that travel in Lissauer's Tract. These axons (small, lightly myelinated A delta and unmyelinated C fibers) innervate thermo-receptors, high threshold mechanoreceptors, or polymodal nociceptors located in skin or deeper tissues. Polymodal Receptors, innervated by C fibers in primates, respond to noxious mechanical, thermal or chemical stimuli. Some of these marginal zone neurons are nociceptive specific (NS), some are Thermal Specific (TS) "WARM" or "COOL" Neurons,

while others are polymodal nociceptive neurons that respond to heat, to high-threshold mechanical stimuli or to cold stimuli: Heat, Pinch & Cold (HPC) Neurons. The TS, HPC and NS projection neurons send their axons into the crossed Spinothalamic Tract. Marginal Zone projection neurons are influenced by local Substantia Gelatinosa interneurons that, in turn, are driven by peripheral afferent input, other local interneurons, & by certain descending pathways. Projection neurons in the marginal zone have a strong influence on thermal & pain responsive brainstem centers, parietal opercular cortex, cingulate cortex and the insula. These dorsal horn neurons may provide signals regarding changes in internal states, homeostasis, arousal and perhaps internally referenced objective and subjective feelings, e.g., see Craig references.

NUCLEUS PROPRIUS: DORSAL COLUMN AND SPINOTHALAMIC TRACT (SPTH) NEURONS

The Nucleus Proprius is located in the most ventral portion of the dorsal horn. It contains ascending long tract projection neurons. Low Threshold Mechanoreceptive (LTM) projection neurons form a post-synaptic projection to the dorsal column nuclei by sending their axon into the ipsilateral dorsal column to join primary afferent axons coming from dorsal root ganglion cells. The LTM neuron has input from large myelinated axons that innervate low-threshold tactile mechanoreceptors in glabrous or hairy skin.

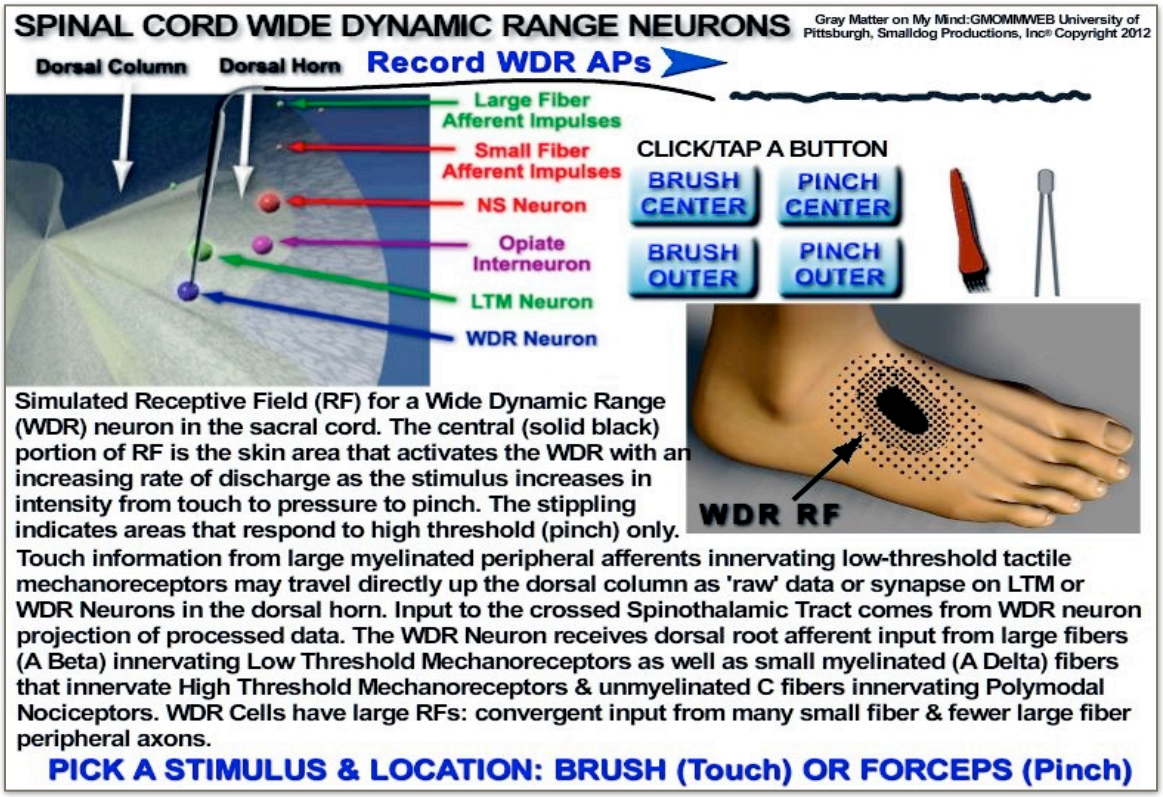

Fig 9-7. Wide Dynamic Range (WDR) Neuron Receptive Field Properties-An Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig9-7_Interactive Media]

LTM neurons are influenced by descending corticospinal tract axons and by local interneurons. Wide Dynamic Range (WDR) projection neurons send their axon into the Contralateral Spinothalamic Tract. Both large and small caliber dorsal root ganglion cell axons synapse on this class of neuron. WDR Neurons are so named because of their complex response properties, responding to a wide variety of somatosensory modalities, having dynamic receptive field properties. WDR neurons are influenced by local interneurons, and by descending axons from the cerebral cortex and brainstem. Other projection neurons in the Nucleus Proprius respond to high threshold inputs only (not shown). In addition, some neurons may project their axons to brainstem nuclei as uncrossed or crossed pathways (spinoreticulodiencephalic or spinotectal pathway)

SUBSTANTIA GELATINOSA: GABA INHIBITORY INTERNEURONS

The substantia gelatinosa (SG) is the middle zone of the dorsal horn containing Interneurons (INs) that modulate the discharge properties of projection neurons located in the marginal zone and the nucleus proprius. There are both excitatory and inhibitory interneurons that are influenced by peripheral afferent, descending pathway & spinal neuronal inputs. One of the inhibitory interneurons (GABA IN) postsynaptically inhibits Spinothalamic Tract Neurons (HPC, TS and WDR) and the Low Threshold Mechanoreceptive (LTM) Neuron. In addition, GABAergic INs may presynaptically inhibit peripheral afferent axons as they synapse on dorsal horn neurons (axo-axonic synapses not shown). GABA interneurons are influenced by Lateral Corticospinal Tract axons originating from Pyramidal Tract Neurons living in the Parietal Lobe, Frontal Lobe or Cingulate Gyrus. Thus, the cerebral cortex can modulate (gate) sensory transmission at the earliest stage of data processing. Descending control optimizes information flow.

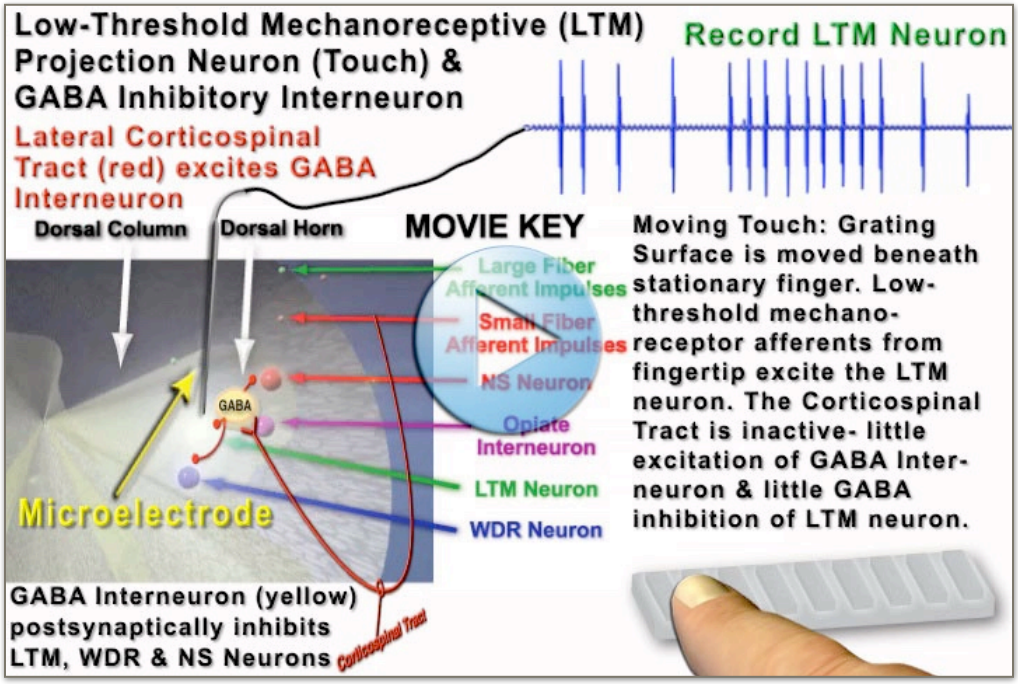

Fig 9-8. Low Threshold Mechano-receptive Neuron (LTM) and Descending Corticospinal Control Movie (gec). GO TO: gmomm.pitt.edu

Fig9-8 Video

SUBSTANTIA GELATINOSA: OPIATE INHIBITORY INTERNEURONS

The substantia gelatinosa (SG) is the middle zone of the dorsal horn containing Interneurons (INs) that modulate the discharge properties of projection neurons located in the marginal zone and the nucleus proprius. There are both excitatory and inhibitory interneurons that are influenced by peripheral afferent, descending pathway & spinal neuronal inputs. Besides GABA inhibitory interneurons, a second important group of inhibitory interneurons in the SG are "Opiate" Interneurons, so called because they utilize endogenous opiates (enkephalins) as neurotransmitters. "O" INs provide presynaptic inhibition (axo-axonic synapses) of small peripheral afferent axons as they synapse on Spinothalamic Tract Neurons in the dorsal horn. "Opiate" INs are activated by small fiber peripheral input and powerfully excited by descending Reticulospinal Tract axons originating from serotonergic projection neurons in the Nucleus Raphe Magnus and from other adrenergic brainstem nuclei. This "opiate" neuron mechanism selectively inhibits small but not large peripheral afferent input. Thus, pain may be inhibited while touch is still transmitted to the brain. Play Opiate Presynaptic Pain Inhibition Movie.

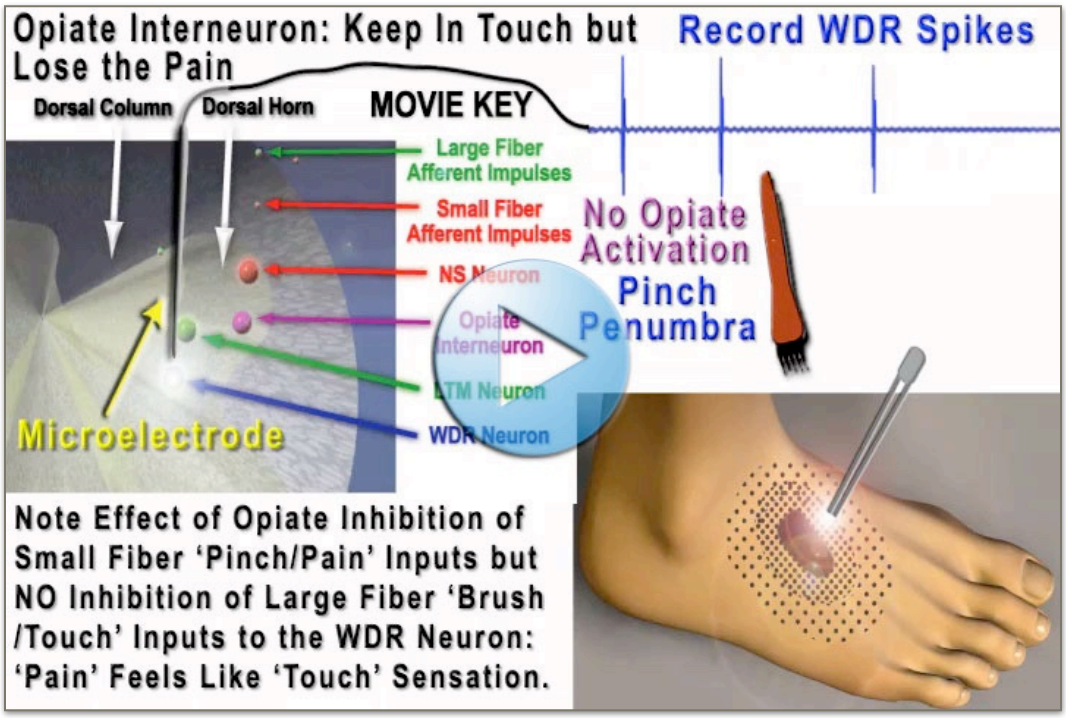

Fig 9-9. Opiate Pre-synaptic Pain Inhibition Movie: Keep in Touch But Lose the Pain (gec, dh). GO TO: gmomm.pitt.edu Fig9-9_Video

Pain afferents may be selectively inhibited before their signals can be passed along to the brain. Touch inputs signals survive and are transmitted to the brain. This selective axo-axonic pre-synaptic inhibition of small but not large fibers is illustrated in the Opiate Presynaptic Pain Inhibition Movie and the Pain Gating Movie.

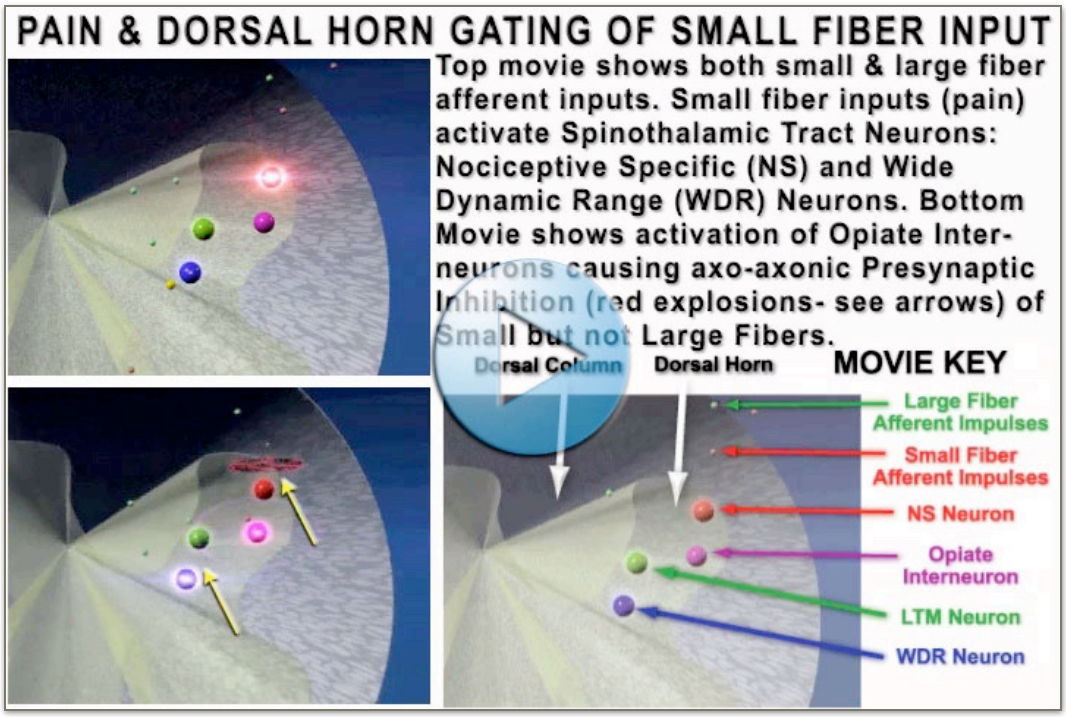

Fig 9-10. Pain Gating Movie (gec, dh). GO TO: gmomm.pitt.edu Fig9-10_Video

DESCENDING SEROTONERGIC SELECTIVE MODULATION OF PAIN AFFERENT INPUT

The Descending Pain Modulation Mechanism Simulation-Interactive Flash File animation shows the effect of this pain modulatory mechanism. The simulated PeriStimulus Time Histograms or PSTHs (spikes = vertical tic mark; figure shows cumulative spike count) are from a WDR Spinothalamic Tract Neuron in the dorsal horn of the sacral cord. The first animation shows discharges from the WDR neuron when electrically stimulating the sural nerve with low intensity (only fast, large A Beta fibers respond). The second animation shows responses when the sural nerve is stimulated with high intensity (fast, large A Beta and slower A Delta plus C fibers respond). When both the sural nerve and the Nucleus Raphe Magnus (NRM) in the Brainstem Reticular Formation are stimulated, the responses of the WDR neuron changes but only with high intensity sural nerve stimulation. The NRM provides a descending serotonergic activation of Opiate (O) Interneurons in the dorsal horn of the spinal cord.

When the Sural Nerve is stimulated along with the NRM, only small fiber input is inhibited (compare low to high intensity sural nerve stimulation animations). Note that only large fiber input continues to activate the WDR Neuron (loss of A delta and C fiber responses when sural nerve is stimulated with high intensity pulses plus NRM stimulation). This selective inhibition of the small fiber input is thought to be due to a descending serotonergic pathway from NRM (in brainstem reticular formation) to the opiate (enkephalin) interneuron in the substantia gelatinosa of the dorsal horn. This opiate (O) interneuron presynaptically inhibits small (but not large) fiber axon terminals as they synapse on WDR and other Spinothalamic Tract Neurons. Thus, touch (large

fiber input) is still signaled to the brain by WDR Neurons but pain is selectively blocked. See: K.D. Gerhart, T.K. Wilcox, J.M. Chung and W.D. Willis, 1981.

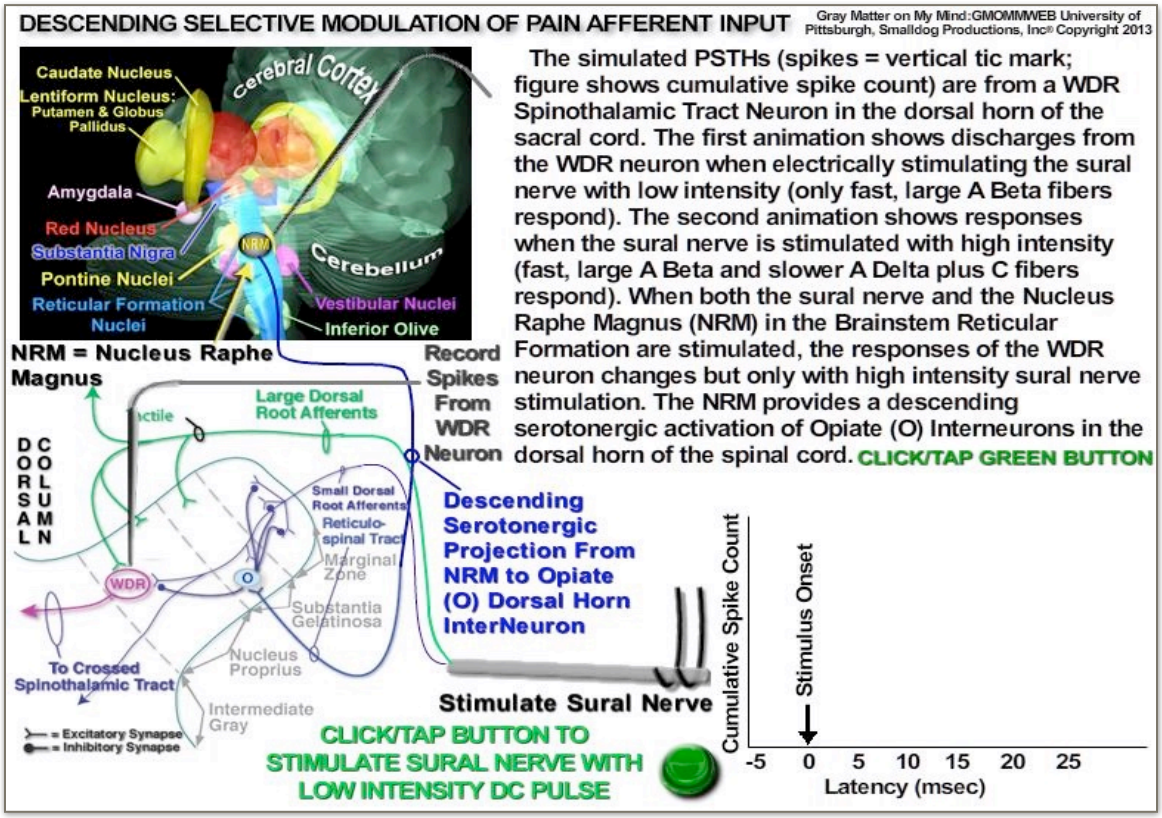

Fig 9-11. Descending Pain Modulation Mechanism Simulation-Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig9-11_Interactive Media]

SPINOTHALAMIC TRACT (SPTH): ASCENDING PAIN, TEMPERATURE AND "CRUDE" TOUCH SENSATIONS ARISING FROM DORSAL HORN PROJECTION NEURONS

The Spinothalamic Tract (SPTH) is the ascending pathway for pain, temperature and touch. It originates from Spinothalamic Tract Neurons in the contralateral dorsal horn. Some SPTH Neurons receive input from large myelinated and from small lightly myelinated or unmyelinated peripheral afferents. Other SPTH Neurons receive input only from small fibers innervating thermal or pain receptors. SPTH provides information to localize pain and identify gradients of both temperature & noxious stimulus. SPTH "processed" data are modulated by local interneurons and by descending pathways. Additional SPTH neurons are located in the Intermediate Gray and a few in the ventral horn. SPTH has input to Motor, Limbic and Integrative Higher Order Thalamic Nuclei. Insular, Second Somatosensory, MI and Cingulate Motor Cortex are targets of these thalamic nuclei receiving inputs from SPTH. The SPTH has collaterals to brainstem pain

centers, autonomic centers and some axons synapse on neurons in midline thalamic nuclei that project to somatosensory pain areas, insular cortex and neuroendocrine brain structures. These subcortical structures often receive inputs also from the spinoreticulodiencephalic pathways as part of the anterolateral system.

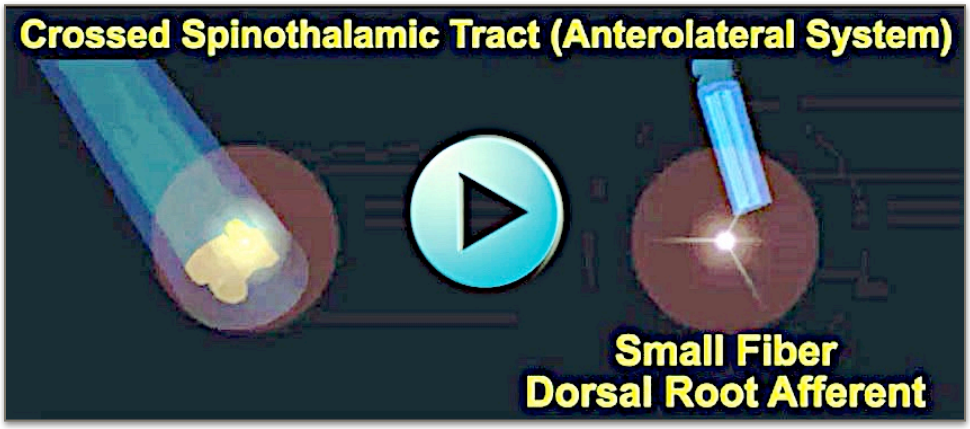

Fig 9-12. Spinothalamic Tract 3D Movie (gec, dh). GO TO: gmomm.pitt.edu Fig9-12_Video

The SPTH Movie shows this spinothalamic highway to you as if you are a participant in the impulse traffic and as an observer from above. The point of this movie is to give you a sense of the dynamic flow of information as it travels from periphery to SPTH neurons in the dorsal horn, then to thalamus and finally to somatosensory cortex.

BRAIN AREAS RESPONSIVE TO PAIN & THERMAL INPUTS

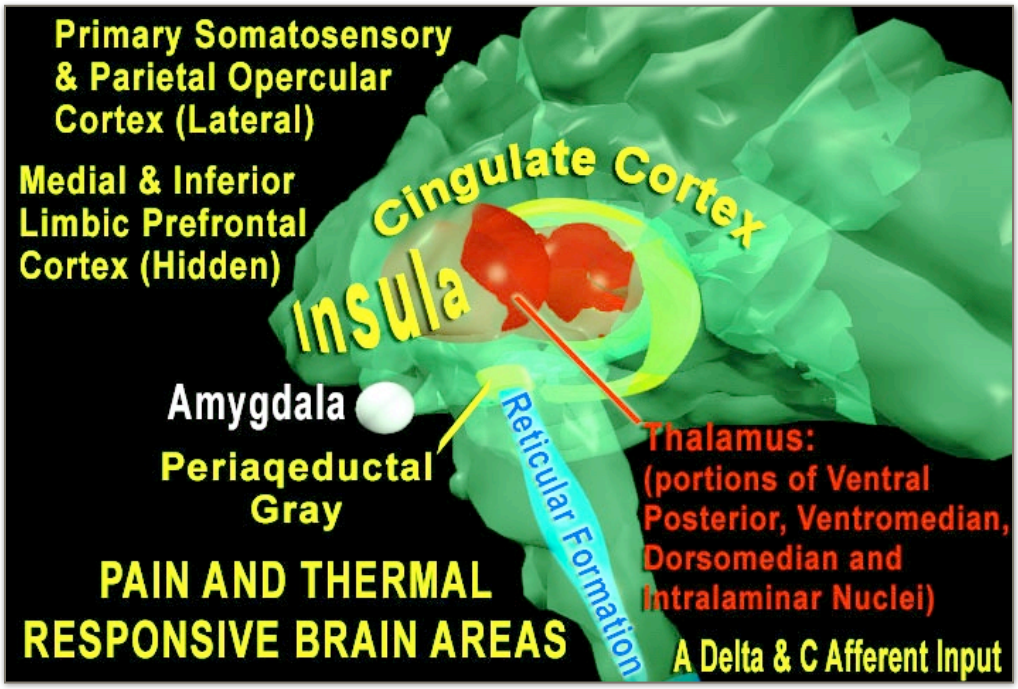

Fig 9-13. Cerebral Cortical and Brainstem Areas Responsive to Pain and Thermal Inputs. See also Limbic Labeled Movie (gec). GO TO: gmomm.pitt.edu Fig9-13_Video

Small fiber A delta and C afferent inputs to the spinal gray and brainstem cranial nerve nuclei influence multiple CNS centers within the brainstem, thalamus and cerebral cortex. Few of these brain areas are

classically defined as sensory areas. Most are limbic and non-limbic integrative areas which helps to explain pain as an emotional as well as a sensory experience and as a strong drive for autonomic and motor behaviors. Moreover, pain provides a powerful drive to activate complex endogenous opiate pain modulatory circuitry at multiple levels of the neuraxis.

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Chapter 10

CEREBRAL CORTEX CIRCUITRY INTRODUCTION

The human cerebral cortex if lifted from the underlying white matter and flattened to remove its "wrinkles" would be a thin (between ~1.5-4.5 mm thick) expanse of gray matter that would cover the surface of a ~29" widescreen display. The number of cells "nixels" contained within that sheet of biological circuitry would exceed the pixel count of almost all high resolution digital screens. *Disclosure: washing and then ironing your cerebral gray matter into a flat sheet is NOT recommended.*

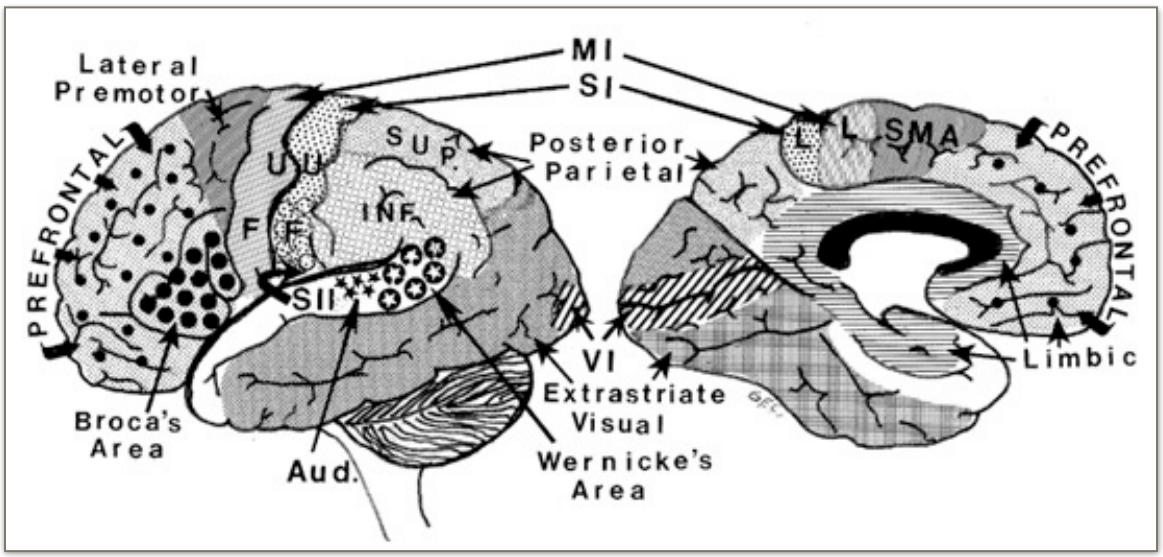


Fig 10-1. Cerebral Cortical Areas. KEY: Aud. = Primary Auditory Cortex, INF. = Inferior Parietal Lobule, MI = Primary Motor Cortex, SI = Primary Somatosensory Cortex, SII = Second Somatosensory Cortex, SUP. = Superior Parietal Lobule, SMA = Supplemental Motor Area, VI = Primary Visual Cortex (Striate), F = Face Area of SI & MI, L = Lower Extremity Area, U = Upper Extremity Area (gec). ***SEE: Brodmann Areas Interactive Media File:*** *GO TO: gmomm.pitt.edu* Fig10-1_Interactive Media

Estimates range from 20-30 billion neurons in the intact adult human cerebral cortex. If one considers a minicolumn (microcolumn) as the smallest individual integrative processing unit within the cerebral cortex (see below) and each minicolumn contains ~60-100 neurons then our human cerebral cortex would contain hundreds to thousands of millions of *CCPUs (Cerebral Cortical Processing Units)* to process & store our cherished data. The neurons are accompanied by perhaps twice as many glial cells (astrocytes, oligodendrocytes and microglia), as well as an abundant pericytes and microvasculature that perfuses all of these cortical cells with nutrients and oxygen and removes "waste products" of energy production, hormones and byproducts of damaged cells. If vascular endothelial tight junctions are compromised blood supply may deliver toxins and pathogens to brain parenchyma. The gross structure (macrostructure) was

presented in earlier chapters. Here we will concentrate on the microstructure of the cerebral cortex, link microstructure to neural network function, relate cerebral cortex to the thalamic nuclei that connect with specific regions of the cerebral cortex and introduce the concept of distributed processing within and among different areas of the cortex (see Cerebral Cortical Areas).

CEREBRAL CORTEX LAMINATION: NEOCORTICAL SIX LAYERED MODULAR POWERHOUSE FOR BEING, THINKING AND DOING

The cerebral neocortex of mice and men (and other mammals) has six layers (laminae I-VI); it is the bulk of surface gray matter on your conscious mind. Illustrated above is the laminar pattern for agranular motor cortex and granular sensory cortex of the rat (lissencephalic or smooth brain). Cell bodies (seen as blotchy dots) are visible due to a Nissl stain. Differences in the density and distribution of neuronal soma define one cytoarchitectonic brain area from another (e.g., Brodmann Areas). The cerebral cortex contains several varieties of glial cells and neurons. As discussed previously, neurons come in two basic flavors: pyramidal and nonpyramidal. Pyramidal neurons are typically projection neurons that send their axons to other cortical areas (corticocortical and callosal neurons) or to subcortical structures (corticofugal neurons). Most pyramidal cells have recurrent collateral axonal branches that form local (intra-columnar and inter-columnar) network connections. Non-pyramidal neurons are typically interneurons whose short axons form only local intrinsic network connections. These interneurons are either excitatory or inhibitory. The characteristics of neuron types has been described in previous chapters.

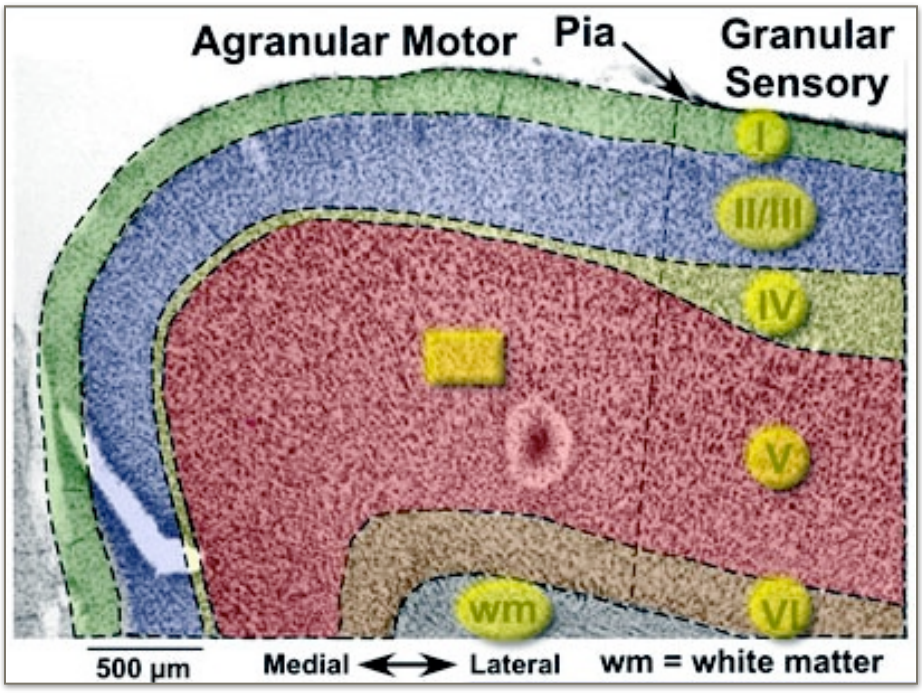


Fig 10-2. Cerebral Cortical Lamination: Layers I-VI (CHOOSE A LAMINA FROM THE INTERACTIVE Media FILE (gec). GO TO: *gmomm.pitt.edu*

Fig10-2_Interactive Media

Most cerebral cortical excitatory interneurons are spiny stellate cells. Inhibitory interneurons are smooth stellate cells

or one of a variety of other distinguishable inhibitory neurons. The supragranular layers (II/III) and infra-granular layers (V/VI) contain pyramidal cells and some inhibitory interneurons. The granular layer (IV) is almost nonexistent in Agranular Cortex but forms a well-defined middle layer packed with stellate cells in Granular Cortex. Your gyrencephalic "wrinkled" cerebral cortex if sectioned and stained with a Nissl stain would look similar to the mouse cerebral cortex on the stage of a light microscope (minus the dashed lines and the colors that designate laminar boundaries). White Matter = wm in photomicrograph of rat cerebral cortex. Of course you have a much greater expanse of cerebral cortex compared to that of the small rodent brain. Click/tap the yellow rectangle in the Cerebral Cortical Lamination Review Interactive Flash File to see cortex unlabeled and a magnified view of Nissl stained pyramidal cells.

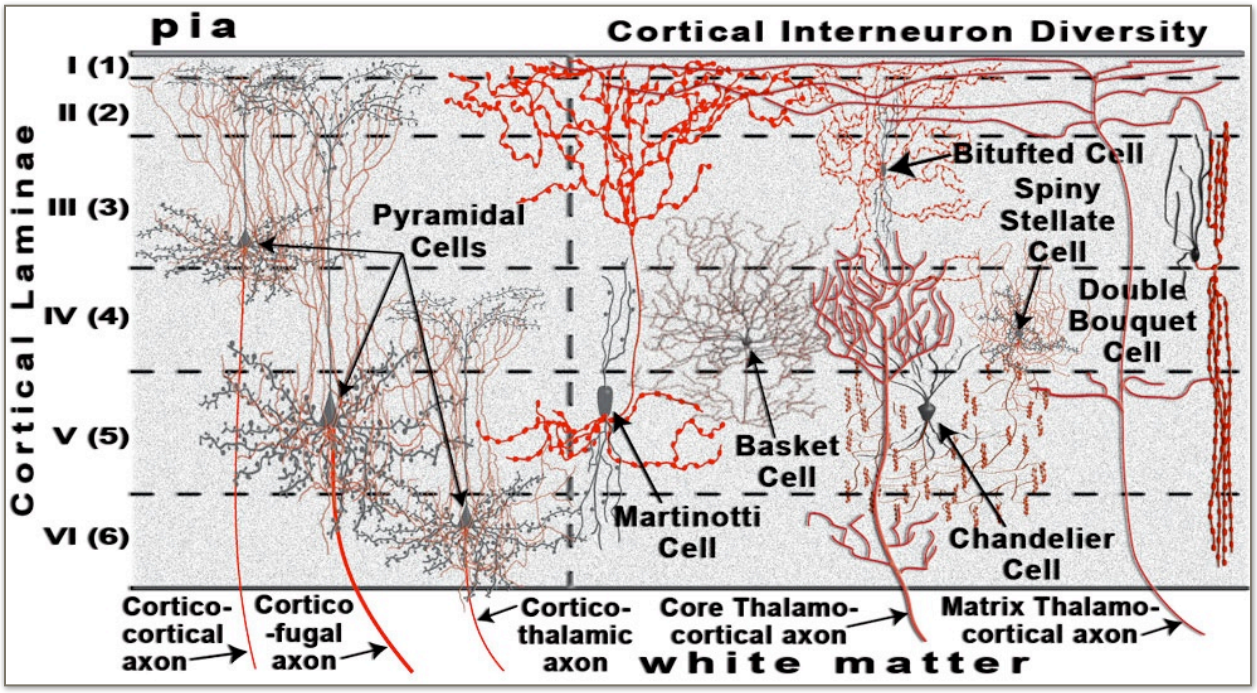


Fig 10-3. Cell types and the Inputs + Outputs of Six-layered Cerebral Neocortex. The two major cell types are illustrated: Pyramidal projection neurons (left of vertical dashed line) and non-pyramidal neurons local interneurons (right of dashed line). Different cell types are actually near neighbors, not segregated as in this illustration. Two general types of thalamocortical (corticopetal) afferents (from core thalamic cell or from matrix thalamic cell) are shown. Note pyramidal cell outputs: corticocortical, corticofugal and corticothalamic efferent axons. Neuronal dendrites and soma are dark, axonal arbors are red. Cerebral & Cerebellar Cortex Neuron Type Review Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig10-3 Interactive Media*

LAYER I

Layer I in the adult cortex is a cell sparse lamina located just beneath the pia. It contains a few horizontal (non-pyramidal) neurons that have widespread horizontal connections. The distal apical dendrite branches (tufts) plus axonal collaterals of

Pyramidal Cells located in deeper layers and some GABA interneurons, e.g., Bitufted and Martinotti Cells project axon branches to Layers I & II. Input from thalamocortical axons from "nonspecific" nuclei of the thalamus and from *matrix* cells in *first-order* and *higher-order* thalamic nuclei project to lamina I. The precise role of this most superficial layer has not been well established. It has been suggested that these horizontal connections contribute to “binding” of neural activity across widespread areas of cortex. Such binding may synchronize neural activity among widespread networks during perception, “willed” action and other cognitive tasks. Superficial depolarizations of pyramidal dendritic tufts may include Ca^{++} potentials that propagate back to layer 5 pyramidal somas to induce burst firing at the axon hillock. We might envision horizontal connectivity in layer 1 as a “signal bus” to share data among adjacent and distant cortical modules.

Anatomical studies of primate cerebral gray matter have shown an age-dependent collapse of upper cortical layers (layer I and upper layer II) in old but not young adult monkeys. For the areas studied in detail, this deficit is more prevalent in association areas (prefrontal cortex) than in primary cortical areas (striate cortex). The upper laminae provide circuitry for horizontal spread of activity across broad regions of cortex. A loss of superficial cortex may have profound implications regarding higher level processes that use such connectivity to sustain higher level mental processing. Taken together with other gray matter changes in connectivity and white matter pathology seen in aged monkey brains, one might expect cogitation to be more challenging as we age.

SUPRAGRANULAR LAYERS (II-III)

The supragranular cortex (layers II and III) contains small to medium pyramidal neurons. Some of these neurons project their axon to nearby cortical columns to form local networks. Other supragranular pyramidal cells project axonal branches to other functional cortical areas e.g., motor to somatosensory cortex. These represent two forms of corticocortical connectivity (local and global). Corticocortical connections are critical for network communication that forms the basis of distributed processing in the cerebral cortex. Many of these pyramidal cells have axon collaterals that influence interneurons and apical dendritic trees of layer V pyramidal cells. Some Pyramidal Neurons project their axon to homologous cortical regions in the opposite hemisphere: callosal connections for inter-hemispheric communication. A very small subset of Pyramidal cells in layer III are corticofugal neurons that send their axon to subcortical structures. GABAergic Interneurons within the supragranular layers provide intrinsic local connections to modulate pyramidal cell activity within a functional cortical column. A diversity of layer II & III interneurons may cause both inhibition and disinhibition of layer 3 and 5 pyramidal cell dendritic tufts. Such interactions may alter gain and firing patterns of deep pyramidal neurons. Layer III Pyramidal cells in agranular cortex, e.g., motor cortex receive specific thalamic input from core thalamic nucleus neurons located in the appropriate first-order thalamic nucleus.

GRANULAR LAYER (IV)

Layer IV contains excitatory cells (E, spiny stellate or star pyramid) and inhibitory interneurons (I, smooth stellate or other GABAergic cells) that are heavily interconnected in a local network. There are many more excitatory than inhibitory neurons but the GABAergic smooth cells have a powerful inhibitory effect on the spiny cells. Spiny cells receive excitatory synapses on their dendritic spines from other spiny stellate neurons and from thalamocortical afferents. On the other hand, inhibitory synapses from smooth cells occur on the cell body, proximal dendrites, and dendritic branch points of spiny cells and thereby have enormous controlling influence. Smooth cells have dense thalamocortical inputs to their proximal dendrites and soma. Spiny cell excitatory inputs to smooth cells are distributed all along the dendrites. Layer IV is the major lamina for abundant thalamocortical afferent termination. This afferent input from a 'specific' thalamic nucleus provides a powerful drive to the layer IV interneuronal network. Layer IV is thin in agranular motor, cortex. Layer IV is thicker with densely packed cells in granular sensory, e.g., primary somatosensory, primary auditory and primary visual cortices and anterior frontal cortex.

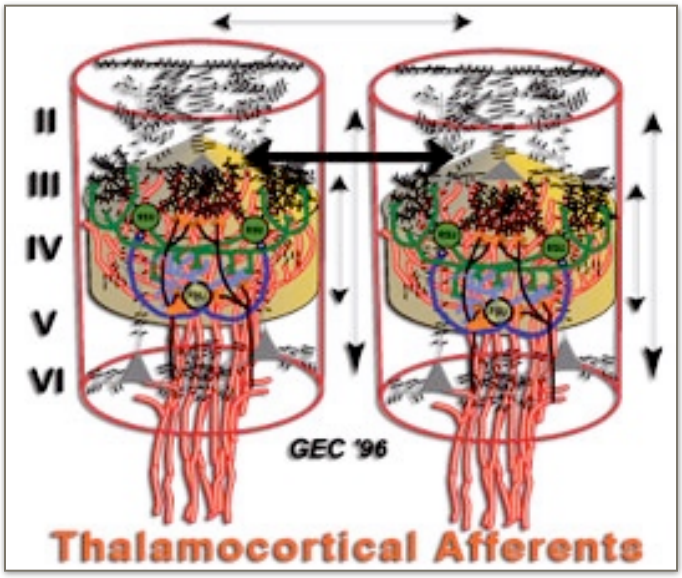


Fig 10-4 (left). Layer IV Barrel Network in Rat Primary Somatosensory Cortex: Two Adjacent Barrel Columns (gec).

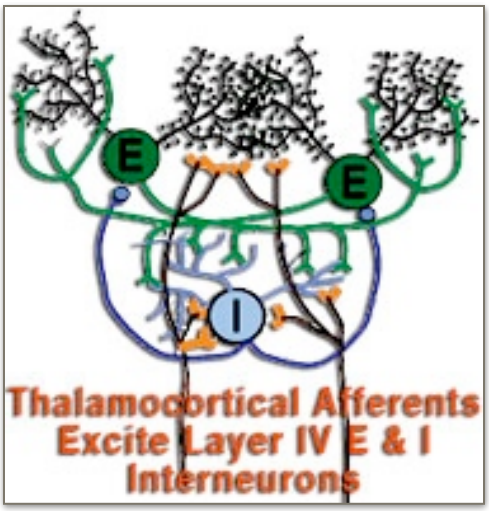


Fig 10-5 (right). Layer IV Excitatory (E) Spiny Stellate and Inhibitory (I) Smooth Stellate Cells and Driving Thalamocortical Afferents (gec).

INFRAGRANULAR LAYER (V)

Layer V contains Pyramidal Neurons that project their axons to subcortical brain structures. These corticofugal projections have targets in the Striatum, Thalamus, Cranial Nerve Nuclei, Dorsal Column Nuclei, and Brainstem Nuclei subserving “sensory,” “motor” and “integrative” functions.

These cortical output neurons represent ~80% of all corticofugal pyramidal cells and are called are non-PTNs. A subset of corticofugal pyramidal neurons project their axons

into the Pyramidal Tract. These Pyramidal Tract Neurons (PTNs) provide a direct link from cerebral cortex to the spinal cord. Only ~ 20% of Corticofugal Pyramidal Cells are PTNs. PTNs are found in motor cortical areas and somatosensory cortical areas. Pyramidal Neurons have a characteristic basal dendritic arbor as well as an apical dendrite that typically extends up to superficial layers with branch points along the way. Deep Pyramidal Neurons also have axon collaterals that project back to other neurons in the cortical column (there is considerable information sharing in the cortical column). Intercolumnar connections from Pyramidal Neurons provide important links to other local networks, to the motor cortex, to other somatosensory cortical areas and to networks located in the opposite hemisphere. Corticofugal connections allow the cortex to influence how it gets its information (perception) by modulation/gating ascending sensory inputs, and how it assists other subcortical areas in the control of behavior (action). Layer 5 contains multiple inhibitory interneurons which regulate pyramidal cell activity. These GABAergic neurons target the soma, dendrites or the axon hillock of pyramidal cells.

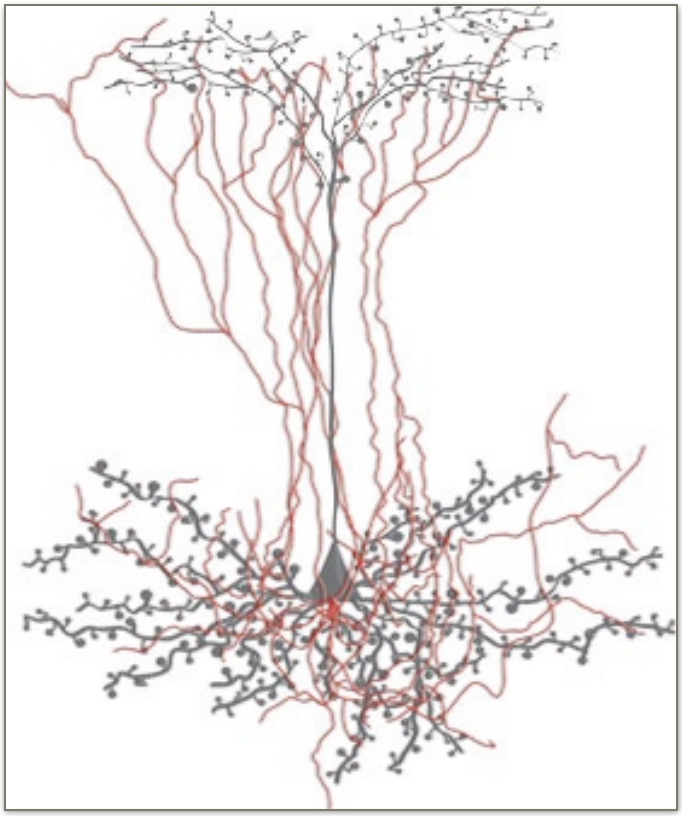


Fig 10-6. Layer V Pyramidal Cell: Corticofugal Output Neuron for Perceptions, Intentions and Actions (gec).

In addition to the subcortical brainstem or spinal cord targets of layer V pyramidal cells many, perhaps all of these corticofugal neurons, send a collateral axon to the thalamus: a corollary signal of intentions & actions to the diencephalon. Some neuroscientists suggest that layer V is "*motor*" everywhere due to its corticofugal influences on the subcortical brain and spinal cord. Figure shows a pyramidal cell (axonal arbor in red).

INFRAGRANULAR LAYER (VI)

Layer VI contains Corticothalamic Neurons that project their axons to thalamic nuclei that have direct thalamocortical projections to that part of the cerebral cortex. Layer VI projection neurons have a variety of shapes. Pyramidal, triangular, and fusiform cell bodies are found in this deepest of cortical laminae. Interneurons especially inhibitory cells are found in lamina 6. Layer VI receives thalamocortical axon

collaterals, corticocortical inputs, and input from more superficial cells in the cortical column.

Corticothalamic connections allow the cortex to influence how it gets its information by modulating/gating ascending sensory, motor or integrated signals arising from first order and higher order thalamic nuclei (see below). This influence may be directly upon thalamic interneurons and thalamocortical projection neurons in specific thalamic nuclei, or indirectly by influencing the Thalamic Reticular Nucleus (R). The Reticular Nucleus is composed of a thin layer of cells that forms a partial 'shell' around the rest of the thalamus. It contains inhibitory neurons that project to specific thalamic nuclei; thus R has powerful inhibitory influences on thalamic cell discharge properties.

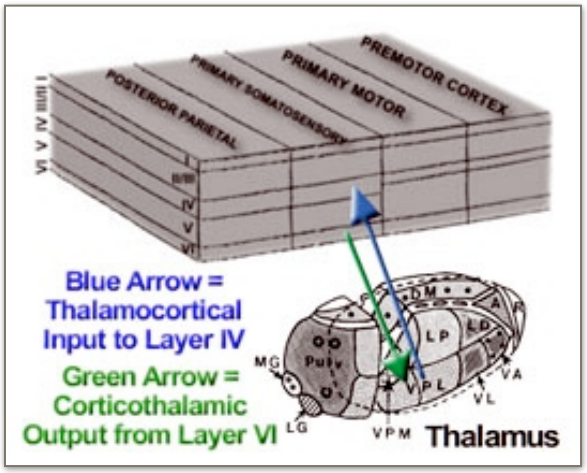


Fig 10-7. Layer VI Topographic Cortico-thalamic Input to Thalamic Nucleus of Origin for Specific Thalamocortical Drive (gec).

WHITE MATTER BENEATH THE GRAY

The white matter beneath the gray matter of the cerebral cortex contains axons that travel to and from the neurons in the cerebral cortex. Some of these axons are corticocortical, an ipsilateral pathway for cooperation among different cortical areas. Some axons are callosal, a pathway for connections between hemispheres (corpus callosum). Other axons are corticofugal, a pathway for cortical signals to influence subcortical brain areas (corticostriatal, corticorubral, corticobulbar, corticoreticular, corticopontine axons, etc.) or the spinal cord (corticospinal axons).

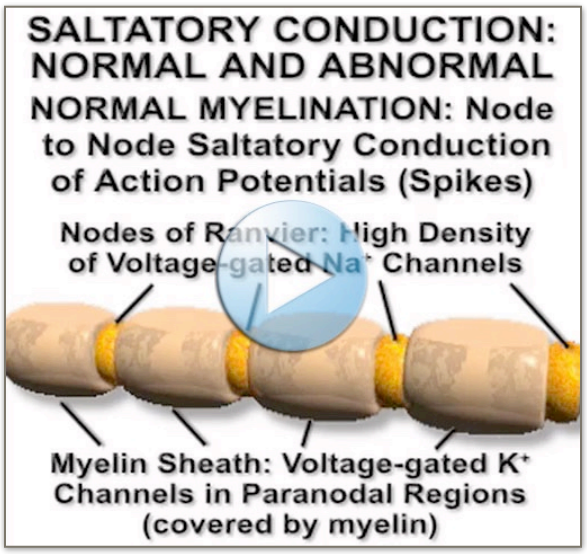


Fig 10-8. Demyelination-Remyelination Simulation: Plasticity in Nerve Conduction Mechanisms (gec). GO TO: gmomm.pitt.edu
Fig10-8_Video

Still other axons are corticothalamic, a pathway for the cerebral cortex (the major recipient zone of thalamic output) to adjust its extrinsic afferent drive from below. Neural activity may influence the extent of myelination to optimize signal transmission along pathways of differing lengths, e.g., see Fields, 2005. Lesions of the white matter e.g., plaques typical of the central demyelinating disease-Multiple Sclerosis,

can produce complicated disconnection syndromes, sensory deficits, motor deficits, or cognitive deficits. Anatomical studies of primates have shown an age-dependent reduction in white matter density in the aged cerebrum. There is a recurrent process of demyelination and partial remyelination in old but not young adult monkeys: e.g. see Demyelination-Remyelination Simulation Movie). This process is more prevalent in an association areas (e.g., prefrontal cortex) than in primary cortical areas (e.g., striate cortex). Oligodendrocytes appear to replicate to a greater extent in older than in younger adults.

RESTRICTIVE VERTICAL COLUMNAR PLUS EXPANSIVE HORIZONTAL CEREBRAL CORTICAL LAMINAR TIER SPECIALIZATIONS

The cerebral neocortex is organized in a vertical (columnar) fashion (see columns and radial dashed lines in figure 10-9B below) and in horizontal (laminar) fashion: "stratified fractured slabs." Superficial cortical layers provide intrinsic horizontal connections critical to higher functions of your personal brain/mind lintel (Fig 10-9A).

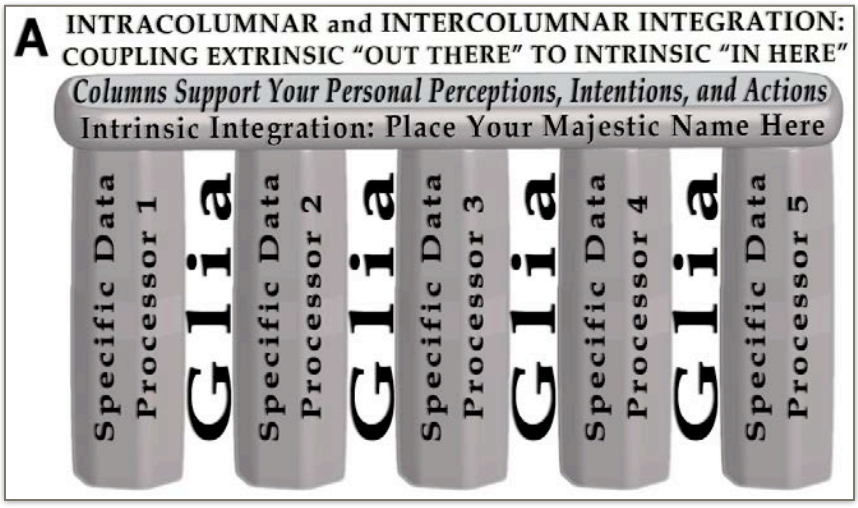
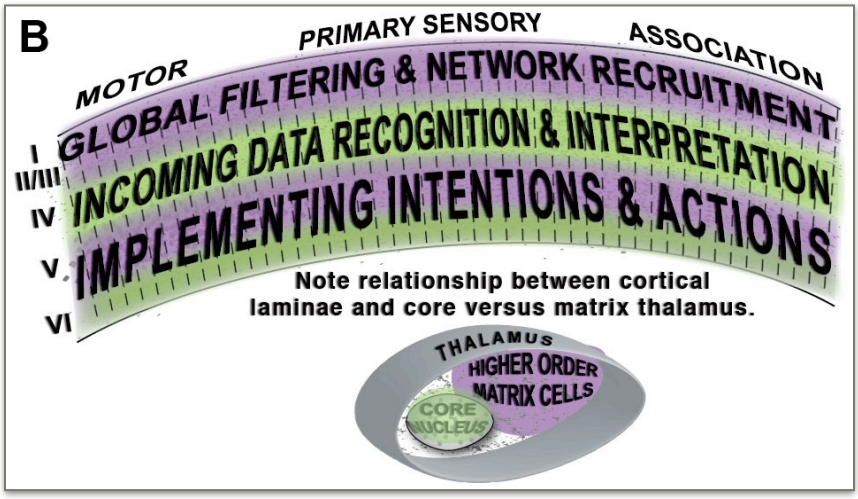


Fig 10-9 A, Neuronal Columns & Glia Supporting Your MajesticBrain/Mind Lintel; B. Functional Relations of 3-Tiered Cerebral Cortex (superficial, middle, deep) to Thalamic Core (green) and Matrix (purple) Cells - Dashed lines indicate radial columnar parsing of cortex across layers 2 - 6 across all areas (gec).



A normal structure-function relationship likely depends on both types of intrinsic vertical and horizontal corticocortical connections plus extrinsic connectivity (corticopetal inputs from core or matrix thalamic cells or neuromodulatory brainstem center

projections to cortex and loop effects of corticofugal outputs to subcortical targets). Glia support columns. Structural laminar organization may be complemented by overlapping functional segregation. A nonhierarchical three-tiered functional organization is hypothesized based on data from a number of experimental studies.

Laminae 1 & 2, & perhaps upper layer 3 may be most important for more global “intensity” control and filtering of engaged circuits and perhaps the successive or concurrent recruitment of large scale selected cortical networks. The superficial tier layers have extensive horizontal connections related to Global Filtering and Network Recruitment. These integrative processes require broad recruitment of many cortical networks: a “neurobiological signal bus” distribution of data. Superficial layers are influenced by local neurons and by a corticothalamocortical loop. This upper tier of the cortical slab (Lintel) is supported by columns and may be essential for broadly distributed neural processing responsible for attention and intention. These topmost layers may provide the broad distributed processing necessary for higher level processing to make your brain “mindful”.

The middle laminar tier (lower layer III & layer IV) in primary sensory and motor cortex may be most important for recognizing the specific type and precise source of incoming data. Within association cortex the middle tier provides an initial interpretation of integrated data for higher level functions (e.g., perception, cognition). Depending on the cortical area, incoming data may arise from a variety of sources. Thalamic input to middle tier layers III and IV may be related to current information from external sources, e.g., sensory receptor inputs, “motor” signals from spinal cord, brainstem motor centers or from the cerebellum. Middle tier laminae of association areas receive integrated sensorimotor data from thalamocortical inputs and from corticocortical connections with non-primary sensory or motor association areas or “recall” of previously accumulated data from association cortex that integrates behavior repertoires. Most often data inputs are not limited to one source. For example, thalamic input from specific core nuclei are directed to layer 4 interneurons in primary sensory or motor areas while corticocortical inputs often come from sensory association cortex and from intrinsic networks in nearby primary cortical columns to target primarily layer III neurons. Within association cortex the majority of inputs to layer 3 and the thin layer 4 come from core thalamic cells in higher order nuclei, from non-primary sensory or motor association cortex or from limbic or non-limbic “cognitive” association cortex.

Laminae 5 & 6 (deep laminar tier) may be most important for distributing integrated intentions and actions to the most appropriate subcortical brain or spinal target centers. In addition, lamina V pyramidal cells form local connections with neurites and neurons in the upper tier. Laminae V and VI corticofugal outputs primarily arise from Pyramidal Cells in those deep layers of the cerebral cortex. Only a minority of these corticofugal pyramidal cells project their axons to the spinal cord or brainstem nuclei capable of directly activating skeletal muscle. The vast majority of corticofugal projections influence

subcortical brain areas which process sensory, sensorimotor or integrative data. These deep laminae enable our most precise thoughts and plans to engage appropriate brainstem & spinal neural resources for implementing intentions. Many layer 5 pyramidal cells have axon collaterals which provide excitatory drive to matrix thalamic neurons which in turn project to upper tier apical dendrites of pyramidal cells-a corticothalamocortical loop.

None of these neocortical laminar tier "duties" can be implemented at any level of precision until both feedforward and feedback (reentrant) looping of information optimizes the cortical columnar and laminar processors. Such networked loops are not restricted to corticocortical circuitry; they incorporate extrinsic, subcortical processors at input, output & integrative stages of information flow. The majority of incoming data to middle layers (deep layer 3 and layer 4) of the cerebral cortex comes from one or more thalamic nuclei which determines the type of information that will influence any cortical area. Likewise, infragranular corticofugal output does not always result in an observable physical action. Much of the cortical output may provide "mental" intentional signals related to cognitive or behavioral events in response to internal "will" or external triggers. The significance of the first order versus higher order thalamic cell connections with the cerebral cortex will be described below.

Finally, all three laminar tiers are influenced to some degree by data coming from brainstem nuclei which modulate neuronal function in a relatively broad manner both structurally and functionally. These nuclei include those that contain neurons classified as serotonergic, noradrenergic, dopaminergic or cholinergic. These nuclei are typically influenced heavily by signals that originate within our bodies concerning basic physiological data about our homeostasis, our *well-being* or an *out-of-bounds* physiology that often is accompanied by feelings of discomfort, distress or frank pain. These brainstem modulatory inputs to the cerebral cortex may be filtered through nonspecific midline thalamic nuclei or arrive at the cortex by direct projections from these brainstem nuclei that by-pass the thalamus altogether. These modulatory inputs are distributed is such a way that their influences are not categorized easily into those attributes defined above where more specific information must be retained. These are signals about our very being and relate to fundamental biological principles of survival for the biologic entity in which these neurons reside. However, these neuromodulatory signals may be co-opted at this level to represent our more *primitive feelings* plus more noteworthy human feelings/emotions of ourself related to others, e.g., compassion and empathy. In addition, these signals may be vital to success from the standpoint of either reinforcing those behaviors that result in positive outcomes or stifling those things we *might* do that, *if done*, would result in negative outcomes for ourselves or others. These modulatory influences may be facilitatory or suppressive within cerebral circuitry by influencing a variety of chemically-gated and voltage-gated protein complexes.

THALAMIC NUCLEI AND THEIR RELATIONSHIP TO LOCALIZED CEREBRAL CORTICAL AREAS

The thalamus is a bilateral diencephalic deep gray matter structure containing subnuclei: see diencephalon labeled movie. The human thalamus may be a critical "hub" linking (gating) cortical networks for "routine" and higher level "creative" cortical processes: e.g., see Hwang, et.al., 2017.

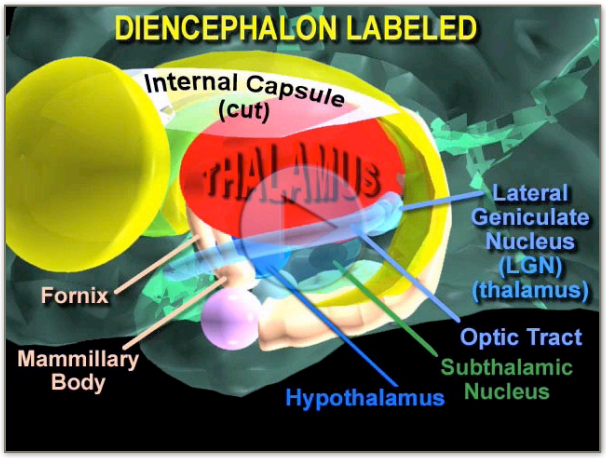


Fig 10-10. Diencephalon Labeled Movie (gec). GO TO: gmomm.pitt.edu Fig10-10 Video

The Thalamocortical Relations Interactive Media File allows you to explore the specific relationship between a defined thalamic nucleus and the area or areas of the cerebral cortex that have reciprocal thalamocortical and corticothalamic connections. You may explore this relationship by selecting (clicking/tapping) a thalamic nucleus and discovering the cortical area or areas connected. Alternatively, you can select (click/tap) a cerebral cortical area and discover which thalamic nucleus is or thalamic nuclei are related to that particular cortical area.

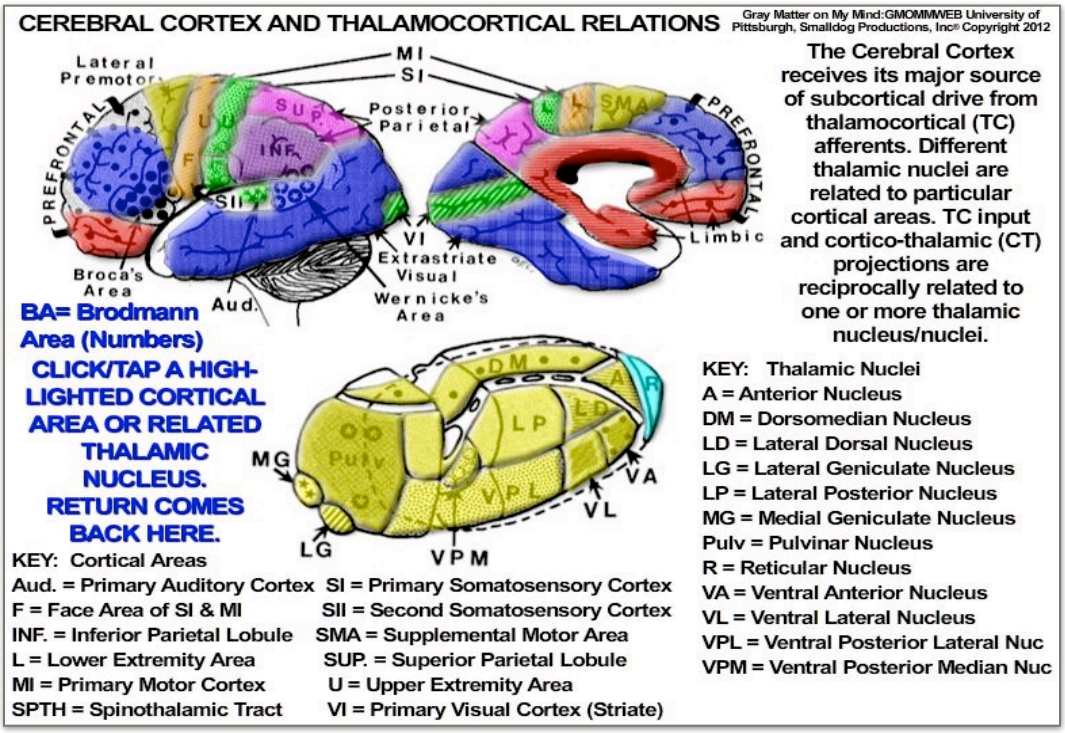


Fig 10-11. Thalamo-cortical Relations Interactive Media File (gec). GO TO: gmomm.pitt.edu Fig10-11 Inter-active Media

Most first order and higher order thalamic nuclei are identified. For most nuclei a button is provided to reveal a summary of the major functions of the selected nucleus/ nuclei. Thalamocortical projection patterns shown here are not exhaustive but represent major connections as revealed by anatomical studies. Thalamocortical projection patterns shown here are not exhaustive but represent major connections as revealed by anatomical studies.

CEREBRAL NEOCORTEX: PROPOSED LAMINAR & COLUMNAR LINKS WITH THALAMUS
FIRST ORDER NUCLEI AND HIGHER ORDER NUCLEI: TC, CT & CTC RELATIONS

Recent evidence, far from being complete or universally accepted, has suggested that thalamic drive to the cerebral cortex may differ depending on the type of thalamic cell and the particular thalamic nucleus in which that cell lives. First-Order (FO) specific thalamic nuclei receive ascending input from cerebellum, brainstem or spinal cord. Core cells in these FO nuclei provide a highly ordered topography and are driven by spatially and temporally specific sensory, motor or sensorimotor data. These thalamocortical (TC) neurons provide a dense axonal projection to middle cortical layers (layer 4 and deep layer 3) as well as deep layer 5 (5b) and 6 cortical cells (see green tint in figure above and movie below). This is the “classic” TC connectivity that provides two-way links between our brain and the external world (willed actions & cortical perceptions of our world at least as our brain interprets the real world).

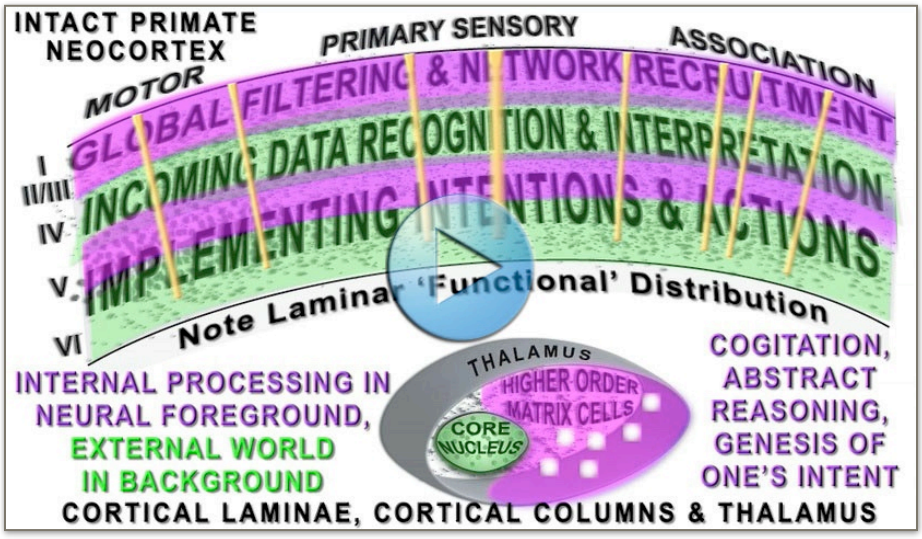


Fig 10-12. Cortical Columnar and Laminar Functional Links with Core and Matrix Thalamus Movie (gec). GO TO: gmomm.pitt.edu
Fig10-12_Video

Ascending pathways from subcortical brain and spinal cord are “routed” through the thalamus before influencing cortical networks. Recent research suggests that there are two groups of thalamic cells. One group contains larger cells that are grouped into First Order (FO) CORE nuclei that receive specific spatiotemporal inputs from ascending pathways. These CORE FO Nuclei include: Lateral Geniculate (LG), Medial Geniculate (MG), Ventral Posterior

Lateral (VPL), Ventral Posterior Medial (VPM) and Ventral Lateral (VL) Nuclei. The second group are matrix cells located in FO and Higher Order (HO) nuclei (see below).

Cortical Columns activated by Core inputs appear to send a copy of corticofugal output to Higher Order (HO) Thalamic Nuclei. HO thalamic nuclei are large and contain abundant Matrix Cells in the human thalamus. Axons of Matrix TC projection neurons terminate in upper layers: 1, 2, upper layer 3 and in superficial layer 5 (purple tint). Unlike FO Core Cells, HO Matrix Cells have few discrete ascending inputs from brainstem or spinal levels but do have significant inputs from corticothalamic axons and from corticofugal axon collaterals (see below). Matrix cell inputs to layer I provide a spreading influence across wide regions of the cortex. Switching between brain states dominated by internal events versus attention to events generated within the world external to our being seems to require cerebral loop connections (corticocortical and corticothalamocortical).

The corticofugal axon collaterals to FO matrix cells are "*FYI*" data sent to the thalamus reflecting our intentions and/or actions that may be implemented by brainstem and/or spinal centers concerned with our will being done or maintaining our sense of well-being. Thus, HO Matrix cells may provide a distributed message that may be better associated with the internal cerebral neural processing (e.g., cogitation, abstract reasoning, feelings, personal ideations & genesis of a willed intent to act).

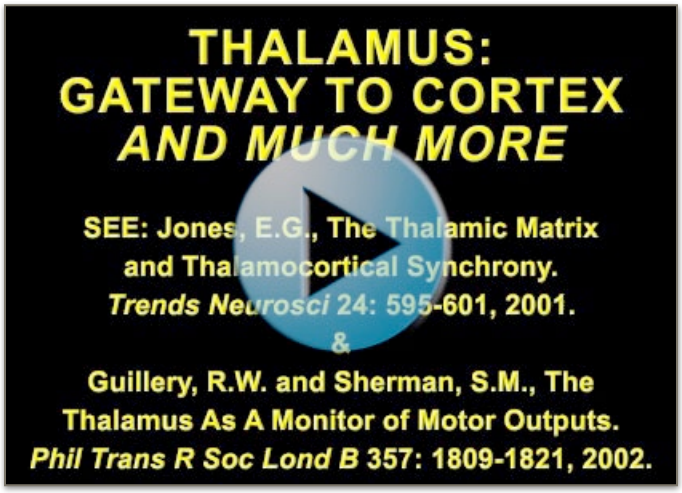


Fig 10-13. Thalamic Core Matrix Galaxy Movie (LARGE MOVIE, PLEASE BE PATIENT) (gec). GO TO: gmomm.pitt.edu Fig10-13_Video

The Thalamic Core Matrix Galaxy Movie shows the main features of these thalamocortical & corticothalamocortical relations; enjoy the "edutainment". You may find a particular musical theme brought to mind as you play this movie.

The first animation in the First Order Core Thalamus Movie shows activation of the Ventral Posterior Lateral (VPL) Nucleus by ascending axons in the Medial Lemniscus & Spinothalamic Tract. VPL neurons are primarily CORE large cells that project thalamocortical (TC) axons in a topographic fashion to the granular layer (IV) of the Primary Somatosensory Cortex (SI). TC input to granular layer (IV) spreads in a restricted vertical, columnar fashion to supragranular (II-III) and to infragranular (V & VI) layers. A less dense TC projection goes to layer VI. A Layer VI corticothalamic projection specifically targets VPL. The CORE thalamocortical projection is not only somatotopically organized but is necessary to get detailed spatial

and temporal tactile & proprioceptive information from the contralateral body to SI. It is critical for high tactile acuity (discriminative touch) & stereognosis.

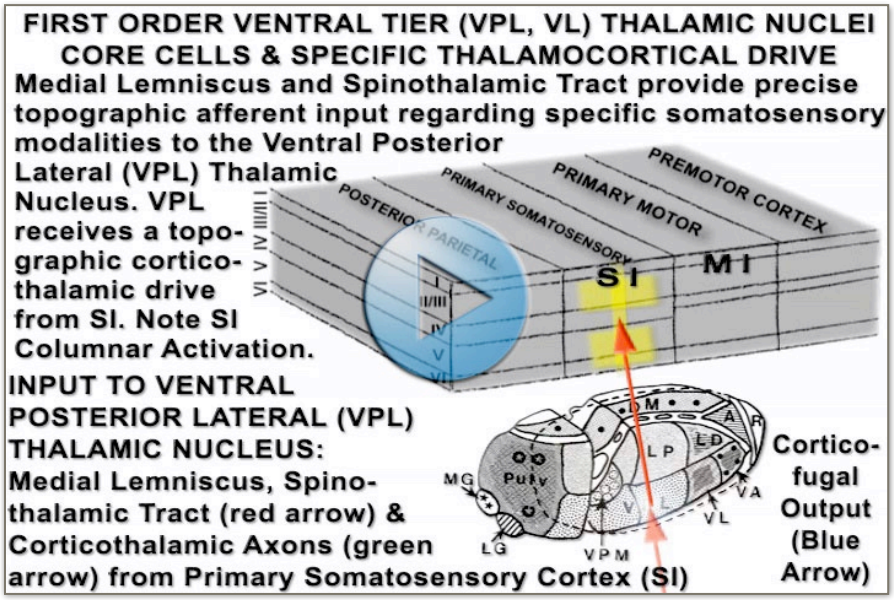


Fig 10-14. First Order Core Thalamus Movie (gec). GO TO: gmomm. pitt.edu [*Fig10-14 _Video*]

The second animation in the First Order Core Thalamus Movie shows activation of the Ventral Lateral (VL) Nucleus by ascending axons from the Cerebellum, Basal Ganglia & Spinothalamic Tract (SPTH).

VL neurons are primarily CORE large cells that project thalamocortical (TC) axons in a topographic fashion to layers III/IV of the Primary Motor (MI) and Premotor Cortices (Lateral Premotor Areas & Supplemental Motor Area). TC input to middle layers spreads in a vertical, columnar fashion to supragranular (II-III) and to infragranular (V & VI) layers.

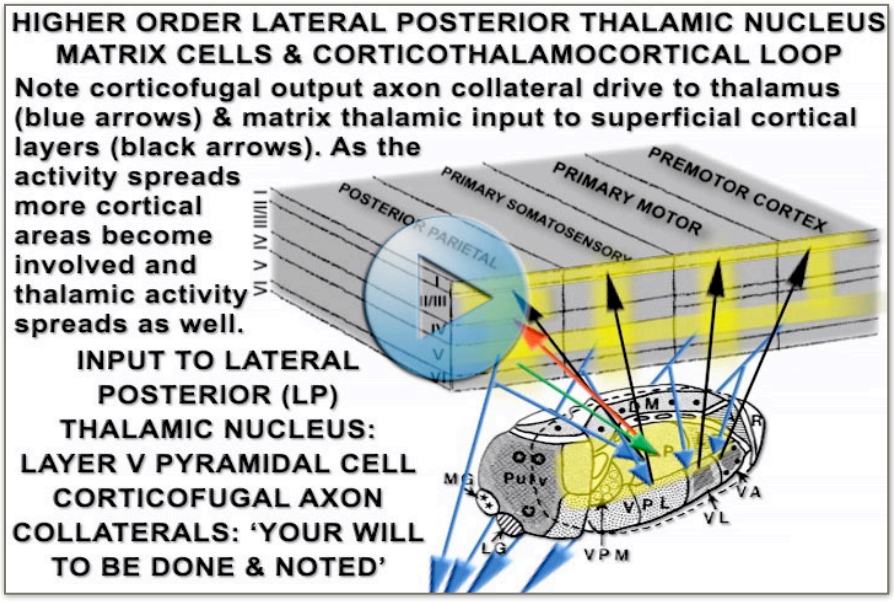


Fig 10-15. Lateral Posterior Higher Order Thalamic Nucleus and Cortico-thalamocortical Loop Movie (gec). GO TO: gmomm.pitt.edu [Fig10-15_Video]

A less dense TC projection goes to layer VI. A Layer VI corticothalamic projection specifically targets VL. The VL CORE nucleus is a major "MOTOR" relay to get detailed spatial and temporal information of planned or *in-progress* actions from subcortical brain & spinal cord areas to motor cortices.

The Lateral Posterior Higher Order Thalamic Nucleus Movie shows activation of the Lateral Posterior (LP) Nucleus from collateral branches of Layer V pyramidal cell axons that project to brainstem or spinal cord. Matrix cells in LP project back to superficial cortical layers in parietal and occipital cortex (only posterior parietal cortex illustrated here), e.g., see Roth, et.al., 2016.

Many LP neurons are small MATRIX thalamocortical cells that project in a non-topographic fashion to superficial layers of the cerebral cortex: layers I-III. Fewer CORE cells in LP project thalamocortical axons (red arrow in movie) to the granular layer (IV) of the Posterior Parietal Cortex (PPC). Note the expansion of activity across multiple cortical areas and the expansion of thalamic neural activity to other nuclei surrounding LP. Thus, MATRIX cells have a broad impact on multiple cortical areas by way of a corticothalamocortical loop that may generate synchronized gamma (40-70 Hz) rhythms typical of a "thinking" brain.

EXAMPLE OF THALAMOCORTICAL AXON PROJECTION FROM A CORE NUCLEUS NEURON-SINGLE THALAMOCORTICAL (TC) AXON TERMINATION IN SI LAYER IV FROM VPM TC NEURON IN THE RAT

The rat face (particularly its whiskers) is well represented in SI. The whisker map is topographic; see the Whisker to Barrel Topography Movie.

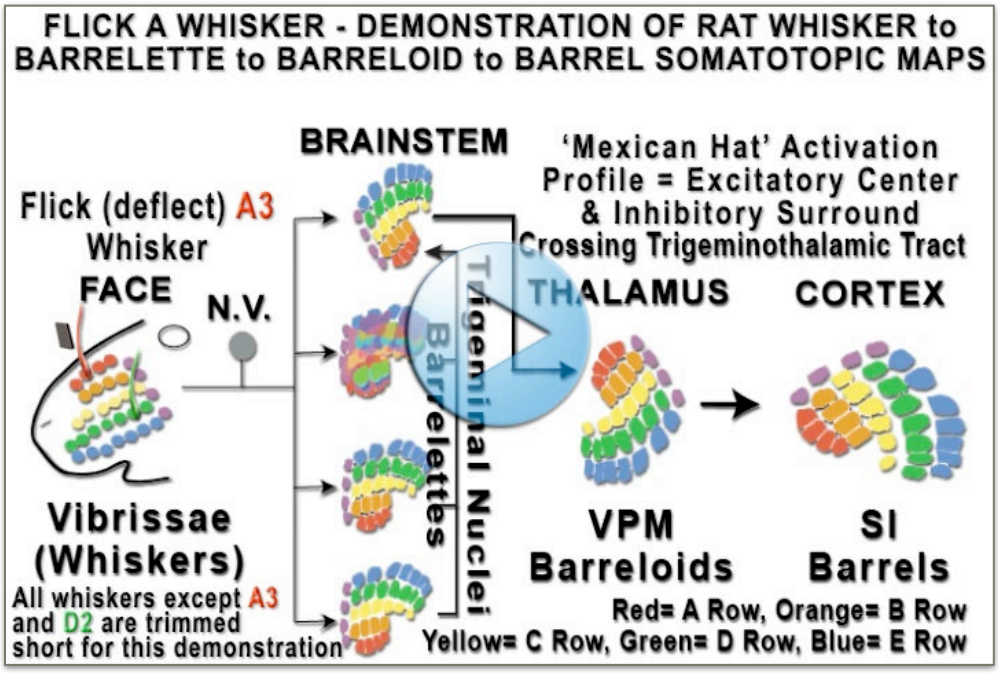


Fig 10-16. Whisker to Barrel Topography Movie (gec). GO TO: gmomm.pitt.edu Fig10-16_Video

Within layer IV, thousands of cortical neurons form a network called a barrel. Each barrel corresponds to a particular whisker on the contralateral face (see Whiskers to Barrel Topography Movie). The SI barrelfield map can be visualized in tangential sections of layer IV using a metabolic marker: cytochrome oxidase (CO) staining. Outlines of individual CO barrels within a

portion of the total barrelfield are illustrated and 4 barrels are identified (B1, B2, C2, D1) in the Thalamocortical Projection figure.

The thalamocortical projection figure shows a single thalamocortical (TC) axon and its arborization in layer IV is reconstructed following injection of a single VPm neuron with Biocytin label. The axon ascends obliquely in the infragranular cortex beneath the B2 & B3 barrels. Note the dense axonal arborization and many axonal swellings within the C1 barrel.

Axonal swellings are presumed presynaptic boutons. A glass micropipette filled with Biocytin recorded action potentials from a single TC cell in the VPm nucleus. Deflections of the C1 whisker on the contralateral face produced a strong response while stimulation of neighboring whiskers evoked little or no response. Following physiological identification, the cell was injected with a cellular marker called Biocytin (juxtasomal) using DC pulses. The labeled cell body and a portion of its dendritic tree are shown in the photomicrograph inset. The TC cell's axon is digitally reconstructed in the barrelfield drawing. Maximal branch ramification occurs in layer 4 of the C1 Barrel.

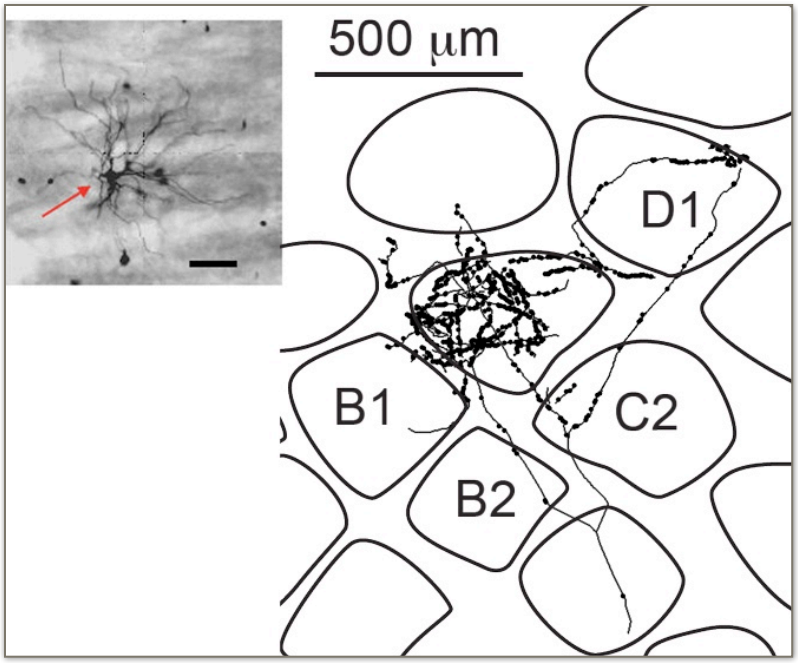


Fig 10-17. Thalamocortical projection. Left panel inset- photomicrograph of injected thalamic cell. Red arrow points to injected thalamocortical neuron soma surrounded by dendrites in the ventral posterior medial thalamic nucleus (C1 Barreloid). Scale bar in left panel photo = 25 microns. Right panel is the reconstructed axonal arbor (viewed from above) in the SI "barrel" cortex projecting from the identified cell. Axon ramifies most extensively in the middle (granular) cortical layer of the C1 Barrel. "Decorations" on the axon represent locations of axonal swellings (suspected synaptic axon boutons) (gec). Data courtesy of A-J. Su, H.T. Kyriazi, G.E. Carvell & D.J. Simons, Dept. Neurobiology, University of Pittsburgh School of Medicine, 2008.

CLASSIC BOTTOM-UP & TOP-DOWN SENSORY TO MOTOR TRANSCORTICAL "REFLEX" SENSORIMOTOR CONTROL

Classical concepts of sensation begin with sensory input to spinal and brainstem nuclei that then project sensory information to the thalamus by way of ascending pathways.

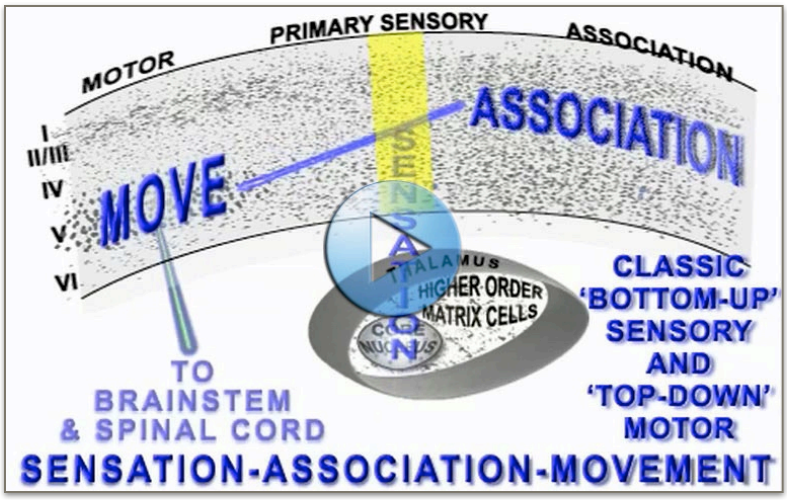


*Fig 10-18. Classic SR Movie: Bottom-Up, Cortical Association, Top-Down Stimulus-Response Control (gec). GO TO: gmomm.pitt.*edu
Fig10-18_Video

The most important path for Discriminative Touch is the Dorsal Column Medial Lemniscal (DCML) Tract whose ascending axons synapse on neurons in the Ventral Posterior Lateral (VPL) Nucleus of the Thalamus. Ascending thalamocortical axons synapse on middle layer cells in the Primary Somatosensory Cortex (SI). SI then projects corticocortical axons to synapse on neurons in Association Cortex (Posterior Parietal Cortex for Discriminative Touch). Association Cortex then projects to Motor Cortex that sends descending axons to Brainstem & Spinal Motor Centers to produce movement. First order thalamic nuclei have an important role to act as the major gateway for afferent input to the Cortex from ascending pathways, e.g., somatosensory, auditory, visual sensory data and sensorimotor data from the cerebellum: a “bottom-up” drive to cortical networks.

This Classic S-R concept of information flow depends on external input as a trigger for movement as opposed to Intention-Action-Perception Cycle concept of information flow (see below).

VOLITION: INTENTION-ACTION-PERCEPTION (I-A-P) CYCLE DRIVES OUR WILL

Volition begins with the Intention of the Subject. This is thought to be generated within Higher Order Association Cortex (e.g., Posterior Parietal, Inferior Temporal or Prefrontal Cortex). Information rapidly spreads to Somatosensory and Motor Cortices. All of these cortices project corticofugal axons from layer 5 Pyramidal Cells to Sensory & Motor Brainstem and/or Spinal Centers. Note the functional distribution according to superficial, middle and deep tiers across cortical areas in the Intention-Action-Perception Cycle Movie.

Recent evidence shows that many if not all corticofugal descending axons have collateral axonal branches that synapse on cells in various Higher Order Thalamic Nuclei. The first set of events in Sensorimotor Skill may be motor not sensory. Descending axons to subcortical brain & spinal centers have collateral branches to thalamic matrix cells: an “efferent copy” of ACTION/INTENTION Signals. Note that INTENTION is “converted” to ATTENTION as Thalamic Matrix Cells project back to

superficial cortical layers and neural engagement in the cerebral cortex spreads. This conversion marks the garnering of neural resources for your brain to gather information and possibly to do your will. This conversion to ATTENTION may lead to a conscious perception under certain circumstances while non-conscious processing may occur if there is a minimal salient sensory component. The former is illustrated in the Intention-Action-Perception Cycle Movie. The thalamus may act as a subcortical "monitor" for Intended Actions. It is primed for receipt of sensory information from ascending pathways. Those data are modulated before being sent on to Somatosensory Cortex (see SENSATION in the movie). The simulation shows this as a continuing cycle: INTENTION, ATTENTION, ACTION and PERCEPTION require cooperative interactions.

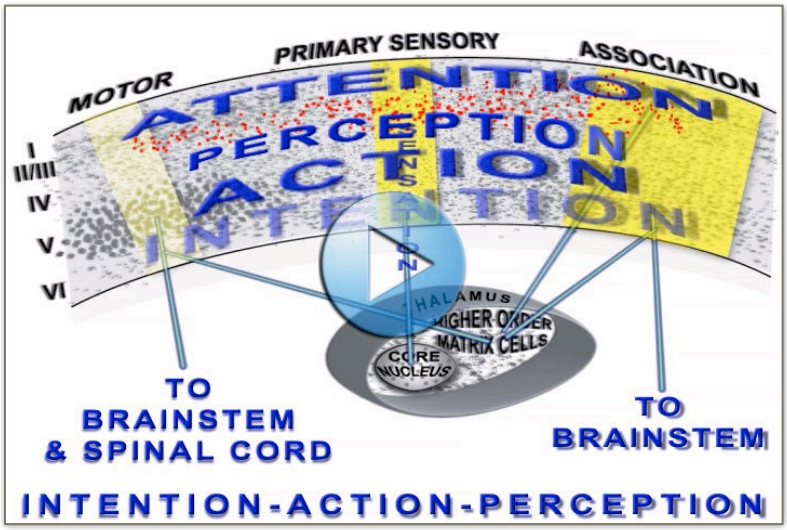


Fig 10-19. Intention-Action-Perception Cycle Movie (gec). GO TO: gmomm.pitt.edu Fig10-19_Video

Rhythmic oscillations may synchronize activity among cells at multiple levels of the neuraxis. This BINDING (superficial layer red particle spray in movie) may link neural activity in the Intention-Action-Perception cycle & improve efficiency of Sensorimotor Skill over time (learning).

VERTICAL & HORIZONTAL ORGANIZATION OF CEREBRAL CORTEX-NO NEURON IS AN ISLAND UNTO ITSELF*

Neuroscientists studying the organization of the nervous system investigate the anatomic and physiologic bases of neuronal interactions. Cooperation amongst a collection of interconnected cells appears to be critical for normal nervous system function. These collections are referred to as nests, colonies, cell assemblies, centers, blobs, nodes, columns, etc. Special properties are attributed to the collective that may be either weakly represented by individual neurons or absent in any cell by cell analysis. For example, a population code of some property may emerge when one looks at the whole group despite its absence when examining individual units. Researchers state that this emergent property is dependent upon a network. This network may include a local group of cells or it may require a distributed group of cell assemblies located some distance apart.

One of the pioneers of these studies is V. B. Mountcastle who recorded, in detail, properties of single cells in the Somatosensory Cortex. He proposed that neurons

interconnected in radial columns from the pia to the white matter form a functional column. Mountcastle proposed that columns are interconnected in a distributed network (distributed neural processing). Others have confirmed and expanded Mountcastle's findings re: Columnar Organization in cortical circuits using micro-electrodes & other probes of neural function. It has been hypothesized that primates have a finer-grained columnar organization; minicolumns or microcolumns: think High Definition (HD) TV versus conventional, Standard Definition (SD) TV.

The Columnar Organization Movie illustrates classic intracolumnar & intercolumnar communication in adjacent columns of the primary somatosensory cortex. The major extrinsic afferent drive comes from the ventral posterior thalamic nucleus to cortical layer IV (granular layer) where excitatory and inhibitory interneurons live. These interneuronal Stellate cells form a local network within the center of the column. This "*node*" extends its influence to supragranular (II-III) and infragranular (V-VI) layers which contain pyramidal neurons (and others, not shown). Layer III pyramidal cells form inter-columnar connections. Some Layer III Pyramidal cells are callosal neurons that link right & left hemispheres (not shown). Layer V & VI Pyramidal neurons have efferent (corticofugal) projections to subcortical CNS structures.

Classic concepts of columnar organization incorporates a serial processing mode where thalamocortical drive activates layer IV networks which then activates supragranular cells above.

Fig 10-20. Columnar Organization Movie: Vertical (Intracolumnar) and Horizontal (Intercolumnar) Macrocolumn Connections (gec). GO TO: gmomm.pitt.edu Fig10-20_Video

Those supragranular neurons then provide inputs to infragranular neurons which provide an output from the cortical column to subcortical structures. A recent study (Constantinople and Bruno, 2013) revises this concept suggesting thalamocortical inputs to infragranular neurons provides a separate pattern of parallel granular and infragranular activation.

*See J. Donne, Devotions Upon Emergent Occasions. *Meditation* 17, 1623.

VERTICAL AND HORIZONTAL ORGANIZATION OF CEREBRAL CORTEX-CREATING HIGH DEFINITION (HD) CORTICAL NEURAL IMAGES: FUNCTIONAL MINICOLUMNS

A minicolumn or microcolumn is a vertically interconnected narrow column of neurons bridging all layers of the cerebral cortex. These structural/functional cortical cell groups are hypothesized to be basic cell assemblies in primate neocortex. Minicolumns/ microcolumns have been described for many mammalian species. Primate neocortex has the advantage of a large number of double bouquet inhibitory interneurons that align their axonal “horsetails” in a narrow vertical pattern: a crucial delimiting factor that may define the longitudinal border of a microcolumn, e.g. see Peters & Sethares, 1997.

One hypothesis suggests that the microcolumn is centered on the soma of a layer V pyramidal cell (PC); the structural/functional unit is only ~25-50 microns in diameter centered on the infragranular pyramidal cell's corticofugal output rather than being centered on the corticopetal afferent input from the thalamus as has been suggested for a 'macro' column (hundreds of microns in diameter). Illustrated in the Primate Cerebral Cortical Minicolumn is a hypothetical minicolumn (microcolumn) containing a representative sample of the cell types that would comprise the column in granular cortex: layer III pyramidal cell, layer IV spiny stellate cell, layer IV basket cell, layer V pyramidal cell and double bouquet cell whose's soma is located in upper layer III. The actual microcolumn (minicolumn) would contain perhaps 60-100 or fewer cells within the vertical column, see Mountcastle, 1997; Jones, 2000; Buxhoeveden & Casanova, 2002.

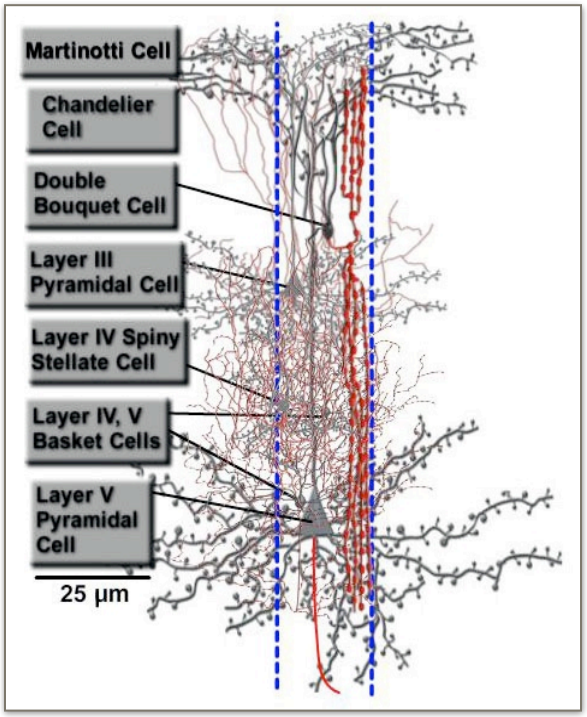


Fig 10-21. Primate Cerebral Cortical Minicolumn: Interactive Media File Shows Macrocolumns Minicolumns & Their Neurons (gec). GO TO: gmomm.pitt.edu

Fig10-21_Interactive Media

What is the advantage of a microcolumn? Presumably a neural image could be represented in “Standard Definition (SD)” as a coarser-grained macrocolumn or as a “High Definition (HD)” image with a much finer-grained resolution among select microcolumns: think HD versus SD TV.

Double Bouquet Cells (DBCs) and other dendrite-targeting GABA cells, e.g., Martinotti Cells in primate cortex could provide a mechanism to dynamically regulate the extent of a microcolumn's sphere of influence, e.g., see Gupta, et.al., 2000; Markram, 2004. Chandelier cells may also assist in activating quiet pyramidal cells while simultaneously silencing highly active PCs: see Woodruff, et.al., 2011; a powerful source of selective inhibition of PC clusters. Selective-attention and/or learning could

serve to generate HD neural networks having rapid “refresh” rates; see Leo-LowRes to High Res Image Movie.

Fig 10-22. Leo (2002-2018): Proposed Low Resolution (SD) to High Resolution (HD) Transition in Neural Image within Primate Visual System Movie (gec). GO TO: gmomm.pitt.edu *Fig10-22_Video*

DOUBLE BOUQUET GABA INTERNEURONS: PARSING HIGH DEFINITION (HD) CORTICAL MINICOLUMNS FROM STANDARD DEFINITION (SD) MACROCOLUMNS

The two movies (Double Bouquet Cells No & Double Bouquet Cells Yes) illustrate the effect of DBCs on columnar organization in a sensory association cortical area. These areas receive strong corticocortical drive and a more generalized modulation of excitatory inputs to superficial cortical layers from thalamocortical (TC) input from matrix cells living in a higher-order thalamic nucleus, e.g., Pulvinar.

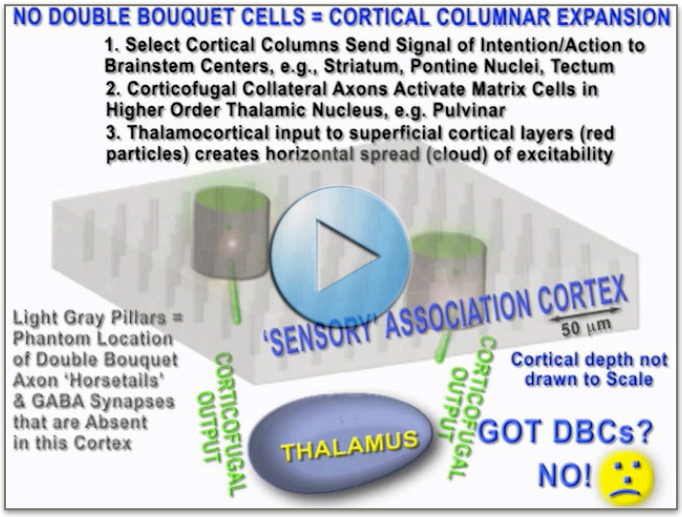


Fig 10-23. Proposed Lack of Cortical Double Bouquet Cells: Macrocolumn Activation Movie (gec). GO TO: gmomm.pitt.edu *Fig10-23_Video*

When DBCs are present and active they may provide shunting inhibition of pyramidal cell apical dendritic trees to delimit columnar processing to microcolumns. If DBCs are absent, columnar size may be related to the extent of overlapping pyramidal neuropil in supragranular cortex = macrocolumns.

Primary sensory cortex may utilize layer IV (4) GABA neurons to define the columnar space since the major drive for these columns arises from strong TC input to layer IV from core cells in a first-order thalamic nucleus. The processing takes some time to “fracture” the macrocolumn into selective

activation of some minicolumns and suppression of others: high resolution processing takes time to be realized as a consciously attended, unified perception.

Fig 10-24. Proposed Effect of Activating Cortical Double Bouquet Cells: Minicolumn Activation Movie (gec). GO TO: gmomm.pitt.edu
Fig10-24_Video

PROPOSED CORTICAL CIRCUITRY FOR CREATING MINICOLUMN FRACTURE PATTERN

Recent advances in patch-clamp electrophysiology and in optogenetic methodology allow neuroscientists to study cortical circuitry in detail (*in-vitro* & *in-vivo*).

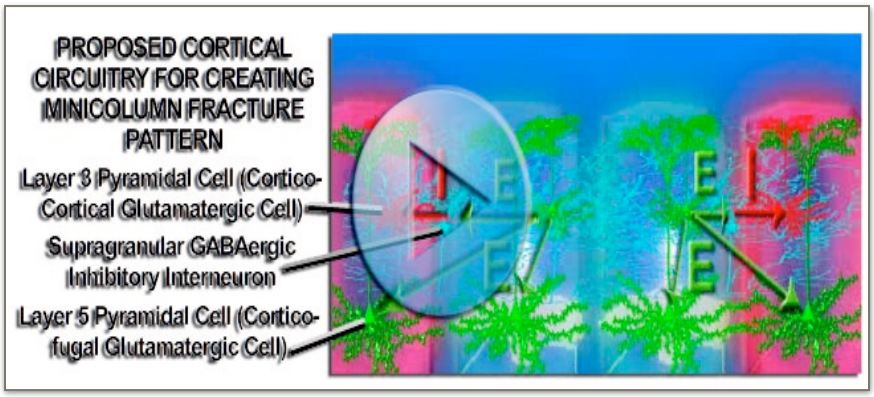


Fig 10-25. Circuit Connections for Laminar Differences in Minicolumn Fracture Movie (gec). GO TO: gmomm.pitt.edu
Fig10-25_Video

Optogenetic methodology utilizes genetic modification of particular types of neurons in such a way that these cells are not only visible using 2-photon microscopy but such genetically engineered cells can be specifically activated using discrete light stimuli of a particular wavelength. The animation below shows four minicolumns that are connected horizontally by layer 3 pyramidal cells.

The pattern of activation across minicolumns differs according to inter-laminar and intra-laminar connections of Glutamatergic (E) pyramidal cells and GABAergic (I) Inhibitory Interneurons. The net effect of supragranular (Layers 2 & 3) horizontal connections is Inhibitory (I) > Excitatory (E) due to the strong influence of GABA neurons suppressing the influence of surrounding minicolumns. By contrast, those excited layer 3 pyramidal cells facilitate many layer 5 pyramidal cells where horizontal connections have a net E > I influence. Such a differential pattern of laminar activation will 'fracture' the cortical column allowing a discrete subset of inputs to influence the

output of many layer 5 corticofugal pyramidal cells: a discrete columnar integration magnified by a facilitated corticofugal output. Laminar differences relate to supragranular GABA neurons that are driven in a robust oscillatory, coupled fashion. Such oscillations have an ~40 Hz frequency even if the input has no spatiotemporal pattern that would evoke such periodicity: GABA gamma binding at the local circuit level. These findings must be replicated across various species & various cortical areas.

COMPARTMENTALIZED PYRAMIDAL CELL ACTIVATION: SUPERFICIAL APICAL VS. DEEP BASAL DENDRITIC INPUTS

Initial intracellular recording from individual neurons was accomplished by sharp microelectrodes with very fine tips that impaled the cell to gain access to intracellular depolarizing and hyperpolarizing potentials. Methodology initially designed by Bert Sakmann, (see Neher & Sakmann, 1976; Stuart & Sakmann, 1994 references) allows the investigator to record intracellular events without entering the cell by patching onto the neuronal membrane with a microelectrode and opening a very small part of the membrane within the lumen of the microelectrode. Such patch electrode recordings may occur at the soma, dendrite or both. This technique allows for simultaneous recordings from different compartments of a neuron to reveal greater details about the form and temporal profile of membrane potential changes at the soma and at distant locations, e.g., basal dendrites or distant apical dendrite of a pyramidal cell. Such recordings *in-vitro* occur by direct visualization of fluorescent-labeled neurons which reveal the soma and dendritic tree of an individual cell. These investigations have shown a critical differential effect of excitatory (depolarizing) and inhibitory inputs (hyperpolarizing) to the proximal basal dendrites and soma of a layer 5 pyramidal neuron vs. inputs to the distal apical dendritic arbor of that cell. The deep inputs appear to be related to specific sources of input (modality, and source localization of data) while inputs to the superficial layers (Layer 1 & 2) appear to be related to long-range horizontal cortical axonal inputs coupled to local dendritic and axonal arbors of pyramidal cells and several inhibitory interneurons. Layer 1 also receives widespread thalamocortical inputs from matrix cells within higher-order thalamic nuclei cells. Thus, layer 1 inputs to the apical dendrites of layer 5 pyramidal cells appear to be related to more integrated information thought to be crucial for the layering of “higher level” perceptual and cognitive processes onto more specific data accessed by basal dendrites of those layer 5 corticofugal pyramidal neurons. An important mechanism seems to be the forward propagation of Ca^{++} spikes from the distal apical dendritic tree to the pyramidal soma which initiates a burst of axonal spikes.

Patch-clamp recordings from distal apical dendritic tufts *in-vitro* have revealed long-duration depolarizing plateau potentials (spikes?) due to NMDA channel activation. The Martinotti cell may limit Ca^{++} spiking. The Compartmentalized Pyramidal Neuron Activation Movie simulates several of these compartmentalized influences as revealed by investigators using patch-recordings of dendrites and soma of pyramidal cells and

patch recordings from several types of inhibitory interneurons in the cerebral cortex of rodents (see references).

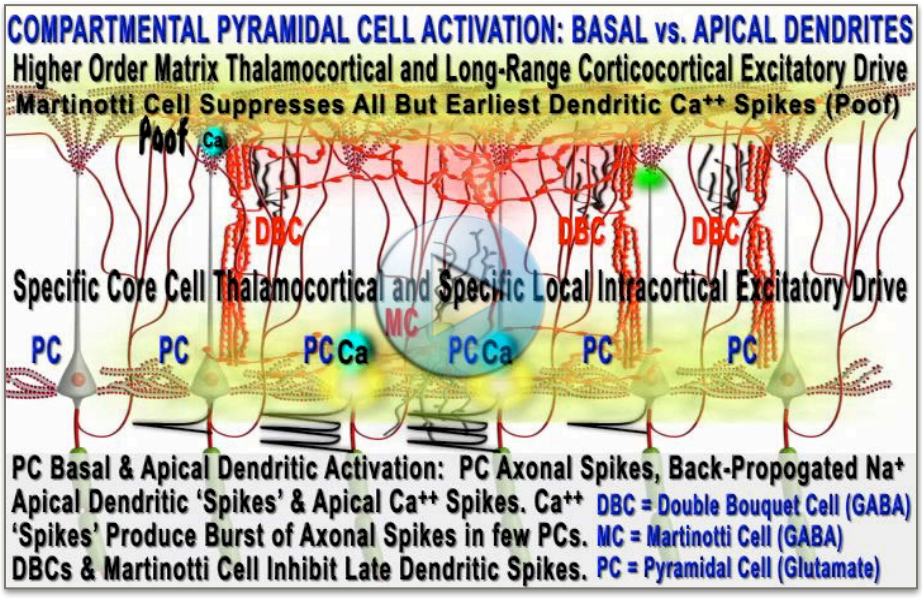


Fig 10-26. Compartmentalized Pyramidal Neuron Activation Movie (gec). GO TO: gmomm.pitt.edu *Fig10-26_Video*

DISTRIBUTED CORTICAL NETWORKS- FUNCTIONAL

LOCALIZATION: PROPOSED ROLES OF KEY CORTICAL AREAS - GET JAVA

Function appears to be distributed across a number of cortical areas for both perceptions and actions. Despite this parceling of function, images and behaviors are not normally fragmented. We do have unified perceptions and actions. How do we coalesce our resources for such unity (the binding problem)? This question is still unanswered. One hypothesis suggests that transient local oscillations (~40-70 Hertz) plus a relative synchrony of neuronal discharge (~4Hz) across multiple areas forms the basis for unification of firing among cell assemblies distributed across the cortex. Under these conditions, coincidence detection among neurons (correlated discharge) may be more important than a simple integrate and fire mechanism. Reaching for an object is a common visually guided task. However, there is still uncertainty regarding the role of the eyes versus. the arm & hand as a reference point for such a synergistic task. Certainly, we do not usually expend extensive conscious effort to follow the hand to cup or cup to mouth. Internal models of reference appear to be critical for efficient function.

READY, SET, GO: REACH, GRASP, DRINK, AH!

Reaching for a coffee cup, grasping it, and successfully drinking from the cup seems like a very straightforward activity. However, this visually guided task requires tremendous cooperation among neuronal networks distributed across all cortical lobes and many subcortical areas.

Before the first motor unit is recruited to move the arm, many brain areas are active to prepare for the reach & grasp.

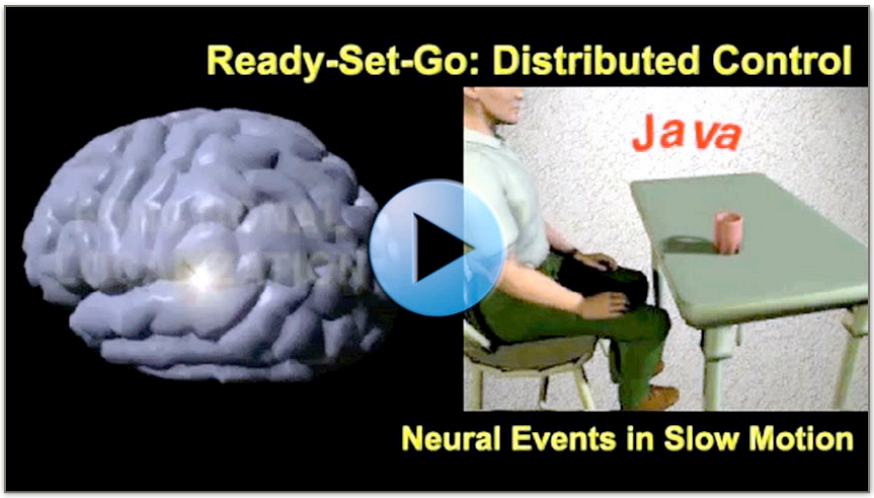


Fig 10-27. Ready-Set-Go Movie: Getting Java - A Distributed Control Process (gec, jec). GO TO: gmomm.pitt.edu *Fig10-27_Video*

These include primary cortical areas (VI, SI, MI), Premotor Areas and Association Areas in all cerebral lobes. In addition, some Cerebellar & Basal Ganglia Circuits are incorporated into planning, programming: "compiling & signing the will" and in doing volitional actions: "executing the will." Action unfolds by neural control of posture, reach and grasp in parallel.

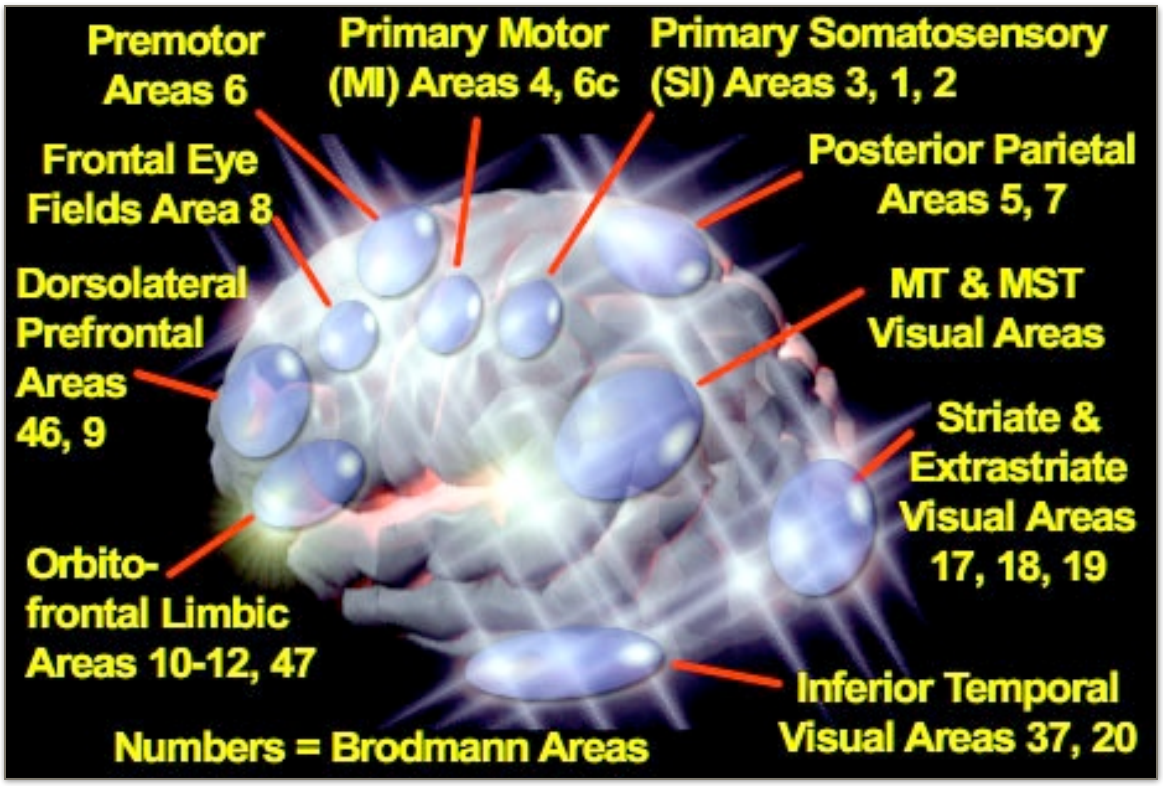


Fig 10-28. Functional Localization: Each of the designated cortical areas indicated by the blue "bubbles" will be discussed below (gec). Open the Interactive Media File. GO TO: gmomm.pitt.edu *Fig10-28_Interactive Media*

The brain frames (left) of the Ready-Set-Go Movie shows the major cortical areas that are active for such a task (activation = spotlight). Not all areas are included, e.g,

trunk muscles maintain postural support while the subject leans forward. The actual task is animated in the 2nd set of frames of the Ready-Set-Go Movie (right). No attempt is made to show subcortical participation. Functional roles are “crude” simulations of actual events (spatially & temporally): play Ready-Set-Go Movie.

PRIMARY MOTOR CORTEX (MI: AREAS 4, 6C)

Pyramidal Tract Neurons (PTNs) in layer V of MI contribute a major projection to the spinal cord (Lateral and Anterior Corticospinal Tracts). The Pyramidal Tract is critically involved in skilled volitional movements especially those requiring fine-hand control (hand dexterity). The distal limb representation in MI has few if any callosal connections which contributes to a specialized 'handedness' in fine motor control of the digits. MI is important in reaching movements, both in the 'mental' representation of direction, and control of synergistic arm movements. Not all pyramidal cells project their axon into the pyramidal tract. Most layer III pyramidal cells have corticocortical or callosal connections, & the majority of layer V pyramidal cells are non-pyramidal tract neurons (non-PTNs).

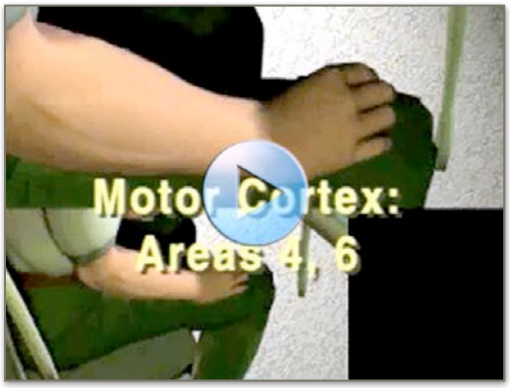


Fig 10-29. Motor Cortex Function Movie (gec). GO TO: gmomm.pitt.edu *Fig10-29_Video*

Non-PTNs represent probably 90-95% of the total cerebral cortex output and have corticofugal projections to supratentorial & posterior fossa brainstem nuclei. Corticomotoneuronal (CM) Cells in Motor Cortex that provide strong, monosynaptic drive directly to spinal alpha motoneurons by way of the pyramidal tract are the “*one per-centers*” of cerebral cortical control of skilled motor tasks.

PRIMARY SOMATOSENSORY CORTEX (SI: AREAS 3, 1, 2)

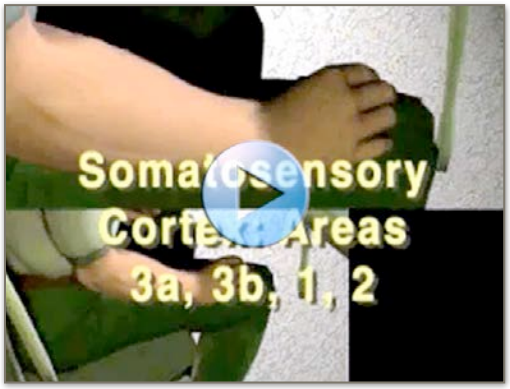


Fig 10-30. Somatosensory Cortex Function (gec). GO TO: gmomm.pitt.edu *Fig10-30_Video*

SI is represented by Brodmann's Areas 3, 1, and 2, such that there are multiple representations of the same body region across these areas. Area 3 has been subdivided into Area 3a which has a major deep representation (joint, muscle receptors) It is located along the bank of the Postcentral Gyrus within the Central Sulcus. Area 3b (located on exposed rostral portion of the Postcentral Gyrus) receives primarily tactile input. Thalamocortical (TC) inputs associated with deep receptors synapse on neurons in Brodmann Areas 2 & 3a of SI

and a portion of MI. Cutaneous TC afferents travel to Areas 3b and 1 of SI and a portion of Area 4 located within the Central Sulcus. Compared to Brodmann Area 3, Areas 1 and 2 have more complex interactions of thalamocortical and corticocortical inputs. SI neurons are critical for 'conscious' proprioception, active touch and localization of somatosensory inputs.

STRIATE AND EXTRASTRIATE OCCIPITAL VISUAL AREAS (AREAS 17, 18, 19)

Most of the Primary Visual Cortex (VI) is located along the banks of the Calcarine Sulcus of the Medial Occipital Lobe. VI is the Striate Cortex (Area 17). Extrastriate Visual Areas (V2, V3, V4, V5 = Areas 18,19) include the Lateral Occipital Gyri, portions of the Cuneus and the Lingual Gyrus of the medial Occipital Lobe. The Striate Cortex is the first cell station in the visual pathway where binocular vision is processed.

Fig 10-31. Visual Cortex Function (gec). GO TO: gmomm.pitt.edu *Fig10-31_Video*

The Magnocellular Pathway (concerned with motion, depth, & general form) projects to the Dorsal Stream. The fast Magnocellular Pathway maintains high temporal resolution of visual information. The slower Parvocellular Pathway (concerned with color, high acuity form, and depth) projects to the Ventral Stream. It carries high spatial resolution of visual inputs. Extrastriate Visual Areas perform higher level processing of visual information to ultimately form a unified perception of the visual world.

DORSAL STREAM: MOTION-SENSITIVE MIDDLE TEMPORAL (MT) & MEDIAL SUPERIOR TEMPORAL (MST) VISUAL AREAS

MT and MST are important areas of the Dorsal Visual Stream Pathway for processing motion. Neuronal activation in these areas is Context- and State-Dependent. For example, neurons modulate their firing according to directional preferences of object motion, and firing may be enhanced or suppressed according to attentional states (objects may be present in the visual field but their blips on the radar may disappear with diverted attention). MT and MST project to the Intraparietal and Superior Parietal Visual Areas that form the “end-point” of the Dorsal Stream Visual Pathway concerned with the "where" and "how" of visually guided tasks (Action-Oriented Pathway). The Dorsal Stream has major connections with Frontal Lobe Areas involved in the generation and control of visually guided actions and active touch. MT, MST receive fast magnocellular visual pathway cortical (striate and extrastriate cortex) and subcortical

(superior colliculus) inputs that allow for a rapid preconscious response to moving objects in the visual scene and assist in tracking moving objects.

Fig 10-32. Middle Temporal (MT) & Medial Superior Temporal (MST) Cortex (Dorsal Visual Stream) Function (gec). GO TO: gmomm.pitt.edu
Fig10-32_Video

DORSAL VISUAL STREAM: THE POSTERIOR PARIETAL CORTEX- "TERMINATION" OF THE DORSAL VISUAL STREAM

The Posterior Parietal Cortex (PPC) consists of a Superior Parietal Lobule (Areas 5, 7) and an Inferior Parietal Lobule (Supramarginal Gyrus-Area 40 & Angular Gyrus-Area 39) separated by the Intraparietal Sulcus & Intraparietal Cortex (IP). The PPC is thought to be a critical cortical area for representation of our "body image" or "body schema." Neuronal networks provide a four-dimensional spatial reference system (3 spatial dimensions dynamically represented over time) to allow us to relate one body part to another and relate ourselves to the external world. These perceptual processes provide a means to navigate in a changing environment and engage objects in the environment with a high degree of precision. PPC is multimodal; it receives somatosensory, visual, auditory, and vestibular inputs and neuronal firing here is state- and context-dependent. The PPC is the "end-point" for the dorsal visual stream and defines the "where" and/or "how" in utilization of visual input to guide our actions, e.g., reaching. It has significant connections with the Frontal Lobe, Basal Ganglia and the Cerebellum.

Fig 10-33. Posterior Parietal Cortex (Dorsal Visual Stream) Function (gec). GO TO: gmomm.pitt.edu
Fig10-33_Video

VENTRAL VISUAL STREAM: INFERIOR TEMPORAL VISUAL AREAS: AIT, PIT, TE, TEO

Inferior Temporal (IT) Visual Areas process details of form, color, and depth cues of our visual world ('Parvocellular' Pathway). Neuronal activation in these areas appears to be Context- and State-Dependent. For example, neurons modulate their firing according to the specific features of an object that define it as an entity or as a member of a class of objects (including faces).

Fig 10-34. Inferior Temporal Visual Cortex (Ventral Visual Stream) Function (gec). GO TO: gmomm. pitt.edu Fig10-34_Video

Here a rose by any other name is still a rose. Placing a face with a name would not be possible without IT. Firing may be enhanced or suppressed according to attentional states (e.g., objects may be present in the visual field but their blips on the radar may disappear with diverted attention). IT Visual Areas form the “end-point” of the Ventral Stream Visual Pathway concerned with the "what" of the object of interest in visually guided tasks (Perception Oriented Pathway). IT receives input from the Parvocellular pathway. This pathway is relatively slow compared to the Magnocellular pathway in the Dorsal Stream. The Parvocellular pathway is critical for conscious visual perceptions where we define objects and people in our world.

LATERAL PREMOTOR AREA, SUPPLEMENTAL MOTOR AREA (SMA) & CINGULATE MOTOR AREAS

The Premotor Cortex and SMA are critically involved in “programming” skilled “volitional” movements especially those requiring sequential actions from groups of muscles coordinated in synergistic fashion (e.g., reaching, grasping and drinking).

Fig 10-35. Premotor Cortex (Lateral premotor, SMA, CMA) Function (gec). GO TO: gmomm.pitt.edu Fig10-35_Video

A motor program is thought to be a neural representation of the pattern of action not necessarily the specific muscles activated. Some believe the program represents a motor schema or set of rules to follow (see animated “program” Cartoon). The Lateral Premotor & SMA are major cortical targets for portions of the Basal Ganglia, Cerebellum, SI, Posterior Parietal and other “Association” Cortices. These are critical areas in preparation for upcoming movements and are active prior to Primary Motor Cortex for learned activities.

Most neurons continue to fire as the action unfolds, i.e., during the execution of the task. Premotor Areas project axons into the Lateral Corticospinal Tract to synapse on

ventral horn neurons. SMA and adjacent Cingulate Motor Areas may contribute to the neural “code” for the “urge” to move.

FRONTAL EYE FIELDS (FEF)

Fig 10-36. Frontal Eye Fields (FEF) Cortex Function (gec). GO TO: gmomm.pitt.edu
Fig10-36_Video

The Frontal Eye Fields (Area 8) located rostral to Area 6 in the inferior portion of the Superior Frontal Gyrus and in the Middle Frontal Gyrus is an important area for cortical control of conjugate eye movements (Visual Scanning and tracking of Visual Objects: see movie). The FEF along with the Supplemental Eye Fields adjacent to the FEF are active from the beginning of a visually guided reaching task. FEF receive inputs from the Posterior Parietal Lobe (the dorsal visual stream target area), MT & MST, Superior Colliculus, and Basal Ganglia. Rapid saccadic conjugate eye movements allow us to rapidly move our eyes to acquire a visual target. This is often done in a preconscious fashion well before any conscious reaction to specifically identify the object. After "locking-on" to the visual object of interest we then use slower smooth-pursuit conjugate eye movements to willfully track the target of interest and identify the specific characteristics of the object (conscious perception).

DORSOLATERAL PREFRONTAL AREA (DLF): AREAS 46 & 9

The Dorsolateral Prefrontal Cortex (DLF) is critically involved in the planning of self-initiated, goal oriented tasks that require an intact working memory. The executive function is thought to be one of cognitive monitoring of intended actions and temporal organization of events to realize a specific goal. The executive function is not a single declaration of intent, but an ongoing process that requires good working memory over the duration of the task (“*thou shalts*” are not simply commands with no “hands-on” involvement).

Fig 10-37. Dorsolateral Prefrontal Cortex Executive Function (gec).

Recent studies suggest that over-learned tasks require relatively little DLF activation since basal ganglia and cerebellar circuits may automate the over-learned skill. The DLF is well connected. The DLF has major connections with portions of the Basal Ganglia, Lateral Cerebellum, Posterior Parietal Cortex & other “Association” and “Limbic” Cortices.

The DLF is a “higher” level area with access to “privileged” information and networks built for working memory. Connections between the DLF, Cingulate Cortex & Orbitofrontal Cortex may add some flavor to the task; the DLF isn't haughty, it has a “dry” or “wry” sense of humor layered upon its decision-making capabilities.

ORBITOFRONTAL GYRI: LIMBIC AREA

The Orbitofrontal Gyri are often considered to be part of the limbic system; these gyri include the medial orbitofrontal gyri on the ventromedial aspect of the frontal lobe and the orbital gyri on the inferior surface of the frontal lobe. These prefrontal gyri are thought to be important in control of behaviors that have a high affective, emotional component, require memory of past behavioral events and weigh behavioral choice selection based in reward value. This Limbic Area along with others, including the cingulate gyrus are important in control of basic drives and motivation of our behaviors. They add some flavor to our actions (reward arbitration).

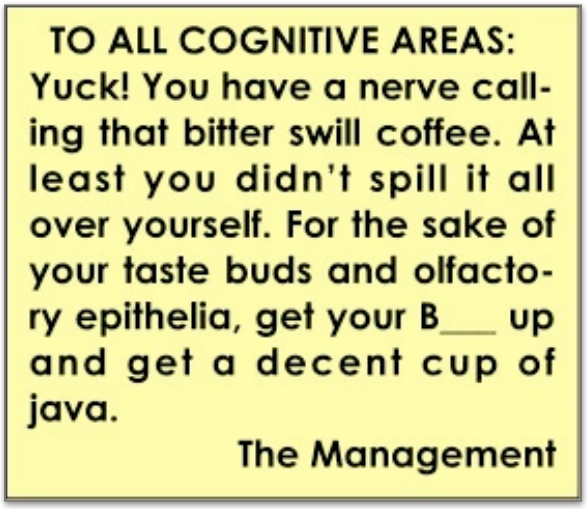


Fig 10-38. Limbic Cortex (Tongue-In-Cheek) Function (see Ready-Set-Go: Getting Java Movie above) (gec).

The orbitofrontal gyri may at once bring out the animal in us and make us human. As suggested by the MEMO these gyri can be quite ‘*opinionated*’ and influential. These limbic gyri have important connections with olfactory areas, other Limbic Structures, e.g., Cingulate Cortex, the Basal Ganglia (BG), the Dorsolateral Prefrontal Cortex & the Medial & Inferior Temporal Lobe. Many prefrontal areas cooperate with BG in deciphering reward-based intentions and actions and Dopamine (DOPA) is their favorite ‘flavor of the month’: DOPA influences the frontal lobe by direct connections from the Ventral Tegmental Area in the brainstem and indirectly by way of a basal ganglia-cerebral cortical loop.

BINDING: UNIFIED PERCEPTION - RED BALL BOUNCING

The Binding in Distributed System: Red Ball Bouncing Movie is an attempt to illustrate the sequence of events when a moving object appears in a viewer's peripheral vision. A rapid saccade provides a first glimpse of the object and then the identify the object becomes apparent if gaze lingers and then sufficient brain resources are brought “on-line.” The scenario begins as a preconscious saccade to an object located somewhere to the viewer's right.

Then a more precise location and other features of the object begin to be recognized by the viewer's visual brain. Finally, when the cortical dorsal stream and ventral stream extrastriate visual areas are active and functionally joined by corticocortical connectivity

and the linked higher order thalamic matrix cells establish a viable corticothalamocortical loop, the multiple areas show synchronous activity. The relevant brain areas are now bound together to establish a conscious, unified perception.

Now the necessary network coalitions have been established so that the appropriate brain areas are “on the same page at the same time.” Rapid visual input to the superior colliculus (SC) can initiate a 'preconscious' saccade that moves eyes to the right but does not precisely target the object. Then visual input to the forebrain provides data that allow for more precise localization & tracking of the object: transition from preconscious to conscious state.

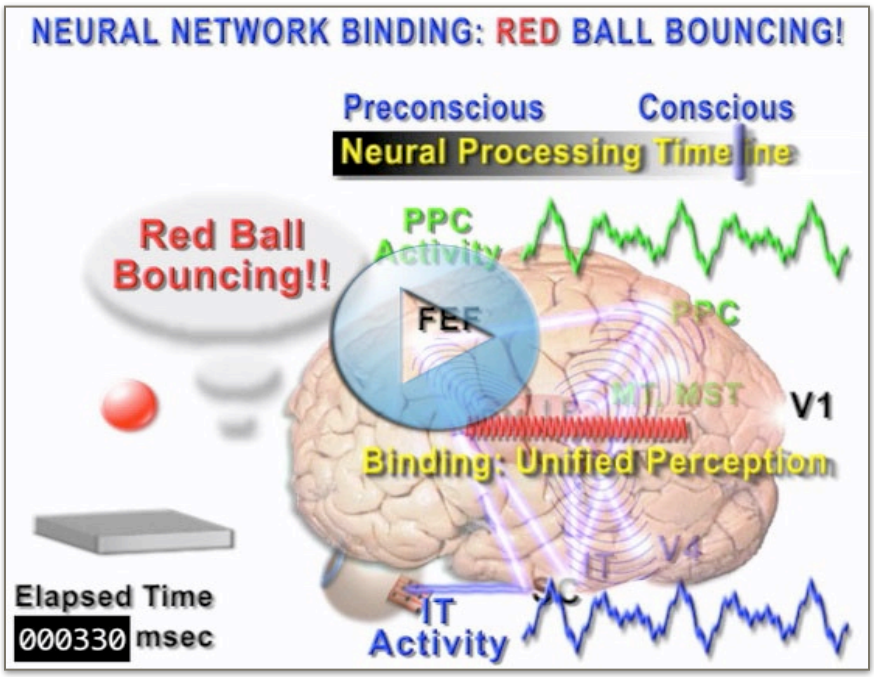


Fig 10-39. Binding in Distributed System: Red Ball Bouncing Movie (gec). GO TO: gmomm. pitt.edu Fig10-39 Video

Two streams of visual input to the LGN thalamic nucleus are illustrated in the animation: a fast, colorblind, motion-sensitive magnocellular input that targets the dorsal visual stream (to V1, MT, MST, PPC cortical areas) followed by a slower high acuity, color sensitive parvocellular input that targets the ventral visual stream (to V1, V4, IT cortical areas). Binding occurs when select neural networks within all components are brought “on-line” to be synchronously active. This takes some time for forward and backward connections among distributed cortical areas.

AMERICA THE GRAY: AGING HUMAN CEREBRAL CORTEX

Americans are coming of age – literally. “Baby-boomers” will soon swell enrollment in Medicare, and draw social security from coffers that may be unable to meet demand. Health care demands will parallel the rise in median age of our society. The number one risk factor for a number of neurodegenerative diseases, e.g., Parkinson’s Disease (PD) and Alzheimer’s Disease (AD) is age. There is good news and bad news.

A number of very bright neuroscientists are working furiously to define pathological processes, create targeted diagnostic tools, and establish potential treatments (lifestyle & medication) for neurodegenerative diseases. There are scientists who believe that AD

is not only treatable but also preventable. Contrary to older ideas, normal aging does not appear to be associated with significant cell loss in most cerebral gray matter. While this older idea appears to be unfounded in normal aging, profound cell loss is characteristic of AD and other forms of dementia and a number of progressive neurodegenerative disorders, e.g., Huntington's Disease.

1. Of all layers, layer I of the cerebral cortex appears to atrophy in normal aged primates. For young adults, Layer I is cell sparse but has many horizontal long-range corticocortical axonal projections and apical dendritic tufts from supragranular and infragranular pyramidal cells. A number of neuromodulatory chemicals may have profound effects on these synaptic connections. Many of these dendritic branches and synaptic connections appear to be lost with age. Who cares? Remember that superficial cortical layers receive substantial input from matrix projection neurons in higher order thalamic nuclei. Through thalamocortical loops, this connectivity may be essential when coupled with intrinsic cortical connections in solving the “binding problem” for normal cognitive function. Apical dendrites of layer V pyramidal cells under certain conditions may generate dendritic NMDA and Ca++ potentials that induce persistent “burst” firing in these neurons. Recent findings in rodents suggest such activity may be critical for “global” binding across multiple cortical areas involved in perceptual and cognitive processes. In addition, a recent study of human cerebral cortex has characterized a GABAergic interneuron called a Rosehip cell (RC) located in cortical layer I. RCs have not been identified in other species and evidence suggests RCs have a critical role in regulation of excitability in apical dendritic tufts of pyramidal cells. RCs are electronically coupled and may participate in generating rhythms important for higher level (top-down) processing critical for cognition (see Boldog, et.al., 2018). Collapse of human cortical layer I with aging would remove these influences for higher level functions.

2. By middle age our gray matter may have a nonuniform “thinning” that may be due to cell shrinkage and/or neurite loss but not substantial neuron loss; the prefrontal cortex is particularly affected. Certain neurotransmitters and neurotrophins may be altered or diminished and some axospinous synapses may be lost. Synapse loss may be nonuniform in both location and type. For example, small axospinous synapses onto small spine heads are reduced more than synapses with large spine heads in pyramidal cells of prefrontal cortex. The losses appear to greater in upper layers of the cortex (layer1> 2/3). It is suggested this more selective loss of small spine head synapses is correlated with deficits in working memory, see Morrison and Baxter, 2012. Based on monkey electron micrographic studies, presynaptic axosomatic GABAergic boutons on pyramidal cells in Area 46 of prefrontal cortex may actually be enhanced in aged monkeys who show cognitive impairment (e.g., see Soghomonian, et.al., 2010). Thus, too little depolarizing input may have to compete with excessive strong inhibition in cognitive circuitry; now add impaired mechanisms to generate

persistent firing in pyramidal cells and we have a potentially disastrous combination for thinking brains, see: Peters, 2002; Peters et.al., 2008; Peters & Kemper, 2012.

3. White matter does seem to diminish to some extent in normal aging. Gray and more so white thinning may account for slightly enlarged ventricles and a reduced brain volume (but not overall weight) in normal aging brains. Myelin abnormalities appear to be substantial in association cortex, e.g., prefrontal cortex in aged monkeys. Demyelination and remyelination is accompanied by an increased number of oligodendroglia and the level of myelin abnormalities in Prefrontal Cortex is correlated with cognitive decline (as measured in aged monkeys). Since cognition may depend upon correlated firing of cerebral neurons to solve the binding problem, a variable conduction velocity may tax neurons struggling to function within the distributed network. Slowed or disrupted temporal sequencing of thought (altered executive function) occurs in many elderly. Paradoxically, while association cortex is critical for higher functions, it is the evolutionary "weak-link" in the human brain since myelination is poor there and thinning of gray greater compared to primary cortical areas even in young adults. The cerebral cortex is not the only region influenced by age. Volume as measured by MRI decreases with age in the caudate nucleus, cerebellum and hippocampus, all regions of importance in cognitive function, e.g., see Raz, et.al., 2005. With longevity, the organ that best defines us as human is susceptible to insults that have little impact on other species.

4. Dementia including Alzheimer's Dementia is related to a neuronal cell loss particularly in association cortex. Not all neurons are susceptible and left hemisphere is typically involved more than the right hemisphere in AD (see references). AD shows abnormal function in neurons 'attacked' by Beta Amyloid plaque formation and neurofibrillary tangles. Such changes are not restricted to neurons. Glia are involved in this degenerative neuropathology as well. Indeed, normally helpful glia may turn to the dark side in AD, e.g., see Deszkowka, et.al., 2018.

5. Although the aging brain movies are "tongue-in-cheek" animations, accumulating evidence suggests that in addition to genetic factors there is an important role for lifestyle factors in preservation of brain structure and function as an individual ages due to "reserve", compensation and/or maintenance of brain function: for recent review see Cabeza, et.al., 2018.

The second movie suggests also that making lifestyle changes while beneficial in theory, in practice may be difficult to achieve for many individuals. Nevertheless, meeting the physical and mental challenges of aging may provide sufficient rewards to be worth the effort.

Neuroprotective effects of exercise, diet and other "lifestyle" factors are now being investigated in earnest by a dedicated cadre of scientists in the USA and in a number of other countries. **See also: Alzheimer's Dementia: ''The Thief In The Night'' Section in Chapter 19**.

Fig 10-40. Old View (Tongue-In-Cheek) of Normal Aging of Cerebral Cortex : Substantial Loss of Cerebral Cortical Neurons. Evidence now rejects this substantial neuron loss in normal aging (gec). GO TO: gmomm.pitt.edu *Fig10-40_Video*

Fig 10-41. New View (Tongue-In-Cheek) of Normal Aging of Cerebral Cortex: Keep the Neurons (gec). GO TO: gmomm.pitt.edu *Fig10-41_Video*

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Chapter 11

SOMATOSENSORY SYSTEM: CENTRAL REPRESENTATION OF BODILY SENSES

"Sensory is sensory and motor is motor and nary the two shall meet except perhaps in the psychologist's mind." *GEC* This old idea of a structural or functional separation between "bottom-up" sensory data and "top-down" motor drive will be challenged in the following pages. Such a conceptual separation of sensory and motor function was challenged early by at least one psychologist: see J. Dewey, 1896 .

PERIPHERAL TACTILE AFFERENT INPUT: RAPID "BOTTOM-UP" DRIVE WITHIN THE SOMATOSENSORY SYSTEM

Somatosensory inputs from cutaneous and deep receptors are processed at various levels of the CNS including spinal, supraspinal (posterior fossa brainstem, thalamus and cerebellum) and most importantly for our conscious being at the cerebral cortical level. Although classic descriptions of this information transfer was often represented as an ascending only process from "lower" CNS (subcortical brain and spinal cord) areas to "higher" ones (cerebral cortical areas), current evidence shuns such a unilateral, one-way "hierarchical" transfer of information from the standpoint of behaviorally relevant function. Nevertheless most instructors still see this simplified ascending rule to be useful when describing the structural components of the somatosensory (or any other sensory) system to students being introduced to neuroscience.

"TOP-DOWN" RECURRENT PROCESSING: A PRESUMED REQUIREMENT FOR CONSCIOUS PERCEPTION

Recording a local field potential (LFP) recorded from the surface of the primary somatosensory cortex (SI) shows both early and late components in the evoked waveform. The earliest component is associated with cortical activity due to strong ascending peripheral excitation from the first order core thalamus (Ventral Posterior Median Nucleus in this illustration of SI recording of an evoked potential due to trigeminal nerve stimulation in the rat). Later components reveal depolarizing and hyperpolarizing intracortical processing due to both local and long-range connections: see Panel A of LFP & ERP Recordings figure. The LFP represents activity within a population of neurons; later components may reflect behaviorally relevant discrimination processing due to recurrent cortical & corticothalamocortical projections (see refs).

A scalp recording using electroencephalographic (EEG) electrodes shows a similar evoked potential commonly referred to as an Event Related Potential (ERP) in awake subjects: see Panel B of the LFP & ERP Recordings figure. This panel shows an animation which simulates a hypothetical experiment to block the later components of the ERP associated with long range feedforward and recurrent intracortical connectivity.

Mounting evidence shows that the longer latency components of the ERP are related to the behaviorally relevant conscious awareness of the sensory input, i.e., the early latency components less than ~100-150 msec ***alone*** do not give rise to conscious perception (play movie and see references at end of movie). However, early somatosensory components define the source, location and type of external sensory data and these early externally-driven responses are critical for non-conscious automatic sensorimotor mechanisms, e.g, grip-slip adjustments.

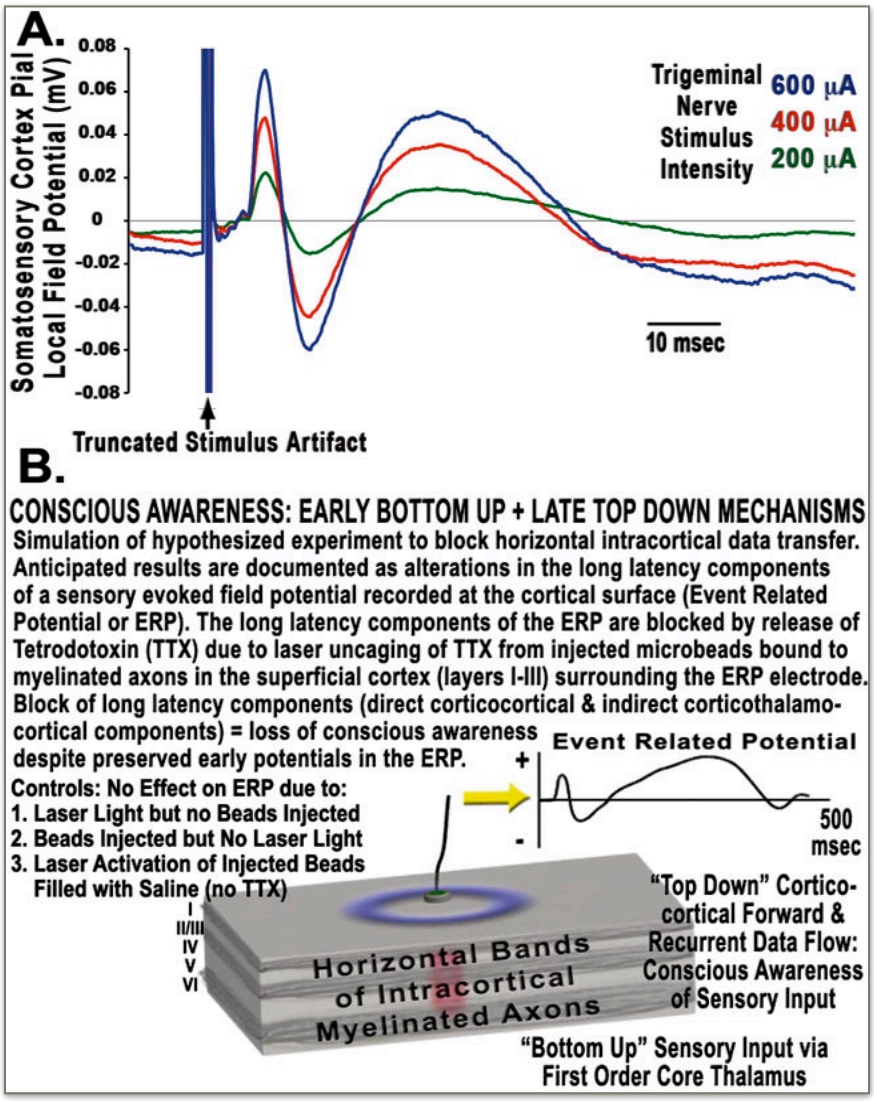


Fig 11-1. LFP & ERP Recordings. A. SI Cortical Surface Local Field Potentials Evoked by Three Intensities of Peripheral Trigeminal Afferent Stimulation in Anesthetized Rat . B. Simulation of Hypothesized Experiment to Inactivate "Top-Down" Intracortical Connectivity and Therefore Block Conscious Awareness of Sensory Input in Awake Subject (gec). GO TO: gmomm.pitt.edu
Fig11-1_Video

Therefore, one must be cautious not to oversimplify the somatosensory CNS structural-functional relationships as if they are strictly a bottom-up one-way street of touchy traffic. Bodily information travels on busy multilane highways that under certain circumstances may resemble "rush hour" traffic with all the "multitaskers" doing other things as well as driving. Thankfully, the CNS has GABA interneurons at each of these processing centers that bring some degree of order out of potential chaos when our bodies are in motion and we are actively engaging animate and inanimate objects within reach. This central control of traffic may under certain circumstances be extreme; for example, when POTUS (President of the United States)

comes to town and there are rolling traffic stoppages for all vehicles except the president's party. Some data may have privileged access to communication routes compared to others according to the saliency of the information at any one time (we do not feel, hear or see everything that activates the modality-specific sensory receptors). Such top-down influences may alter perception due to predictive inferences that are matched to postdictive sensory data perhaps using Bayesian principles of data translation, e.g. see Geldard & Sherrick, 1972, Goldreich & Tong, 2015, see also Roth, et.al., 2016.

PERCEPTION/ACTION GESTALT

Let's investigate our central representation of bodily senses at the "top," i.e., at the level of perceptual realization of sensory phenomena and utilization of such information to gain knowledge about the world within reach (expanding our personal "bubble" to physically engage the world).

Having lived in a time & place when "more is better" was a national obsession, one must now look at the nervous system's role in perception and volition from a slightly different perspective. Gestalt theory suggests "the whole is greater than the sum of its parts" in perceptions and actions that underlie volition. Though this theory is difficult to put to the proof, the implication might be that, ultimately, more is better. Neuroscientists have not yet agreed as to the role of synaptic interactions in neural networks underlying perceptions and actions. Some conclude that networks amplify incoming data, while others suggest that at least some cortical networks operate as damping circuits. What if the network operations actually distill the fine liquid from the mash as is true for processing many alcoholic beverages? Now the refined/filtered network "whole" actually may be less than the sum of the incoming data mash (negative Gestalt?). While a number of peripheral receptor systems do amplify transduced signals and the motor unit, by definition, amplifies the neural impulse for action, the ***Central*** Nervous System may need to suppress a potential information overload & distill incoming and outgoing signals. Both Perception and Volitional Action may require a critical weighing and filtering to extract the exact "bouquet" to satisfy the discriminating palate of beings capable of such fine, smooth, seemingly effortless skilled behavior and refined perceptions (that refers to us humans). Cerebral Cortical control appears to be critically dependent on local circuit GABAergic inhibitory synapses and Cerebellar plus Basal Ganglia Circuits will not function without GABA neurons to do their job. For a high level action-perception cycle of events, a refined lesser "whole" may be better than any greater sum of many parts. Perhaps, "*do more with less*" is a more appropriate motto! *Debate is encouraged*.

INTENTION-ACTION-PERCEPTION CYCLE: LIFETIME LEARNING

The somatosensory system provides tactile and proprioceptive information from our body (soma) and the world that we physically contact. The visual system provides

information about extra-personal space and the animate and inanimate objects within it. Information processing is not a simple bottom-up transference of data from periphery to perception. The realization of the intentions for our actions provides the opportunity for purposeful engagement of the environment and objects within it. The motor system is continuously altering our sensations and sensations often modulate motor output. This has been modeled as an action-perception cycle that provides the basis for increasingly sophisticated "impressions" of internal and external states as we gain experience over a lifetime. Recent studies emphasize the plasticity & malleability of our sensorimotor system even in adulthood. Some changes may occur rapidly, others only after repeated events. Although early neurophysiological studies suggest that neuronal activity in cortical association areas are state- and context-dependent, evidence was less compelling for neurons in early stages of sensory processing. More recent investigations suggest that the CNS may modulate its own afferent drive in the early stages of information gathering (e.g., spinal cord, dorsal column nuclei). This includes mechanisms for surround inhibition and motor gating of somatosensation, see Chapman, 1994; Ghez & Lenzi, 1971; Guillery, 2003; Lee, et.al., 2013; Schroeder, et.al., 2010; Williams & Chapman, 2000, 2002.

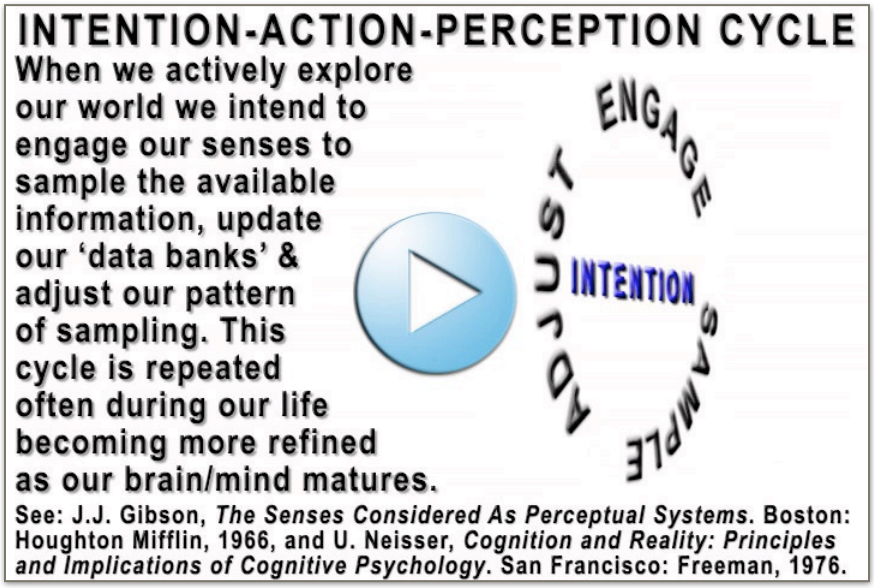


Fig 11-2. Intention-Action-Perception Cycling Movie (gec). GO TO: gmomm.pitt.edu
Fig11-2_Video

Attention, intention, motivation and reward may all have a critical role in defining salient aspects of our senses. The Action-Perception (AP) Cycle (see Gibson, 1966; Neisser, 1976) hypothesizes that what we experience is related to our ability to explore and gain information about our world: see also Cisek & Kalaska, 2010; Schroeder, et.al., 2010. Based on our own intent, there is an evolution of sampling, modifying/adjusting CNS resources and engaging our world to gather further information. Here intention is added as another component to this cycle; one's intent typically is directly related to one's own will. One supposes that a repetition of a willed Intention-Action-Perception (IAP) Cycle results in learning. Learning allows for increased sophistication in our perceptions & actions as our "schema" of the present environment and the cognitive "map" of the world grow to become fine-tuned [more

mature?] over our life cycle, see: U. Neisser, 1976. Play Intention-Action-Perception Cycling Movie.

ATTENTION-INTENTION AND SOMATOSENSATION: TOP-DOWN VERSUS BOTTOM-UP PROCESSING

The glabrous surface of the hand contains a very high density of low-threshold tactile mechanoreceptors critical for discriminative touch. The central representation of the volar but not the dorsal surface of the hand is magnified. Despite this robust cutaneous representation, the tactile receptors for glabrous surface of the hand are rarely activated without our "permission." We do not stand or walk in the anatomical position such that the forearm is supinated and our palms are facing forward. Distance receptors (eye, ear and sometimes nose) most often make "first contact" with our world. Nevertheless, our hands represent a particularly relevant source of somatosensory data in our daily lives (according to our own needs: volitional discriminative active touch).

Now consider the following scenario.

> You are attending a "formal" gathering of friends, coworkers and other people that you have not previously met. While you are holding a beverage with your right hand and conversing with a friend, something suddenly touches your left palm. You react to find that someone has "handed" you his business card without introduction. You turn and look at the person with a mixture of surprise and disgust on your face. The person is well-dressed and seems to be of no particular threat. You read the card and see that he is a financial advisor for a reputable firm but seems to be "clueless" to your reaction. As you look at this individual for scars and full dentition, you wonder how often he has done this before; perhaps most of his sales are done "on-line." Compare this to a more socially acceptable scene where he introduces himself and extends his hand which you accept with a firm handshake. He then hands you his card which produces a less intense tactile sensation as he "makes his pitch". You thank him and let him know that you are in no need of his financial assistance at this time.

Both circumstances lead to touch of your hand and your full attention to tactile input but the "feel" is completely different. Your intentions and actions are essential to your interpretation of tactile inputs to the hand and elsewhere. This requires cerebral top-down processing that substantially modulates the effect of and interpretation of bottom-up sensory data: perhaps a prime example of Bayesian predictive & postdictive modeling, e.g., see Goldreich and Tong, 2013.

MAY I HAVE YOUR ATTENTION PLEASE! TOP-DOWN INFLUENCES ON SENSATIONS.

Some real events in your life are so sensational that you are compelled to experience and remember them. Such events often have an emotional overtone so

intense you "*burn*" a "condensed" version in your memory; remembrances over time are not exact replay. Other events are virtually experienced by proxy through the media: movies, social media, TV, internet and written accounts of "real" or fictional events.

What all of these have in common is the combined "assault" on your sensorium by a bottom-up activation of peripheral sensory receptors and a top-down activation of attentional and intentional central nervous system resources to "focus" on selective neural events at the expense of other fleeting signals of no particular consequence to you. Writers are especially challenged since they must convince you of the experience by quite abstract means-words! Since a picture is said to be worth a thousand words, publications such as the National Geographic are quite compelling to many audiences. When all is said and done, information flow is unlikely to be a one-way process in the engaged brain.

If you ask a young child how she sees, she will point to her eyes. However, it does not take long for a child with insight to discover the "mind's eye." Dreams may contain vivid images that persist upon waking; characters & scenes are "seen" even if words in one's favorite book are the only point of reference. Although many psychologists have long conceptualized context- and state-dependent neuronal activity even in the earliest stages of sensory processing, only recently have single cell sensory cortex recordings & brain imaging in awake subjects confirmed some of these hypotheses. Not only do peripheral receptor inputs influence receptive fields of somatosensory cortex cells, but also the central inputs from other cortical areas (association and motor areas) reciprocally connected with these neurons via corticocortical and/or cortico-thalamocortical loops, e.g., see Aukstulewicz, et.al., 2012; Cauller, 1995; Chapman, 1995; Guillery and Sherman, 2002; Jones, 2001, 2009; Lederman & Klatzky, 1990; Manita, et.al., 2015; Niebur, et.al., 2002; Schroeder, et.al., 2010.

Neuroscientists believe that our ability to attend to our world is limited in space (we cannot attend to details of all that reach our sensory organs at any one time). However, we are capable of rapidly shifting our attention from one thing to another and thus, time permitting, we may take in the details from all parts of a scene if we put our mind to it. Of course some things are more deserving of our attention than others and we tend to dwell on what is interesting and/or critical to our well-being (saliency). One theory suggests involvement of a corticothalamocortical loop and a transient binding of activity among connected cells as a mechanism for "the guiding light." What we consciously perceive is not the same as what we touch, since preconscious sensory processing may provoke action without conscious awareness, e.g., automatic grip-slip adjustments when using tools.

The Selective Attention Animation movie describes the effect of selective attention on the firing pattern of connected neurons located in the second somatosensory cortex (SII). The scenario is simulated as if the experiments were done with human subjects;

but the animation is based on interpretation of data collected from individual neurons in SII of monkeys (e.g., see Niebur, et.al., 2002; Steinmetz, et.al., 2000).

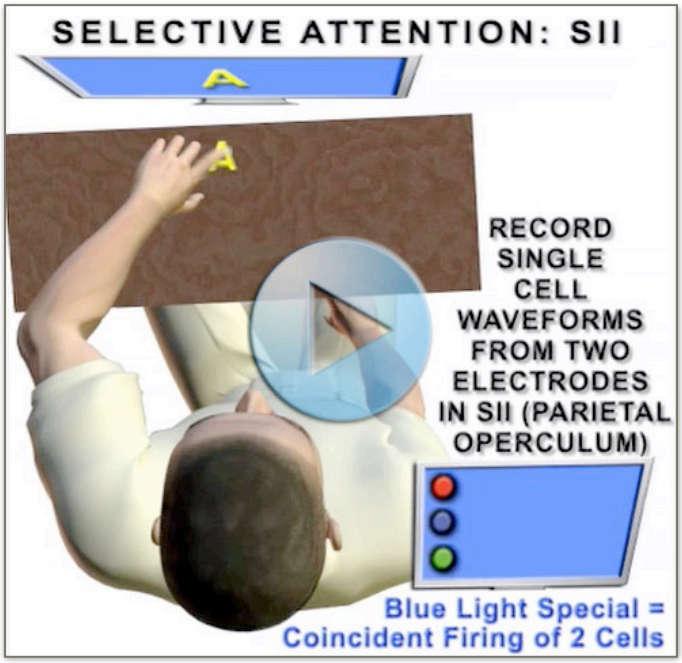


Fig 11-3. Selective Attention Animation Movie (gec). GO TO: gmomm.pitt.edu [Fig11-3_Video]

Note difference in the response pattern for the two SII cells when the subject attends to a visual cue versus a tactile cue presented simultaneously to the subject. SII contains a topographic representation of the body but its neurons tend to represent more integrated information compared to the high spatial & temporal detail represented in the primary somatosensory cortex (SI). SII neurons are considered to be highly task- and state-dependent (certain tasks produce high firing but if the subject is not attentive neurons show reduced firing or even cease responding). If recordings occured in extrastriate visual cortex the increased synchrony may be seen when the individual attends to the visual letter rather than the palpated letter, e.g., see Moran & Desimone, 1985; Motter, 1993; Petersen & Posner, 2012.

SOMATOTOPIC ORGANIZATION: DISTORTED TOPOGRAPHY

The tactile periphery is organized in a topographic fashion. This topography differs however for the peripheral and central representation of touch. Dorsal roots are organized in a segmental fashion; these segmental peripheral axons to trunk and limbs are ordered according to a dermatomal map (see Composite Dermatomal Map figure).

The central ascending pathways are organized according to body region such that adjacent or non adjacent dermatomes may be represented in adjacent ascending axons of the somatosensory pathways, i.e., dermatomes are not contiguous in central somatosensory representations of the body. Centrally, each side of the body is represented in the contralateral somatosensory cortex as a roughly continuous body map (see Somatosensory SI HOMUNCULUS figure). An early map of body representation in precentral and postcentral gyri was published as a result of cortical surface stimulation during neurosurgery in awake subjects: see Foerster, 1936. The afferents representing arm, trunk, or leg are “bundled” as largely separate entities within the major ascending tracts. This somatotopic organization is maintained for the major tracts from spinal cord, through the posterior fossa brainstem to the thalamus. It is

projected topographically to the Primary Somatosensory Cortex by thalamocortical axons. There is some disagreement on the details, but neuroscientists agree on the major features of the map. The central representation of the body is not a simple proportional point to point map. The homunculus is distorted such that the skin areas innervated by the highest density of somatosensory receptors have a proportionally greater extent of neural machinery (neurons) devoted to them. At the level of the cerebral cortex this takes the form of a Cortical Magnification of the hand, digits, face and tongue compared to other body regions.

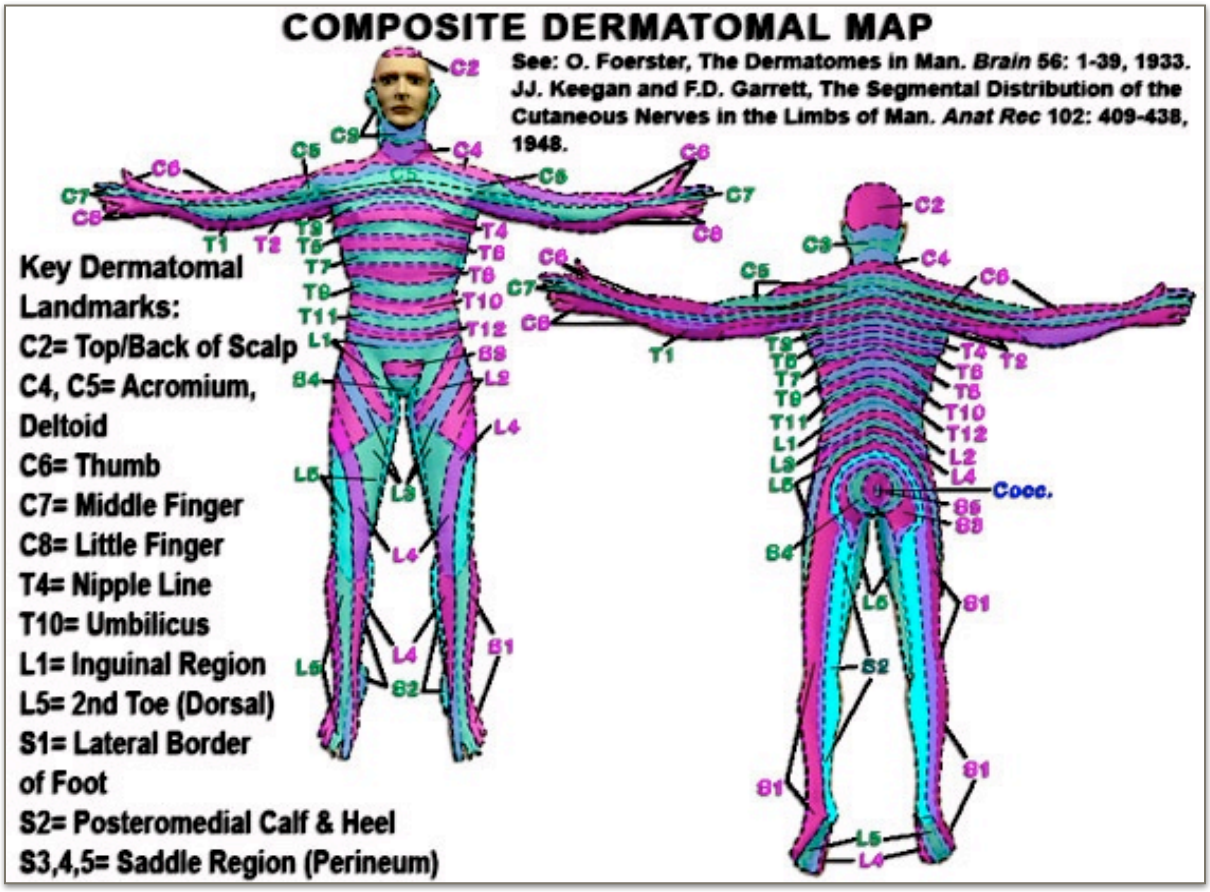


Fig 11-4. Composite Dermatomal Map: Peripheral NOT Central Distribution of Afferent Inputs (gec).

PRIMARY SOMATOSENSORY CORTEX (SI) HOMUNCULUS: STRUCTURE MEETS FUNCTION

The homunculus is an artistic rendition of the representation of the body in the Primary Somatosensory Cortex (SI). This drawing and many other homunculi are based upon the findings of Wilder Penfield, MD. Penfield was a neurosurgeon who, in the 1950s, mapped the precentral and postcentral gyri and other cortical areas of human subjects undergoing neurosurgery. The subjects were awake and the map represents the site where the person felt the effects of stimulating the cortex at each postcentral

cortical location. these topographic maps are quite similar to those obtained during neurosurgery by Foerster, 1936.

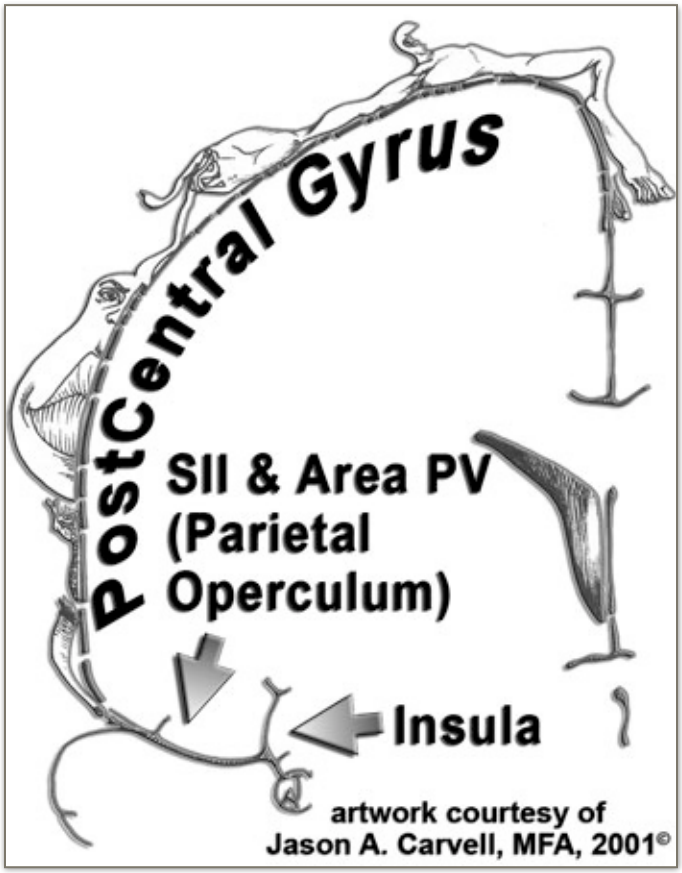


Fig 11-5. Somatosensory (SI) Homunculus - Postcentral Gyrus Distorted Topography (gec, jac).

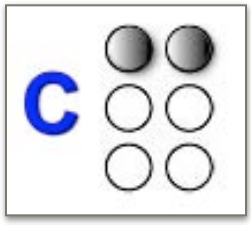
At the end of the twentieth century neuroscientists used a variety of methods to determine if this map was mutable. Many animal and human studies have provided evidence that the map is much more dynamic than that suggested by static drawings. There is now considerable evidence to show that both age and experience can modify the map on an individual basis. This should be welcome news to health care providers who attempt to 'retrain' the nervous system following disease or injury. Additional representations of the somatosensory periphery exist within the parietal operculum. This includes the Second Somatosensory Area (SII) and Area PV (Parietal Ventral). The SII map is not as detailed as the SI map. Area PV and portions of the Insula are areas activated by high threshold stimulation, visceral stimulation and pain. Note the distortion of the SI map such that the hand (glabrous skin) and the face (especially the lips are magnified in their territory compared to other body areas. This cortical magnification of hand and face are related to the high density of low-threshold tactile mechanoreceptors in the glabrous skin of the hand (volar surface) and the lips.

PERIPHERAL INNERVATION DENSITY VERSUS CORTICAL MAGNIFICATION

Receptor Innervation Density Corresponds to 2-Point Discrimination and Extent of Cortical Representation of Skin Area. Your fingertips and lips are the "fovea" for "20/20" tactile acuity in discriminative touch.

Fig 11-6. Interactive Media File of Braille Letters and importance of SAI to read Braille (gec). GO TO: gmomm.pitt.edu

Fig11-6_Interactive Media



Braille includes letters formed by a raised dot pattern. A high density of Merkel Disc Complexes in the fingertips plus SAI afferents that innervate these receptors and an intact dorsal column medial lemniscal ascending tract are critical for reading Braille. Braille dots are typically placed within a 6 cell pattern.

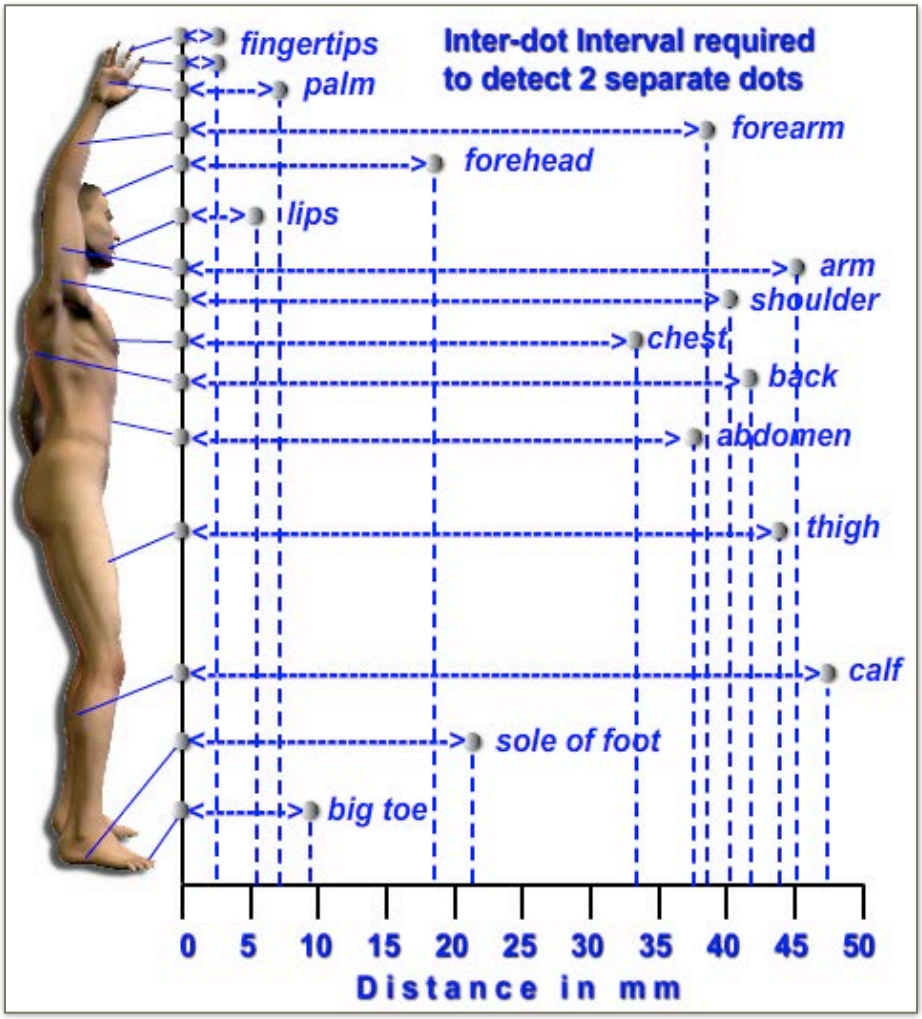


Fig 11-7. Two-point discrimination is closely paired with extent of cortical magnification of body parts (gec).

PRIMARY SOMATO-SENSORY CORTEX: MAPPING THE BODY IN A PRECISE SPATIAL AND TEMPORAL FASHION

The Primary Somatosensory Cortex (SI) is a 6-layered, homotypic granular neocortex. Layer I is located just beneath the pia and contains neurons that have widespread horizontal connections. Layers II and II represent the Supragranular Cortex and contain Pyramidal Neurons that project their axons to other cortical areas (corticocortical) connections; some of these connections are to the contralateral cortex (callosal connections). The granular layer (layer IV) contains excitatory and inhibitory interneurons that are heavily interconnected in a local network called a Barrel in rodent SI (gold cylinder extending as a cone into lower layer III in Rat Somatosensory Cortex figure) that then influences neurons in the supra- and infra-granular layers within a Cortical Column (open red cylinder in the diagram). The infragranular cortex (layers V and VI) contains Pyramidal Neurons that project their axons to subcortical brain structures. These corticofugal projections have targets in the Striatum, Thalamus, and Brainstem Nuclei subserving “sensory” and “motor” functions.

The Primary Somatosensory Cortical representation of the many contralateral vibrissae (whiskers) in the rat is called a Vibrissal Barrelfield.

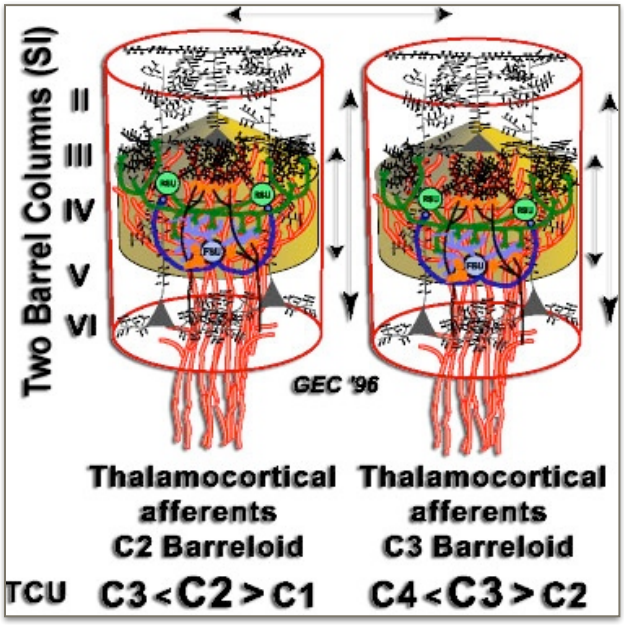


Fig 11-8. Rat Somatosensory Cortex: Barrels as Topographic Networks (gec). GO TO: gmomm.pitt.edu
Fig11-8_Video

The cortical vibrissal representation is called the barrelfield since a topographic representation of the rat's face is revealed when the brain is appropriately stained and sectioned. A similar pattern is seen in the mouse somatosensory cortex. Individual barrels can be revealed by metabolic markers,, e.g., Cytochrome Oxidase since the activity within them is greater than for surrounding (septal) cortex. The layer IV barrel is thought to be an important nodal point that processes thalamic input and then relays this networked/ processed information to the supra- and infra-granular neurons, where data may then be shared with other SI cortical columns, with other cortical areas, or with subcortical neural centers. Layer IV barrel neurons tend to restrict their influence locally and vertically within their parent barrel/barrel column (see vertical double-headed arrows). TCU = Thalamocortical Unit (VPM projection neuron): note that a dominant PW and to a lesser extent several adjacent whiskers provide excitatory drive to thalamic barreloid neurons (TCUs). A cytochrome oxidase (CO) stained tangential section of layer IV of the mouse cerebral cortex is illustrated in SI CO Barrelfield Photomicrograph.

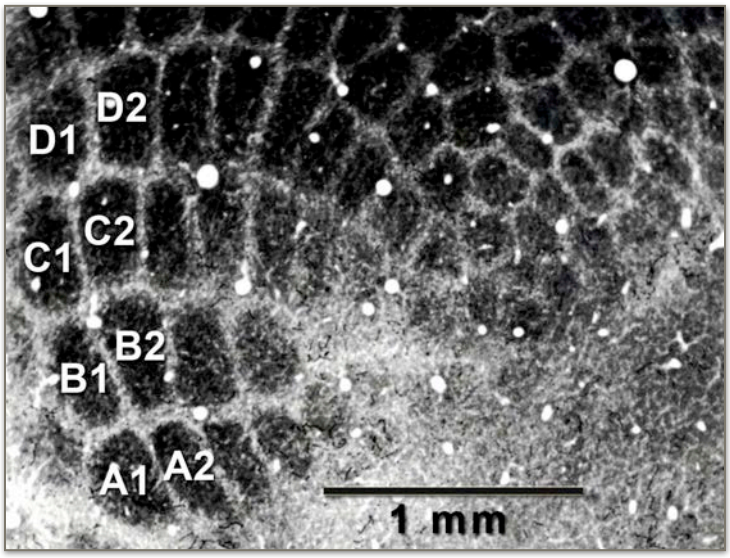


Fig 11-9A. Mouse SI CO Barrelfield (Whisker Representation) : Row A through D, Arc 1-2 Barrels are labeled. Medial is up; Anterior is Right (gec unpublished photomicrograph).

Barrels in the cortex and Barreloids in the thalamus are named according to the one whisker on the opposite side of the face that provides the most dominant excitatory drive; this whisker is named the Principal

Whisker (PW). Each layer IV barrel, as seen in transverse 3D section (gold filled cylinder+cone), is a collection of blood vessels, thousands of glia & interneurons, local dendritic & axonal fields, and a massive arbor of thalamocortical axon terminals from projection neurons in the Ventral Posterior Medial (VPM) Nucleus of the Thalamus.

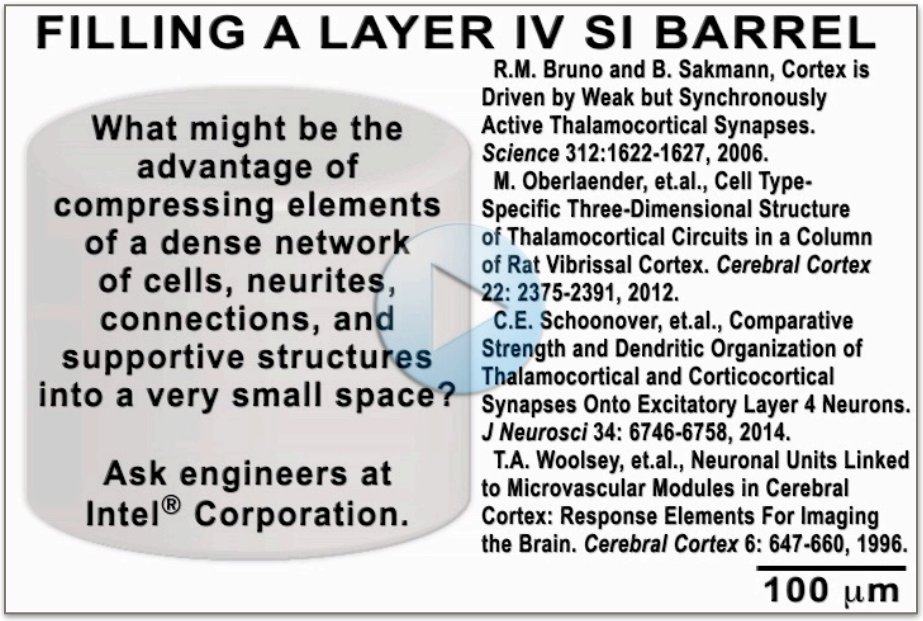


Fig 11-9B. SI Barrel Fill Movie (gec). GO TO: gmomm.pitt.edu Fig11-8_Video

WHISKER TO BARREL TRIGEMINAL TOPOGRAPHY: MODEL FOR SOMATOTOPIC ORGANIZATION

The rodent trigeminal system is a model for somatotopic organization. Rats have 30-35 large mobile mystacial vibrissae (whiskers) on each side of the face. Whiskers are arranged in a precise pattern on the muzzle of a rat (see stylized rodent face).

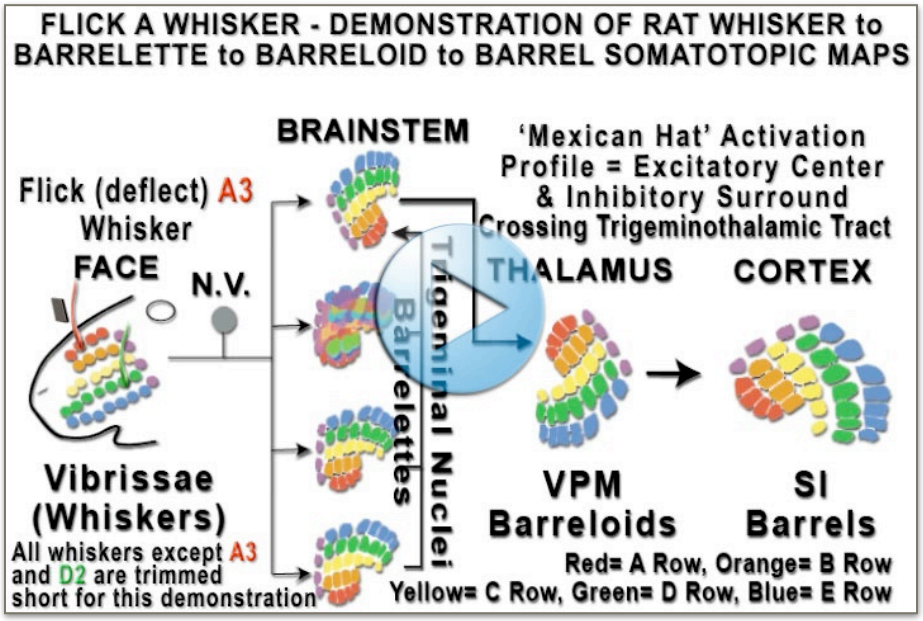


Fig 11-10. Whisker to Barrel System: Model of Somatotopic Organization Movie (gec). GO TO: gmomm.pitt.edu Fig11-10_Video

This precise topography is conserved in the trigeminal lemniscal representation within the somatosensory system.

The somatotopic

pattern is seen as separate networks of neurons arranged in tight cell groupings in the brainstem trigeminal nuclei (Barrelettes), the Ventral Posterior Medial Nucleus of the thalamus (Barreloids) & in SI Cortex (Barrels). This arrangement is critically dependent on the Prenatal innervation of the rat's muzzle. If a whisker follicle fails to develop its trigeminal innervation is not present and the corresponding barrelette, barreloid and barrel will not appear. On the other hand, if an extra whisker grows from an additional whisker follicle, the whisker will be innervated in a discrete fashion (normal innervation). This will add the extra whisker representation to the somatosensory pathway in a correct topographic pattern.

Rats are nocturnal animals in the wild and depend on their vibrissae to navigate and explore their environment. The large mystacial vibrissae (whiskers) emerge from a specialized sinus-hair follicle innervated by hundreds of low-threshold slowly adapting or rapidly adapting tactile mechanoreceptors. These specialized whiskers are as sensitive as your fingertips. Rats palpate objects by repetitively sweeping their whiskers forward and backward (active whisking). Individual or groups of whiskers can be activated in a precise, controlled fashion using a mechanical apparatus to deflect the whisker and activate the low-threshold rapidly adapting and slowly-adapting mechanoreceptors in the sinus-hair follicle in the rat's muzzle: see Whisker Bimorph Movie, for details see Simons, 1983. Excitatory and inhibitory receptive field properties of single cells in the trigeminal ganglion (excitatory only), VPm barreloids and SI cortical barrels have been characterized, e.g., see Simons & Carvell, 1989.

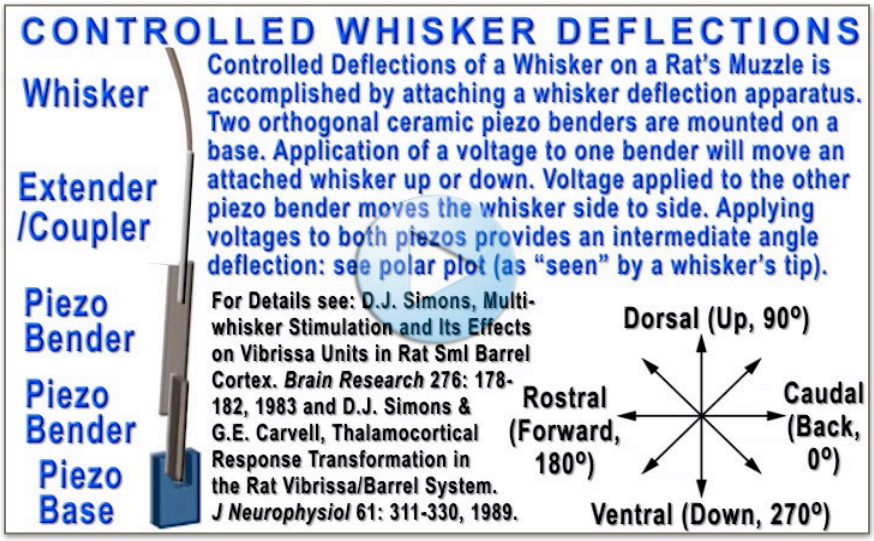


Fig 11-11. Whisker Bimorph Movie. Mechanical apparatus to deflect a whisker in different directions in a precisely controlled fashion (gec). GO TO: gmomm.pitt.edu
Fig11-11_Video

Each Thalamic Barreloid in Rat Ventral Posterior Median nucleus (VPm) contains ~250-300 excitatory thalamo-cortical (TC) projection neurons. Each Layer IV Barrel in the Rat SI Vibrissal Barrelfield contains ~3000-4000 neurons. Most Layer IV Barrel neurons are excitatory Spiny Stellate Regular-Spiking (RS) Cells, a minority (15-30%) are GABAergic Inhibitory Smooth Stellate Fast-Spiking (FS) Cells. Estimates suggest each RS cell within the layer 4 barrel receives ~250-350 synapses from ~90 VPm thalamic neurons. The local intracortical Spiny to Spiny Stellate connections outnumber thalamocortical to spiny cell

synapses by an ~10:1 ratio within the barrel. Topographic input from the appropriate Barreloid to its recipient layer IV Barrel involves a massive coincident convergence and divergence of TC afferents driving a network of Excitatory (RS) & Inhibitory (FS) Barrel neurons (~10-15 fold increase in cell number from thalamus to cortex). The layer IV barrel network transforms a multiwhisker thalamic input into a single whisker (PW) representation of repeated whisker deflections. FS cells are thought to receive massive convergent input from ~160 VPm thalamic neurons (strong inhibition within the barrel), see Simons, Carvell & Kyriazi, 2015.

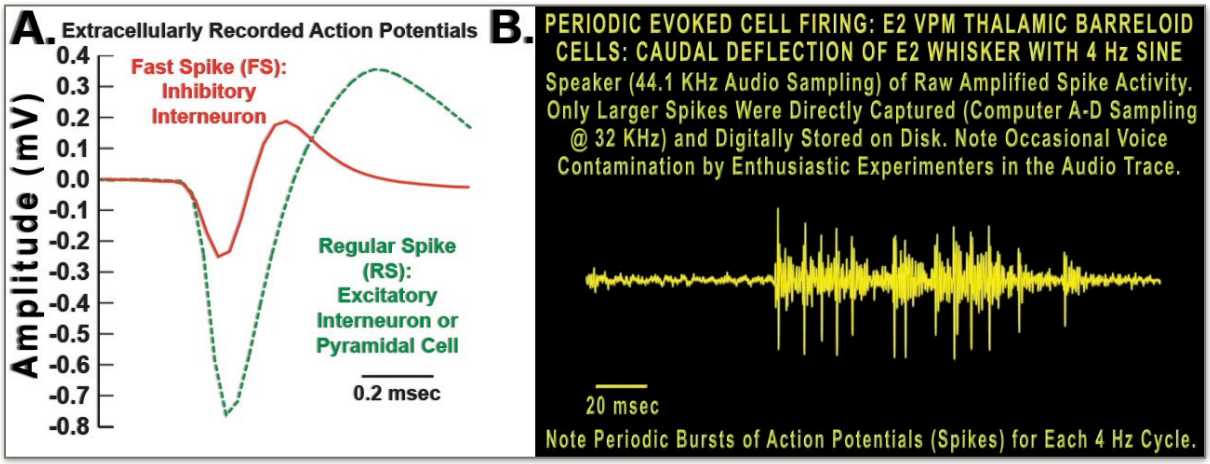


Fig 11-12. Panel A. Fast Spiking (FS) GABAergic Interneuron Action Potential and Regular Spiking (RS) Glutamatergic Neuron Action Potential: Digitized Spikes from Rat Barrel Cortex; Panel B. Extracellular Recording of VPM Thalamic Barreloid Cell-Activity Evoked by 4 Hz Sinewave Movie (gec). GO TO: gmomm.pitt.edu *Fig11-12_Video*

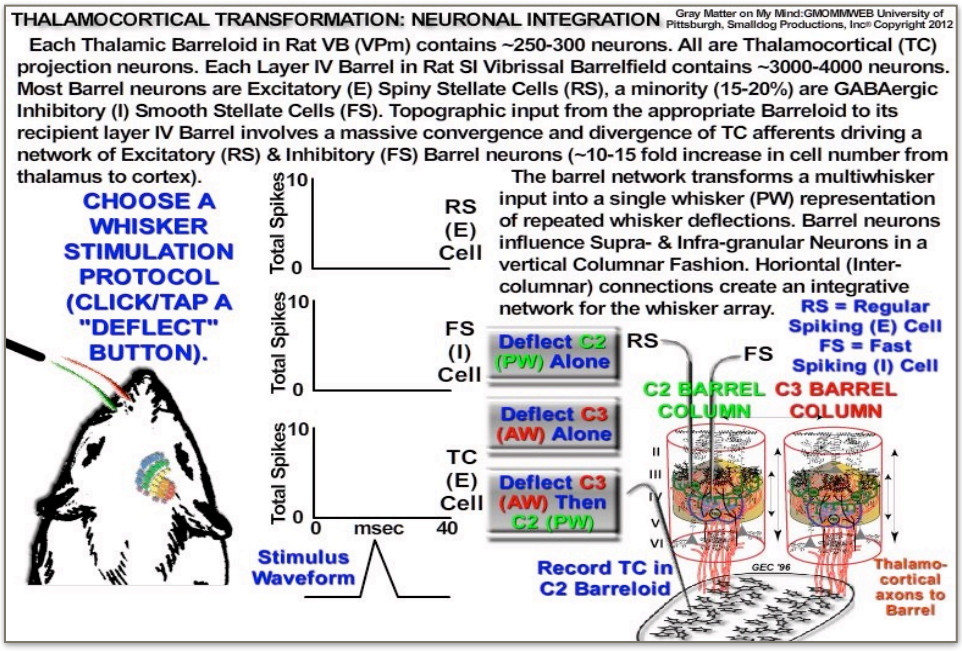


Fig 11-13. Rat Whisker to Barrel Thalamocortical Response Transformation Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig11-13_Inter-active_Media

Barrel neurons influence Supra- and Infra-granular Neurons in a

vertical Columnar Fashion. Horizontal (Intercolumnar) connections create an integrative network for the whisker array. Play the movie below to see the Thalamocortical Response Transformation simulated for Rat Whisker to Barrel Pathway. This illustrates the transformation of multiwhisker excitatory onto thalamic cells from adjacent whiskers into single whisker responses in the large interconnected ensemble of excitatory barrel neurons due, in large part, to the active inhibition by FS GABA interneurons of all but the strongest coincident excitatory thalamic inputs from the PW stimulation.

COLUMNAR ORGANIZATION OF SOMATOSENSORY CORTEX: VERTICAL INTRACOLUMNAR AND HORIZONTAL INTERCOLUMNAR INFORMATION FLOW

The concept of a vertical (radial) columnar organization within the cerebral cortex has been described previously.

This model of connectivity states that for most cortical areas that receive a dominant extrinsic excitatory drive from First Order (FO) thalamic nuclei, information flow rises from core nucleus thalamic cells to middle layer cortical interneurons that then influence other cells within a narrow vertical column of cells located above and below the thalamocortical recipient zone. In addition, thalamic matrix cells project to superficial and infragranular layers which is thought to provide a separate form of information: less topographic and less modality specificity data than for FO core thalamic inputs.

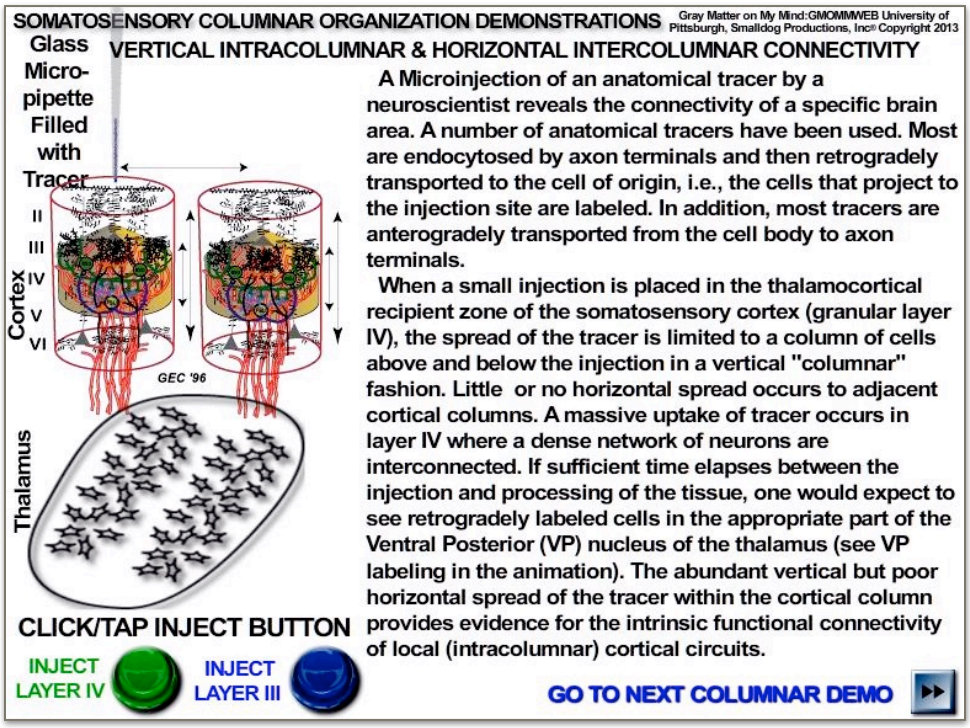


Fig 11-14. Cerebral Cortical Columnar Demonstration Animations- Interactive Media File-(gec). GO TO: gmomm.pitt.edu

[Fig11-14 Interactive Media]

This intracolumnar processing is rapidly followed by column to column connectivity derived primarily from supragranular pyramidal cells that contribute to corticocortical synapses. In addition, intracolumnar spread of information will lead to excitation of

infragranular pyramidal cells that provide the output from columnar processing to subcortical brain and or spinal cord recipient zones for these corticofugal projections. The Interactive Flash file lets you perform three virtual simulations that emphasize these principles of cortical columnar organization. These simulations describe anatomical and physiological aspects of columnar organization based upon research done using the rat whisker to barrel pathway as a model.

SURROUND INHIBITION & GABA NEURONS: TONIC & PHASIC TACTILE SPATIOTEMPORAL TUNING

Discriminative active touch requires a high degree of spatial and temporal accuracy in the central representation of the tactile periphery. The level of tactile acuity is influenced by the density of specialized mechanoreceptors in the skin and the relative expanse of CNS territory devoted to representing that skin area. For example, our fingertips, lips, and tongue have the highest density of tactile mechanoreceptors per square mm of all skin areas and these areas have a magnified central representation in the somatosensory system (see above). However, individual receptors typically do not have separate labeled lines to the somatosensory cortex.

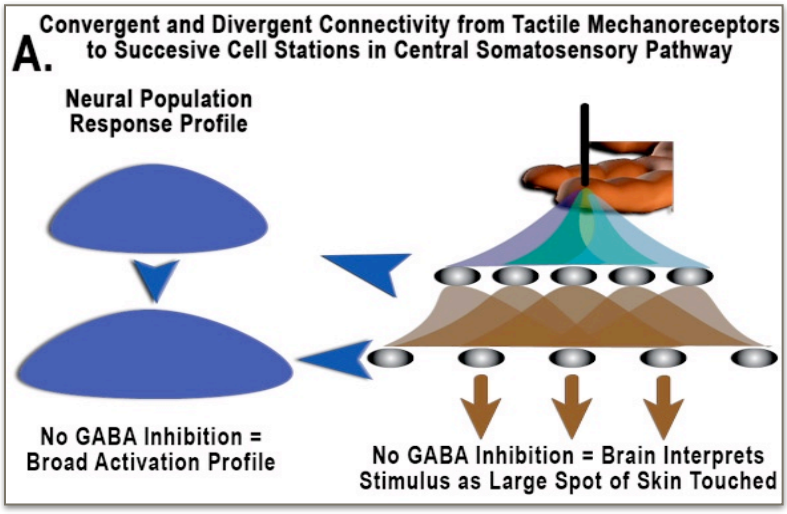


Fig 11-15A. Convergent-Divergent Nature of Somatosensory Neuron Receptive Fields Effect of NO GABA Inhibitory Modulation (gec).

There is significant convergence and divergence of afferent inputs to a number of neurons at each cell station in the pathway, e.g., in the spinal cord dorsal horn, dorsal column nuclei, thalamus and somatosensory cortex. A blending of inputs from adjacent skin areas could distort any precise point to point representation by spreading each point's excitation broadly over many neurons. Each neuron has the potential to "service" many adjacent skin areas. The nervous system regains a high degree of spatial and temporal precision by the process of surround inhibition. Thus, only the strongest, most secure excitatory input will be passed along to the next center, while weaker inputs are actively suppressed by GABAergic inhibitory interneurons. This provides a dynamic mechanism to regulate the extent of spatiotemporal constraints on inputs; there may be circumstances where detail is not critical but the total area of skin stimulation and the maximal amplitude of contact are the most important data.

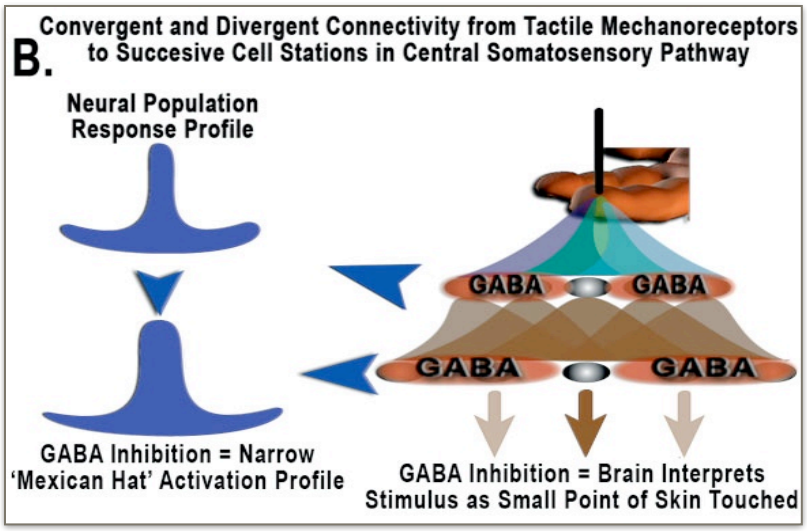


Fig 11-15B. Convergent-Divergent Nature of Somatosensory Neuron Receptive Fields GABAergic Surround Inhibition Present (gec).

The Dorsal Column Medial Lemniscal Pathway is illustrated in 3-D with Cell Stations (locations of synapses) labeled in the following DCML movie.

Fig 11-16. Dorsal Column Medial Lemniscal (DCML) 3D Pathway Movie. Note Cell Stations (where synapses occur): Dorsal Column Nuclei, Ventral Posterior Lateral Thalamus, Primary Somatosensory Cortex (SI) (gec). GO TO: gmomm.pitt.edu

Fig11-16_Video

SURROUND INHIBITION: TACTILE SPATIOTEMPORAL TUNING IN DORSAL COLUMN NUCLEI

Inhibitory interneurons located in the dorsal column nucleus allow the brain to adjust the size of the receptive fields that will be found at higher levels. The following two movies illustrate the effect of NO GABA Inhibition followed by a movie illustrating the significance of GABA neurons producing a surround inhibition. The inhibitory interneurons are excited by ascending dorsal column afferents (clover and violet inputs) and by descending axons that originate in pyramidal cells located in the parietal cortex (yellow corticofugal inputs). The descending pathway excitatory drive to the inhibitory interneurons provides the "cerebral cortical seat" of somatosensory perception, the parietal cortex, an opportunity to adjust what information it needs at any one time.

For example, there is some evidence to suggest that some ascending input is gated out when certain sensorimotor events are evolving. Note that the output from the dorsal column projection neurons is reduced due to the local GABAergic inhibitory (red) inputs to the projection neurons. The projection neurons may also have axon collaterals that

excite the inhibitory interneurons (not shown). This recurrent inhibition from medial lemniscal axons would be an effective way to self-limit the output of the dorsal column nucleus to the thalamus. The effect of this surround inhibition is to reduce the total depolarization of the projection neurons.

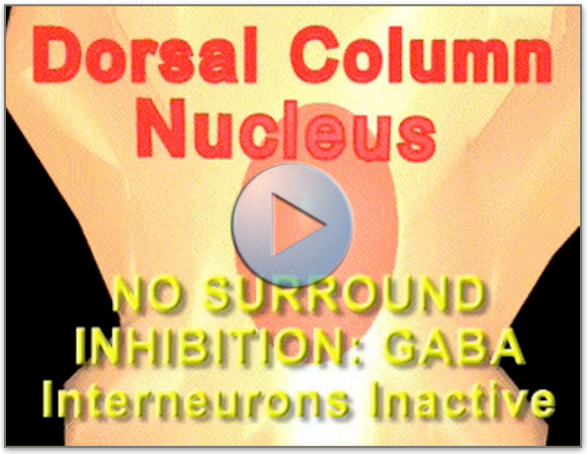


Fig 11-17. Dorsal Column Nuclei NO GABA= Impaired 2-point Discrimination Movie (gec). GO TO: gmomm.pitt.edu *Fig11-17_Video*

Therefore, the output represents the strongest, most secure afferent drive to these cells (green-left & purple-right). Now there are fewer neurons discharging action potentials and the inhibition defines a separate clover and violet output to the thalamus. This will be interpreted as two distinct, adjacent points of skin stimulated at about the same time rather than a single broad stimulus to the skin. The process of inhibitory modulation occurs in the spinal dorsal horn (e.g. GABA neurons in the substantia gelatinosa), the somatosensory thalamus, and within and across the cortical columns. Surround inhibition offers a dynamic solution to the problem of adjusting the effective receptive field size according to changing task demands.

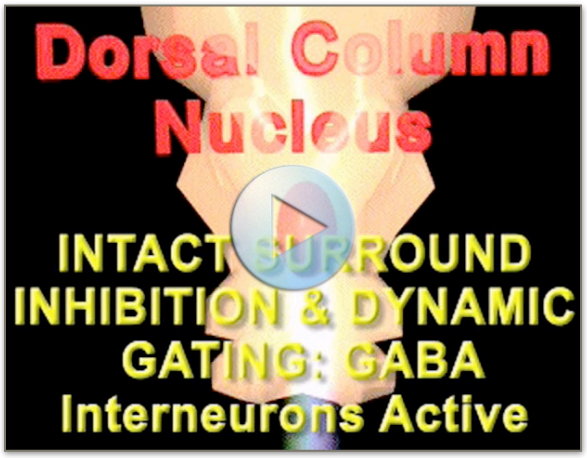


Fig 11-18. Dorsal Column Nuclei GABA Surround Inhibition= Intact 2 point discrimination Movie (gec). GO TO: gmomm.pitt.edu *Fig11-18_Video*

SURROUND INHIBITION: TACTILE SPATIOTEMPORAL TUNING IN DORSAL COLUMN MEDIAL LEMNISCAL (DCML) PATHWAY TO PRIMARY SOMATOSENSORY CORTEX

The following animations portray an imaginary isomorphic representation of the Braille letter "f" as the neural profile ascends from the fingertip to the Dorsal Column Nucleus, the Ventral Posterolateral Thalamic Nucleus and the Primary Somatosensory Cortex. The three dots that represent the Braille letter "*f*" are color coded to assist in the identification of the neural profile (neurons activated by the particular dot) at each stage of the pathway. The arrowhead moves across the dot pattern in a manner similar to the motion of the fingertip as the letter is being read. The neurons that will be activated are

shown beneath a threshold plane prior to the arrival of ascending input and then peaks of activity rise above threshold as they receive excitatory drive.

Output from the Somatosensory Cortex is to other Cortical Areas and to subcortical sensory and motor areas. In the first movie (left) Inhibitory Interneurons located at each station (Dorsal Column Nucleus, Thalamus, and Somatosensory Cortex) are silent (no surround inhibition). Many neurons are activated at each cell station (domes = population of responding neurons). As the signal rises to the thalamus and cortex the profile expands (telescoping of the convergence & divergence at successive stages = larger domes). The second movie (right) shows the influence of strong activation of the local inhibitory circuitry (which is normally present in active touch).

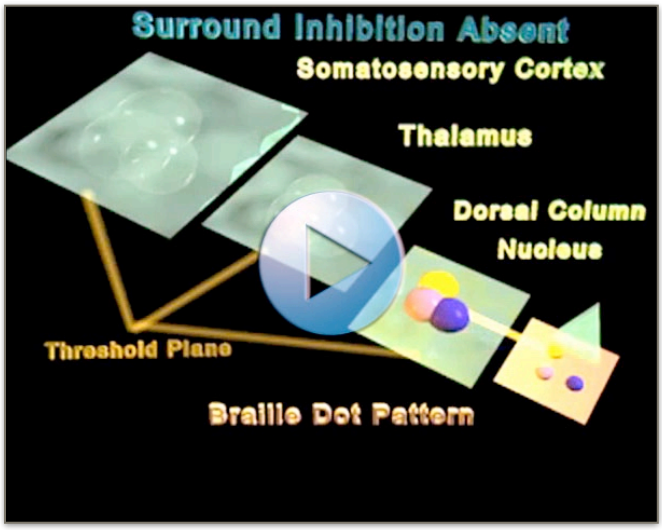


Fig 11-19. Movie shows neural pattern when "reading" a Braille letter "f" with No Surround Inhibition (gec). GO TO: gmomm.pitt.edu Fig11-19_Video

Note that although the same expanse of neurons respond, the neural profile changes from an excitatory dome to an excitatory center + inhibitory surround profile. The effect of surround inhibition is to keep all but the most strongly driven neurons below the threshold plane.

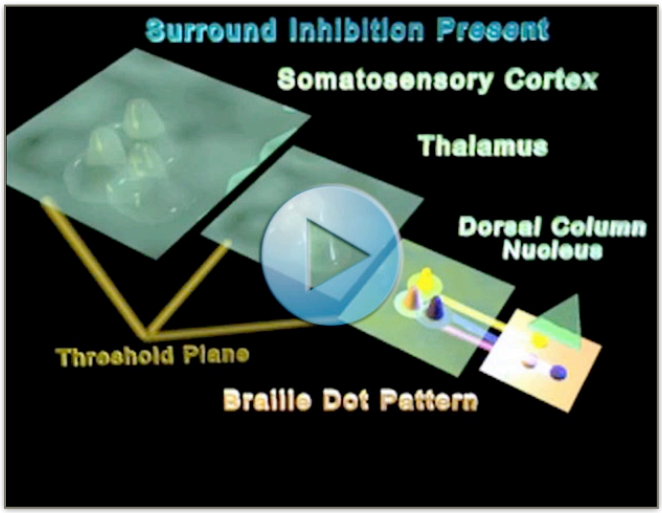


Fig 11-20. Movie shows neural pattern when reading Braille letter "f" with Surround Inhibition Present (gec). GO TO: gmomm.pitt.edu Fig11-20_Video

Thus individual population peaks (representing the individual Braille dots) are expressed in an 'isomorphic' "dot" profile at each cell station. It should be self-evident that, without surround inhibition, the likelihood of confusing one Braille letter with another of similar form increases dramatically.

PASSIVE VERSUS ACTIVE TOUCH & MOTOR GATING OF SOMATOSENSATION: CNS RESOURCES

Our somatosensory system in daily life does not function independently. Bottom-up sensory signals originating in transduced tactile or proprioceptive receptors will meet internally generated CNS signals related to attentional demands and motor system activity that gets us to interact with our environment. This interaction modulates the peripheral signals in a way that presumably optimizes those data upon which we learn about and interact with our world. A prime example of this interaction is the process by which we use our peripheral sensory organs to discriminate differences in the texture, form and other physical properties of objects that we palpate.

Discriminative Active Touch requires the cooperation of a number of CNS Pathways plus Sensory & Motor Centers:

1. Dorsal Column Medial Lemniscal (DCML) Tract carries ascending information to the brain that is critical for Discriminative Active Touch. Tactile and Proprioceptive information ascends in this tract from the upper extremity.

2. Ventral Posterior Lateral Nucleus of the Thalamus processes Somatosensory information ascending from Dorsal Column Nuclei in the Medulla by way of the Medial Lemniscus.

3. Parietal Cortex (Anterior Parietal or SI and Posterior Parietal Lobe) if lesioned often produce impairments in one or several forms of discriminative active touch processes. Posterior Parietal Lobe lesions may produce severe deficits in skilled hand tasks (finger agnosia, reaching & grasping deficits and more profound spatial perceptual problems).

4. Motor Cortices (Primary and Secondary Motor Areas) plus the Pyramidal Tract are critical for regulating precise finger movements as may be required in skilled hand function (precise force modulation of the hand, fractionation of finger movements).

5. As the level of skill required for fine hand control increases so do the demands on other subcortical and association cortical areas; the learned skill requires a distributed sensorimotor network. Small differences in somatosensory input used for guidance of fingers and changes in recruitment of precisely selected motor units can produce profound alterations in performance. *Previous experience and a sound knowledge-base play a critical role. You would not want your mechanic doing brain surgery just as you would not want a neurosurgeon rebuilding a $15k high performance engine in your favorite sports car (assuming you own one). However, there are always exceptions to the rules, for example, see Luke Dittrich's descriptions of his grandfather's multiple talents, Dittrich, 2016.*

PASSIVE MOVING TOUCH (moving the object under the finger) replicates the pattern of somatosensory input as seen in ACTIVE TOUCH if motion parameters are the same. Motor System is inactive and there is no GATING due to "top-down" Motor Pathway activation. For some detection or simple discrimination tasks PASSIVE MOVING TOUCH may provide equivalent perceptual accuracy as does ACTIVE

TOUCH. The sensory signal can still be regulated by feedforward inhibitory processes and/or feedback from Somatosensory Cortex, both of which contribute to classical surround inhibition that optimizes strong but suppresses weak signals. Activation is primarily a bottom-up sensory driven process with the motor system inactive and the somatosensory system highly active. The Passive Moving Touch Movie illustrates the concepts described above.

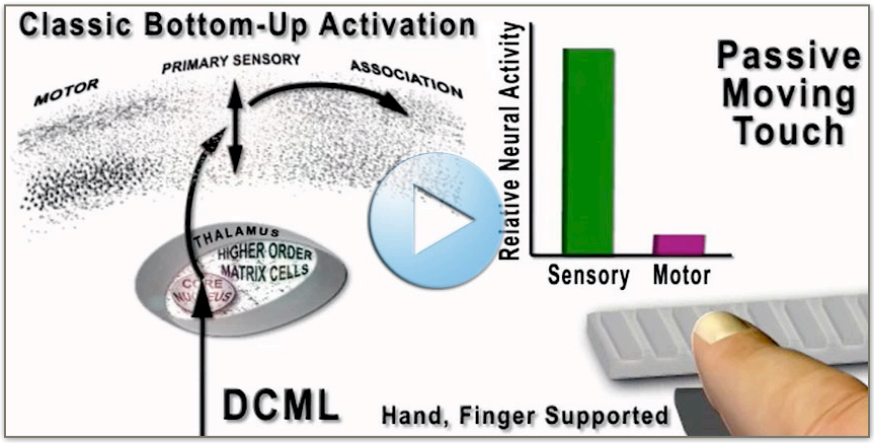


Fig 11-21. Passive Moving Touch Movie (gec). GO TO: gmomm. pitt.edu *Fig11-21_Video*

ACTIVE TOUCH in real-life tasks provides a critical advantage to the individual. The person volitionally regulates information acquisition during the performance of the discrimination task (e.g., reading Braille). This offers a skilled performer the advantage of rapid yet accurate sampling of the object's surface features. ACTIVE TOUCH provides a critical mechanism for us to explore, appreciate and learn about the animate & inanimate objects in our environment (ACTION PERCEPTION CYCLE).

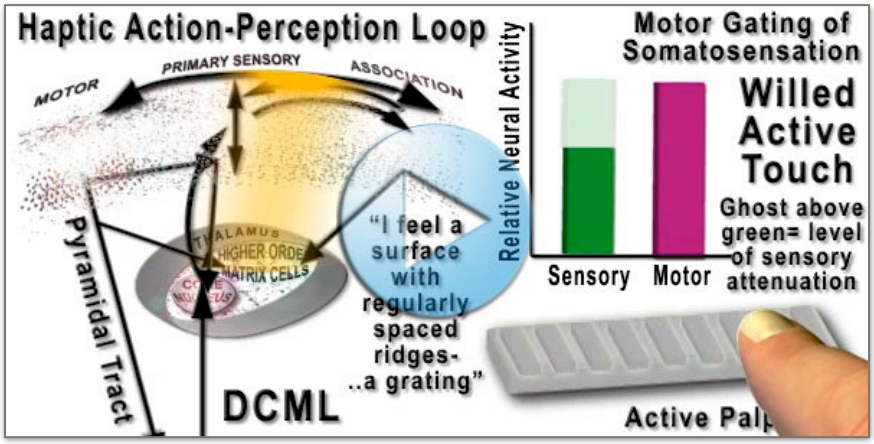


Fig 11-22. Willed Active Touch Movie (gec). GO TO: gmomm.pitt.edu *Fig11-22_Video*

Active Touch by definition requires neural activity in both sensory and motor systems. Passive touch by contrast activates sensory system in isolation. Movement attenuates somatosensory potentials at multiple levels of the neuraxis. This attenuation is called GATING and gates are in place at the spinal, brainstem and cortical levels. Thus, motor and sensory systems are not just turned on together but are inextricably linked during active touch. MOTOR GATING (attenuation) of somatosensory information is thought to occur at multiple levels of the neuraxis: spinal cord, dorsal column nuclei, the thalamus and cerebral cortex. Both presynaptic

inhibition (axo-axonic synapse) and postsynaptic inhibition by way of GABA interneurons is suggested as a mechanism to reduce the size of the somatosensory signal as it passes up the neuraxis. GATING is not evident if the Motor System is inactive (compare Sensory Activity for WILLED ACTIVE TOUCH Movie versus PASSIVE MOVING TOUCH Movie).

Layer V Pyramidal Tract Neurons in MI & SI that project to dorsal horn, ventral horn & intermediate zone spinal gray provide collateral axons to cells in the cerebral cortex, thalamus, and dorsal column nuclei as the axons descend to the spinal cord (a top-down regulation of sensory processing). A Corticothalamocortical loop may provide a "binding" mechanism to link those brain areas responsible for Integration of Willed Actions and Conscious Perceptions. Uncontrolled loops may lead to abnormal rhythms such as tremor.

MOTOR GATING OF SOMATOSENSATION: GABA INTERNEURONS PROVIDE CRITICAL CONTROL OF SOMATOSENSORY SIGNALS

The Gating GABA Yes-No Movie illustrates role of GABA Neurons for MOTOR GATING OF SOMATOSENSATION. INTENTION & ACTION attenuates (gates) somatosensory potentials at multiple levels of the neuraxis. GABA inhibition attenuates signal as it ascends neuraxis. The weakest signals are those suppressed to the greatest extent by the GABA neurons.

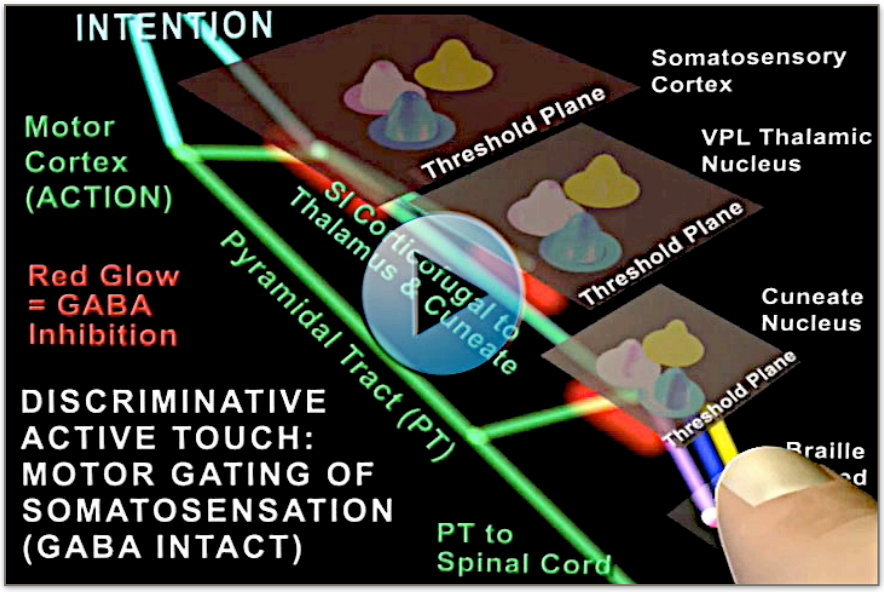


Fig 11-23. Gating GABA Yes-No Movie: GABA Neurons for Motor Gating of Somato-sensation (gec). GO TO: gmomm.pitt.edu Fig11-23_Video

Both ascending somatosensory data and top-down descending influences from somatosensory, posterior parietal and motor cortices may activate the GABAergic suppressive effects at multiple cell stations in the ascending DCML pathway.

TWO EXAMPLES OF MOTOR GATING OF SOMATOSENSATION

The following examples of motor gating of somatosensation should convince the reader that any artificial separation of sensory information flow and motor information flow is not functional in an awake behaving brains of many mammalian species.

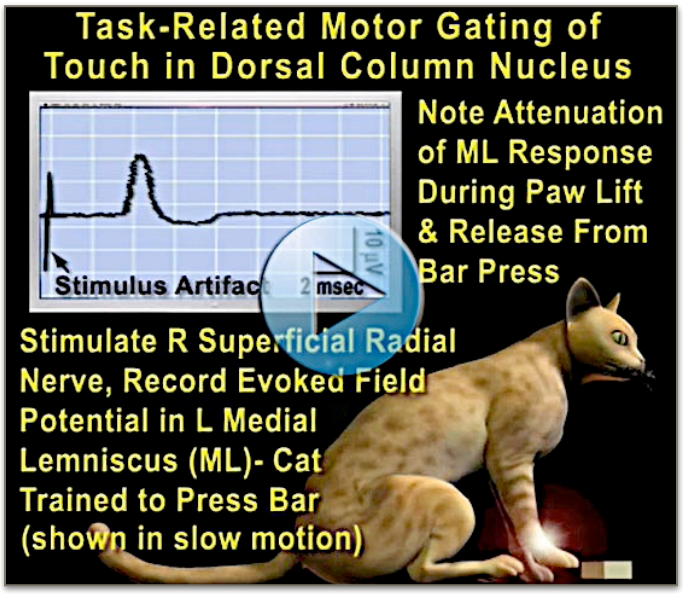


Fig 11-24. Motor Gating of Somatosensation in Dorsal Column Nucleus-Cat Bar Press Movie (gec). GO TO: gmomm.pitt.edu
Fig11-24_Video

Cats were trained to lift a paw and press a bar for a food reward when they heard a tone. Evoked Local Field Potentials (LFPs) were recorded in the Medial Lemniscus (ML) due to periodic stimulation of the superficial radial nerve. Recordings were obtained while the animal performed the task. Remember that the ML is the crossed output tract from the dorsal column nuclei. The compound action potential (LFP) recorded in the ML represents a summed output sent to the Ventral Posterior Lateral Thalamic Nucleus from the Cuneate Nucleus. ML responses were attenuated (depressed) when the animal lifted its paw from the ground or from the bar (see cat movie). Experiments by Ghez & Lenzi, 1971 showed that response suppression begins ~100-200 msec before the onset of the lift. Subsequently, many investigators have shown similar findings of context-dependent motor modulation of somatosensory input in many species including human subjects. NOTE: Evoked field potentials (also called Local Field Potentials or LFPs) are population responses. Therefore, LFPs represent correlated neural activity among many neurons not single cell events. LFPs reflect the net excitatory and inhibitory events within a local network including subthreshold depolarizing EPSPs & hyperpolarizing IPSPs plus suprathreshold neural events (Action Potentials).

Motor gating of somatosensory signals has been demonstrated in the trigeminal lemniscal system (brainstem trigeminal nuclei) that project to the Ventral Posterior median (VPm) thalamic nucleus. The VPm is the major source of specific (core) thalamic drive to the whisker representation in the Primary Somatosensory Cortex. An animated representation of gating experiments in rats (see rat movie) simulates the stimulation of whisker (vibrissal) afferents and recording of evoked field potentials in the VPm thalamus. VPm recordings show a gating (attenuation) of whisker input signals when the animal is whisking vs. when the animal is not whisking. However, it is known that the somatosensory cortex projects an excitatory corticothalamic input to VPm that facilitates whisker input signals. This facilitation is not obvious in the behaving animal

until it is unmasked by artificially removing the attenuating influence of inhibitory interneurons in the brainstem trigeminal nuclei: see inactivation of GABA neurons in the trigeminal nuclei in the whisking gating movie; see S-H. Lee, et.al., 2008.

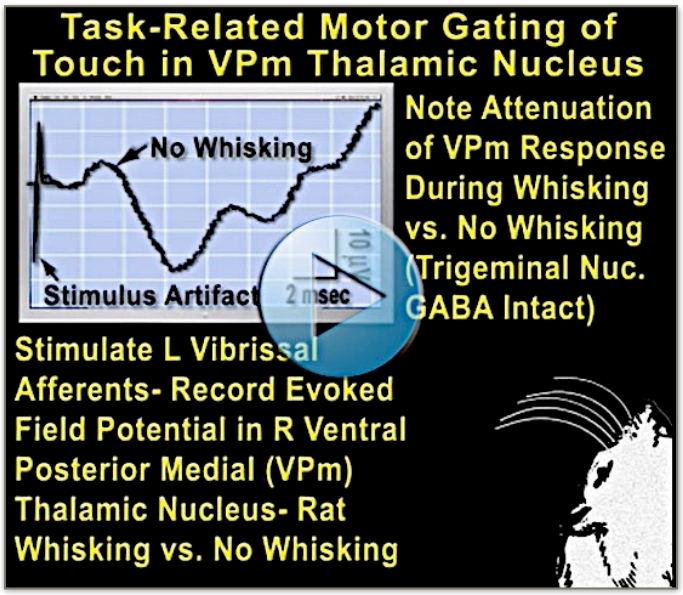


Fig 11-25. Motor Gating of Somatosensation in the Trigeminal System-Rat Whisking Movie (gec). GO TO: gmomm.pitt.edu Fig11-25 Video

BEYOND THE POSTCENTRAL GYRUS-POSTERIOR PARIETAL CORTEX: ACTION-ORIENTED SENSORY INTEGRATION

The Posterior Parietal Lobe consists of a Superior Parietal Lobule (Areas 5, 7) and an Inferior Parietal Lobule (Supramarginal Gyrus-Area 40 & Angular Gyrus-Area 39) separated by the Intraparietal Sulcus. The Posterior Parietal Lobe is thought to be a critical cortical area for representation of our body image/body schema that is represented best in the Right Hemisphere in most individuals. Neuronal networks in the Posterior Parietal Lobe provide a four-dimensional spatial reference system (3 spatial dimensions dynamically represented over time) to allow us to relate one body part to another and relate ourselves to the external world. The Intraparietal (IP) Sulcus separating the Superior from the Inferior Parietal Lobule contains several IP areas associated with visually-guided actions, e.g., AIP, LIP, VIP for reaching and grasping objects located in 3D space. These parietal areas are heavily connected with portions of the frontal cortex including premotor areas anterior to the precentral gyrus.

These higher level perceptual processes provide a means to navigate in a changing environment and engage objects in the world with a high degree of precision. To accomplish this task the Posterior Parietal Lobe must be multimodal; it receives somatosensory, visual, auditory, and vestibular inputs. It has significant connections with the Frontal Lobe, Basal Ganglia and the Cerebellum. In addition, the Inferior Parietal Lobule (Left Hemisphere > Right) is a major area for higher level communications: spoken language, reading, writing skills; and mathematical skills. Taken together, the right and left posterior parietal cortices helps us link our being to the physical world and to a more abstract world represented by words, numbers and mental concepts. It has been proposed that neural networks in the Superior Parietal Lobule provides a storage mechanism for an internal representation of the body (in motion) that is based on

iterative matching of motor commands and updated sensory data (Bayesian?), e.g., see Wolpert, Goodbody and Husain, 1998.

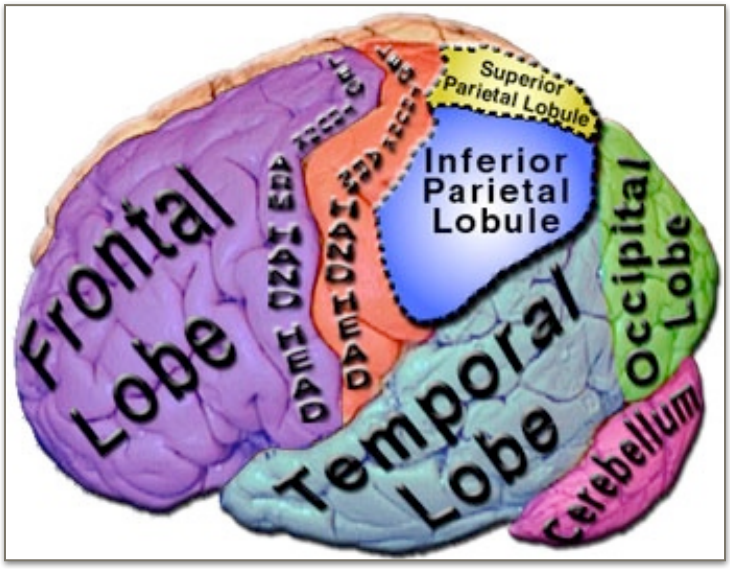


Fig 11-26. Anterior (SI) and Posterior Parietal Cortex (Superior & Inferior Parietal Lobules) (gec) Remembering that the retina is actually the embryologic diencephalon pushed out into the periphery (the eye in the orbit of the skull), the CNS has two parallel pathways that process different aspects of our visual inputs.

One pathway, the Parvocellular (P) Pathway, provides the best information about spatial detail (visual acuity) and color.

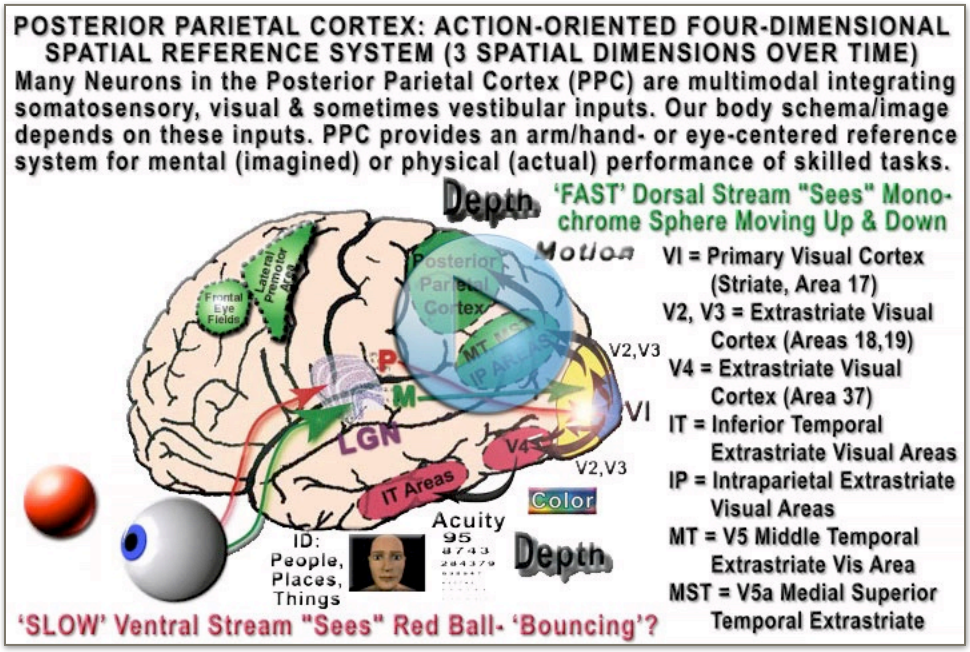


Fig 11-27. Posterior Parietal Cortex (PPC): Simulation of PPC's role in reach & grasp task (gec). GO TO: gmomm. pitt.edu Fig11-27 _Video

The second pathway, the Magnocellular (M) Pathway provides less absolute spatial detail but provides critical information about the overall size, shape and location of an object plus temporal aspects of vision including object motion. The M Pathway has a major routing of information to extrastriate visual areas that eventually converge upon neural ensembles in the Posterior Parietal Cortex (Dorsal Visual Stream). Parvocellular input tends to gravitate to more ventral extrastriate areas that ultimately connect with visual association areas in the Inferior Temporal Cortex (Ventral Visual Stream). While

perception suggests conscious attention, the dorsal stream may operate at subconscious or preconscious levels. The Dorsal Visual Stream and the Posterior Parietal Cortex (PPC) may utilize sensory information to trigger or guide actions in extrapersonal space with no conscious awareness of this integrative processing. Although only feedforward connections are shown in the PPC movie, most areas have reciprocal connectivity. A significant portion of the primate cerebrum is devoted to or somehow linked to vision. Thus, when we experience the world in the light, our senses are integrated to form a more robust perception of extrinsic signals.

MEDIAL POSTERIOR PARIETAL CORTEX: PRECUNEUS-ARE YOU INTROSPECTIVE?

I can see it in your eyes. I can read your body language. If your head was in a fMRI scanner I would see a distinctive shift in brain state. You have been concentrating on the material that has been presented to your visual and auditory systems regarding complex neuroscience principles and your brain now has had enough and you have fundamentally zoned me out. Time for a break.

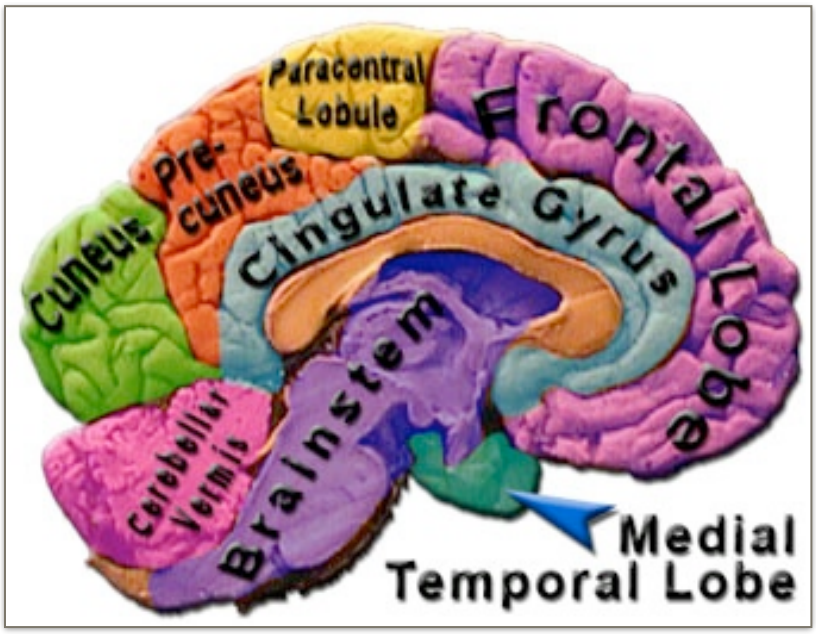


Fig 11-28. Medial Cerebral Cortex: Precuneus and Inner Thoughts (gec).

Electroencephalographers (those who study EEG patterns in the human brain) have known for some time that when a human subject is just "resting" there is no absence of brain activity and in fact there may be a shift in frequency and/or amplitude of brain waves from some EEG electrodes compared to others. Neuroscientists who now study brain activity using fMRI imaging have proposed that there is a global brain network where activity increases in the "resting" brain regions that otherwise are either inactive or even suppressed when we attend to external events. This "resting" brain network has been called the Default Mode Network or DMN for short by some scientists. One of the areas involved in this DMN is the Precuneus (along with portions of medial prefrontal & orbitofrontal cortex, posterior cingulate cortex and parieto-occipito-temporal association cortex). This appears to be for the most part a bilateral phenomenon.

While there is disagreement regarding the actual brain functions related to the DMN, this brain state appears to be associated with situations where the subject has shifted from attending to external stimuli and has become more "focused" on introspective or self-referential brain states (thinking?, daydreaming?, self-reflection?, meditation?).

The brain abhors a vacuum and even if we seem to be "zoned-out" or even asleep much of our brain remains quite active. If subjects are deprived of external stimuli for long periods of time (sensory deprivation experiments) or are in certain stages of dementia, the brain appears to confabulate scenarios if there is insufficient access to data from the "real" world. In modern societies where individuals are *wired* or "*wirelessed"* to others for much of their waking hours, then any opportunity for the brain to enter the DMN state may be minimal. If neuroscientists are correct in theorizing that the DMN state is a critical component of normal brain function, then the brain that does not have much opportunity to undergo introspection may have little time to consolidate and integrate all those data that have flooded and potentially overloaded brain circuits. This could lead to plenty of isolated facts but little deep understanding of how those bits of data might fit together. Remember that if the brain cannot make sense of the data from without, it may opt for confabulating from within.

Could these medial cortical areas including the precuneus relate to brain states where we turn our neural resources to introspection? Some of these fMRI studies suggest that to be the case while others suggest resting state brain activity is unrelated to such lofty matters, e.g., see: Deco, et.al., 2011; Northoff & Bermpohl, 2004; Raichle, 2015.

MIRROR NEURONS: I KNOW WHAT YOU ARE DOING!

Neuroscientists have identified a network of neurons within the parietal and frontal cortex known as the Mirror Neurons System. These neurons are activated when a person actually performs an action AND when a subject observes another doing that action. The neurons do not appear to be highly responsive to just the visual information inherent in the task nor by actual motor execution of the task but seem to be integrating the sensorimotor event as a whole (gestalt?). Mirror neurons have been best studied in the Intraparietal Sulcus and portions of the lateral premotor cortex in monkeys. Results from human fMRI studies appear to be consistent with the monkey data and such studies reveal the potential for these neurons to not only represent the action of others as if the actions were performed by the observer, but some scientists suggest that the Mirror Neuron System may also contribute to our ability to "read" the intentions of others at least to the extent that the observed actions convey some intent that we have experienced ourselves (suggesting species specific mirroring: see below). Thus, the Mirror Neuron System may truly contribute to the cognitive domain of our being such that we could state with some degree of certainty what another brain intends to do: "I know what you are doing or are about to do." The capacity to correctly identify not only the actions of others but the intent behind such actions would provide an evolutionary

advantage. It would allow us to expand our social skills to include empathy or distrust or other affective bonds between 2 biological entities. A recent study recorded activity in individual neurons as related to observed actions and actions actually performed by human subjects. Task-related neurons in the medial frontal cortex, particularly SMA neurons, and medial temporal lobe task-related neurons would either increase or decrease firing related to observed actions and performance of imitated actions: see Mukamel, et.al., 2011.

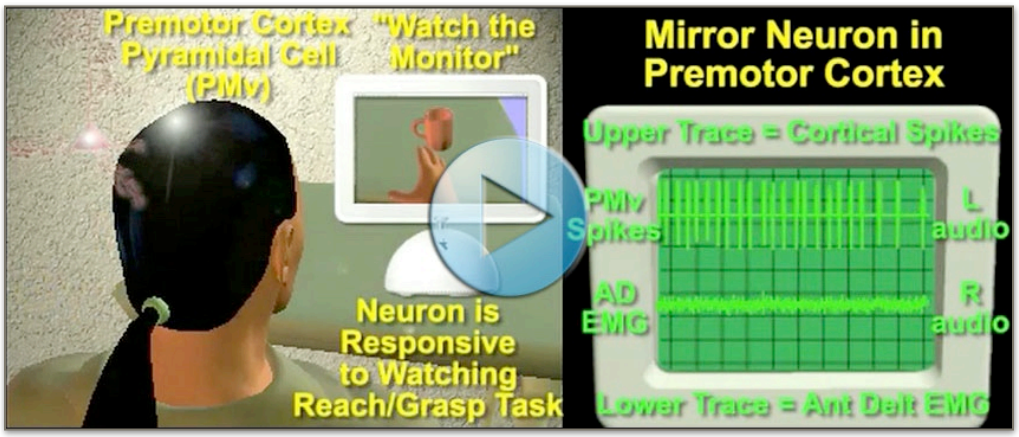


Fig 11-29. Mirror Neuron System Movie: Watching and Performing Task (gec). GO TO: gmomm.pitt.edu Fig11-29_Video

Of course, we cannot fully read another person's mind; much of the mental driving force behind the intent is invisible or seen only through a veil of relative uncertainty. I am told that, on occasion, "I roll my eyes" when I am skeptical about the information presented to me by another in a dogmatic fashion. ***Are you rolling your eyes?*** Autism Spectrum Disorders (ASDs) seriously compromise the individual's capacity to "fully read" the emotional/social intent of others. ASD in many cases may also degrade the Mirror Neuron System's capacity to imitate the actions of others particularly related to communication and social skills. However, many individuals who are "on the spectrum" have an uncanny ability to imitate characters in animated films. For a first-person account of presumed mirror-neuron deficits see Grandin, 2006.

Mirror Neurons appear to be task-dependent (particularly tasks that require precise interaction with objects in our environment). Many of these mirror neurons in the Lateral Premotor ventral (PMv) Cortex are active also when the subject actually performs the task (see MOVIE simulation below). This lends support for mental practice of motor tasks and suggests that imitation may activate a neuronal network that subsequently will be active when the task is transformed from an internal neural representation to an actual motor performance. It has been suggested that the Lateral Premotor Dorsal Area (PMd) is active when we orient our hand and open it (hand aperture) to be able to grasp an object. The change in hand aperture normally occurs as we are reaching for the object. Would you benefit from watching an expert perform a motor sequence before actually doing it? Orientation of the observer versus action matters. While the movie simulates neuronal activity in the PMv portion of the Mirror Neuron System in a human

subject (which has not been done), recordings from single neurons have been documented in PMv and in Intraparietal Sulcal (Posterior Parietal) neurons in monkeys which show similar patterns of activity. Finally, studies of the mirror neuron system in monkeys and humans suggest that our ability to use this system is dependent upon our implicit knowledge of species-specific behaviors.

Consider this squirrelly example:

While you may have some understanding of the intentions of a squirrel sitting on a fence holding an acorn with its little forepaws, you do not activate a neural motor program to replicate the squirrel's posture or actions. First, you are unlikely to be sitting on a fencepost to eat your lunch unless you are a cowboy(girl). Second, you are unlikely to be restricting your diet to acorns unless you have a specific food fetish. Third, you do not have a gray furry tail that you can position as a question mark to help you balance yourself on such a precarious lunchroom stool (see photo).

On the other hand, you would understand and be able to replicate the obscene gesture of a single raised digit from one driver to another when the one cuts off the other in traffic. One might wonder whether this particular human gesture is learned or now is a genetically programmed rage behavior.

OUT-THERE INTERACTING WITH IN-HERE: PYRAMIDAL CELL INTEGRATION OF BOTTOM-UP & TOP-DOWN INFLUENCES

Recent research has revealed two possible mechanisms for bringing a layer 5 pyramidal cell to threshold for firing one or more axonal action potentials.

Suprathreshold excitatory input from first order core thalamocortical input and intracolumnar inputs (Granular & Supragranular Inputs) to basal dendrites of a layer 5 pyramidal cell produces individual axonal spikes. This "extrinsic" input source relates to "bottom-up" specific sensory drive (Out There Drive).

Alternatively, excitatory inputs to the superficial apical dendrite tufts of the layer 5 pyramidal cell within layers 1 & 2 originates primarily from long range intracortical or higher order matrix thalamocortical inputs to the superficial cortical layers. These "top-down" inputs may have a powerful influence if the A-type K^+ apical dendritic channels are closed (see Cyan). When the K^+ channels are closed a Ca^{++} "spike" can be initiated and propagated along the apical dendrite to the pyramidal soma. The propagated dendritic Ca^{++} "spike" produces a prolonged depolarization of the soma such that a

burst of axonal APs is generated (In Here Intrinsic Meets Out There Extrinsic Influences). This pyramidal cell burst firing may be an important code related to higher level perceptual processing.

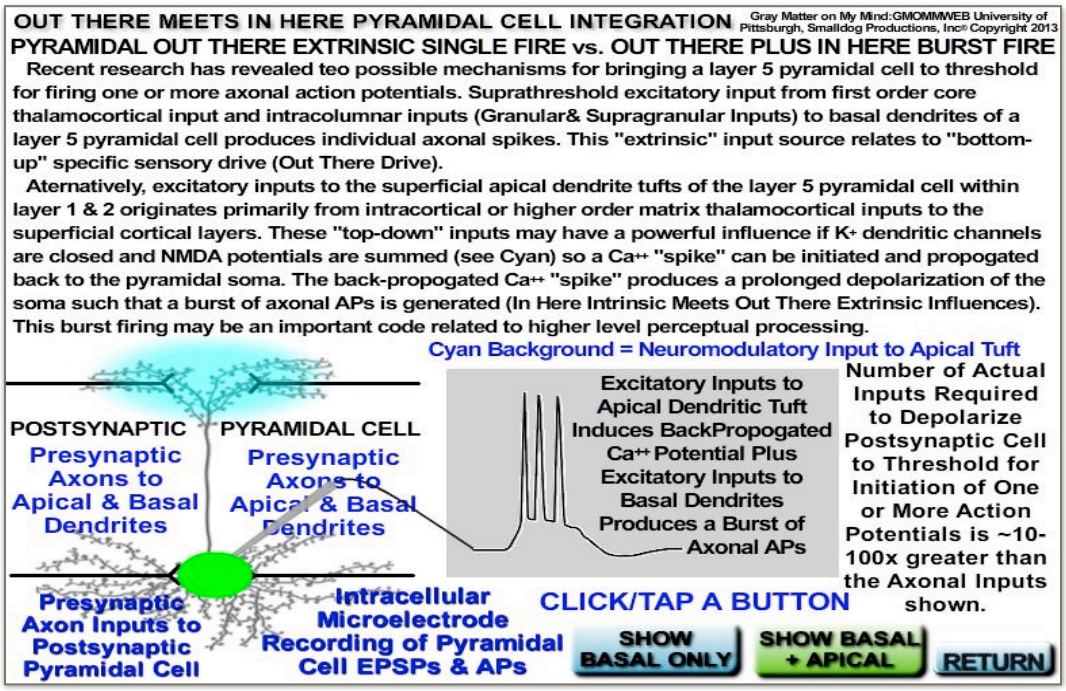


Fig 11-30. Top-Down and Bottom-Up influences on Pyramidal Cells (gec). GO TO: gmomm.pitt.edu

Fig11-30 Inter-active Media

SOMATOSENSORY SYSTEM PLASTICITY

Somatosensory System Plasticity involves malleable circuitry as it does elsewhere in the nervous system. It is thought to be one component in reaction to injury, or the response to repeated exposure to tasks/environments that command our attention or demand change to improve performance. Implicit learning and memory are likely to use similar if not identical mechanisms to those that will be described on the following pages. Plasticity infers adaptability, an ability to change. Recent research suggests a malleability of the nervous system that at one time was unimaginable to most scientists studying neural connections. Evidence suggests an age- and activity-dependent nature to neural plasticity; adaptability is not restricted to the very young. Mechanisms may differ for immature versus mature nervous systems, for early versus. late modifications and for changes due to lesions versus experience. Our current understanding of those biochemical, connectional and physiological modifications that express themselves as plasticity is limited. Nevertheless, we will present examples of plasticity within the somatosensory system that have been the signature studies of a malleable brain. Examples show changes in the human, actual data are based on studies in non-human subjects.

PLASTICITY FOLLOWING PERIPHERAL NERVE LESIONS

Loss of peripheral nerve input results in an early and a delayed reorganization of the somatosensory system. Some of these changes may be seen in spinal cord circuits and

dorsal column nuclei, but major changes in tactile representation appear to be the result of reorganization of the SI map.

Early map changes, as expected, include “silent zones” where there is no response to stimulation of the denervated skin area. However, over time some adjacent skin area representations appear to invade the cortical area originally activated by the now denervated skin. This is thought to be a consequence of unmasking of the normally weak convergent projections from adjacent skin. The mechanism(s) responsible for the unmasking may include changes in excitatory and inhibitory synaptic strength. Later changes where there is significant invasion of the previously inactive cortex by adjacent skin areas may represent both physiological & anatomical mechanisms that partially “rewires” the map.

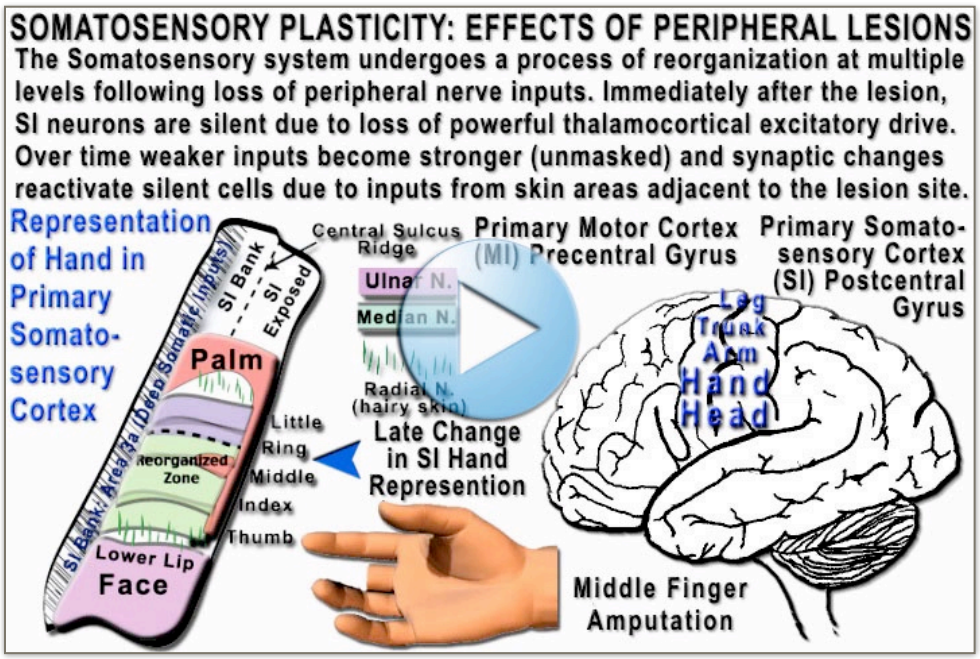


Fig 11-31. Somato-sensory Plasticity: Cortical Reorganization Following Peripheral Nerve Lesions (gec). GO TO: gmomm.pitt.edu Fig11-31_Video

A question that is central to the issue of neural plasticity is related to the effects of experience on brain circuitry. While plasticity has been accepted for some time as a natural form of experience-dependent circuit building in the developing brain, until recently no such alteration in neural connections was thought to occur in the mature brain. Early evidence of the power of the environment to shape the nervous system came from William T. Greenough and colleagues at the University of Illinois, Urbana. Greenough has provided evidence that an enriched environment can modify certain areas of the cerebral cortex of adult rats. Rats that were placed in a rat “playground” (probable equivalent of going to a variety of amusement parks every day for months on end) had anatomical changes that were not seen in rats that were housed in typical cage environments. Changes included expanded dendritic fields and increased synaptic density in sensory cortex of the enriched rats.

PLASTICITY: MAP EXPANSION DUE TO REPEATED USE

Repeated exposure to a tactile stimulus may reorganize the somatosensory map. A number of studies have shown that experience in the form of repeated exposure to a specific active touch task results in an expansion of the representation of the 'trained' tactile skin.

This may require a long period of exposure to the task, or a short intense period of training, depending on the task at hand. Some studies suggest that the expanded representation may include adjacent Area 3a SI Cortex, an area that typically maps only deep somatic inputs. The scenario presented here is loosely based on a monkey study by W. M. Jenkins and colleagues in M. M. Merzenich's laboratory at the University of California, San Francisco (see W.M. Jenkins, et.al., 1990).

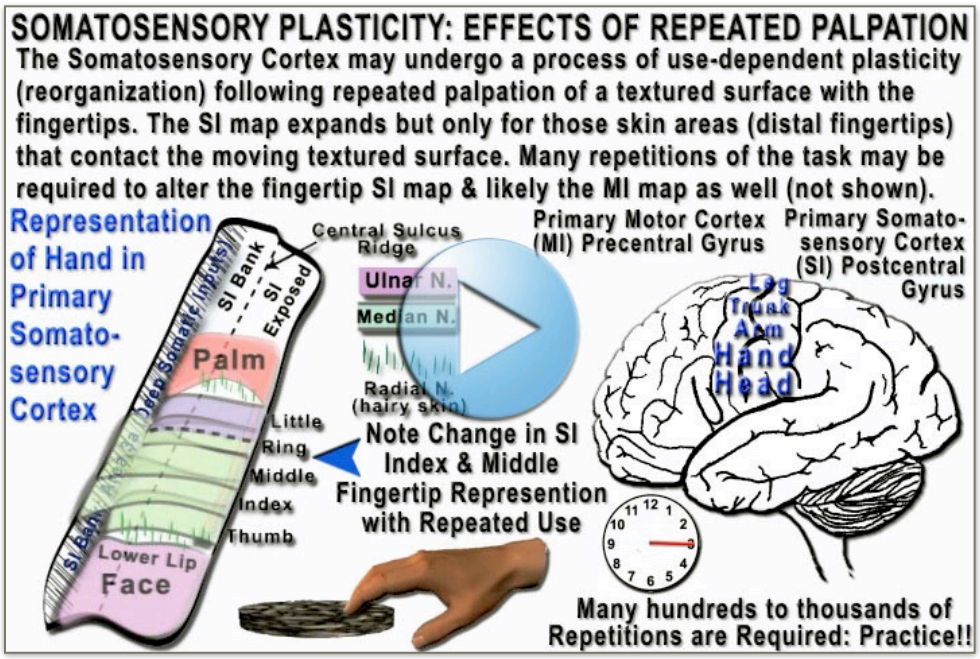


Fig 11-32. Somato-sensory Plasticity: Cortical Reorganization Following Repeated Tactile Palpation (gec). GO TO: gmomm.pitt.edu Fig11-32_Video

PLASTICITY: NETWORK TEMPORAL COHERENCE IMPROVES WITH PRACTICE

While bigger may be better concerning the extent of cortex devoted to a peripheral tactile receptive field, neural discharge modulation may be the stronger influence on neural network function. Few studies have addressed the question of experience-dependent modulation of the firing properties of neurons exposed to a discriminative tactile task.

One such set of experiments were conducted by Gregg H. Recanzone and colleagues at UCSF (see G.H. Recanzone, et.al., 1992). Recanzone trained monkeys to discriminate between a 20 Hz sinusoidal tapping versus tapping at frequencies of 22-30 Hz. As animals learned the task, their discrimination improved (reduced errors) correlated with a concurrent alteration in the discharge profile of the “trained” neurons in

SI. Over time, as behavior improved, the discharge profile of activated SI neurons showed an increased coherence, a sharpening of the peak of activity with each stimulus cycle. An increased response synchrony (seen as a rapidly rising “front-loaded” peak of activity) was directly correlated to improved performance. While it may be tempting to suggest that the improved discrimination was the result of the neural modulation, there are other interpretations. Monkeys performed the task for a reward. As they got better, the brain's reward system (limbic and basal ganglia circuitry?) could adjust levels of metabotropic neurotransmitters that, in turn, altered synaptic profiles in the “trained” cortex. Rewarded behavior could induce the sensory change, not vice-versa.

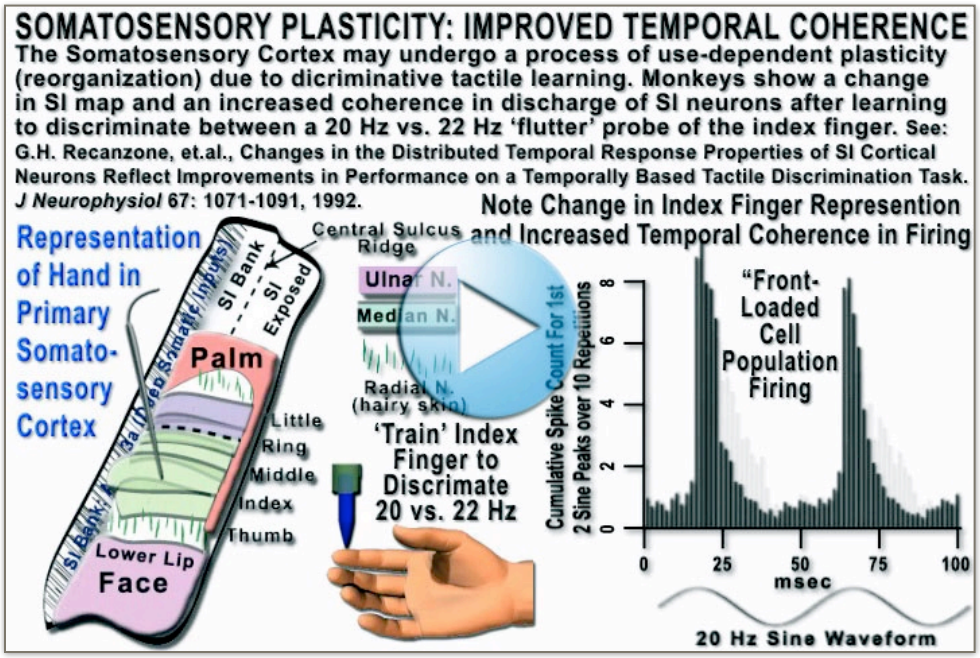


Fig 11-33. Somato-sensory Plasticity: Cortical Reorganization Following Discriminative Tactile Learning (gec). GO TO: gmomm.pitt.edu *Fig11-3_Video*

AGE- AND ACTIVITY-DEPENDENT SOMATOSENSORY PLASTICITY: WHISKER TO BARREL SYSTEM

What role does activity-dependent plasticity play in the developing somatosensory system? Evidence accumulated since the 1960s supports the concept that activity-dependent adjustments of synaptic connections is required for normal development of the visual system. A series of experiments related to the somatosensory system of the rat has provided evidence that normal development of somatosensation requires experience during a sensitive period in the life of a young rat pup.

Rats are nocturnal animals that rely upon their mobile vibrissae (whiskers) to navigate and interact with their environment in their normal habitat. If the vibrissae are deafferented at birth, the somatosensory system undergoes extensive anatomical and physiological reorganization. What would happen if the vibrissae were merely trimmed during this critical period and then allowed to regrow in adulthood? Simple whisker trimming does not remove touch receptors and their afferent innervation, and the rat still

has some touch input through the shortened tactile organs. The difference with whisker stubs versus full length whiskers is the lack of a normal spatial and temporal pattern of input that is acquired normally by the animal whisking its surroundings with long flexible tapered vibrissae. Infant whisker trimming with adult regrowth increases responsiveness of excitatory neurons to whisker deflections, expands receptive fields and reduces inhibition of these cells in somatosensory barrel cortex: see Simons and Land, 1987; Y. Jiao, et.al., 2006; Q.Q. Sun, 2009; Simons, Carvell and Kyriazi, 2015.

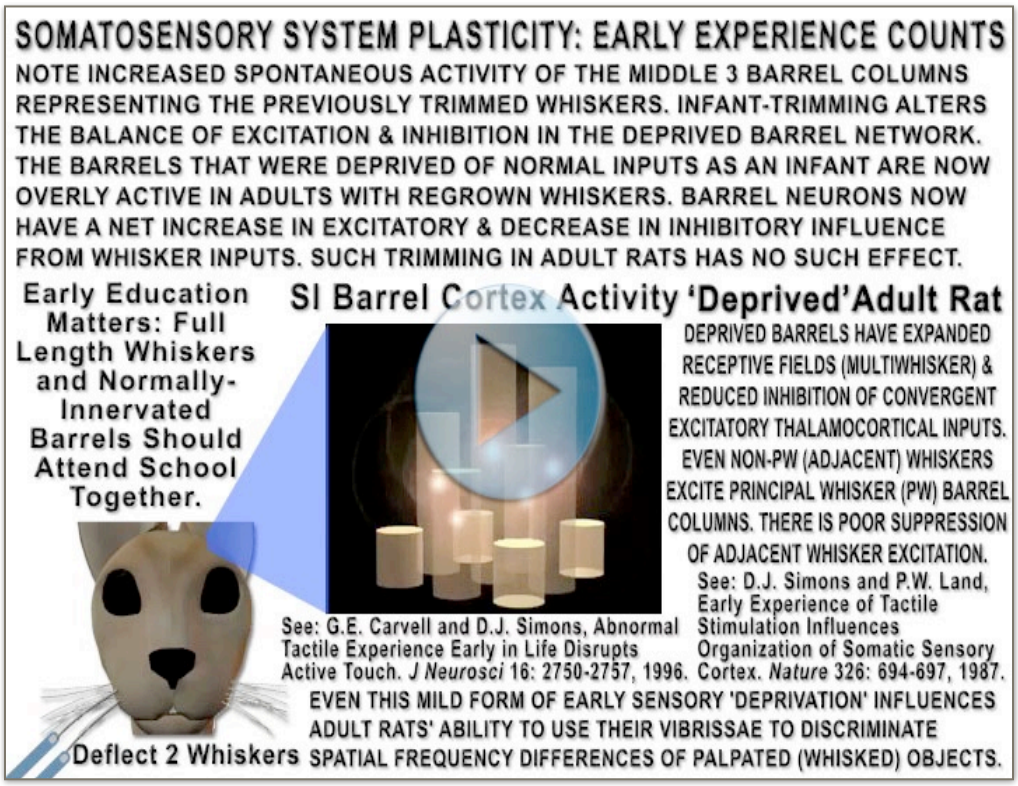


Fig 11-34. Somatosensory Plasticity: Importance of Early Tactile Experience to Fine Tune Somatosensory System (gec). GO TO: gmomm.pitt.edu *Fig11-34_Video*

SOMATOSENSORY AND MOTOR SYSTEM ALTERATIONS DUE TO EARLY SOMATOSENSORY DEPRIVATION

Blindfolded rats placed on an elevated platform are trained to stretch across a gap to palpate discriminanda attached to the front of choice platforms with their outstretched vibrissae (see Behavioral Training Apparatus figure).

The animal indicates its choice by jumping to one of these platforms; if correct the animal receives a food reward. The reward discriminandum is matched to another having a different surface texture. Reward and non-reward discriminanda are randomly interchanged between the two choice platforms. Rats are capable of reliably distinguishing differences as little as 50 to 60 μm after training. There are characteristic motor patterns that distinguish good from poor performers, and whisking biometrics

differ for a rough versus smooth (R-S) detection task and a rough versus rough (R-R) discrimination task: See Carvell & Simons, 1990, 1995.

For the R-R task rats must differentiate differences in the spatial frequencies of relatively widely spaced gratings. The latter but not the former R-S task requires multiwhisker inputs. A close-up view of task (Whiskers Bending with Discriminandum Palpation Movie) shows that as the animal palpates a textured surface its whiskers bend, indicating the high level of flexibility of these tactile organs.

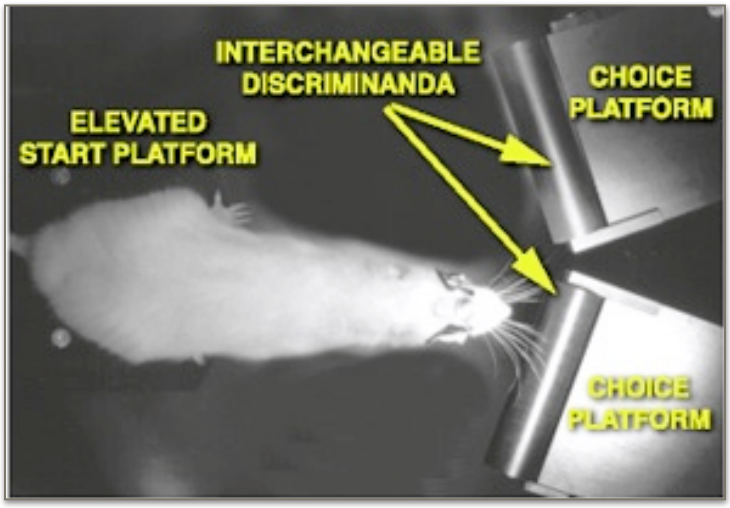


Fig 11-35. Behavioral Training Apparatus for Vibrissal-Based Tactile Discrimination Using Interchangeable Discriminanda (gec).
Animals learn the (R-S) but not the (R-R) task with whiskers regrown in adulthood after a month of trimming as infants; motor patterns are abnormal in those animals that fail to learn the rough versus rough task (see below).

Fig 11-36. Whiskers Bending with Discriminandum Palpation Movie (gec). GO TO: gmomm.pitt.edu Fig11-36_Video

The Abnormal Sensorimotor Biometrics for Whisking in Adult Rats Following Whisker Regrowth after Trimming as Infants figure illustrates average frequency spectra of data from tens of thousands of whisks when normally reared and infant-trimmed groups of rats approached and then palpated tactile discriminanda: Rough versus Smooth task (R-S) or Rough versus Rough task (R-R). Note that animals whether normally reared (no trimming) in the R-S and R-R group or those rats who learned the R-S task as adults following whisker trimming as infants have normal whisking patterns as adults: repetitive whisking sweeps within mid range frequencies (6-12 Hz).

A robust increase of ~2 Hz is seen in mid range whisking for all animals who learned the discrimination tasks after contacting the tactile surface: compare approach (blue) and contact (green) data in panel A of figure. By contrast, as shown in panel B, those

infant-trimmed rats could not learn the more difficult R-R task as adults with regrown vibrissae and these animals whisk at frequencies in the low and high range but actually have a valley in mid range frequency power. Thus both sensory deficits (inability to discriminate object spatial "form") and motor deficits (inability to find/utilize the appropriate "rhythm" of whisking) seem to go hand-in-hand. This should not be surprising for a discriminative active touch task. Whether the sensory or motor deficits cause the poor performance is a "chicken or egg" (which comes first) proposition. Rats who have whiskers chronically trimmed as adults have no such difficulty learning either task with regrown vibrissae: this is an example of age- and activity-dependent neural plasticity. see: Carvell and Simons, 1996.

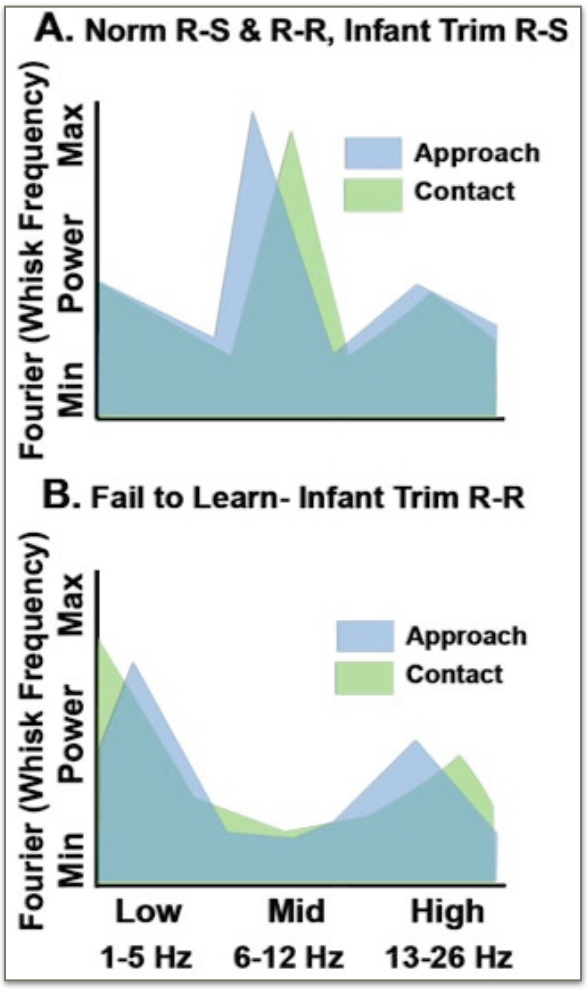


Fig 11-37. Abnormal Sensorimotor Biometrics for Whisking in Adult Rats Following Whisker Regrowth after Trimming as Infants (gec).

Recent studies suggest a transient alteration in thalamocortical connectivity in ***adult*** rat vibrissal cortical barrels when whiskers are trimmed. The onset of these changes appears to be rapid and may be rapidly reversed following whisker regrowth: see Oberlaender, et.al., 2012.

Intrinsic (sling) muscles that tilt the vibrissae forward contain almost exclusively fast twitch muscle fibers. These fast twitch muscles rapidly sweep the whiskers as shown in the Normal Volitional vs. Fictive Whisking Movie.

The Normal Volitional vs. Fictive Whisking Movie shows that patterned electrical stimulation of the facial nerve can artificially move the whiskers although these fictive whisking motions do not replicate the smooth contractions produced by volitional recruitment of facial motoneurons (compare volitional whisking vs. fictive whisking).

Fig 11-38. Normal Volitional vs. Fictive Whisking Movie: unpublished data, Carvell & Simons (gec). GO TO: gmomm.pitt.edu *Fig11-38_Video*

The Whisker To Barrel: Normal & Abnormal Integration Interactive Flash File simulates the effect of infant-trimming (whiskers trimmed short for first 30 days after birth) on layer IV somatosensory barrel cortex neural networks in adult animals following whisker regrowth.

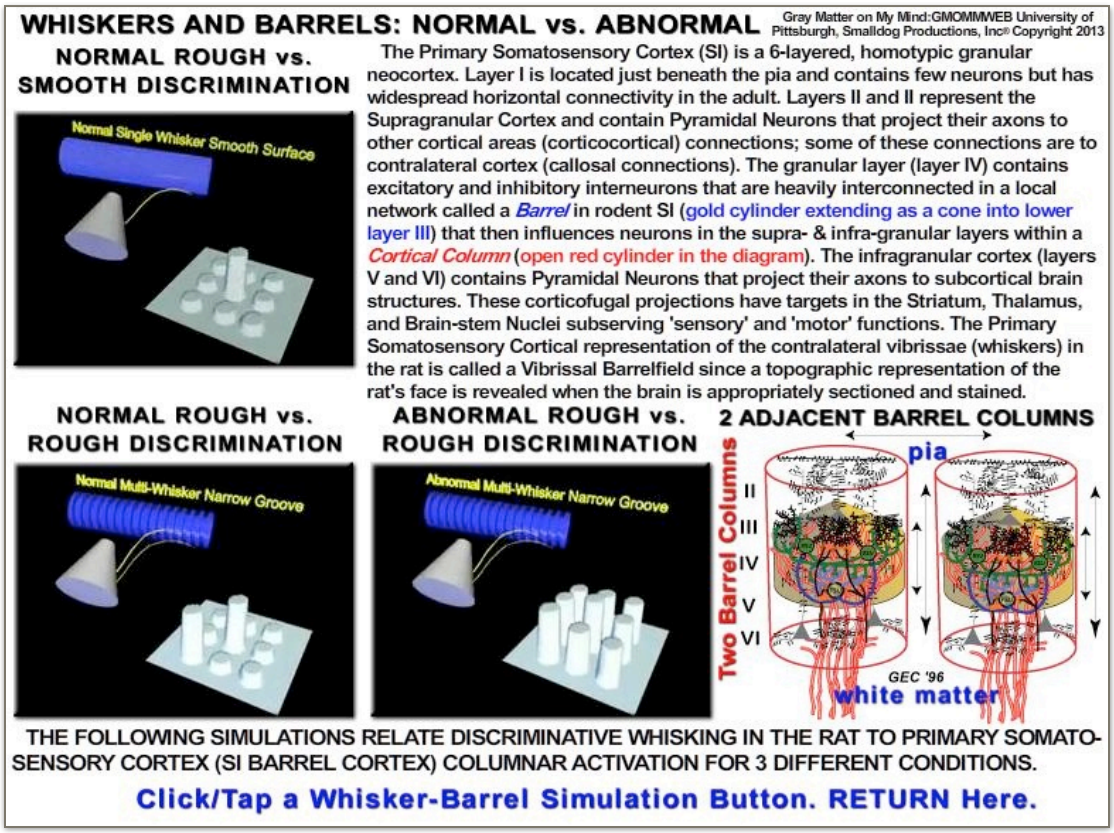


Fig 11-39. Whisker To Barrel: Normal & Abnormal Integration Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig11-39_Interactive Media*

Following infant whisker trimming there is an increased somatosensory cortical barrel neuron excitability, an expansion of receptive field size for layer IV excitatory spiny stellate cells, decreased angular specificity and reduced GABAergic inhibition in barrels of adult rats with regrown whiskers as compared to the columnar neural activity in normally reared rats who grow up with all whiskers at their normal length; this altered neurophysiological cortical processing is accompanied by impoverished vibrissal-based discriminative tactile behavior: see Simons & Land, 1987; Carvell & Simons, 1996; Y. Jiao, et.al., 2006; Q.Q. Sun, 2009; Simons, et.al, 2015.

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Chapter 12

VISION: VISUAL SYSTEM LOOKING AND SEEING

The visual system in higher primates (including us) is arguably the most complex of all the special senses. The complexity begins with the visual system's attempts to "construct" a virtual 3-dimensional representation from photic transduction that occurs within a thin curved sheet of cells located at the back of the eye: the retina. The optics of the eye can regulate the amount of light that enters and then focus that light on the retina. However, as will be emphasized later, there is more to vision than meets the eye.

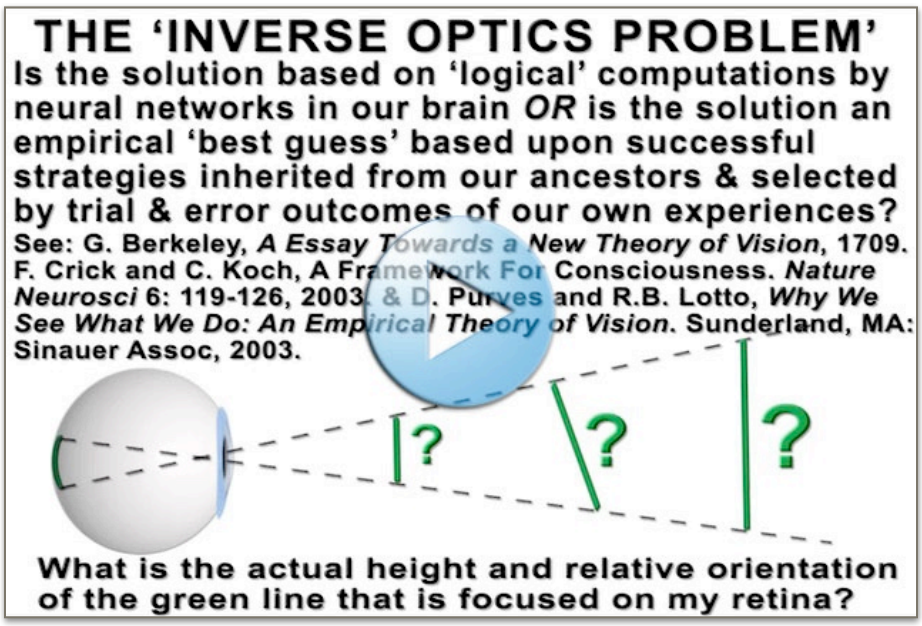

Fig 12-1. Inverse Optics Problem Movie (gec). GO TO: gmomm.pitt.edu *Fig12-1_Video*

The image represented by the photic energy that reaches the retina has ambiguities in orientation (particularly related to the Z-axis position), hue, luminance for reflected light from objects (lightness) or luminance from an emitting source (brightness), motion of objects relative to other moving or stationary objects and incomplete or "fractured" images due to masking. While some neuroscientists insist that the complex neural processing within the many visual areas can explain, *a priori*, the brain's interpretation of these significant ambiguities, others suggest that the visual system has empirically derived trial and error solutions over the lifetime of the individual and by the biasing of trial and error solutions that have provided relevant behavioral outcomes for the species built over a long period of evolution: **some gene assembly required** (see references). It is still unclear how the "history" contained within the DNA/RNA of *individual* cell nuclei can be amassed to create *global* solutions among billions of cells distributed across many visual brain areas: **significant gene assembly required**. *Does this mean that our genes are perceptual geniuses even if we (our conscious selves) are not?*

Of course, none of these solutions directly addresses the other issue related to our "mind's eye" that creates "images" that are based upon our internal not external world,

e.g., an individual writer's creativity that may be shared with others if the author's words can describe those images or the author's rendered images can enhance the understanding of the words; "the lights are on (brain is active) and someone is home (the mind understands)."

The major sensory (afferent) pathway to the primary visual cortex includes the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus (LGN) of the thalamus, optic radiations (geniculocalcarine tract), and the primary visual cortex (striate cortex) located along the banks of the calcarine sulcus in the occipital lobe. The Optic Nerve contains Retinal Ganglion Cell Axons from the corresponding ipsilateral eye.

VISUAL SYSTEM BASICS

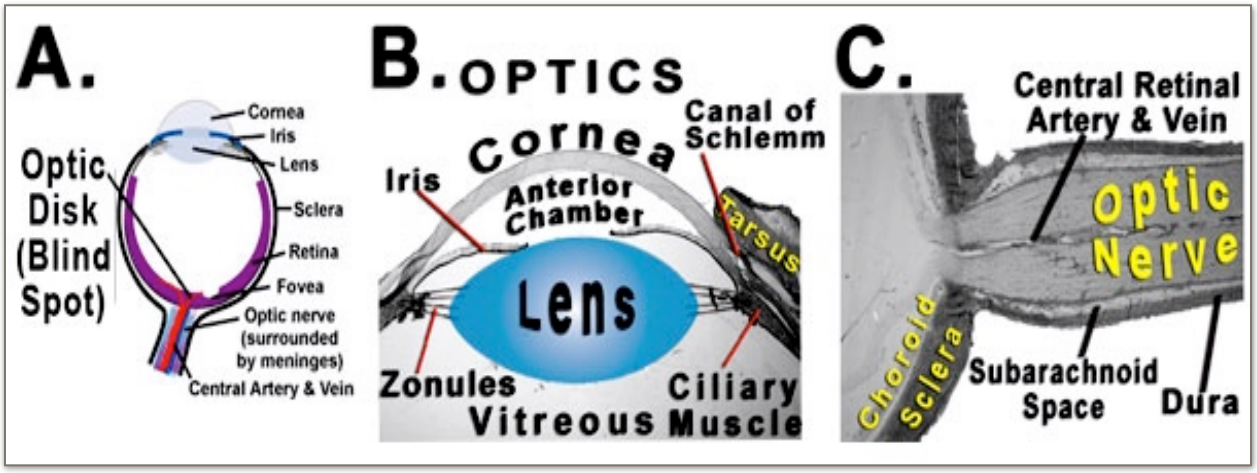

Fig 12-2. A. Architecture of the Eye B. Optics of the Eye. Critical Structures to Transmit Light and Focus Images on the Retina. C. Optic Nerve and Associated Structures (gec).

EYE OPTICS

The anterior portion of the eye provides the optics to 1. control the amount of light that reaches the back of the eye (retina) by dilating or constricting the pupil (changing the diameter of the iris), 2. rounding or flattening the lens to focus the image precisely on the surface of the retina, and 3. determine the form, pressure and transparency of the cornea, anterior chamber (aqueous humor) and vitreous humor. The physical properties of eye optical structures have a direct effect on the visual system's capacity to interpret the world we see, e.g., see Barlow, 1981.

Blocking flow in the canal of Schlemm increases intraocular pressure such that aqueous humor flow is blocked. An untreated increase in intraocular pressure results in glaucoma. Untreated glaucoma results in retinal pathology and loss of vision within a portion of the visual field.

OPTIC NERVE AND DURAL SHEATH

The optic nerve develops as an out-pouching of the embryonic diencephalon (optic stalk). The Optic stalk is continuous with the optic disk that develops into the retina of the eye. The optic nerve contains the major blood supply for the retina (central artery and vein) and it is covered by the meninges like the rest of the brain. Cerebrospinal fluid (CSF) in the subarachnoid space is continuous with that surrounding the brain. Any increase in CSF pressure will be transmitted to the back of the eye. An increase in CSF pressure causes a papilledema where there is a blurring of the optic disk, hemorrhages and congestion of the blood vessels in the back of the eye. These changes are clearly visible with an opthalmoscopic exam. See figure.

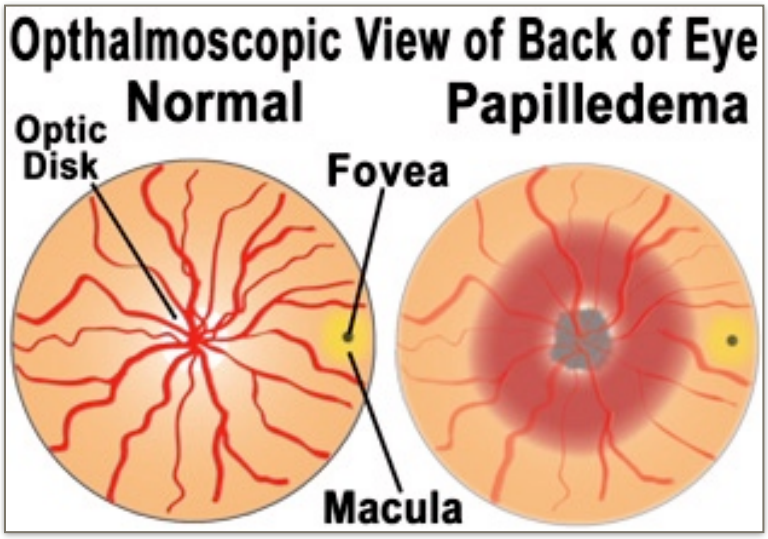

Fig 12-3. Simulation of Normal Opthalmoscopic View of the back of the eye and altered retinal image with Papilledema due to increased CSF pressure (gec)

LOOKING NEAR VERSUS FAR: ACCOMMODATING OPTIC RESOURCES

Accommodation: when the eyes converge upon a near object both eyes adduct (dysconjugate gaze), and a normal reflexive pupillary constriction and a rounding or "fattening" of the lens (due to ciliary muscle contraction) occurs in both eyes.

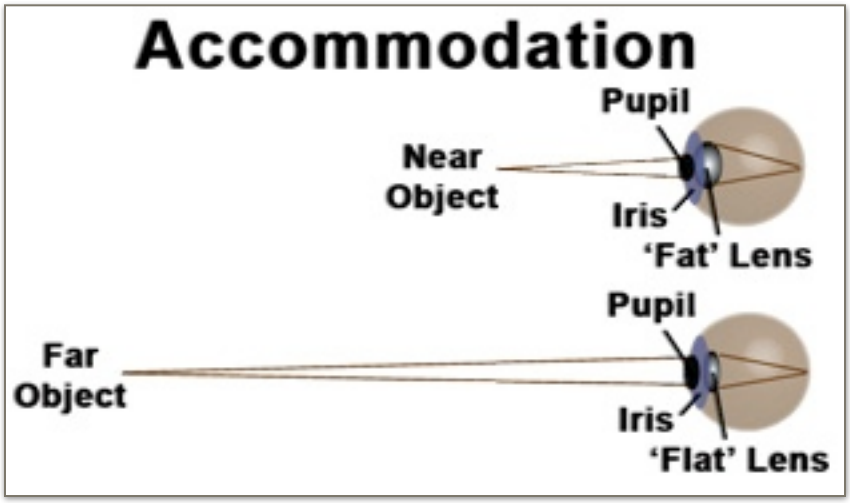

Fig 12-4. Accommodation: Near versus Far Vision (gec).

Looking far away after this near vision will dilate the pupils, abduct the eyes slightly (so they are looking forward for conjugate gaze) and a flattening of the lens as the ciliary muscles relax. The pupillary and lens responses are coupled to autonomic innervation (see below). Eye motion is coupled to extraocular muscles and to gaze control centers

located in the brainstem and in the cerebral cortex. Dysconjugate and conjugate gaze control centers differ.

Fig 12-5. Near vs. Far Vision Simulation Movie (gec). GO TO: gmomm.pitt.edu Fig12-5_Video

EYE OF THE BEHOLDER

It has been said: "beauty is in the eye of the beholder" at least when it comes to art. Yet there is no evidence that the retina has any capability to place a qualitative judgement on the photons transduced into neural signals. On the other hand, the visual cerebrum in cooperation with the limbic system does seem to add an affective overtone to what we see (beauty in the mind's eye).

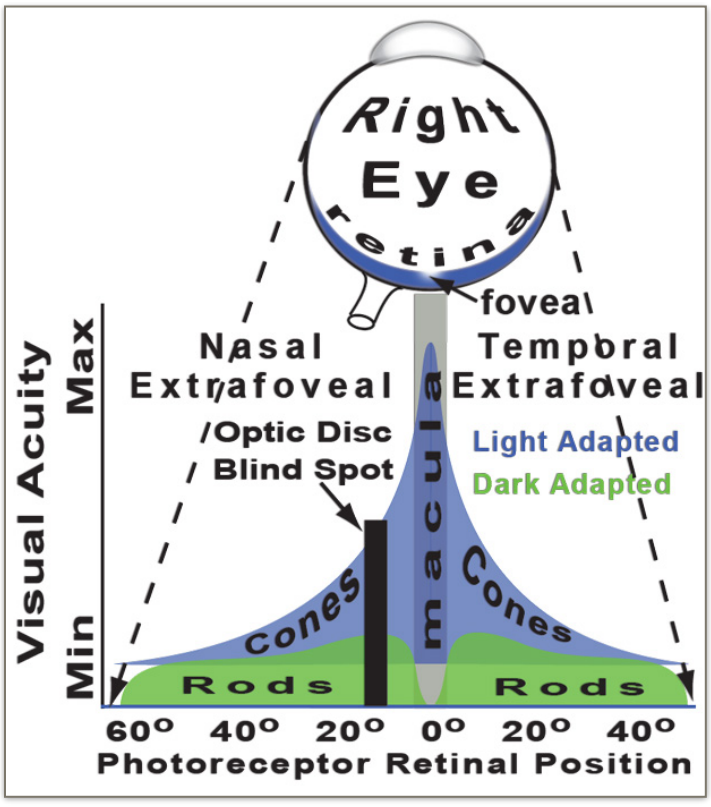

Fig 12-6. Light-Adapted and Dark-Adapted Visual Acuity. Note cone (blue) versus rod (green) eye acuity and the naturally occurring blind spot (optic disk) (gec).

Optics focus images on the retina where photons within the visible light spectrum are transduced to neural signals by photoreceptors (rods & cones). Light hyperpolarizes the rods and cones. The fovea is a small "pit" in the center of the retina where only cones are found. All other cell types of the retina are displaced outside of the fovea. Extrafoveal retina contains all cell types: Cones, Rods, Bipolar cells, Amacrine cells, Horizontal cells & Retinal Ganglion Cells.

The macula, where the fovea is located, provides us our highest visual acuity. Acuity drops sharply outside of the fovea, i.e., nasal and temporal extrafoveal retina (see Light-Adapted and Dark-Adapted Visual Acuity figure). The fovea is the location of the highest density of cones in the retina. Visual motor centers & pathways provide fine control of our eyes and head to bring images into focus on the fovea for tasks requiring high acuity (e.g., reading). Cones provide color vision for the light-adapted eye while rods are color-blind but are sensitive to low light levels to see with the dark-adapted eye. Both photoreceptors distinguish differences in the hue of objects, and retinal circuitry provides an initial processing of visual information that enhances contrast.

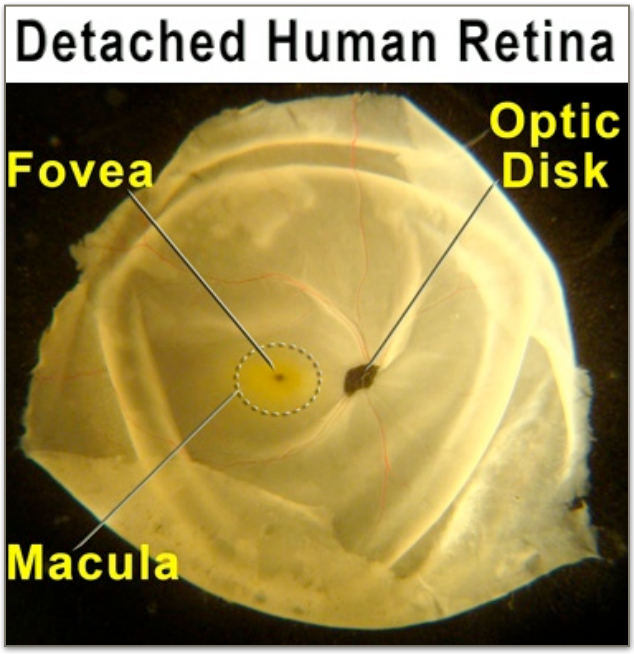

Fig 12-7. Human Retina. Photograph courtesy of Willi Halfter, PhD, Department of Neurobiology, University of Pittsburgh, School of Medicine. Note blood vessels emanating from the optic disk (faint red lines). Dashed line surrounds approximate extent of the macula lutea. Note the small size of the fovea relative to the large surface area of the retina. Macular Degeneration produces profound loss of visual acuity. It is not difficult to imagine the fine motor control necessary for our visual motor system to center our vision on the fovea (gec).

RETINAL LAYERS AND CELL TYPES

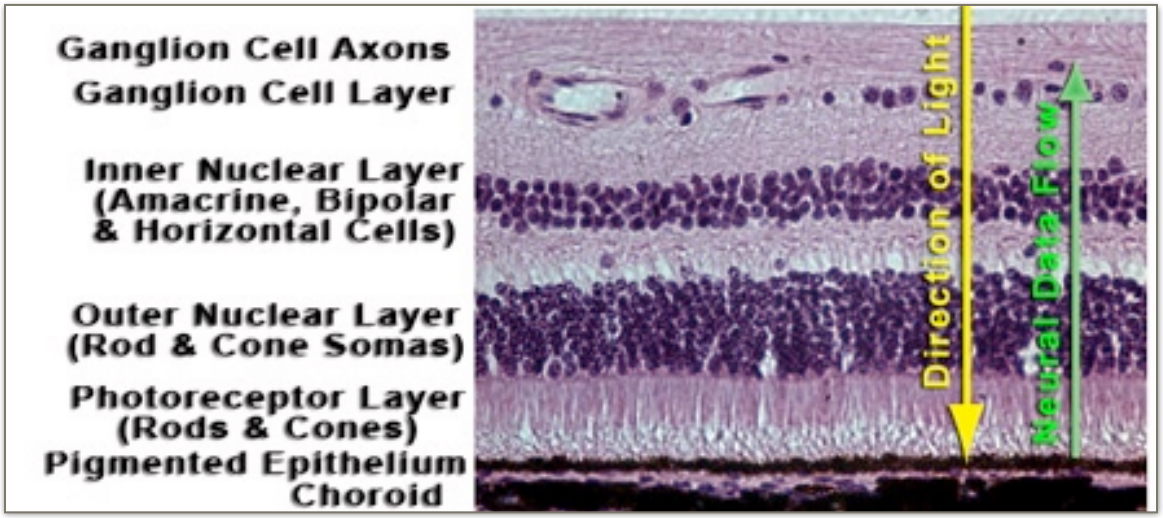

Fig 12-8. Primate Retinal Layers and Associated Cell Types. Top of figure towards vitreous humor (inner portion of eye). Bottom (Choroid) is outside part of eye (gec).

The retina is developed from the optic cup an out-pouching of the embryonic diencephalon. Multiple cell types process the incoming light to build contrast even at this early stage of visual processing. The Cone Vs. Rod View of a Visual Scene Movie presents a simulated situation where a visual scene is seen through the eye of the cones versus the eye of the rods: a situation that does not normally occur with the intact light-adapted eye. Note the difference in the stimulus characteristics "recognized" by these two different phototransducers.

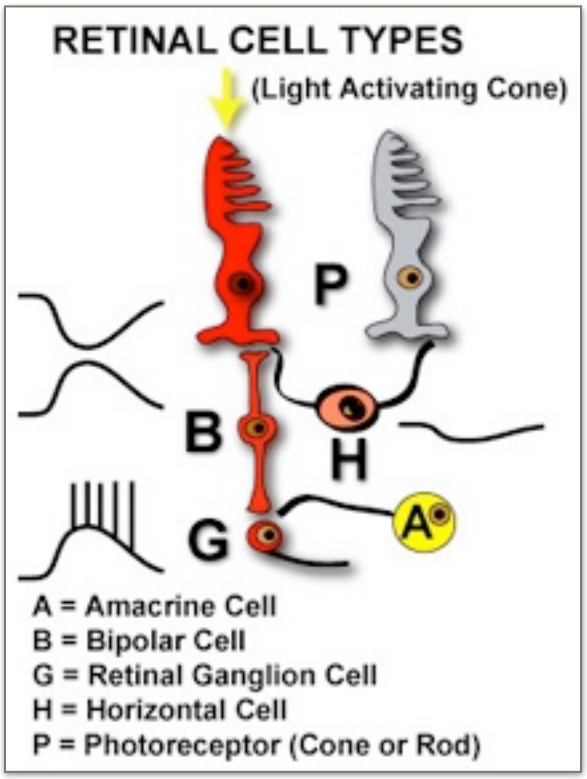

Fig 12-9. Cells of the Retina: Photoreceptors (Cone or Rod), Interneurons & Projection Neuron (Retinal Ganglion Cell) (gec).
Our visual system relies upon contrast within the visual scene to interpret what we see. Activation of photoreceptors will influence bipolar cells that in turn synapse on retinal ganglion cells. Spots of light will either turn-on or turn-off retinal ganglion cells (G) depending upon their location within the center/surround receptive field of each cell. Many cells participate in the formation of the signal that eventually gets transmitted to the thalamic lateral geniculate nucleus by G cell axons. Bipolar (B) Cells provide a link between the photoreceptor (P) and the retinal ganglion cell (G). Both P and B cells are influenced by Horizontal Cells. Horizontal cells (H) are the retinal cells that provide the center/surround sign change for ON-center and OFF-center cells (see movies below).

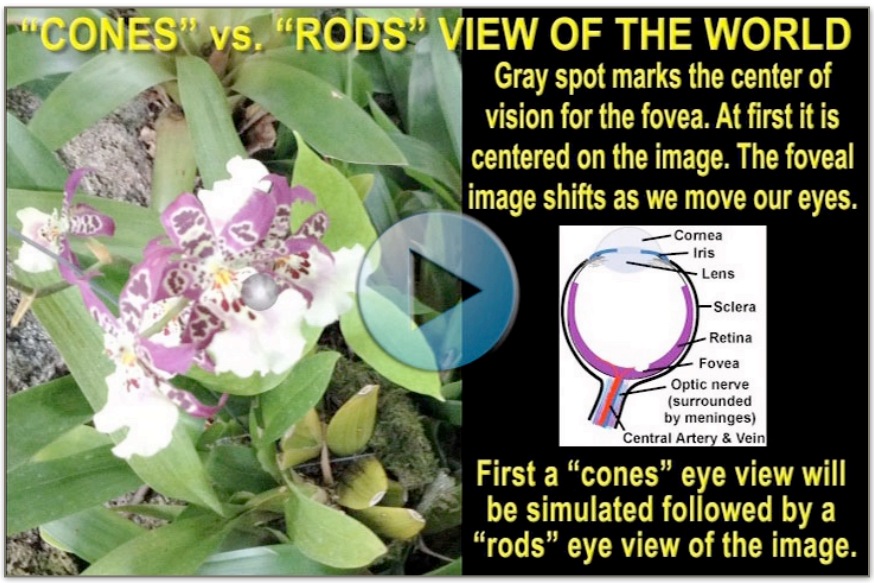

Fig 12-10. Cone Vs. Rod View of a Visual Scene (gec). GO TO: gmomm.pitt.edu
Fig12-10_Video

Amacrine cells (A) appear to be important in detection of light (image) motion that moves across the retina.

The only cell that generates action potentials is the G cell. All other retinal cells

shown in the Cells of the Retina figure produce only local non-propagated potentials.

VISUAL SYSTEM WIRED TO ENHANCE CONTRAST: RETINAL ON-OFF PROCESSING

A small spot of light shown on the center of the Retinal Ganglion (G) Cell's receptive field (RF) turns ON the cell. The best excitatory response occurs when the light fills the center. A spot of light in the surround "donut" produces the opposite effect. Complete illumination of the surround produces optimal inhibition of ON cells due to H cells. Diffuse illumination of center & surround is a weakly excitatory stimulus.

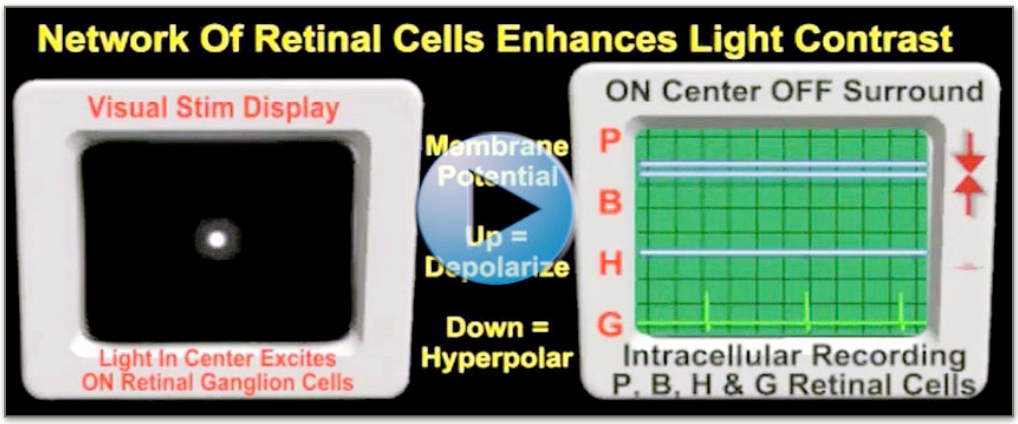

Fig 12-11. ON Center OFF Surround RF for Retinal Ganglion Cell Movie (gec). GO TO: gmomm.pitt.edu Fig12-11_Video

The ON Center OFF Surround Retinal Ganglion Cell Interactive Flash File animation shows the effect of shining light onto either the center or surround portions of a retinal ganglion cell's receptive field (RF). Note the critical role of the Horizontal cell to enhance contrast and limit the size of the effective RF and the ineffective light stimulation represented by a diffuse illumination of a large portion of the retina (no contrast).

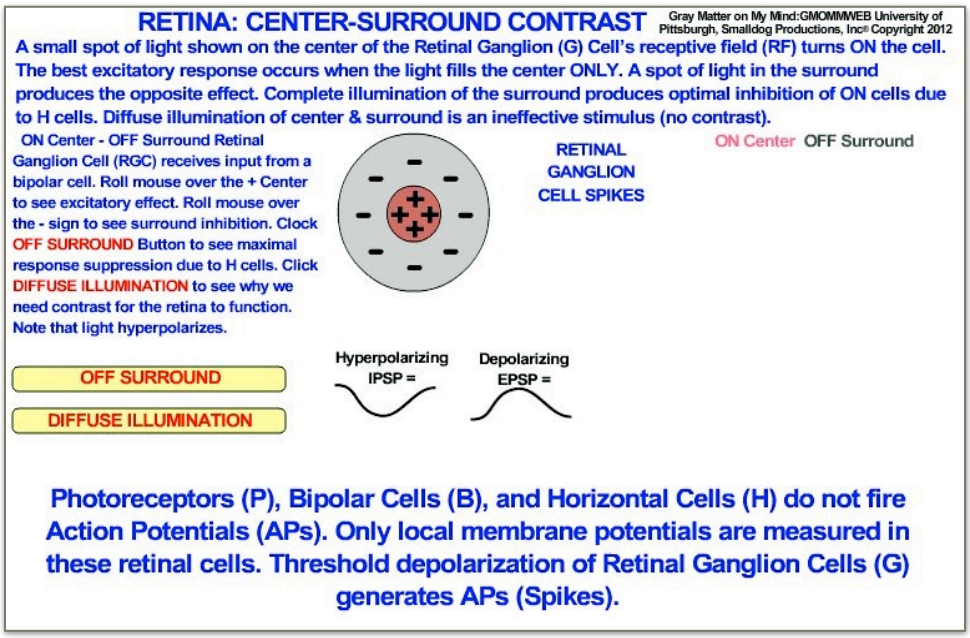

Fig 12-12. ON Center OFF Surround Retinal Ganglion Cell Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig12-12 Interactive Media

EYE MOVEMENTS: EXTRAOCULAR MUSCLES AND BRAINSTEM CONTROL

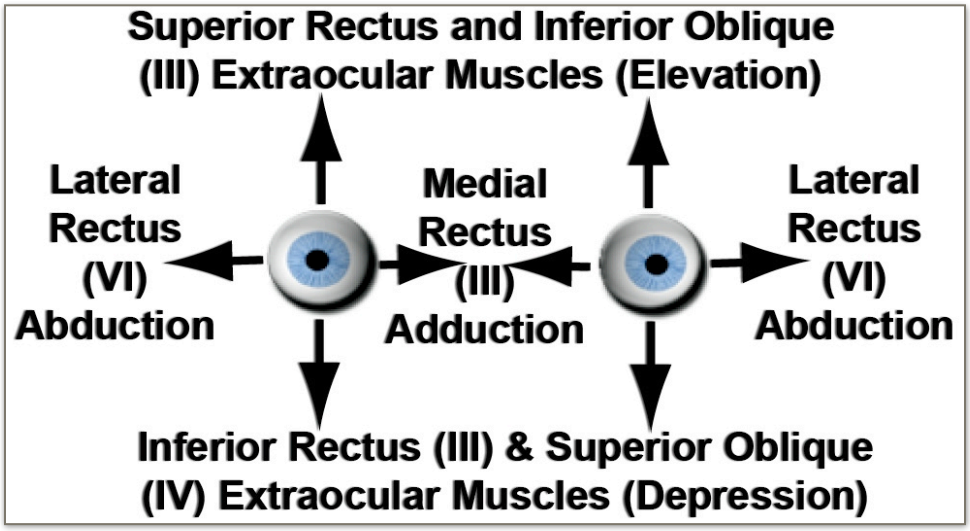

Fig 12-13. Extraocular Muscles, Eye Movements and Cranial Nerve Innervation. III = Oculomotor Nerve, IV = Trochlear Nerve, VI = Abducens Nerve (gec).

A set of six extraocular muscles control the movement of each eye within its orbit. All but two of the muscles are innervated by branches of the oculomotor nerve (cranial nerve III). The superior oblique muscle is innervated by the trochlear nerve (cranial nerve IV), and the lateral rectus is innervated by motoneurons located in the abducens nucleus (cranial nerve VI).

CONJUGATE EYE MOVEMENTS: MOVING OUR EYES FOR BINOCULAR VISION

Movement of our eyes in a conjugate fashion requires a significant coordination of action among extraocular muscles. Vertical conjugate gaze is controlled by vertical gaze centers in the midbrain (not shown here).

Horizontal conjugate gaze is controlled by a brainstem center associated with the abducens nucleus known as the Paramedian Pontine Reticular Formation (PPRF). The PPRF receives input from the contralateral Frontal Eye Fields (FEF) and Supplemental Eye Fields (SEF) in the cerebral cortex by way of connections with the superior colliculus. The PPRF has reciprocal connections with the Vestibular Nuclei in the posterior fossa brainstem. The vestibular nuclei receive direct input from vestibular nerve afferents (cranial nerve VIII), and is reciprocally connected with the Vestibulocerebellum (Flocculonodular Lobe and portions of the Vermis). Animation illustrates three types of horizontal conjugate eye movements: rapid saccade, slow smooth pursuit and the vestibuloocular reflex (VOR). Rapid Saccades and the VOR occur with little or no conscious volitional effort (indeed you are “blind” during fast saccades). Smooth pursuit movements tend to be volitional responses to track a visual target with conscious effort and maintenance of a stable image even if you move your head (VOR).

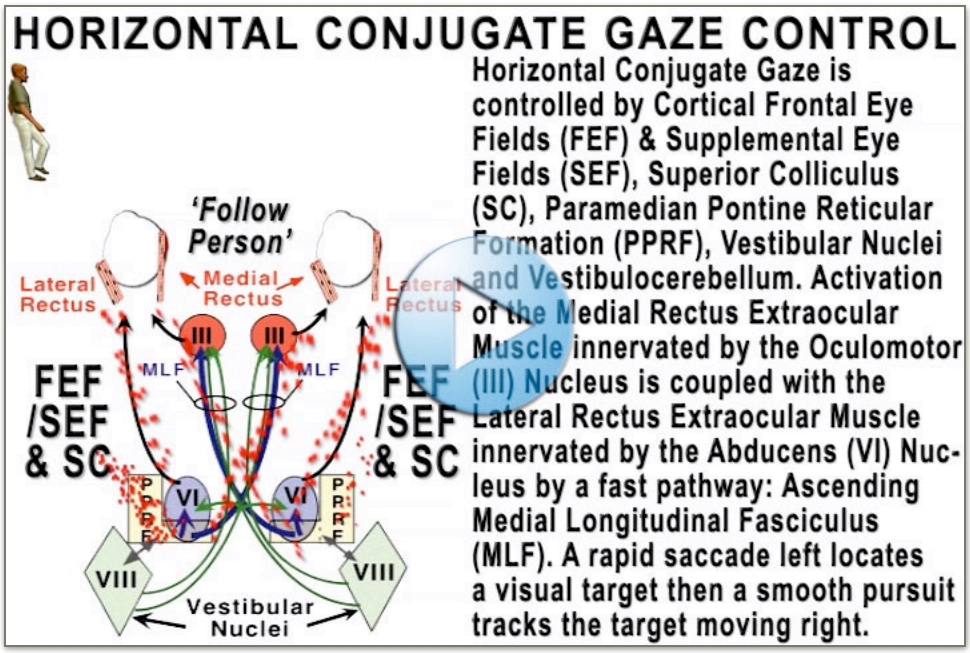

Fig 12-14. Basic Circuitry for Horizontal Conjugate Eye Movements: III = Oculomotor Nucleus, VI = Abducens Nucleus, MLF = Medial Longitudinal Fasciculus, PPRF = Paramedian Pontine Reticular Formation conjugate gaze center) (gec). GO TO: gmomm.pitt.edu Fig12-14_Video

EYE MOVEMENT TESTING: SCREENING EXAMINATION

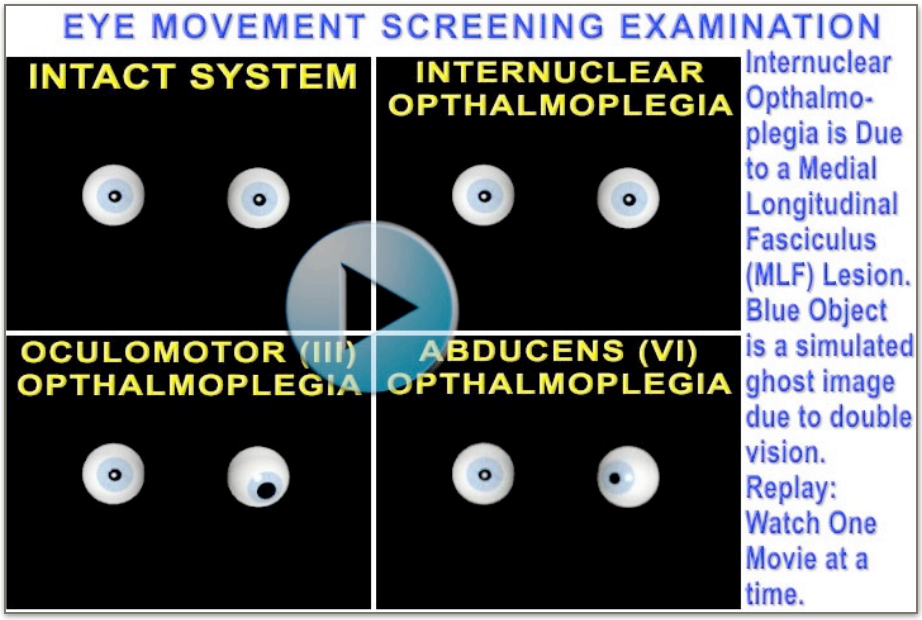

Fig 12-15. Normal and Abnormal Eye Movements: Screening Exam (gec). GO TO: gmomm.pitt.edu Fig12-15_Video

Testing the integrity of eye movements is a critical part of a neurological exam. It provides important information about cranial nerves II, III, IV, and VI, and may reveal potential involvement of nerve VIII (vestibular), or the vestibular nuclei & their connections. In addition, the integrity of central pathways (Medial Longitudinal Fasciculus or MLF), and brainstem or cortical eye movement control centers may be revealed by these simple tests. Brainstem conjugate gaze control centers are located in the midbrain for vertical gaze and in the pons (paramedian pontine reticular formation or PPRF) for horizontal conjugate gaze. The PPRF has reciprocal connections with the vestibular nuclei. These

centers are tested indirectly by assessing a person's gaze. The Frontal Eye Fields provide an important source of cortical control to these brainstem gaze centers.

When you play the movie, note that normally the eyes move in a coordinated (conjugate) fashion and that during the final test for the accommodation reflex, there is a dysconjugate medial deviation of both eyes and a reflexive constriction of the pupil as the lens changes shape to focus on a near object (pencil in this simulation). Normal and opthalmoplegia test results are shown. Opthalmoplegias are described below.

OPTHALMOPLEGIAS: EYE MOVEMENT DEFICITS

An oculomotor opthalmoplegia results from a lesion of the oculomotor nuclei in the brainstem or from a lesion of cranial nerve III (lower motor neuron lesion). A complete lesion of the third cranial nerve produces anisocoria (unequal pupil size), a “down and out” strabismus, loss of accommodation, and eye movement deficits with diplopia (double vision). In addition, there is a ptosis (drooping) of the eyelid. The following animations simulate these deficits (except ptosis).

This movie simulates the movement deficits following a “complete” left III nerve lesion. The resting position of the involved eye is down and out. The eyelid may partially cover the upper iris and typically has to be manually elevated to do these tests (not shown). The pupil is dilated due to loss of parasympathetic third nerve axons. During the tracking portion of the exam “follow the pencil,” a simulation of double-vision that the individual may experience is illustrated by a blue-green “ghost” image displaced to the left of the actual tan-colored image. Note that the diplopia is worse as the person looks up and to their right, and least as the involved eye assumes the resting position. Diplopia is inferred from the reports of the individual which may be difficult to quantify.

An abducens opthalmoplegia results from a lesion of the abducens nucleus in the brainstem or from a lesion of cranial nerve VI (lower motor neuron lesion). A complete lesion of the sixth cranial nerve produces a medial strabismus, and eye movement deficits with diplopia (double vision). The affected eye cannot be moved laterally due to the loss of the lateral rectus extraocular muscle. The diplopia is worse when the individual looks toward the side of the muscle weakness.

The movie simulates the movement deficits following a “complete” left VI nerve lesion. The resting position of the involved eye is medially deviated (medial strabismus). The involved left eye does not move laterally when the individual is asked to look to the left. During the tracking portion of the exam “follow the pencil,” a simulation of double-vision that the individual may experience is illustrated by a blue-green “ghost” image displaced to the left of the actual tan-colored image. Note that the diplopia is worse as the person looks to their left and the left eye cannot move laterally. Double vision is least obvious as they look toward the right. The diplopia is inferred from the reports of the individual which may be difficult to quantify. Many times the diplopia becomes less

apparent to the individual as they compensate for the eye movement deficits; the individual suppresses the distracting visual information from the affected eye.

INTERNUCLEAR OPTHALMOPLEGIA: MEDIAL LONGITUDINAL FASCICULUS LESION

A lesion of the ascending medial longitudinal fasciculus (MLF) results in a dysfunction of horizontal conjugate gaze known as Internuclear Opthalmoplegia (INO). The normal precise coupling of right and left eye movements is lost and abnormal "oscillations" appear as nystagmus. This animation shows the effect of a left MLF lesion. The left eye cannot adduct beyond midline during horizontal conjugate gaze to the right and the abducting right eye shows nystagmus. Gaze to the left is normal as are vertical conjugate eye movements with the eyes in a midline position. INO could mimic a paralysis of the medial rectus extraocular muscle, but a normal accommodation test rules out that possibility. Accommodation: when the eyes converge upon a near object both eyes adduct and a normal reflexive pupillary constriction occurs in both eyes. A lesion of the MLF is a common deficit in Multiple Sclerosis (MS). The MLF contains heavily myelinated axons that are likely targets for the demyelinating process that is a hallmark of MS. MS often produces a bilateral INO.

PUPILLARY LIGHT REFLEX

The pupillary light reflex uses a relatively simple reflex arc.

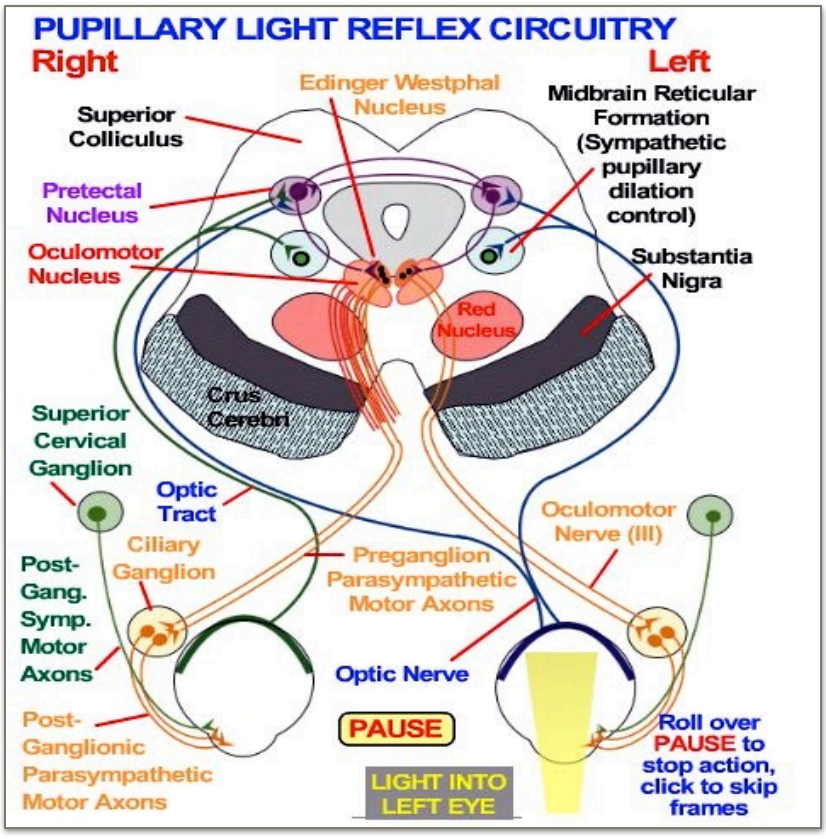

Fig 12-16. Pupillary Light Reflex Circuitry. Interactive Media file (gec). GO TO: gmomm.pitt.edu

Fig12-16_Interactive Media

Retinal ganglion cell axons from both eyes synapse on neurons in the Pretectal Nucleus in the midbrain tectum (superior colliculus). The Pretectal Nucleus projects to the Edinger Westphal (EDW) Nucleus. The EDW nucleus contains preganglionic parasympathetic motoneurons that project their axons by way of the

oculomotor nerve (III) to the Ciliary Ganglion in the orbit of the eye to synapse on postganglionic parasympathetic motoneurons. These postganglionic motoneurons innervate smooth muscle in the eye that constrict the iris. Other autonomic axons innervate smooth muscle in the ciliary body that changes the shape of the lens for near or far vision (accommodation). Light into one eye normally produces both a direct (stimulated eye) and a consensual (unstimulated eye) response. As illustrated here, shining light into the left eye sends input into both pretectal nuclei. The pretectal nucleus activates the EDW on the same side; output goes to both ciliary ganglia. Thus, the pupils of both eyes constrict. The bilateral nature of this reflex is further facilitated by the reciprocal connections between the two pretectal nuclei. See Pupillary Light Reflex Circuitry Interactive Flash File to see the circuit in action.

A compilation of three movies is presented in the Normal and Abnormal Pupillary Light Reflex Movie. The first of three movies below illustrates the normal pupillary light reflex. The second movie shows deficits due to a cranial nerve III lesion involving the parasympathetic innervation of the eye. Light into the uninvolved right eye produces a direct but no consensual response. Light into the involved (left) eye produces no direct response but a normal consensual response occurs in the uninvolved right eye.

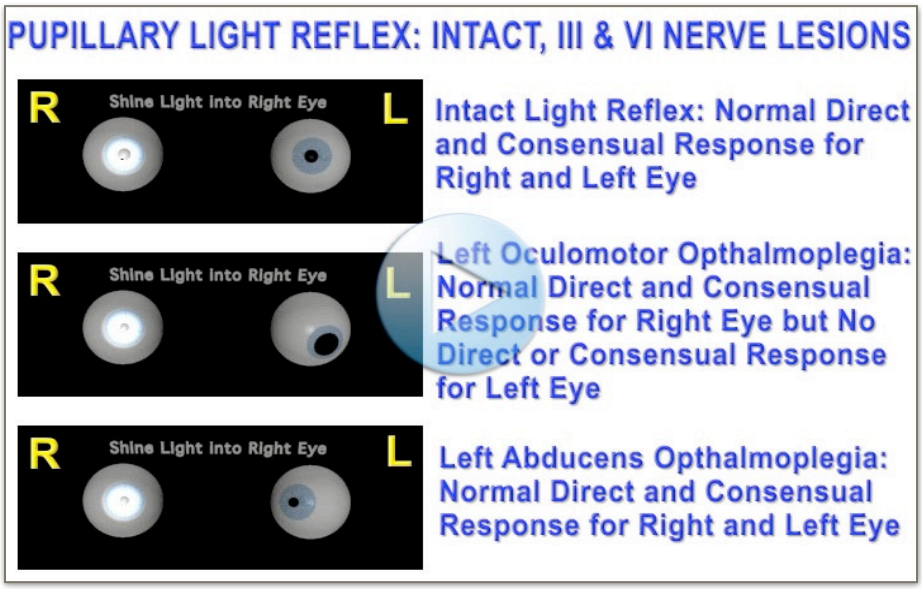

Fig 12-17. Normal and Abnormal Pupillary Light Reflex Movie (gec). GO TO: gmomm.pitt.edu
Fig12-17_Video

The third movie illustrates the normal direct and consensual pupillary light reflex in both eyes in an individual with an abducens nerve lesion. The normal light reflex indicates no involvement of cranial nerve III parasympathetic innervation of the eye.

VISUAL PATHWAY: RETINA TO LATERAL GENICULATE NUCLEUS TO STRIATE CORTEX

The visual pathway includes the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus (LGN) of the thalamus, optic radiations, and the primary visual cortex (striate cortex) located along the banks of the calcarine sulcus in the occipital lobe. Each eye “sees” both a nasal and a temporal visual field. The portion of the retina

that responds will be inverted due to the lens. Thus the temporal visual field is projected to the nasal retina and vice-versa. The most lateral aspect of the temporal visual field is monocular (seen by the ipsilateral eye only) shown here as the lateral crescents labeled (M). Otherwise, both nasal & temporal fields are seen by both eyes (binocular). The superior aspect of the visual fields are projected onto the inferior retina. The inferior retina projects to the striate cortex inferior to the calcarine sulcus by way of optic radiations within Meyer's Loop. Meyer's Loop is found in the temporal lobe. The superior optic radiations travel beneath the parietal lobe to the striate cortex.

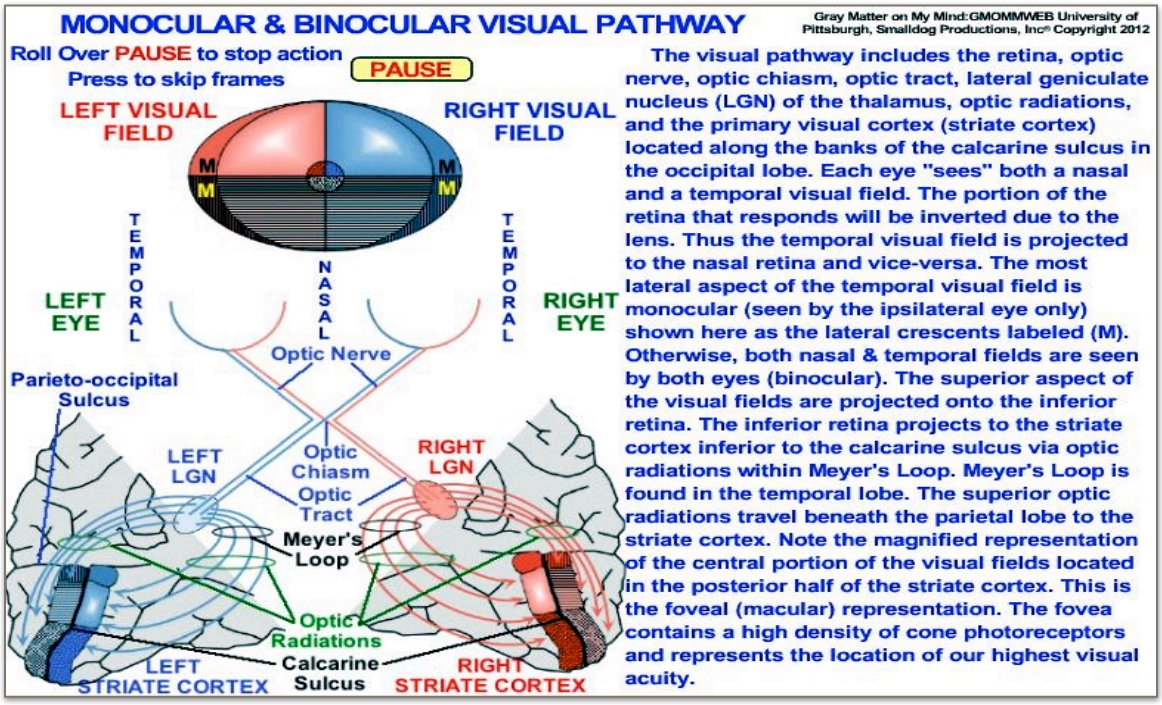

Fig 12-18. Visual Pathway from retina to striate cortex: binocular and monocular visual field retinotopic representation: Interactive Media File (gec). GO TO: gmomm.pitt.edu
Fig12-18_Interactive Media

Note the magnified representation of the central portion of the visual fields located in the posterior half of the striate cortex. This is the foveal (macular) representation. The fovea contains a high density of cone photoreceptors and represents the location of our highest visual acuity.

Retinal Ganglion Cells are projection neurons that send their myelinated axons into the optic nerve. Some of these axons will cross to form the contralateral optic tract. Others do not cross and form the ipsilateral optic tract. Optic tract axons synapse on cells in the LGN. There are 6 layers in this laminated thalamic nucleus separated by Intercalated laminae (I). Each of the six laminae receives P or M Pathway inputs from either the ipsilateral or the contralateral eye. The Intercalated laminae receive color

inputs from the retina. The Optic Tract contains Retinal Ganglion Cell Axons from both eyes (ipsilateral from the temporal hemiretina and crossed axons from the contralateral nasal hemiretina). Axons cross in the Optic Chiasm. Each eye 'sees' both a nasal and a temporal visual field. The fovea contains a high density of cone photoreceptors and represents the location of our highest visual acuity.

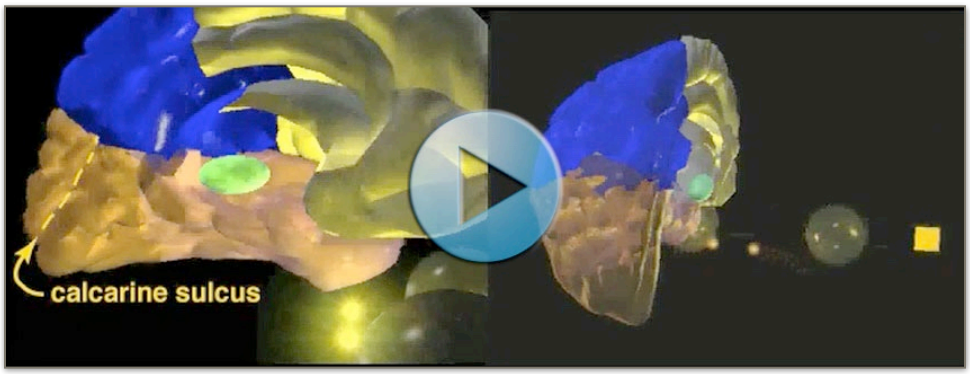

Fig 12-19. Visual Field Movie: two views of information flow. Note: You may have difficulty watching both movies together. Saccadic eye movements that shift attention from side to side may be distractive. Use a piece of paper to cover either the right or left scene to reduce this conflict. Attention tends to be limited due to a "winner take all" mechanism (gec). GO TO: gmomm.pitt.edu *Fig12-19_Video*

The dual scene movie shown above illustrates the visual pathway from the retina of each eye to the contralateral lateral geniculate nucleus (LGN = light green oblong sphere) and from the LGN to the appropriate retinotopic location for the map of visual space in the striate cortex. The cerebellum, brainstem, and right cerebral hemisphere have been removed so you can see the pathway within the left hemisphere for the right visual hemifield. Note input to both eyes from different locations within the binocular zone of vision. Except for the last stimulus presentation, all stimuli are presented in the right half of the visual world. The superior quadrant projects to the striate cortex inferior to the calcarine sulcus (lingual gyrus) while the inferior quadrant projects to the cuneus located above the calcarine sulcus. Note that the peripheral aspect of visual space is represented in the anterior portion of the primary visual cortex (VI), and as the stimuli approach the central, foveal region the input travels to the posterior striate cortex (occipital pole). The last stimulus is positioned in the left visual hemifield; information from both eyes travels to the right LGN and the geniculocalcarine projection to the striate cortex travels off screen (to right VI). The right side view shows input to the eyes from a posterolateral view. The left scene shows information as it proceeds from the retinas to the LGN to the striate (VI) cortex.

VISUAL PATHWAY LESIONS: DEFINED VISUAL FIELD DEFICITS

A lesion at different locations along the visual pathway from retina to optic nerve to optic chiasm to optic tract to optic radiations results in characteristic defects in the visual

field. The portion of the visual world that is involved in each lesion illustrates the monocular and binocular representations that project back through these pathways to the visual cortex. The following Interactive Flash File allows you to “visualize” each of five visual field defects associated with a virtual lesion in 1.) Optic Nerve, 2.) Optic Chiasm, 3.) Optic Tract, 4. Meyer’s Loop in the Optic Radiations (Geniculocalcarine Tract) and 5.) Central Scotoma (Macula of the Retina). Play the Interactive Flash File.

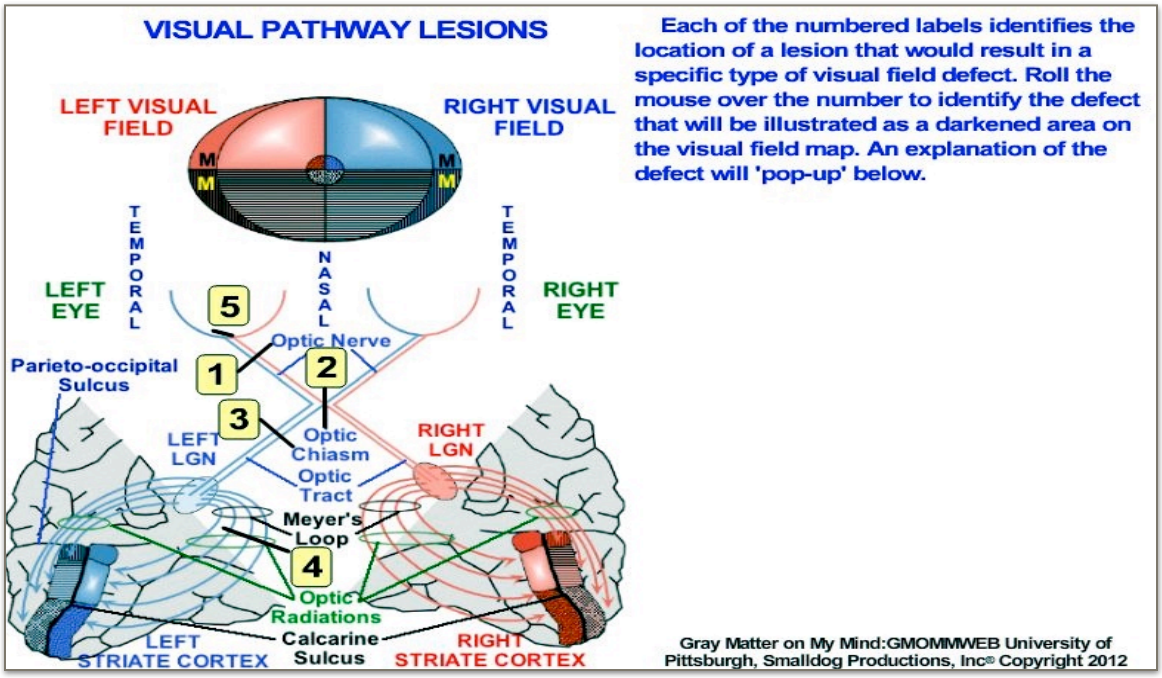

Fig 12-20. Visual Field Deficits Interactive Media File: 5 Visual Pathway Virtual Lesions (gec). GO TO: gmomm.pitt.edu *Fig12-20_Interactive Media*

THALAMIC LATERAL GENICULATE NUCLEUS (LGN) & STRIATE CORTEX (PRIMARY VISUAL CORTEX)

The Lateral Geniculate Nucleus (LGN) receives retinal ganglion cell input from both eyes: Contralateral = Laminae 1, 4, 6 & Ipsilateral = 2, 3, 5.

The input from each eye is segregated at this level of the visual pathway (LGN neurons have monocular receptive fields). There are a number of cell types located in the LGN: I = Intralaminar Laminae of LGN (I Pathway), M = Magnocellular Laminae (1&2) of LGN (M Pathway) and P = Parvocellular Laminae (3-6) of LGN (P Pathway). LGN is a first order thalamic nucleus containing primarily core thalamic neurons.

LGN input monosynaptically excites cells in layers III, IV & VI of the striate cortex. Input is segregated by eye (see Ocular Dominance Columns; actual geometry is more irregular). Neurons in the striate cortex include simple and complex cells as well as

other physiologically classified cells. Layer IV contains spiny stellate excitatory interneurons and smooth stellate cells plus other inhibitory interneurons.

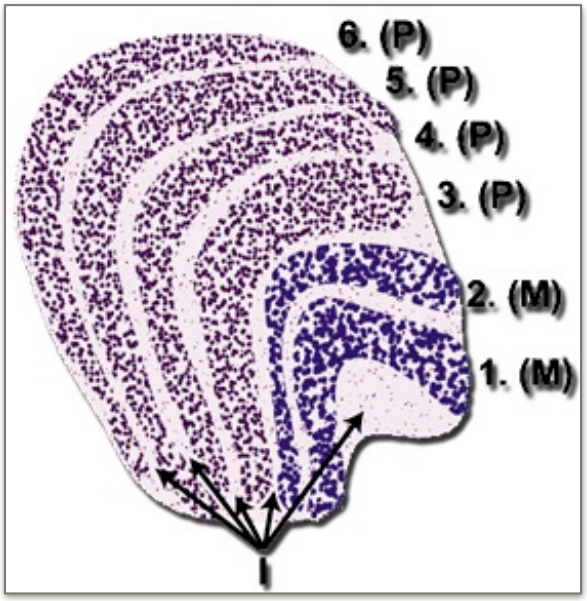

Fig 12-21. Laminae of the Thalamic Lateral Geniculate Nucleus: I = Intralaminar (Koniocellular), M = Magnocellular, P = Parvocellular (gec).

Interneurons influence one another and pyramidal projection cells in supra- and infra-granular layers. Circuitry within the Striate Cortex transforms Circular Center-Surround Receptive Fields (RFs) of LGN Inputs to RFs that respond to oriented bars of light (Note different bar orientations represented here as Orientation Columns). Orientation Columns extend across all ocular dominance columns. The actual geometry is thought to be a pinwheel where orientation specific regions form rays "emerging" from a singularity spot. The geometric arrangement of the pinwheels is complex and likely to be different for each visual cortex possessing such pinwheels.

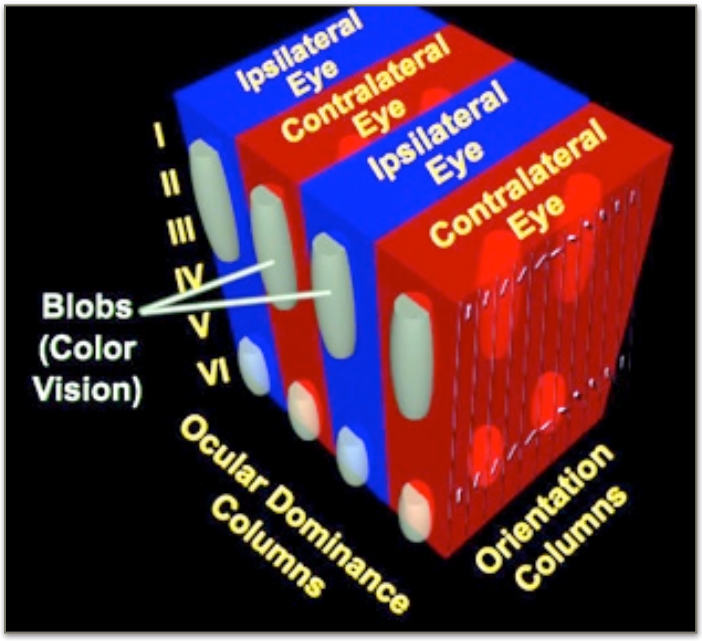

Fig 12-22. Striate Cortex Hypercolumn "Cube" (gec).

Output to other visual areas (Extrastriate Visual Areas) comes primarily from supragranular (layers II & III) Pyramidal Neurons. Output to subcortical structures come from projection cells in infragranular layers (layers V & VI). Blobs in Supragranular Cortex are associated with Color Vision.

STRIATE CORTEX MONOCULAR & BINOCULAR VISUAL FIELD REPRESENTATION

The striate cortex is the primary visual cortex (VI, Brodmann Area 17). The striate cortex of each hemisphere sees only the contralateral half of the visual field through uncrossed inputs from the ipsilateral eye and crossed inputs from the contralateral eye.

Right eye and left eye inputs are segregated in the lateral geniculate nucleus (LGN) and in many layer 4 striate cortex cells that receive monosynaptic LGN inputs. Supragranular and infragranular cells of the striate cortex have binocular interactions. The lens inverts the image horizontally and vertically. Images are focused on the retina of both eyes (binocular zone) except if the image is limited to the far peripheral field of vision (monocular zone = yellow). The monocular peripheral field of view is "seen" by the nasal hemiretina of only one eye. This information is carried to the contralateral hemisphere via retinal ganglion cell axons that cross in the optic chiasm. Information from the binocular zones may be crossed or uncrossed. Note the small central (foveal) representation in the visual field (green) that is much expanded in its representation in the striate cortex (green). This distorted foveal representation is an example of CORTICAL MAGNIFICATION in cerebral representation of high acuity receptors.

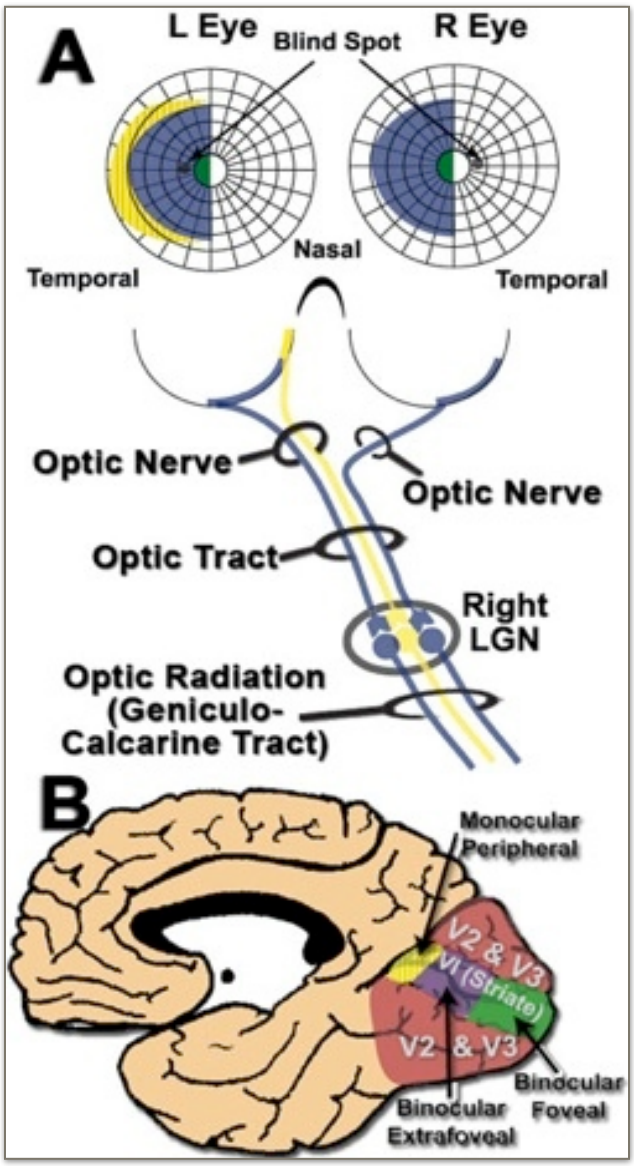

Fig 12-23. A. Primary Visual (VI-Striate) Cortex Monocular and Binocular Visual Pathway Projections Primary Visual (VI-Striate) Cortex. B. Monocular and Binocular Representations of the Contralateral Visual Hemifield (gec).

PRIMARY VISUAL (STRIATE) CORTEX: BRODMANN AREA 17

LGN input monosynaptically excites cells in layers 3 and 4 of the striate cortex. This input is segregated by eye. Neurons in the striate cortex include simple and complex cells as well as other physiologically classified cells. Layer 4 contains spiny stellate excitatory interneurons and smooth stellate inhibitory interneurons. Layer IV is subdivided into 4A, 4B, 4C Alpha and 4C Beta. Different laminae in the LGN have separate targets in Striate Cortex. The Intralaminar Koniocellular LGN cells project to layer III blobs (color vision). Parvocellular LGN cells project to the superficial and deeper sub laminae in the granular layer 4A, 4C Beta). Magnocellular LGN cells project to the middle (4C Alpha) portion of the granular layer.

Striate cortex Interneurons influence one another and Pyramidal projection cells in supragranular and infragranular layers. Output to other visual areas (extrastriate visual areas) comes primarily from supragranular (layers 2 & 3) Pyramidal neurons. Output to subcortical structures come from projection cells (Pyramidal Cells) in infragranular layers (layers 5 & 6).

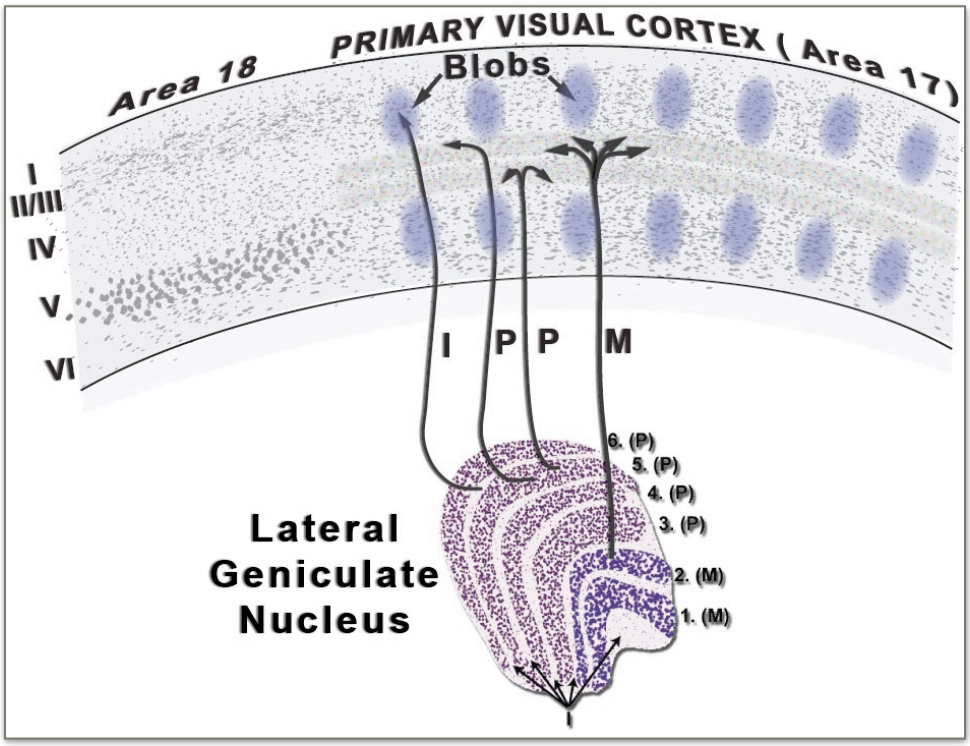

Fig 12-24. Thalamocortical projections from Lateral Geniculate Nucleus to Striate Cortex. I = Intra-laminar (Konio-cellular), M = Magnocellular, P = Parvocellular (gec).

VISUAL SYSTEM: BUILD ORIENTED BARS FROM CIRCLES

Unlike retinal ganglion cells and LGN neurons, most V1 neurons respond poorly to spots of light. The form of visual stimuli that are optimally excitatory for a class of neurons called simple cells (pyramidal cells) is a bar of light oriented in a specific manner. Simple cells may be found in a portion of layer IV or perhaps in layer III.

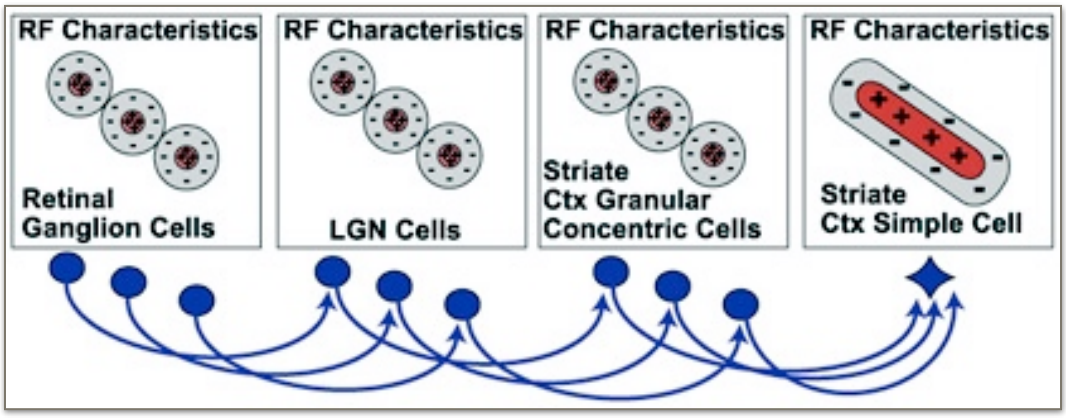

Fig 12-25. The flow of information from Retina to Simple Cell in Striate Cortex. A classic view of Convergence of Circular Center-Surround Receptive Fields to Form Receptive Fields responsive to Oriented Bars of Light in Brodmann Area 17 (gec).

David Hubel and Torsten Wiesel in the 1960s hypothesized that simple cells get their Receptive Field (RF) property by convergence of LGN inputs representing different retinal locations. Concentric Center Surround RFs are characteristic of Retinal Ganglion Cells, LGN Cells and Granular Layer Striate Cortex Concentric (Spiny Stellate) Cells that receive monosynaptic LGN inputs. More recent models include more complex circuitry to build orientation columns including influences of inhibitory interneurons. Layer IV concentric cells and many simple cells have monocular receptive fields.

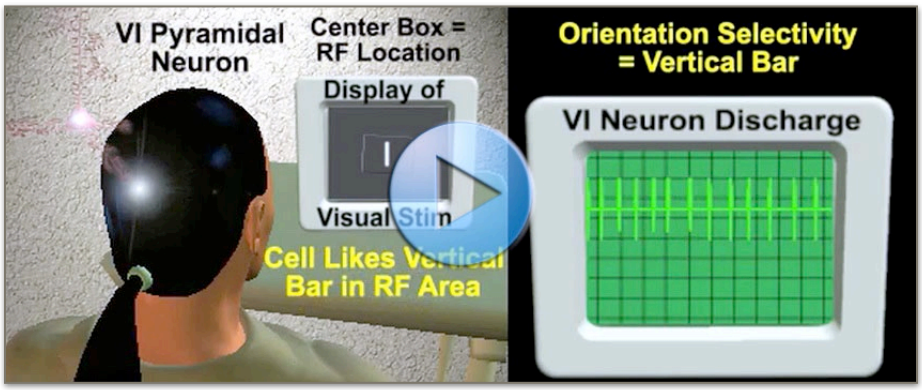

Fig 12-26. Orientation Selective Simple Cell in VI Movie (gec). GO TO: gmomm.pitt.edu *Fig12-26_Video*

Movie shows simulated extracellular recording from an orientation selective pyramidal cell in V1. Unlike Retinal Ganglion Cells, and LGN Neurons, Striate Simple Cells are unresponsive to a spot of light within its Receptive Field (RF). This cell responds vigorously to a bar of light when it is oriented vertically. It is less responsive or unresponsive to other bar orientations in its RF. A vertical bar outside the cell's traditional RF is ineffective.

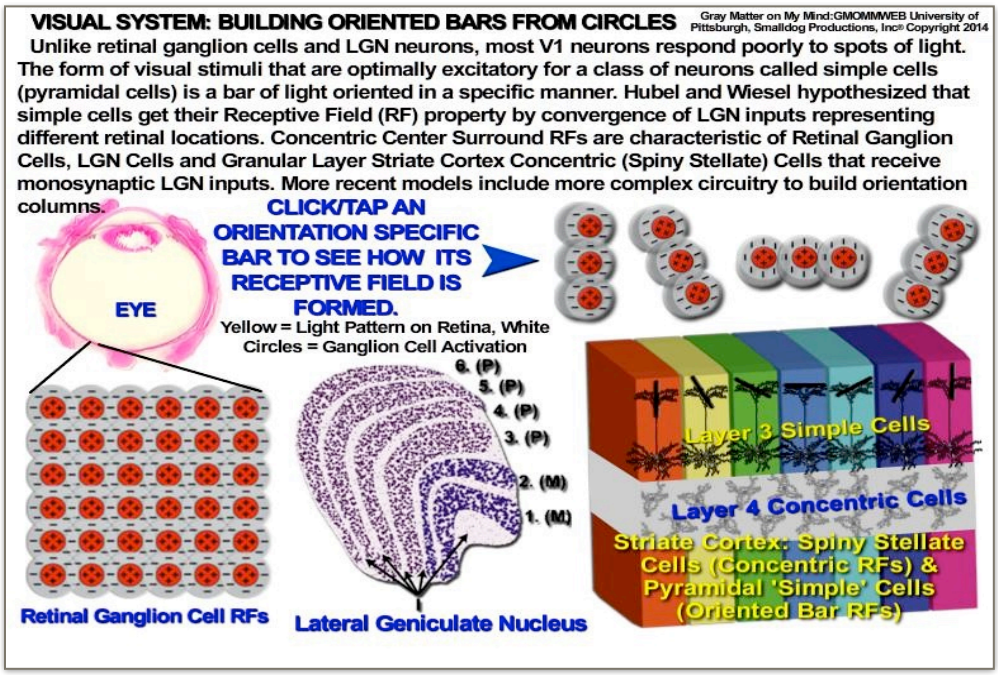

Fig 12-27. Building Oriented Bars of Light in VI Simple Cells from Concentric Circular Receptive Fields Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig12-27_InterActive Media*

The “Visual Cortex: Building Oriented Bars from Spots of Light” provides a virtual experimental platform which “builds” oriented bars from concentric circular receptive fields. The actual geometry of the orientation columns may not be parallel columns as illustrated above but orientation modules arranged in a pinwheel geometry in primate striate cortex. Multiple Pinwheels form complex geometric patterns across the full extent of the striate cortex. The Orientation Specificity Pinwheel Movie simulation illustrates the pinwheel geometry as morphed from the classic parallel columnar pattern (see Blasdel, 1992a,b, Angelucci, et.al., 2002 and Horton & Adams, 2005 references).

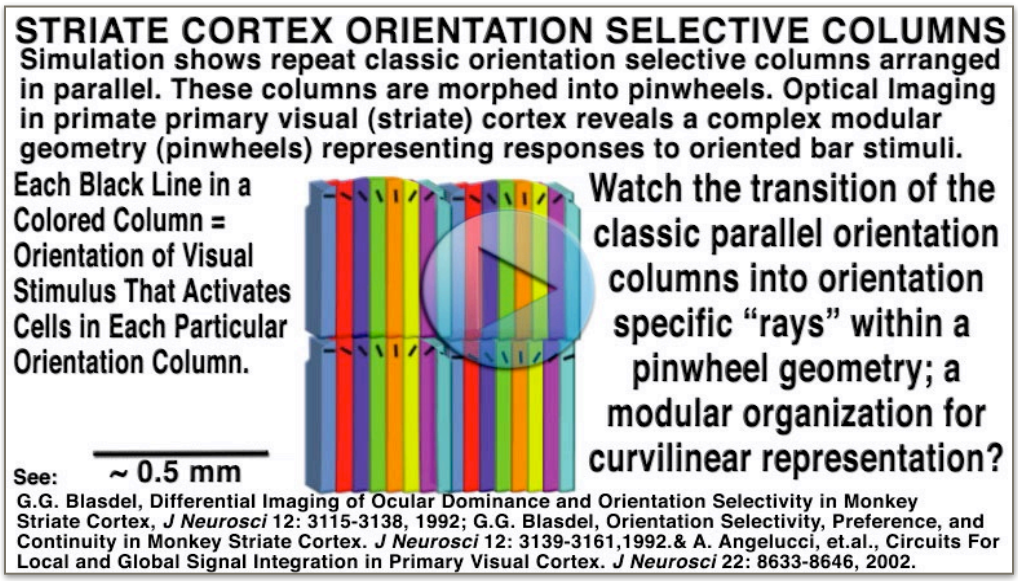

Fig 12-28. Orientation Specificity Pinwheel Movie (gec). GO TO: gmomm.pitt.edu Fig12-28_Video

It is not clear what advantage is gained by such a “radial” geometric pattern. One highly speculative suggestion for a benefit of a radial organization is included in the Orientation Specificity Pinwheel Movie. A line or arc may have color if the pinwheel singularity is co-localized with a blob.

VISUAL SYSTEM: BUILDING INTERCOLUMNAR CONNECTIONS: EXPERIENCE-DEPENDENT HORIZONTAL CONNECTIVITY OF VI ORIENTATION COLUMNS

Horizontal connections provide one mechanism to integrate information across different portions of retinal space. For example, orientation-tuned pyramidal cells in supragranular striate cortex have axon collaterals that travel within the confines of the striate cortex to link like orientation columns. This results in a patchy distribution of axon terminations that if labeled would appear as constrained labeling across supragranular striate cortex. These patches would be in register with 2-deoxyglucose (2-DG) metabolic labeling obtained when a monkey views a repeated pattern of stripes all oriented in the same direction (horizontal bars for this example). Such stimuli would produce the greatest 2-DG labeling in the middle light blue orientation columns shown here. Striate cortex is a mosaic of patchy neural ensembles that provide the basic building blocks of our visual world.

These ensembles share information with extrastriate visual areas and with subcortical structures that provide sensorimotor integration of eye and head movements to direct the visual apparatus to objects of interest in our world. A second animation illustrates the importance of experience in fine-tuning orientation selectivity and in the development of normal modular horizontal connections.

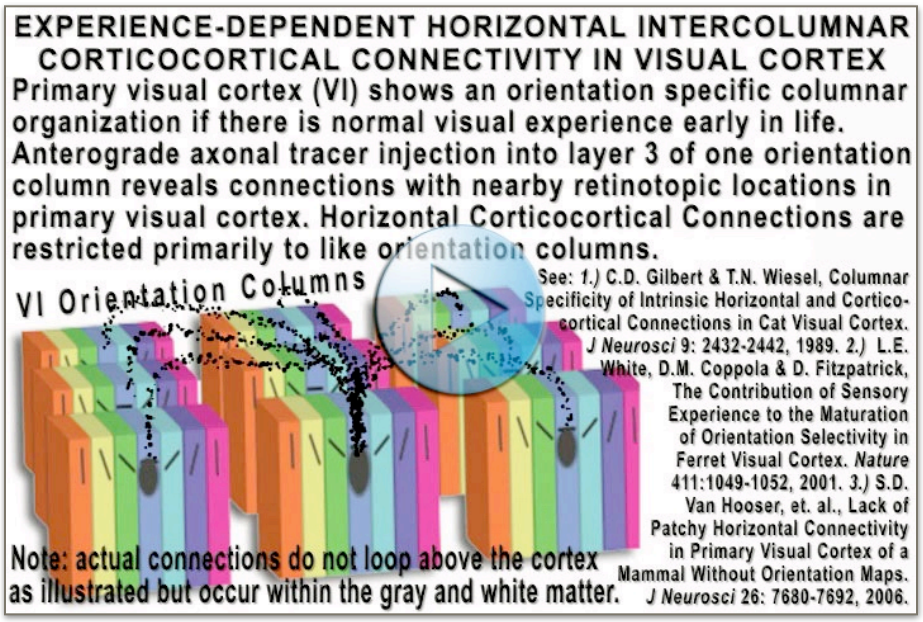

Fig 12-29. Horizontal Connections of Orientation Columns in Visual Cortex. Effects of Normal versus Deprived Early Visual Experience (gec). GO TO: gmomm.pitt.edu [Fig12-29_Video]

The first animation illustrates the spread of horizontal axonal labeling following injection of an axonal tracer in the physiologically defined horizontal oriented column (middle light blue). Note that only like oriented columns are connected as illustrated here by the spread of tracer. The actual axonal connections do not “rise above the cortex” as illustrated here but do travel as axon collaterals for short distances within the gray matter and as longer axonal branches that travel to more distant areas of the striate and extrastriate cortex by way of the white matter (not shown here). The gray spots, which would be found in all horizontal-orientation columns, represent the concentration of 2-DG label and transported label in horizontal oriented columns (middle light blue) within nearby hypercolumns (cubes) of striate cortex. This pattern of specific connectivity and well-defined orientation tuning emerges in the postnatal animal as they mature with normal binocular visual experience. Visual deprivation early in life has profound effects on the anatomy & physiology of these microcircuits.

The second animation illustrates the abnormal horizontal connectivity of poorly tuned orientation columns in striate cortex if the animal had abnormal visual experience early in life. Such binocular deprivation could result from bilateral cataracts or poor binocularity due to a “lazy eye.” Orientation columns show poor tuning (shown as “crows feet” orientation tuning on overlapping orientation columns in the hypercolumn cubes). Actual axonal connections do not “rise above the cortex” as illustrated here but do travel as axon collaterals for short distances within the gray matter and as longer axonal branches that travel to more distant areas of the striate and extrastriate cortex by way of

the white matter (not shown here). The expanded gray spots, would be found in few broadly horizontal+orientation columns; they represent the overlap of 2-DG label and transported label in horizontal+ oriented columns (middle light blue) within only a few hypercolumns (cubes) of striate cortex. Normal visual experience early in life appears to be important for development of normal directional selectivity of simple & complex cells.

COMPLEX CELLS: ORIENTATION AND DIRECTIONAL SELECTIVITY FOR MOVING BARS OF LIGHT

D. Hubel and T. Wiesel described a second class of neurons in the striate cortex called the complex cell. Complex cells respond to oriented objects that move across the cell's RF in a specific direction; RFs tend to be larger than those of simple cells and are sometimes called rectilinear shapes of light. Complex cells are very receptive to edges oriented in a specific orientation and for many complex cells the stimulus must be moving into the cell's RF from a specific direction.

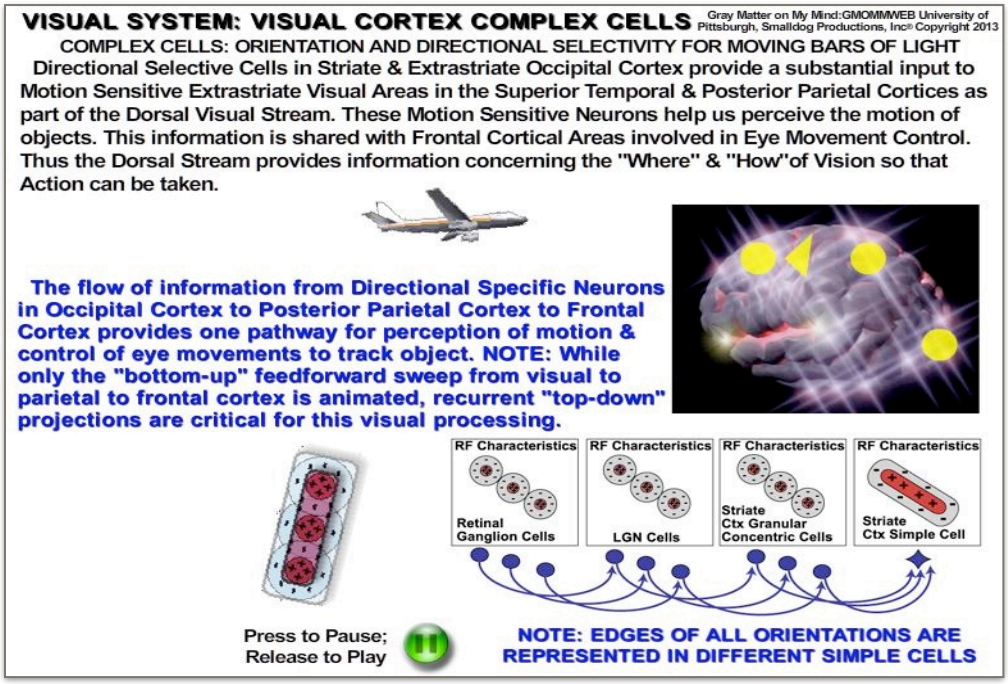

Fig 12-30. Complex Cells: Orientation and Direction Specific Cells- Cues for objects moving in visual receptive fields. Interactive Media File (gec). GO TO: gmomm.pitt.edu

Fig 12-30 Interactive Media

Hubel and Wiesel suggested that complex cells acquire their RF properties due to convergent input from appropriate simple cells. Most complex cells have binocular receptive fields. Although Hubel and Wiesel's original model is built on convergent excitatory connectivity, more recent studies show that inhibitory interneurons are critically involved in shaping RF properties of most visual cortex neurons. Shapes and edges in motion provide cues regarding form, location and motion of objects in our field of view.

Directional Selective Cells in Striate & Extrastriate Occipital Cortex provide a substantial input to Motion Sensitive Extrastriate Visual Areas in the Superior Temporal & Posterior Parietal Cortices as part of the Dorsal Visual Stream. These Motion Sensitive Neurons help us perceive the motion of objects. This information is shared with Frontal Cortical Areas involved in Eye Movement Control. Thus the Dorsal Stream provides information concerning the "Where" and "How" of Vision so that Action can be taken. The flow of information from Directional Selective Neurons in Occipital Cortex to Posterior Parietal Cortex to Frontal Cortex provides one pathway for perception of motion & control of eye movements to track object.

The complex cell movie shows simulated extracellular recording from a directionally selective pyramidal cell in V1. This particular cell responds weakly to a vertically oriented stationary bar of light. It is most responsive when the vertical bar is moving in a particular direction across its Receptive Field (RF). It is less responsive to motion in the opposite direction or to other bar orientations moving in its RF. This cell likes left to right but not right to left motion of the light bar. Complex cells are typically binocular and found in both supragranular and infragranular layers but not in the granular layer of V1.

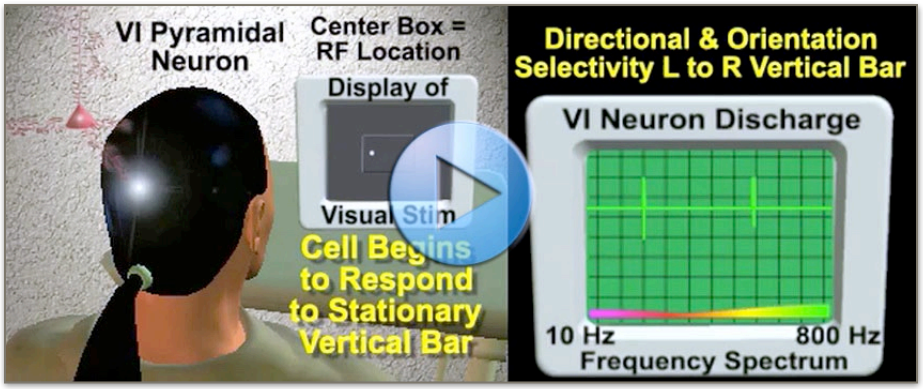

Fig 12-31. Orientation and Direction Selective Complex Cell in Striate Cortex Movie (gec). GO TO: gmomm.pitt.edu *Fig12-31_Video*

VISUAL DEPTH PERCEPTION

Depth perception uses both monocular and binocular cues to provide our Z-axis information. Binocular cues are coded by binocular disparity cells in the visual cortex that are activated when the image is focused on slightly disparate portions of the two retinas (3D movies take advantage of this disparity). While there may be few binocular disparity neurons in the striate cortex there are many in extrastriate visual cortex, e.g., area 18. Stationary monocular cues depend on visual illusions produced by positions of one object compared to another (shadows, occlusion, linear perspective: artists are masters at reproducing these features in their art) and learned information (by you or perhaps by your distant ancestors) about object size, hue and morphology. Motion cues provide illusory motion of near vs. far objects that are opposite one another relative to the object in focus. Optic flow provides an important mechanism for depth perception. Middle Temporal (MT), Medial Superior Temporal (MST) & Intraparietal (IP) extrastriate visual cortex neurons are important in motion detection and perhaps depth perception.

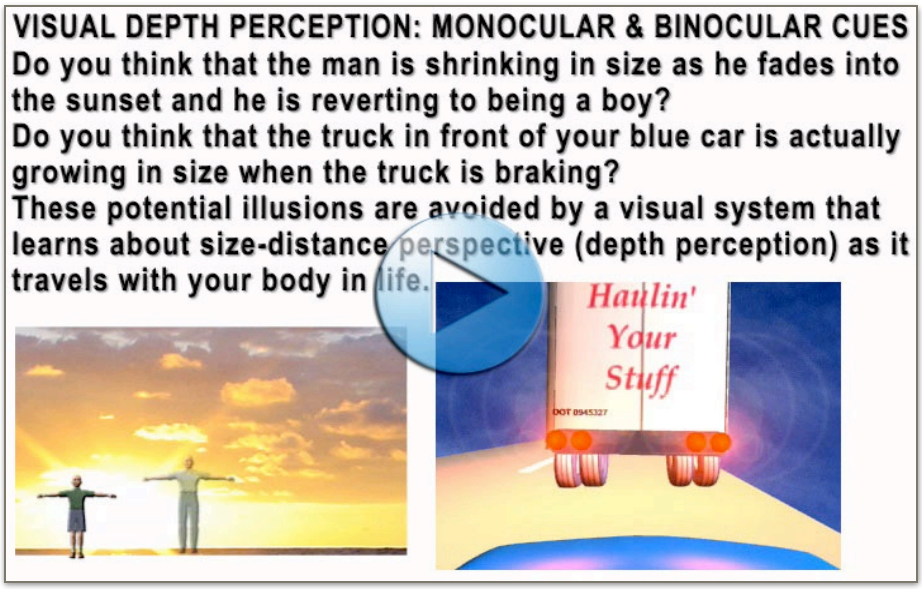

Fig 12-32. Visual Depth Perception Using Monocular/ Binocular Cues Movie (gec). GO TO: gmomm.pitt.edu
Fig12-32_Video

THERE'S MORE TO VISION THAN MEETS THE EYE: "TOP-DOWN" CENTRAL BIAS FOR WHAT WE SEE

If you ask a young child how she sees, she will point to her eyes. However, it does not take long for a child with insight to discover the mind's eye. Dreams may contain vivid images that persist upon waking; characters & scenes are "seen" even if words in one's favorite book are the only point of reference. Although many psychologists have long conceptualized context- and state-dependent neuronal activity even in the earliest stages of visual processing, only recently have single cell visual cortex recordings & brain imaging in awake subjects confirmed some of these hypotheses. Not only peripheral retinal input influences receptive fields of VI neurons, but also central input from extrastriate cortical areas reciprocally connected with VI. Early neurophysiological studies of vision suggested that many visual association area neurons (extrastriate visual) are state- and context-dependent.

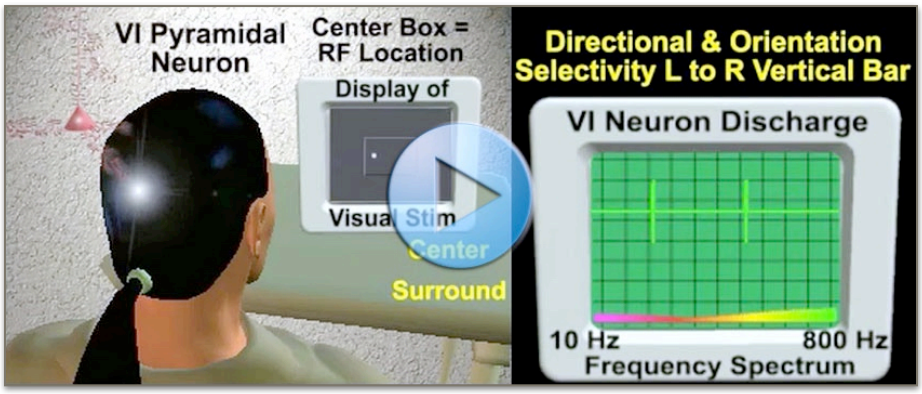

Fig 12-33. Top-Down Influences on Bottom-Up Visual Input. Complex Visual Scene Movie (gec). GO TO: gmomm.pitt.edu
Fig12-33_Video

Only recently have such processes been confirmed for some VI neurons (striate cortex). Most visual areas & many frontal areas are active within 150 ms following visual input. Since conscious reaction time latencies come later, preconscious cortical processing contributes to initial visual responses. Top-

down & bottom-up interactions influence what we see. It appears that a simple serial circuit is inadequate to explain the neural basis for vision. Our fast Dorsal Visual Stream may direct our eyes to a moving object before our slower Ventral Stream can consciously perceive what it is. Our previous experience may influence our perceptions.

The Top-Down Influences on Bottom-Up Visual Input movie shows the effect of a moving background that surrounds the traditional (center box) receptive field of an orientation & direction selective visual cortex neuron. Note a differential effect of a background moving in the same vs. opposite direction to the motion of the center bar of light. Such influences appear to have a central (brain) rather than a peripheral (retinal) origin.

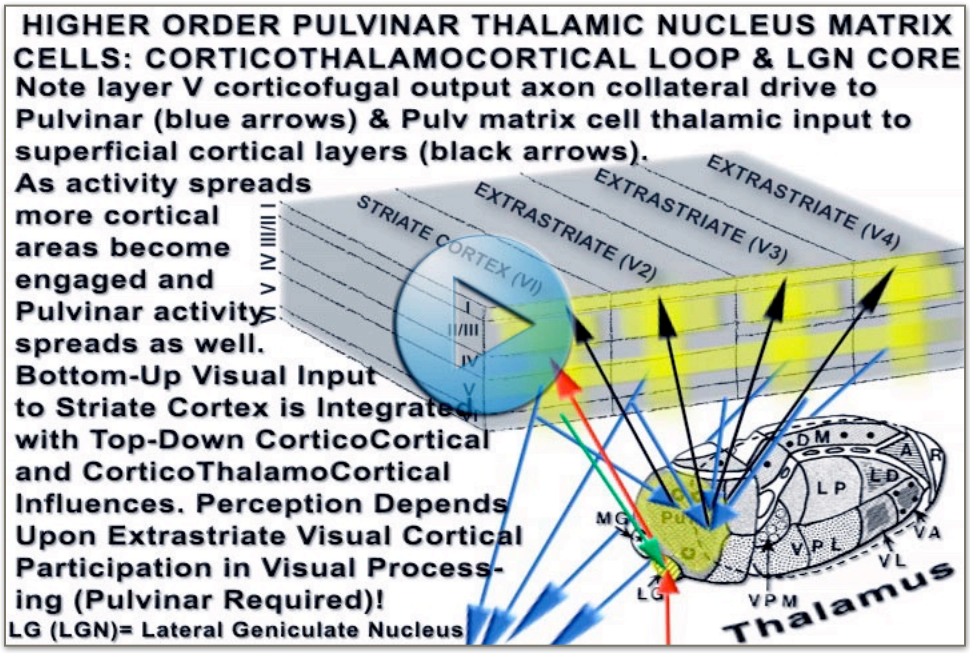

Fig 12-34. Pulvinar "Top-Down" CorticoThalamo-Cortical Influences on "Bottom-Up" LGN Inputs to VI plus Influences on Extrastriate Visual Cortex Movie(gec). GO TO: gmomm.pitt.edu Fig12-34 Video

A recent study shows the importance of higher order Pulvinar thalamic nucleus to response properties of Primary Visual Cortex neurons (see Pulvinar "Top-Down" Corticothalamocortical Influences on "Bottom-Up" LGN Inputs to VI plus Influences on Extrastriate Visual Cortex Movie). Inactivation of even a small portion of the Pulvinar that projects to VI substantially reduces responses in upper layer neurons to peripheral visual inputs. The Pulvinar contains many matrix cells that are driven not by the optic tract but by layer V corticofugal axon collaterals from visual cortex and perhaps from superior colliculus afferents. These matrix cells project to broad regions of VI and V2 superficial cortex (layers 1, 2, and perhaps upper layer 3). Thus these "top-down" excitatory influences incorporated into a corticothalamocortical (CTC) loop have a significant influence on bottom-up signals originating in the retina. The movie illustrates the potential influence of this CTC loop and the hypothesized effect of inactivating visual portions of the large pulvinar nucleus of the thalamus (See Purushothaman, et.al., 2012 and Snow, et.al., 2009 references). Depending upon our intent, top-down influences may precede the

bottom-up retinal signals. Thus, our brain may prepare our sensory cortex for future signals originating in the periphery. Classic visual receptive fields may undergo complex modulation depending upon intrinsic brain state and intentional context as we look at our world related to what we expect to perceive and how we would like to act within visual space. Hollywood takes full advantage of our brain expectations that influence our senses.

Our visual perceptions are influenced by both bottom-up images originating from the retina and by "top-down" influences of attentive processes. Some vision scientists suggest that the two influences are in a dueling match in a winner-take-all battle for our conscious visual perceptions. Since we can move our eyes (and our heads) it is not difficult to imagine the brain guiding the selection of our visual inputs. Neuroscientists believe that our ability to attend to our world is limited in space (we cannot attend to details of all that reaches the retina at any one time). However, we are capable of rapidly shifting our attention from one thing to another and thus, time permitting, we may take in the details from all parts of a scene if we put our mind to it. Of course some things are more deserving of our attention than others and we tend to dwell on what is interesting and/or critical to our well-being (saliency). One popular hypothesis states that our conscious brain uses a spotlight of attention to garner necessary resources to enhance our perceptions for stimuli within the spotlight. We may shift our sweep of the spotlight within visual 'scenes'. One theory suggests involvement of a corticothalamocortical loop and a transient "binding" of activity among connected cells is the mechanism for "the guiding light." What we perceive is not the same as what we see, since preconscious (non-conscious) images may provoke action prior to or without conscious awareness of the event.

A recent study in mice provides compelling evidence that the medial prefrontal cortex and in particular GABAergic interneurons (presumed basket cells) are critical for attention. This study illustrates the critical role of GABA cells in the binding of pyramidal cell firing in the gamma band oscillatory pattern associated with attention leading to correct behavioral choices: see Kim. et.al., 2016. Visual cortex has significant GABAergic synapses on corticocortical Pyramidal cells, e.g., see Freund, et.al. 1983.

MAY I HAVE YOUR UNDIVIDED ATTENTION, PLEASE!

Three movies in the following flash file illustrate the spotlight of attention.

Watch MOVIE 1 first. What did you see? Now watch MOVIE 2. The spotlight shifts from one area of interest to the next as the scene progresses. Watch MOVIE 3; if the spotlight shifts too quickly our brain would see only distracting "stroboscopic" images. Finally, imagine the person in the movie to be your favorite & most attractive movie star. Would your attentional resources shift from brain to person to target? Now the brain could explode for all you knew, since you limit your shift of focus from feature to feature of the attractive person. Your Association Cortices (including Limbic areas), oculomotor

brainstem centers and neuromodulatory brainstem centers influence what you see, when you look with an intention to perceive.

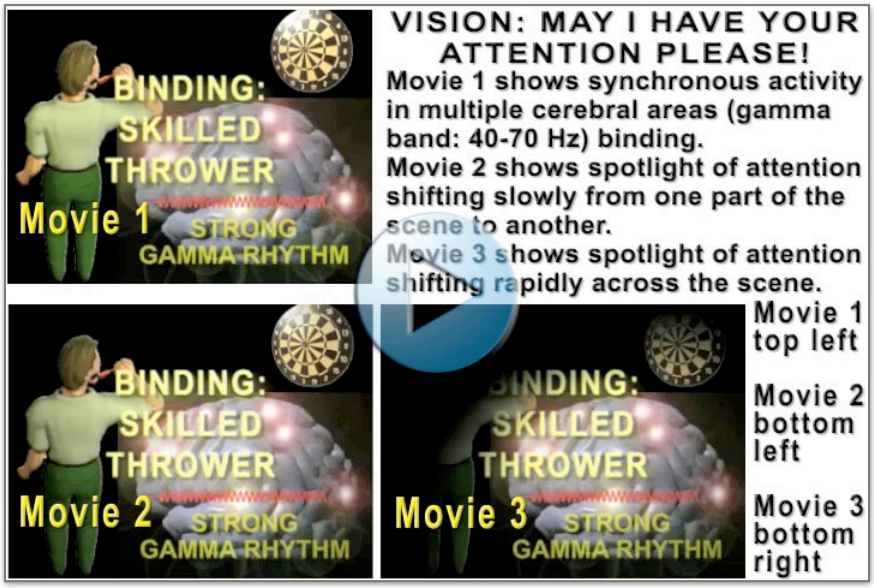

Fig 12-35. Proposed Potential Visual Attentional Mechanisms: Three Movies (gec). GO TO: gmomm.pitt.edu
Fig12-35_Video

If you are attending at least minimally, watching VISUAL ATTENTION MOVIE 1 once should provide the basic context (feedforward). There are three main parts: a brain, a person throwing a dart and a target. If you attend closer to the details, you should see that there is a sequence of events. This will likely require you to watch the movie several more times to extract greater detail (focus of attention shifting with feedforward and feedback processing). The scene: the brain in the movie has multiple areas that flash synchronously and other areas that light up at the end that send impulses to brainstem and spinal cord. The individual throws the dart rapidly and accurately with little excess body motion as expected for a skilled dart thrower. Finally, the dart lodges in the center of the target: an accurate throw. The flashing brain (synchronous flashes) illustrates the “binding” of occipital visual areas (ventral visual stream), posterior parietal (dorsal visual stream) areas, dorsal & ventral premotor areas and dorsolateral prefrontal areas. This transient binding occurs rapidly within the gamma rhythm (~40-70 Hz) during the pre-movement time. At this time, the multisensory perceptual and visuomotor resources are garnered for this well-learned visually guided motor task. Following the preparation to move, motor and somatosensory areas light up as the signals to move are sent to subcortical brain & spinal cord.

VISUAL ATTENTION MOVIE 2 shows the effect of a spotlight of attention as it shifts from the whole scene (centered) to each area of interest (area showing some change to the visual system). First the spotlight shifts to the brain since there is obviously some action going on there (flickering lights). Next, out of the corner of the mind's eye, motion of the person's arm is “seen” and the spotlight shifts (flashes and motion are powerful salient features that get our attention and may rapidly influence actions in a preconscious manner). Finally, after watching the dart come forward and leave the person's hand, the anticipated track of the dart is followed by a shift in the spotlight

towards the target. This shifting spotlight sequence is hypothetical but represents what might be expected if one is familiar with the task and attentive to other dynamic aspects of the scene (e.g., brain flashing). Finally, after watching the dart come forward and leave the person's hand, the anticipated track of the dart is followed by a shift in the spotlight towards the target. This shifting spotlight sequence is hypothetical but represents what might be expected if one is familiar with the task and attentive to other dynamic aspects of the scene (e.g., brain flashing). Saliency of content within visual scenes provides identification of certain objects at a glance (pop-out). Of course the actual spotlight of attention within your brain may not jump so dramatically as illustrated here and the transitions likely will be completely transparent to your conscious perceptions. The concept of the spotlight of attention and binding rhythms are also speculative hypotheses that have yet to be proven “beyond a shadow of a doubt.” Scientists are investigating these hypotheses.

VISUAL ATTENTION MOVIE 3 shows the effect of a spotlight of attention shifting from one portion of the scene to another in rapid and repeated succession. Such a rapid shift in spotlighting produces a stroboscopic effect. If your movie plays at full speed (30 frames per sec) the spotlight shifts every 33 msec. Obviously, the spotlight of attention does not normally shift this fast without some pause on an object of interest before shifting again (our view of the world is not a staccato jumping of images). There are limits to our attentional processing. If the mechanism for shifting of attention requires a corticothalamocortical loop to transiently bind appropriate circuitry, a 33 msec interval would not permit many spikes to be correlated across a neural network that contains delays in impulse conduction & synaptic transmission. The fact that one sees the jumping of the spotlight suggests that our visual system is primed for rapid motion detection although detection of the exact pattern of the spotlight shift requires slower viewing times. The dorsal stream of the visual system provides excellent temporal resolution but our brain's ability to interpret data having high spatial detail may require a longer “look” at specific details of what we see (ventral stream).

VISUAL CORTEX: DORSAL & VENTRAL STREAMS FOR ACTION AND PERCEPTION

Remembering that the retina is actually the diencephalon pushed out into the periphery (optic cup and optic stalk), the CNS has two parallel pathways that process different aspects of our visual inputs.

Reentrant Corticocortical and Corticothalamo-cortical connections provide necessary neural resources for conscious perception.

A Parvocellular (P) Pathway provides the best information about spatial detail (visual acuity) and color. The Magnocellular (M) Pathway provides less absolute spatial detail but provides critical information about temporal aspects of vision including object motion. The Magnocellular Pathway has a major routing of information to extrastriate visual areas that eventually converge upon neural ensembles in the Posterior Parietal

Cortex (Dorsal Stream). Parvocellular input tends to gravitate to more ventral extrastriate areas that ultimately connect with visual association areas in the Inferior Temporal Cortex (Ventral Stream). While perception requires conscious attention, the dorsal stream may operate at conscious or preconscious levels. Although only feedforward connections are shown here, most areas have reciprocal connectivity.

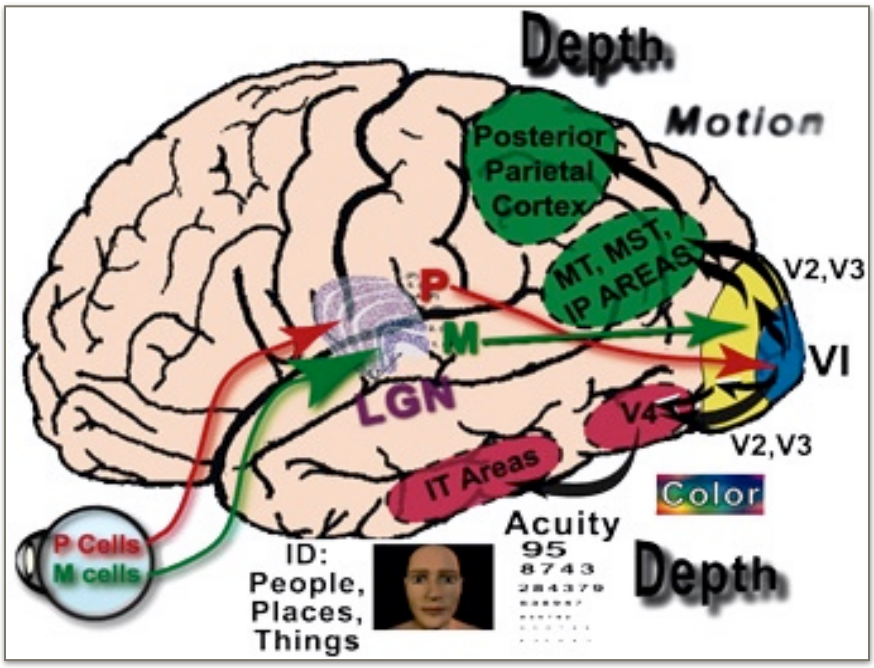

Fig 12-36. Dorsal and Ventral Visual Streams and Their Proposed Functions Related to Vision. Note: Only Feed-forward Connections are Illustrated (gec).

DORSAL STREAM: "Where" & "How" Pathway - Multi-modal Processing for Guiding ACTION; Motion, Depth, Overall Form, & Location of Objects in Space in Black & White.

VENTRAL STREAM: "What" Pathway - Perceptual Processing of Vision; High Visual Acuity, Object and Face Identification, & Color Vision. A significant portion of the primate cerebrum is devoted to, or somehow linked to vision. A brief summary of each stream follows.

MAGNOCELLULAR AND PARVOCELLULAR VISUAL PATHWAYS: IN A FLASH VERSUS ATTENTION TO DETAIL

A flash whether reflected from a surface or generated from a source, commands our attention. Two separate pathways from retina to visual cortex provide different information. The Magno Pathway (via the Magnocellular layers of LGN) is a fast path for information about motion, “flicker,” depth of field and form. The Magno (M) Pathway includes VI output to Dorsal Stream visual areas; note rapid input from the superior colliculus. This pathway is important for the "where & how" of vision. The Parvo (P) Pathway (Parvocellular layers of LGN) provides a slower path for color, object details, spatial acuity and depth of field. The slower Parvocellular Pathway has a major input to the Ventral Stream targeting Inferior Temporal Visual Areas. This pathway is critical for the "what" (perception) of vision. Both Dorsal & Ventral Streams have multiple reciprocal connections and both project to Prefrontal Areas that integrate "what, where & how" info. The Prefrontal Areas plan, program & regulate actions in conjunction with parietal cortex, motor cortical areas, basal ganglia & cerebellar loops.

Consider the following scenario:

"You are thinking about the meeting that you really do not want to attend as you are about to cross the street. Suddenly, out of the corner of your eye there is a flash, a large object moving towards you. You jump back! It is only after you are back safely on the curb that the full perspective of the incident hits you. Now you recognize a person with a portable phone to his ear driving through the intersection (and the red light) in his red sports car. After catching your breath, you have the appropriate response to the situation. The moral of the story? Remember what you have been taught: pay attention, look both ways before crossing. Now are you not glad that you have a fast, preconscious Magnocellular visual pathway for quick action and a conscious (slower, Parvocellular) pathway for high level perception (make of car & license number); and of course a limbic system to react in an 'appropriate' manner." *GEC 2001*

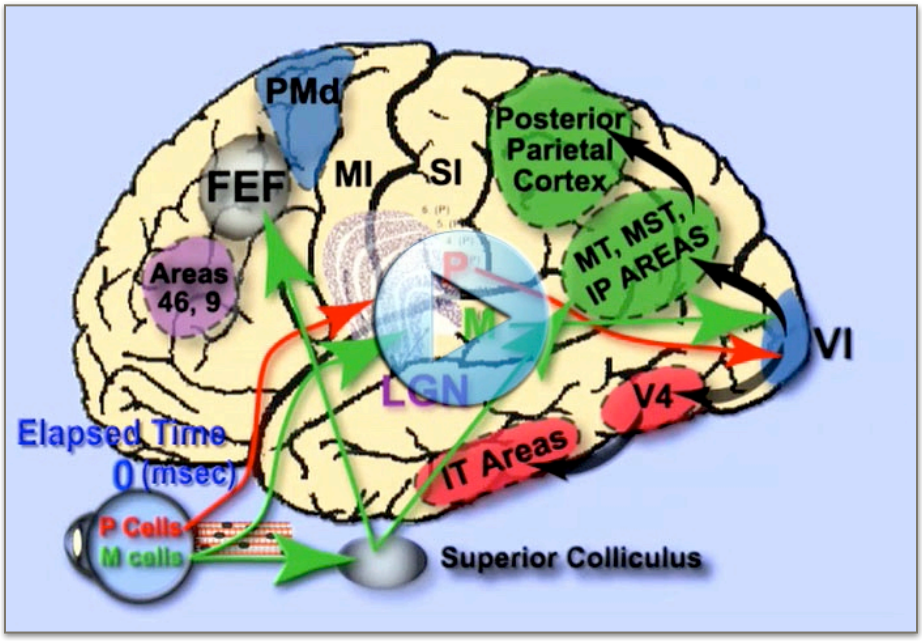

Fig 12-37. Magnocellular and Parvocellular Visual Pathways: In A Flash Movie (gec). GO TO: gmomm.pitt.edu *Fig12-37_Video*

The Magnocellular and Parvocellular Visual Pathways: In a Flash Movie illustrates these two pathways and input to Frontal Eye Fields (FEF) that directs the eyes to the object.

Note the difference in speed & visual cortical targets of the Magnocellular (M) versus Parvocellular (P) Pathways. Input from retina to Superior Colliculus (SC) provides a mechanism for rapid responses to moving stimuli. SC input to the FEF & motion sensitive visual areas (MT, MST & IP) in the Dorsal Stream supplement visual cortical inputs so we can formulate the "how" of action that is projected to frontal cortex where action is regulated (Brodmann Areas 46 & 9). The ventral stream although slower provides the eventual conscious perceptual identification of "what" you are looking at. Each area "broadcasts" its information to other brain areas as both streams of visual processing are engaged and binding occurs within & across appropriate brain areas.

AGE-DEPENDENT & ACTIVITY-DEPENDENT VISUAL SYSTEM PLASTICITY

Neuroscientists who support one hypothesis of visual system development provide evidence that visual cortex has both age- and activity-dependent plasticity.

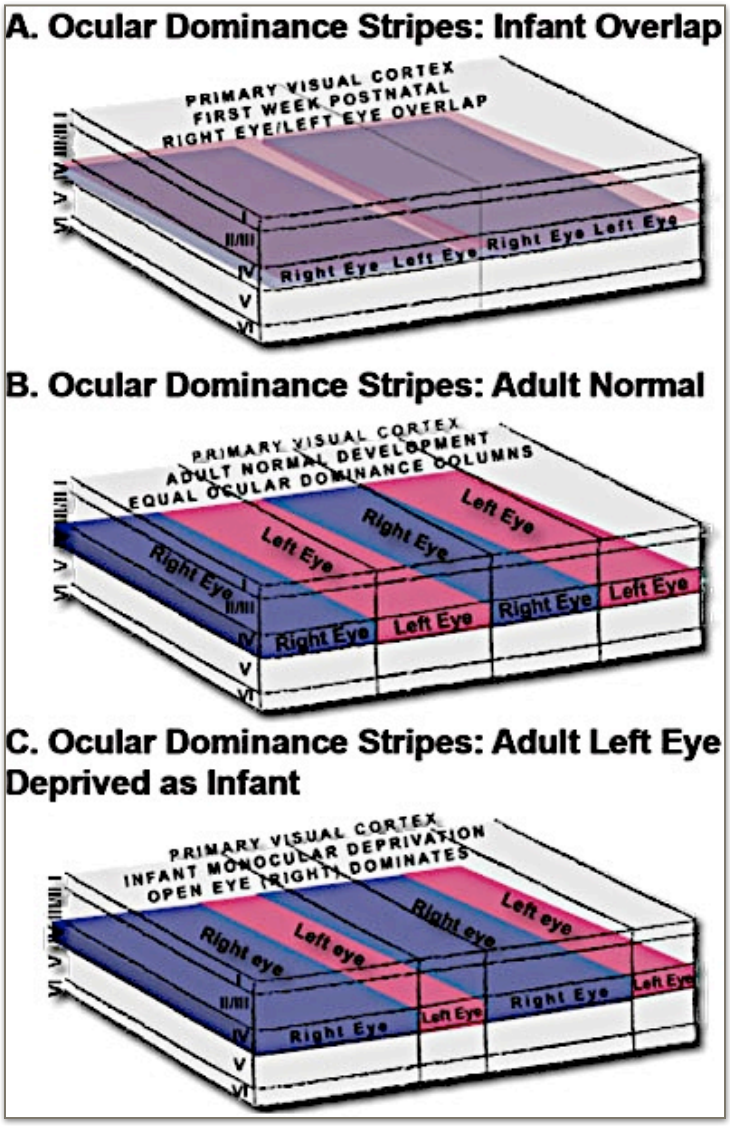

Fig 12-38. Panel A. Ocular Dominance Stripes (Right Eye, Left Eye) Overlap in Infant. Panel B. Ocular Dominance Stripes (Right Eye, Left Eye) are Segregated in Adult with Normal Visual Experience Panel C. Monocular Deprivation Early in Life disrupts normal Ocular Dominance Stripe Formation; Note Expanded Right Eye and Narrow Left Eye Stripes (gec).

Monocular deprivation (e.g., cataract) early but not late in life produces abnormal ocular dominance columns in Primary Visual Cortex (VI). Binocular deprivation just after birth produces no such imbalance of ocular dominance columns and monocular deprivation after a critical (sensitive) period of development does not alter right eye, left eye columns [see figures]. Normal visual activity from the two open eyes competes for space in VI causing retraction of overlapping thalamic inputs (pruning) seen in VI before & just after birth. Competitive synaptic activity strengthens connections for each eye's input to produce clearly defined eye columns (ocular dominance columns). Recent research suggests that both molecular cues (Sperry's Chemo-affinity Hypothesis of connectivity) and Hebbian or non-Hebbian activity-dependent synaptic plasticity contribute to normal visual cortex development; the two mechanisms are unlikely to be mutually exclusive. Although early experience appears to be critical to create optimal circuitry, visual processing continues to be fine-tuned throughout life. In addition, It has been shown that even before the eye has any

visual experience, the mammalian prenatal retina produces spontaneous synchronous discharges to influence visual pathway connections.

THE EARLY RIGHT & LEFT EYE OVERLAP OF INFLUENCE IN VI SEGREGATES INTO RIGHT AND LEFT EYE OCULAR DOMINANCE COLUMNS AS NORMAL VISUAL EXPERIENCE PRODUCES EQUAL COMPETITION FROM THE TWO EYES.

A CATARACT IN THE LEFT EYE OF AN INFANT, IF NOT CORRECTED, HAS PROFOUND & POSSIBLY IRREVERSIBLE CONSEQUENCES. THE NORMAL RIGHT EYE NOW DOMINATES THE PRIMARY VISUAL CORTEX AT THE EXPENSE OF THE WEAKER VISUAL INPUTS FROM THE LEFT EYE.

NO SUCH IMBALANCE OF RIGHT VERSUS LEFT EYE DOMINANCE OCCURS IN ADULTS WHO ACQUIRE A CATARACT; NORMAL EXPERIENCE EARLY IN LIFE "LAYS DOWN" EQUAL OCULAR DOMINANCE COLUMNS IN THE STRIATE CORTEX. RECENT EVIDENCE SUGGESTS AN IMPORTANT ROLE FOR GABA NEURONS IN PLASTICITY AND AN ENDURING CAPACITY FOR SYNAPTIC MODIFICATIONS PERSISTING INTO ADULTHOOD AT LEAST FOR THE MAMMALIAN VISUAL SYSTEM (SEE REFERENCES).

VI OCULAR DOMINANCE: HEBB, NMDA, LTP AGE- & ACTIVITY-DEPENDENT PLASTICITY

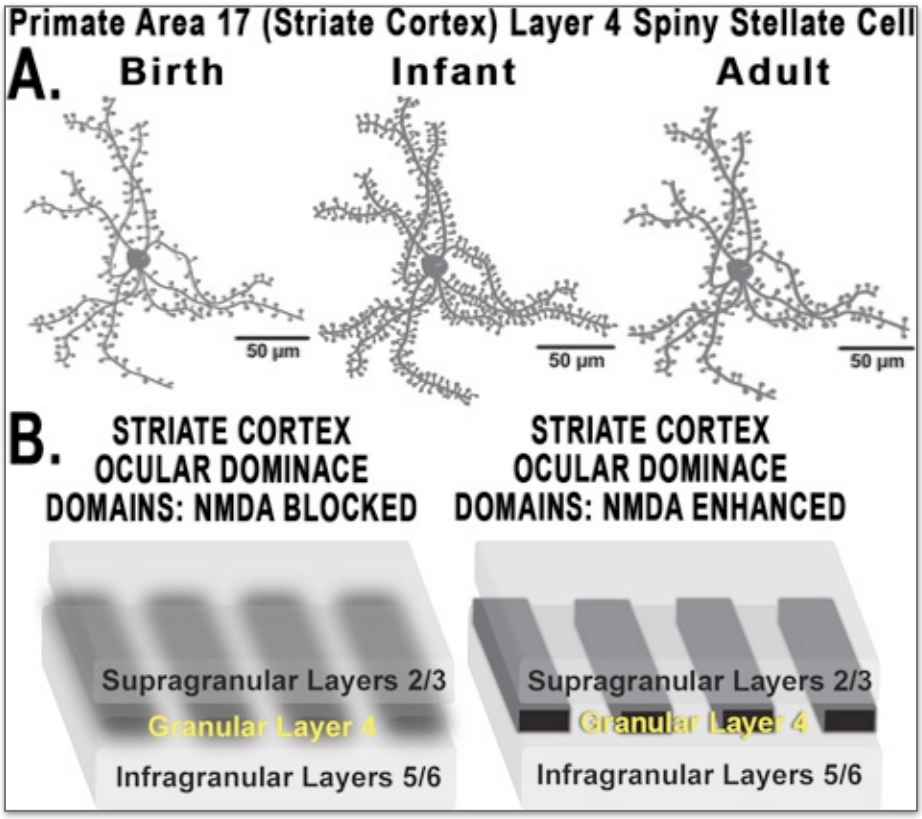

Fig 12-39. A. Development and Maturation of Striate Cortex Excitatory Interneurons B. Activity-Dependent Fine Tuning of Eye Dominance Columns in Primate During the Sensitive Period of Ocular Dominance Development (gec).

During early prenatal life neurons in layer 4 of the striate cortex (VI) have relatively sparse profiles for synaptic connections (e.g., spines on spiny stellate cells). At birth greater numbers of

synapses are made but it not until later in infancy that a dense population of spines occupy each of the dendritic branches. During this critical period right eye and left eye inputs from the lateral geniculate nucleus compete for stable synaptic connections, e.g., see; Lund, Boothe and Lund, 1977 reference.

This process of competition for right and left eye representation in VI appears to be at least partially dependent on “Hebbian rules” such that the strongest and most synchronous synapses grow while weaker synapses are eliminated. Thus in the young adult brain spiny stellate cells have fewer but presumably stronger synaptic connections on those activity-enhanced synaptic spines. Experiments where layer 4 striate cortex is infused with an NMDA blocker show rather “fuzzy” ocular dominance domains while addition of NMDA sharpens each of the ocular domain borders. These effects appear to be mediated through glutamatergic and GABAergic neurons in the striate cortex.

THREE-EYED FROG: VISUAL REPRESENTATION COMPETITION & ACTIVITY-DEPENDENT PLASTICITY

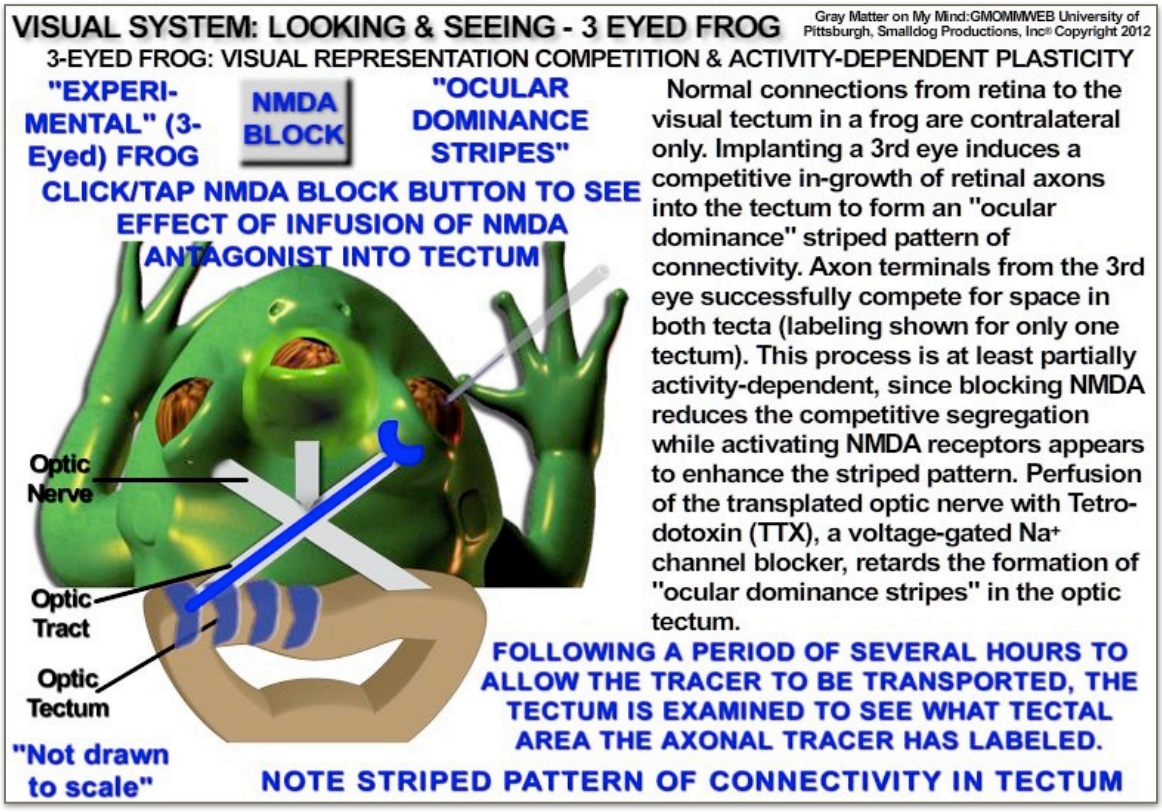

Fig 12-40. Third Eye Transplantation Induces Competition for Retinotectal Synaptic Connections: Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig12-40 Interactive Media]

Normal connections from retina to the visual tectum in a frog are contralateral only. Implanting a third eye induces a competitive in-growth of retinal axons into the tectum to form an “ocular dominance” striped pattern of connectivity. Axon terminals from the third eye successfully compete for space in both tecta (labeling shown for only one tectum), see Constantine-Paton & Law, 1978. This process is at least partially activity-dependent, since blocking NMDA reduces the competitive segregation while activating NMDA receptors appears to enhance the striped pattern. Perfusion of the transplanted optic nerve with Tetrodotoxin (TTX), a voltage-gated Na^+ channel blocker, retards the formation of “ocular dominance stripes” in the optic tectum suggesting the necessity of not only a viable anatomical connection but physiological activation of postsynaptic tectal cells by retinal ganglion cell inputs.

BINDING: UNIFIED PERCEPTION - RED BALL BOUNCING

This Red Ball Bouncing movie is an attempt to illustrate the sequence of events when a moving object appears in a viewer's peripheral vision, a rapid saccade provides a first glimpse of the object and then the identify the object becomes apparent as sufficient brain resources are brought “on-line.” The scenario begins as a preconscious saccade to an object located somewhere to the viewer's right. Then a more precise location and other features of the object begin to be recognized by the viewer's visual brain. Finally, when the cortical dorsal stream and ventral stream extrastriate visual areas are active and the linked higher order thalamic matrix cells establish a viable corticothalamocortical loop, the areas show synchronous activity and are bound to establish a conscious, unified perception. Now the necessary network coalitions have been established so appropriate brain areas are “on the same page at the same time.”

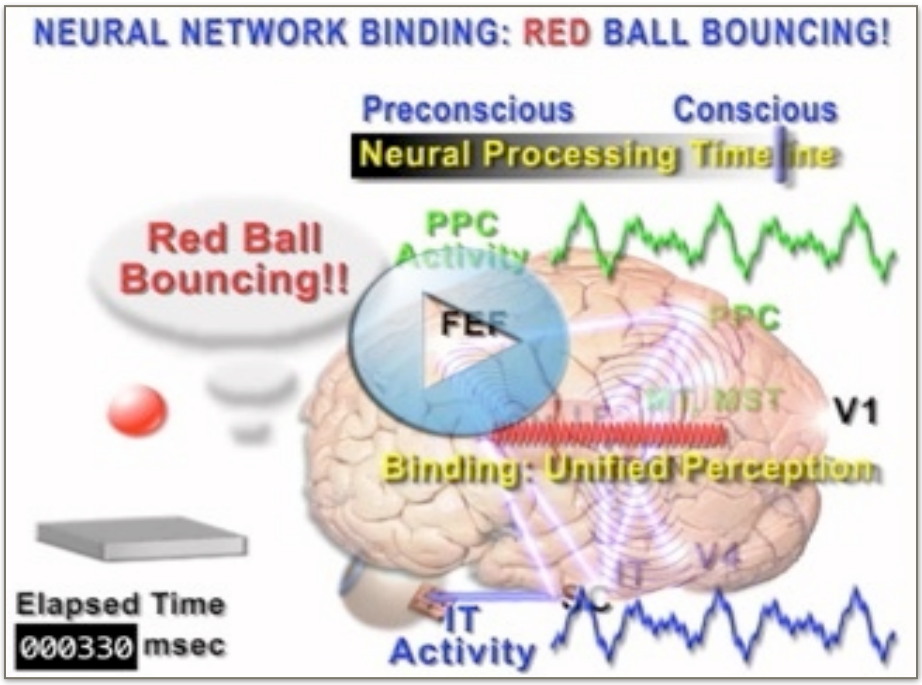

Fig 12-41. Red Ball Bouncing Movie. Perceptual Binding in Vision. GO TO: gmomm.pitt.edu *Fig12-41_Video*

Rapid visual input to the superior colliculus (SC) can initiate a “preconscious” saccade that moves eyes to the right but does not precisely target the object. Then visual input to the forebrain

provides data that allow for more precise localization and tracking of the object: transition from a preconscious to a conscious state.

NOTE: two streams of visual input to the LGN thalamic nucleus are illustrated in the animation: a fast, colorblind, motion-sensitive magnocellular input that targets the dorsal visual stream (to V1, MT, MST, IP, PPC cortical areas) followed by a slower high acuity, color sensitive parvocellular input that targets the ventral visual stream (to V1, V4, IT cortical areas). Binding occurs when all components are brought “on-line” and become synchronously active due to reentrant corticocortical and corticothalamocortical connections (leading to conscious awareness of all aspects of the visual scene).

VISION PSYCHOPHYSICS: SEEING IS BELIEVING?

Our brain tries to make sense of what it sees. Although retinal images play a vital role in capturing photons using high contrast neural circuitry in the retina (color, motion, etc.), it does not simply burn a photographic image onto visual cortex.

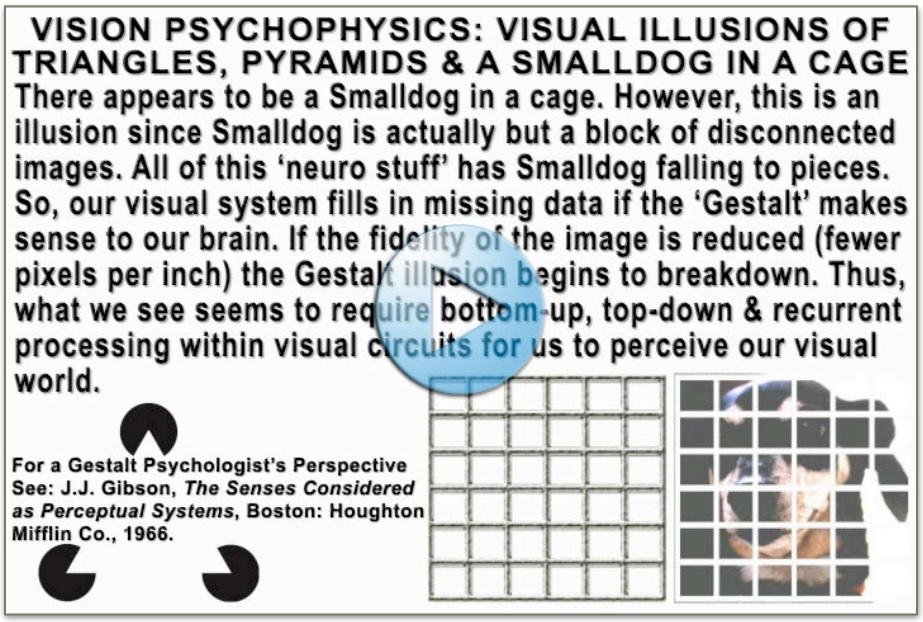

Fig 12-42. Vision Psychophysics: Pacmen, Triangles & Smalldog in a Cage Movie (gec). GO TO: gmomm.pitt.edu *Fig12-42_Video*

Instead, the visual thalamus & striate and extrastriate visual cortex respond to both peripheral data and centrally generated data from both visual and non-visual brain areas. Perceptions are based upon the brain's best interpretation of what it thinks it sees. Because any explicit interpretation of 3D images must come from a 2D sheet of cells, some interesting illusions can be produced to “trick” the brain into seeing things that are not really there.

As long as the bulk of the population “see” what you “see,” these illusions are not considered to be “hallucinogenic,” that is, normally some peripheral image contributes to everyone's perception in a like manner. For example, in the figure below most people see a white triangle formed by three black sectored discs or “pacmen.”

Some individuals see the triangle as “whiter” than the background. This is called a Kanizsa triangle first described by the Gestalt psychologist Gaetano Kanizsa (1979).

When the PACMEN triangle covers the gray square you see that no white triangle really exist but now you see a gray triangle. If the triangle bisects the gray gradient the illusion changes. What do you see? If you look long enough you may now imagine a pyramid rather than a triangle. The gray adds “shading” that turns a 2D into a 3D image just as an artist might do. The next figure appears to be Smalldog inside her cage. However, if you take Smalldog out of her cage, you will see that all this “neuro stuff” has been too much and she is falling to pieces. We use a perceptual process to “fill in” the hidden portion of a whole image. We interpret nearby “puzzle pieces” as forming a unified object (dog). Parts are interpreted as a coherent pattern.

VISION PSYCHOPHYSICS: MOTION ILLUSIONS

Pacman is getting dizzy. The effect of motion on our visual perception is illustrated in the Pacmen In Motion Movie. Three pacmen are set in motion.

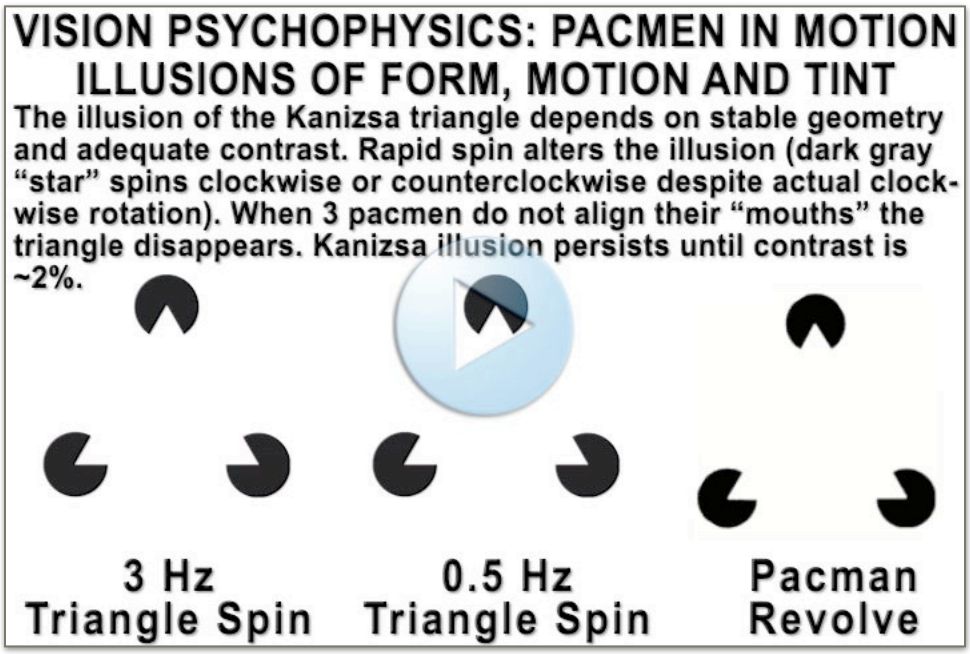

Fig 12-43. Pacmen in Motion Movie. Motion of pacmen and the triangle alters Illusions of form, motion and tint (gec). GO TO: gmomm.pitt.edu Fig12-43 Video

What you should see in the left movie is not a triangle but a spinning star. The spinning pacmen appear gray or alternate gray and black NOT always black. The nominal rotation speed is 3 Hz. Keep looking at the spinning pacmen. Invariably you will eventually see the pacmen/star reverse rotational direction. The actual rotation is clockwise (set within program) but an illusion of a directional shift is strong at this speed. Your perception uses a “winner take all” process so that you see spinning in ONE direction OR the OTHER, never some amalgam of clockwise/counterclockwise.

Shifting your gaze slightly side to side or attending to the right versus left side of the spinning star may bias the rotation that you see. The Dorsal Stream extrastriate motion areas (MT, MST, IP Areas) are strongly driven by fast moving visual stimuli. There are enormous evolutionary pressures for development of this visual perceptual capacity (e.g., cats are most attentive to fast moving, “flashy” toys). CENTER MOVIE: The “star”

illusion falls apart when you can actually “see” each pacman move in slow motion (0.5 Hz). You should see a slowly spinning triangle along with the three pacmen. The slow rotation is clockwise only.

The right Kanizsa triangle (Pacman Revolve) illustrates the importance of relative positional cues to form this illusion. The alignment of the three pacmen's 'mouths' are critical to form the illusory lines of the triangle. As each pacman spins on its own axis, the lines formed by the “mouth” no longer align one to another and the illusion disappears (even when there is minimal misalignment of the notches). A minimal contrast is required to form these illusions.

SPOTS BEFORE YOUR EYES, COLLISION OF STARS AND TRIANGLES: MASKING IN VISUAL PERCEPTION & REENTRANT MODULATION OF WHAT WE SEE

Are you one of those individuals who always pays attention and never misses anything? Try playing the Color Spots Movie. Pay close attention: spots appear & disappear rapidly. There are four movies: MOVIE 1; MOVIE 2; MOVIE 3; & MOVIE 4.

Fig 12-44. Color Spots Movie (gec). GO TO: gmomm.pitt.edu *Fig12-44_Video*

What did you see? Play them more than once. You should use the video control bar to play the movie on a frame-by-frame basis to see what is really there AFTER you watch the movie at full speed. SEE KEY BELOW FOR EXPLANATION AFTER WATCHING MOVIES (don't cheat).

KEY for Color Spots Movie:

COLOR SPOTS MOVIE ONE contains a single red spot that appears for a single frame. The actual color will vary across computer displays. The movie should optimally play at 30 frames per sec so the duration of the spot should be ~33 msec. Actual play may be slower on some computers. Nevertheless, the fact that such a brief spot of color can be recognized suggests that the visual system maintains an afterimage sufficient to activate dorsal (you see a flash) and ventral (you see a red spot) visual stream circuitry beyond the short stimulus duration. Since the ventral stream is thought to be a slower pathway than the dorsal stream, the fact that you perceive a single red spot suggests the afterimage is a composite (unified perception) requiring a “binding” connectivity between parietal (dorsal stream) and temporal (ventral stream) cortices. Localized lesions result in perceptual deficits & a tax on binding.

COLOR SPOTS MOVIE TWO contains a red spot lasting 1 frame immediately followed by 3 frames of a dark gray spot at the same location. Most people report that they see a single dark gray spot. Invisibility of the first stimulus is thought to be due to a

phenomenon called masking. The red spot is masked by the subsequent gray spot. The blocking (masking) of the red spot is thought to be due to recurrent feedback from extra-striate visual areas to striate cortex (backward masking). Most mask experiments use a mask (2nd stimulus) lasting 2 to 3 times the duration of the first brief stimulus.

COLOR SPOTS MOVIE THREE contains a red spot lasting 3 frames, followed by 1 blank frame, followed by 3 frames of a dark gray spot at the same location as the red spot. Most individuals will see a flash of red (red spot) followed by a flash of gray (gray spot). Thus the single blank frame between two longer duration color spots is sufficient to overcome any masking effect seen when two brief stimuli are temporally contiguous. The actual mechanism explaining incomplete masking of the first stimulus is unknown.

COLOR SPOTS MOVIE FOUR contains a dark gray spot lasting 1 frame immediately followed by 1 frame of a red spot at the same location. Most people see a single red or dark red spot. The gray spot is partially masked by the subsequent red spot. In the example used here, there appears to be inadequate time for the first stimulus (dark gray spot) to evoke a response that travels to extrastriate cortex and back before the second (mask) red spot stimulus has ended. Perhaps afterimages are persistent (gray & red fuse = darker red) OR masking occurs within earlier stages of visual processing.

Placing the Kanizsa triangles in motion and merging two rotating separate Kanizsa triangles produces illusions that change according to the speed of the triangle rotation.

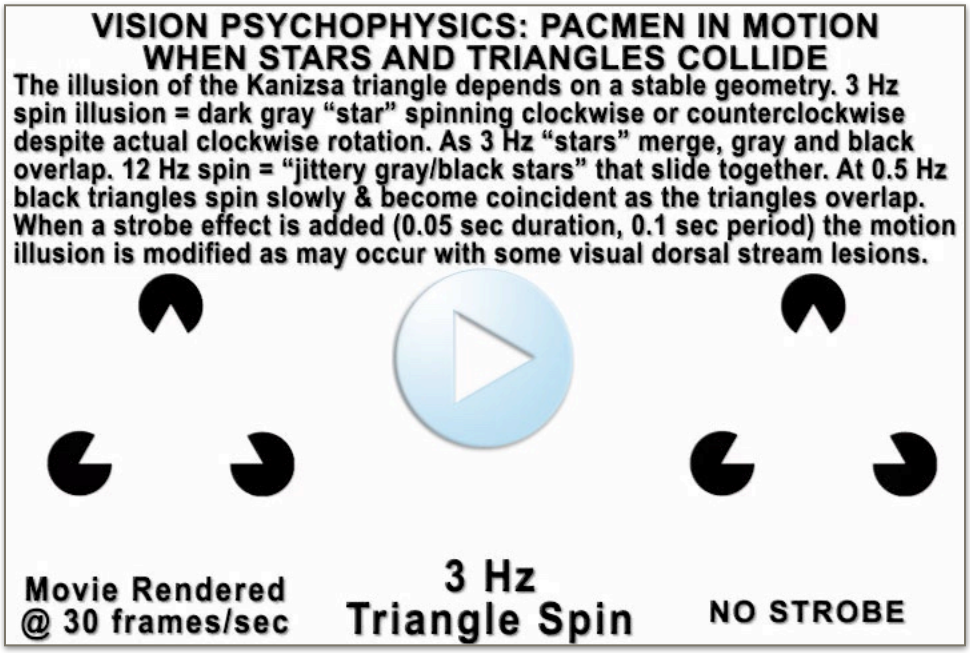

Fig 12-45. Vision Psychophysics: Stars and Triangles Collide Movie (gec). GO TO: gmomm.pitt.edu Fig12-45 _Video

Triangles formed by three black pacmen may look like rotating gray and white stars at one speed (3 Hz). As these stars merge gray and black hue changes for the overlapping spinning "stars". The perception is altered to form a "jittery" gray/black stars that seem to flow together at a faster speed of rotation (12 Hz). Slow speed (0.5 Hz) rotation provides a percept of slowly spinning black pacmen plus white

triangles. As they approach one another they become coincident forms in motion to overlap one another. Play the Vision Psychophysics: Stars and Triangles Collide Movie. These object motion illusions may be the result of conflicting data from “bottom-up” feedforward visual signals interacting with recurrent signals from extrastriate areas back to striate cortex and/or from conflicts within the data of extrastriate integrative areas, e.g., see Moran & Desimone, 1985; Lamme & Roelfsema, 2000; Gilbert & Li, 2013.

VISUAL PERCEPTION: MEMORIES, VENTRAL STREAM & MEDIAL TEMPORAL LOBE (I LIKE WHAT I SEE/SAW)

The Inferior temporal cortex is the “destination” for the ventral visual stream in the classic view of serial processing of conscious visual perception. However, while this view of visual processing may capture the utilitarian goal of identifying the “what” in visual processing, this is not the end of processing of such data (see below).

Brains do not have “wifi” so the axons of projection neurons that provide these long-range connections must have reproducible, “guaranteed” signal transmission. This faithful nerve impulse transmission is a necessary but not sufficient condition for normal brain function. A unified function such as conscious perception of a visual scene depends also upon a distributed parsing of the components that lead to normal perception. In addition, some neuroscientists suggest that these higher functions rely upon genetic history built upon a long-standing empirical learning process by our species. The visual system in primate brains utilizes many different cerebral cortical and subcortical brain areas to code the different aspects of visual signals. It has been proposed that due to the numerous and widely separated areas participating in perception, neuronal activity must be functionally bound together to create a relative synchrony of firing across separate networks (the binding problem).

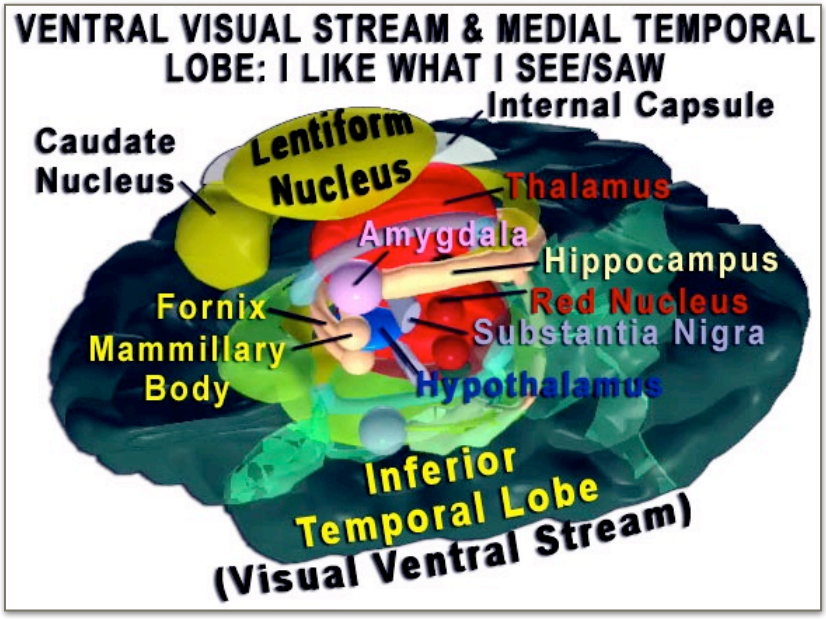

Fig 12-46. Inferior Temporal Cortex: Target of Ventral Visual Stream & Near Neighbors (gec).

Cell assemblies such as cerebral cortical columns provide “integrated circuitry” to accumulate data, transform those data into a neural image and then share that integrated information with other cell assemblies from which meaning is derived.

Even these cell assemblies may be combined at

different scales, e.g., at a macro-columnar scale providing a broader "Standard Definition (SD)" image or in the case of evolved primates a finer grained "High Definition (HD)" neural image that rescales data by fracturing the macrocolumnar representation into selective minicolumnar neural images (see SD to HD Movie). Slow-motion simulation of this hypothesized processing shows the transition from SD to HD neural image that in your brain would occur within a fraction of a second (e.g., recognizing a familiar face). Evidence for such a fracturing into HD neural images in humans is yet to be found and may only be tested when technology advances to allow measurements at this fine-grained level of detail *in-situ*.

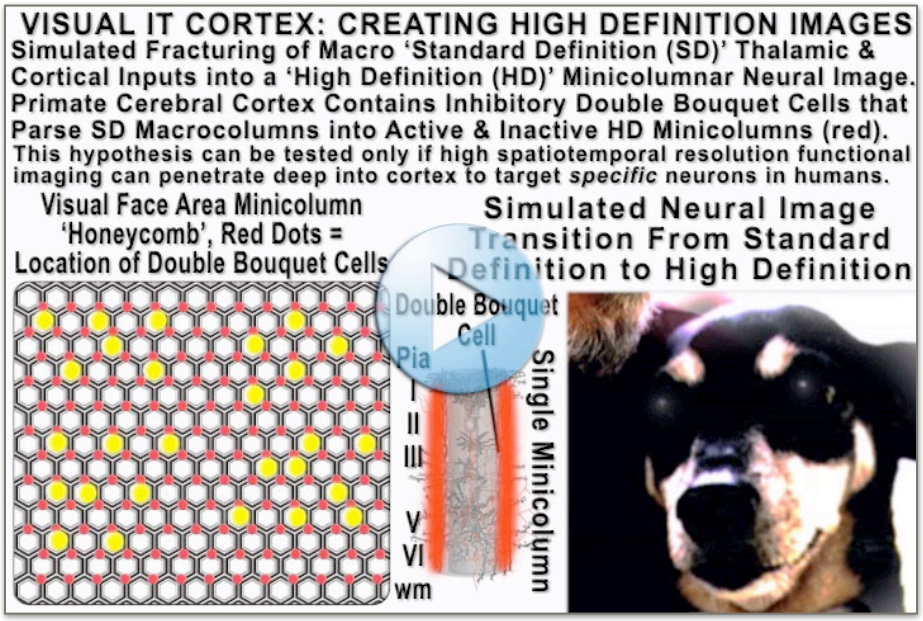

Fig 12-47. Creating High Definition Minicolumnar Images From Standard Definition Macrocolumnar Images Movie (gec). GO TO: gmomm.pitt.edu Fig12-47 _Video

Autobiographical "remembrances" of important events, persons, places and both natural and "man-made" artifacts have affective "value added" qualities layered upon any sensory "image" when data are processed in medial temporal lobe limbic structures. Such limbic affective flavoring of the data makes those events so memorable.

The location of high level visual perceptual processing in the inferior temporal cortex is anatomically convenient in that the Medial Temporal Lobe (MTL) lives next door. MTL is considered to be critical for limbic functions and consolidation/recall of explicit declarative, semantic and autobiographical memory.

The hippocampus, parahippocampal gyrus, entorhinal cortex and the amygdala are located in the MTL. MTL plus its near neighbors (olfactory stria, mammillary body, fornix, tail of the caudate nucleus, hypothalamus and portions of the thalamus) all contribute to limbic function. (Play Limbic Brain Areas Labeled Movie).

A famous case of explicit declarative memory loss tied to MTL is H.M. H.M. has been studied extensively by neurologists, psychologists and neuroscientists from the time of his surgery in 1953 up to and beyond his recent death in 2008. H.M. had *bilateral* anterior MTL resection to alleviate intractable seizures. The surgery which removed the

entorhinal area of the parahippocampal gyrus, amygdala and hippocampus bilaterally had a positive effect related to seizure activity but did not end all seizure activity. However, the ablations had the horrible side effect of severe explicit memory defects. Once the second MTL was surgically ablated H.M.'s biographical history and declarative long-term memory ceased. Following surgery he could no longer form new autobiographical memories and could not add to explicit memory formation, see Scoville and Milner, 1957. He was forced to live in the moment. Despite this sudden severe explicit biographical memory loss he could learn and remember implicit "procedural" motor skills even if he could not recall who taught him to do the new task nor could he remember doing the task the day before. Short-term and working memory were partially spared by the bilateral MTL surgery. H.M. had reduced motivation, initiative and somewhat blunted emotions and poor ability to recognize basic feelings such as thirst, hunger and pain (see Annese, et.al., 2014). A book (2013) for the lay public has recently been written to describe the relationship between Suzanne Corkin (who studied H.M. for decades) and Henry Molaison (H.M.): see, S. Corkin, 2002, 2013.

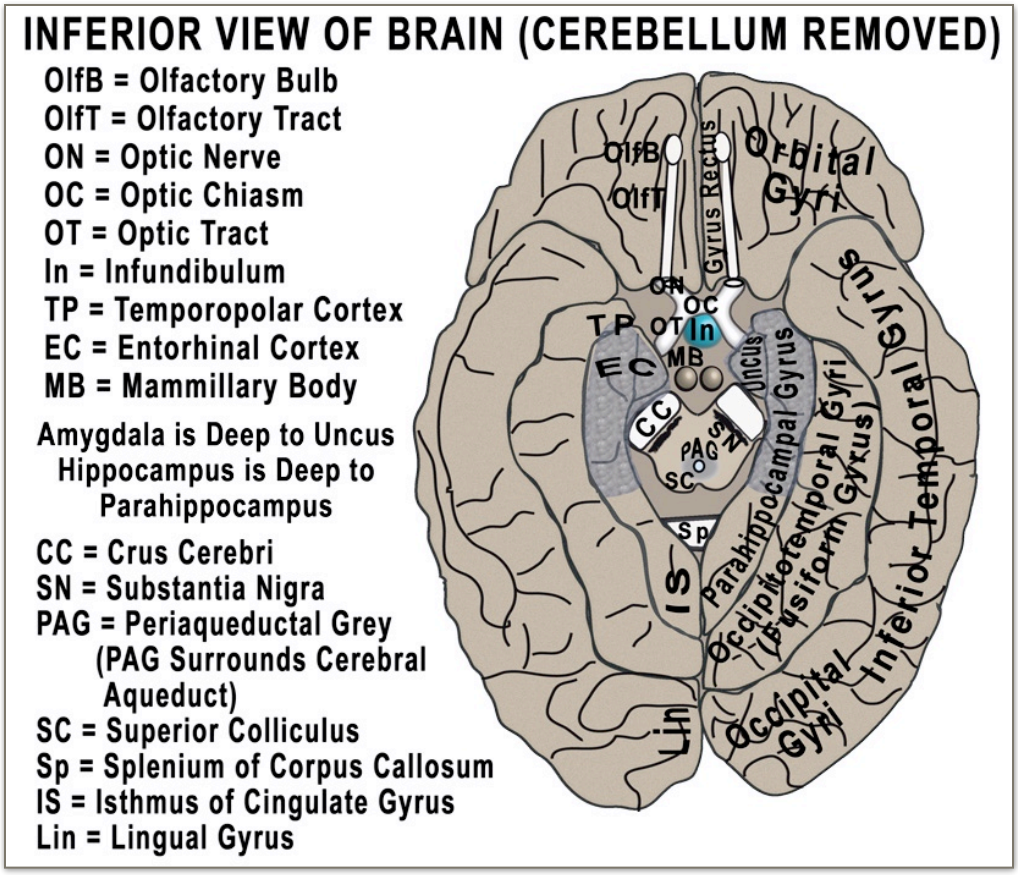

Fig 12-48. Inferior Brain with Bilateral Anterior MTL lesions (see shaded areas representing approximate extent of H.M.'s surgical lesions); see also Limbic Brain Areas Labeled Movie (gec). GO TO: gmomm.pitt.edu

Fig12-48_Video

Postmortem histological study of H.M.'s brain shows sparing of considerable portions of the right and left posterior hippocampus and parahippocampal gyri but loss of most or all the right and left amygdala, anterior hippocampus and overlying *entorhinal* cortices (see shaded areas in Fig. 12-48 and see Annese, et.al., 2014). Thus cortical areas associated with

visual perceptual processing including inferior temporal and posterior MTL were spared bilaterally. Nonetheless, it would appear that visual information tied to an affective overtone as a hallmark of vivid explicit memories seems to have been compromised markedly in H.M., see also recent reviews by Anacker and Hen, 2017; Eichenbaum, 2017. Theories regarding the role of the hippocampus in retrieval of and consolidation of declarative information may have to be revisited considering recent postmortem anatomical & histological findings for H.M.'s MTL: see Annese, et.al., 2014.

Recent recordings from neurons in the MTL of human subjects undergoing electrophysiological testing related to seizures have shown single cells responsive to multiple photos or even the typed name of individual well-known persons, places or architectures. Such neuronal sparse firing seems to be an abstract representation of the identified photo or name. These neurons fire ~300 msec after presentation of the specific token but not when other tokens are presented. Cells have relatively invariant sparse spiking at these long latencies even if the token is displayed for less than a 150 msec duration. Since Inferior Temporal Cortex is active within ~100-150 msec, these MTL long latencies suggests that a simple feedforward input to MTL from the ventral visual stream is insufficient to cause spiking in these cells. Loop (feedforward & feedback) connections with other brain areas, e.g., frontal cortex are most certainly involved. In this regard, both theta band and high gamma band frequencies are identified in firing of MTL single cells or as related to synaptic and spiking activity (local field potentials). These studies suggest that certain neurons in MTL of human brains are capable of coding invariant abstract knowledge that can be recalled when primed. These studies do not provide evidence regarding the minimal cell assembly required for such coding nor do these studies identify the global network that may be activated within the 300 msec prior to MTL cell firing (see Quiroga, et.al., 2005, 2007, 2008; Rey, et.al., 2014; Waydo, et.al., 2006). Nonetheless, these studies do suggest that neural coding of a memory trace for such abstract knowledge may require perhaps hundreds of connected neurons rather than thousands or tens of thousands of well-connected cells. Likewise abstract knowledge is not likely to be coded by a single isolated neuron (a "grandma" cell) since spatiotemporal integration should not require a latency of 150-200 msec for an MTL cell to reach spiking threshold due to feedforward inputs from a nearby single source (inferior temporal cortex, fusiform cortex neurons).

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Chapter 13

AUDITORY AND VESTIBULAR SYSTEMS

The ear is all about motion. Let me *bend your mind's ear* to make the point.

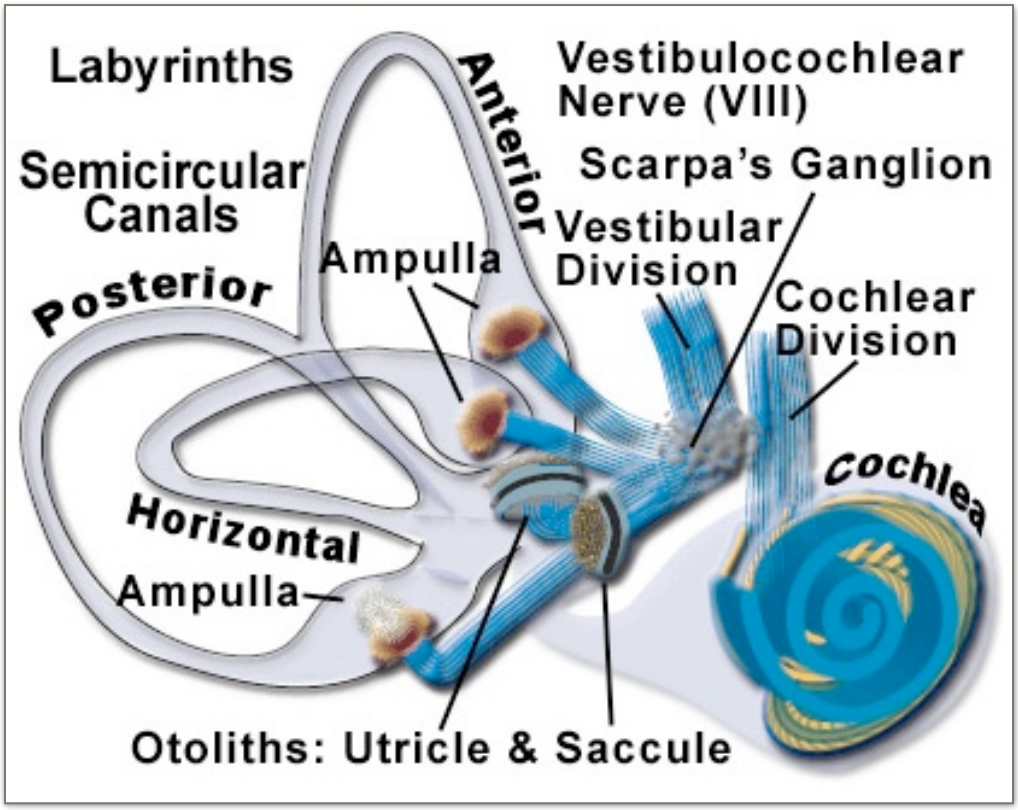


Fig 13-1. Vestibular and Auditory Components of the Inner Ear. Although your inner ear is not this colorful, its 3D morphology is much more elegant than illustrated in this 2D illustration (gec).

HEARING: While a number of animals can move their external ears to "catch" sounds in their environment, most humans have little to show for great effort expended to *wiggle* their ears. The human auricle (pinna) does not have much motion. However, the auricle does collect and reflect traveling waves moving within the medium of air (sound). The airborne traveling waves within the external auditory meatus (ear or auditory canal) vibrate the tympanic membrane (eardrum) deep within the auditory canal. The middle ear contains ossicles (small bones) that are set in motion by sound waves within the auditory canal "beating" against the tympanic membrane. Ossicle motion (stapes attached to oval window) transfers these oscillations into corresponding traveling waves within the fluid-filled chambers of the cochlea within inner ear. The Organ of Corti within the cochlea rocks and the basilar membrane tilts in response to the traveling waves within the inner ear. The Organ of Corti includes hair cells that move with the basilar membrane which in turn is accompanied by a shearing motion of

stereocilia (hairs) that are located at the transduction end of the hair cell. Hair cells are linked to one another through a mechanism called *tip-links* which are thought to open channels to depolarize the hair cell due to the shearing forces. From there action potentials (APs) are generated in the eighth cranial nerve cochlear afferents that innervate the hair cells and those APs are transmitted to the cochlear nuclei in the brainstem. Hearing is all about motion even if our eyes cannot see the micro-dynamics occurring inside our craniums.

BALANCE/EQUILIBRIUM: The vestibular labyrinths along with the cochlea are located within the petrous (rock) portion of the temporal bone and are anatomically associated with the cochlea (as part of the inner ear). The labyrinthine receptors provide an indirect measure of head motion due to motion of fluids within the labyrinths that move the cupula located within each semicircular canal or the macula within one of the otolith organs. The sensory transducers within the cupula or the macula are hair cells similar (but not identical) to the hair cells in the Organ of Corti. Like motion of structures within the cochlea, the motion within the vestibular labyrinths is not detected directly but such motion within the labyrinths certainly has a profound influence on the brainstem, the cerebellum and the eyes. This vestibular afferent input combined with visual and somatosensory inputs provides special proprioceptive cues for balance, equilibrium and an internal reference to the horizon and gravity. When the auditory and/or vestibular apparatus is (are) injured or diseased the individual becomes very aware of the loss of these stealth motion detectors located within the rock of the cranium.

EAR PARTS: GETTING TRAVELING WAVES TO THE ORGAN OF CORTI

The transduction of traveling waves caused by sound occurs in the hair cells located in the Organ of Corti. The hair cells transduce these inner ear fluid and membrane *ripples* into action potentials: the language of the brain. The Organ of Corti does not live at the surface of your skull but resides deep within the protective covering of the petrous portion of the temporal bone. Thus, sound waves must be transmitted through the media of the air in the outer ear, ossicles of the middle ear and fluids and membranes within the inner ear. These structures like the optical portion of the eye regulate the transmission of energy. For the eye this transmission relates to photic energy manipulated by the cornea, lens and iris to focus and transmit the energy onto the retina where light transduction takes place. For the ear, sound is “gathered” by the external ear and *focused/funneled* onto the tympanic membrane. The beating of these airborne traveling waves sets the tympanic membrane into motion that, in turn, oscillates the middle ear ossicles. This mechanism provides a gain increase and an impedance matching of traveling waves across multiple media: from air to bone (ossicles) to fluid in the inner ear. When the ossicles vibrate, the last of these, the stapes, rocks the oval window which generates traveling waves in the perilymphatic and endolymphatic fluids in the cochlea. It is the “waterborne” traveling waves of the inner ear (perilymph and

endolymph) that moves the basilar membrane of the Organ of Corti. Basilar membrane motion tilts the stereocilia of the hair cells of the Organ of Corti which depolarizes these cells to transduce the mechanical energy. What once was initially sound within the external auditory meatus (auditory or ear canal) of the external ear is now coded by the auditory branch of the eighth cranial nerve (Vestibulocochlear Nerve) as a stream of action potentials sent to the cochlear nuclei.

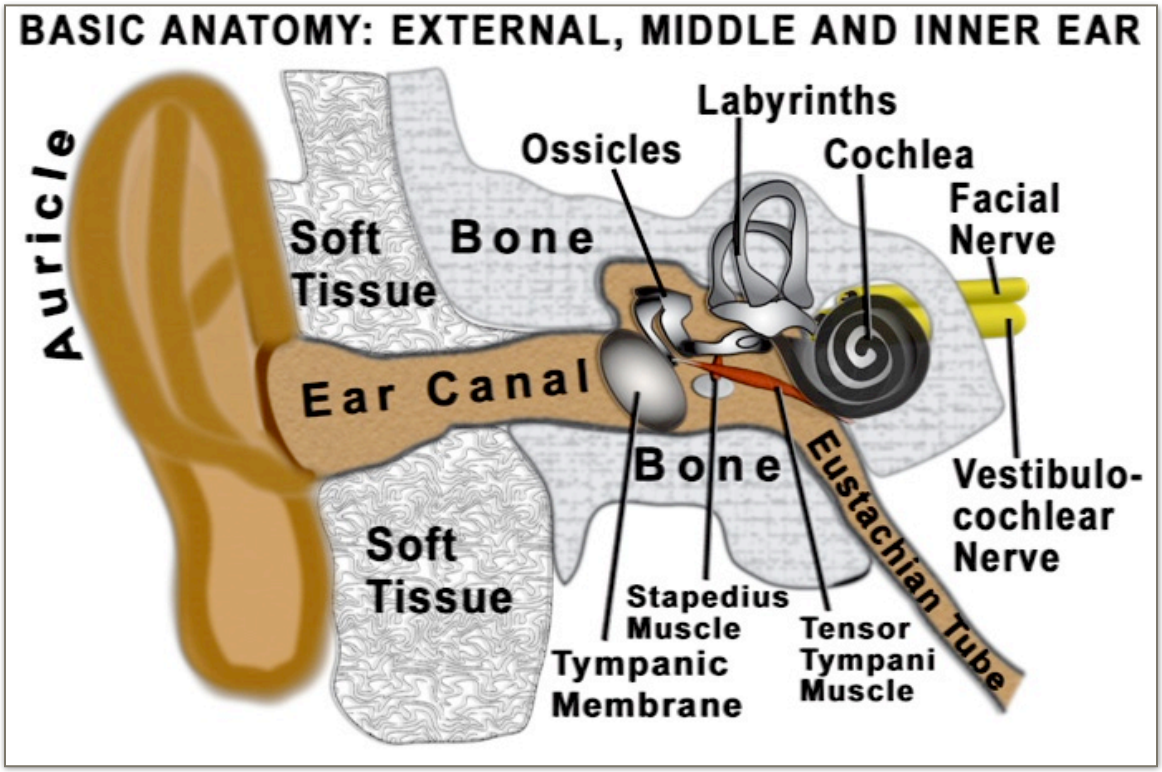


Fig 13-2. External, Middle and Inner Ear. Tympanic Membrane separates the external from the middle ear. Within the middle ear the Stapedius Muscle is innervated by a branch of the facial nerve. The Tensor Tympani Muscle is innervated by a branch of the mandibular division of the trigeminal nerve. The Eustachian (auditory) tube opens into the nasopharynx (gec).

EXTERNAL EAR: MORE THAN A JEWELRY STORE RACK OR AN EYEGLASSES PROP

The human auricle (pinna) although it is not very mobile nevertheless provides a baffle for sound transmission into the external auditory meatus. Both direct and reflected sound waves are funneled into the ear canal and the difference in timing of the two waves may help us localize the source of a sound within the vertical dimension of space. Bats, for example perform echolocation with a significant contribution of the pinna as a physical structure to provide vertical localization cues, e.g., see Lawrence and Simmons, 1982. The ridges and valleys of the cartilaginous pinna covered by skin provide the “soft” surfaces that direct reflected sounds into the external auditory meatus

at slightly different latencies dependent upon which ridge and valley is involved (superior, lateral or inferior). The head may act also as a baffle that creates a sound *shadow* when a sound source is located to one side or the other of the head in a horizontal plane. Except for low frequencies below ~1 Kilohertz (KHz) sound will arrive at the leading ear (same side as sound source) before that for the lagging ear (opposite one). Lower frequencies have wavelengths which "bend" around the head that would substantially reduce the sound shadow baffle effect. Sounds directly in front will reach both ears at the same time.

MIDDLE EAR: BONES, MEMBRANES AND PRESSURE VALVE

The middle ear contains three ossicles that are linked, the malleus (hammer), incus (anvil) and the stapes (stirrup). The transition between the outer and middle ear is created by a membrane known as the tympanic membrane to which the malleus is attached. The stapes as the third bone is attached to one of the membranes that separates the inner and middle ear, the oval window. The other membrane separating these two portions of the total ear is the round window (no attachments). Finally the middle ear has a tunnel that connects the middle ear to the nasopharynx, the Eustachian tube. This tunnel is normally closed by a "valve" that can be partially opened by yawning or altered pressure in the nasopharynx to reduce pressure differences between the middle ear and the nasal cavities, e.g., due to changing atmospheric pressure in high altitude air-flights. The ossicles partially amplify the vibrations set in motion by the tympanic membrane oscillation. The ossicles also provide a semi-stiff transference of energy that prevents a mismatch in impedance between the airborne traveling waves and those to be induced within the higher pressure perilymph fluid in the inner ear. The effect is thought to be an ~20 fold stronger 'rocking' motion of the oval window compared to that of the tympanic membrane.

The stapedius muscle and the tensor tympani muscle have been classically cast in the role of a protective reflex. When these muscles contract they tend to stiffen the middle ear transducers (tympanic membrane and ossicles) to attenuate loud sound transduction to protect the inner ear from dangerous levels of environmental sounds/ noise. Recent hypotheses suggest that these muscles have a role in traveling wave transduction for sounds below the pressure level that would cause harm. Tonic/phasic activation of these muscles may provide a more continuous modifier of mechanotransduction. Their activation may include not only bottom-up driving signals (sounds) but also top-down driving of the musculature according to central signals that reflexly or intentionally modulate transmission of incoming data. Like many other skeletal muscles these middle ear muscles may perform functions that are not simple reflexes but include brain-derived actionable regulation of data.

BASIC COCHLEAR ANATOMY AND PHYSIOLOGY

The cochlea is a spiral structure that if unwound would be ~4 cm. long. There are three fluid filled "tunnels" along the length of the cochlea. The stapes of the middle ear

is attached to the oval window that leads into the scala vestibule filled with perilymph fluid. At the far end of the cochlea an opening provides continuity with the scala tympani filled with perilymph fluid. The round window is located at its "termination" where the inner ear meets the middle ear (see figure). The middle tunnel is the scala media filled with endolymph fluid. The scala media is separated from the scala vestibule by Reissner's membrane and textbooks state that it is separated from the scala tympani by the basilar membrane. However, the hair cells (cell bodies) are said to be "bathed" in perilymph fluid not endolymph fluid. Endolymph **does** surround the stereocilia of the hair cells. Thus the fluid boundary may be related to the tight cell junctions between supporting non-hair cells in the Organ of Corti and the reticular lamina located along the "surface" of the Organ of Corti.

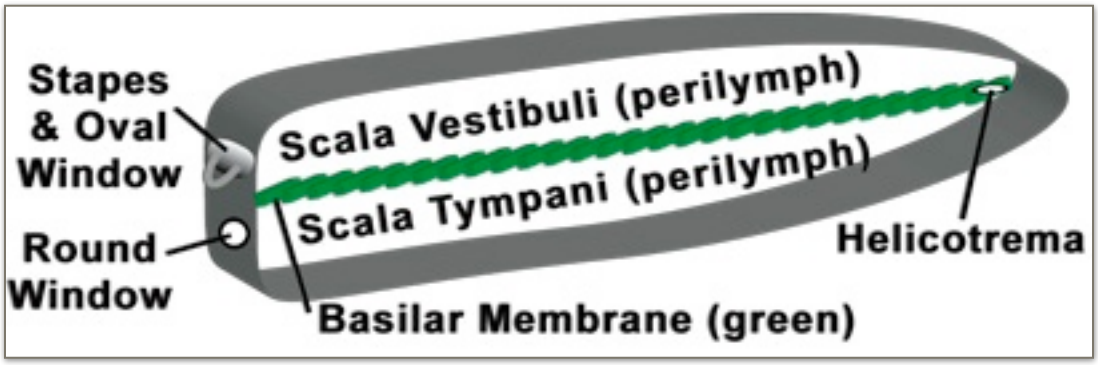


Fig 13-3. Basic Cochlear Architecture as imagined if the cochlea was unwound (gec).

BASILAR MEMBRANE TONOTOPIC ORGANIZATION: LOCATION, LOCATION, LOCATION!?

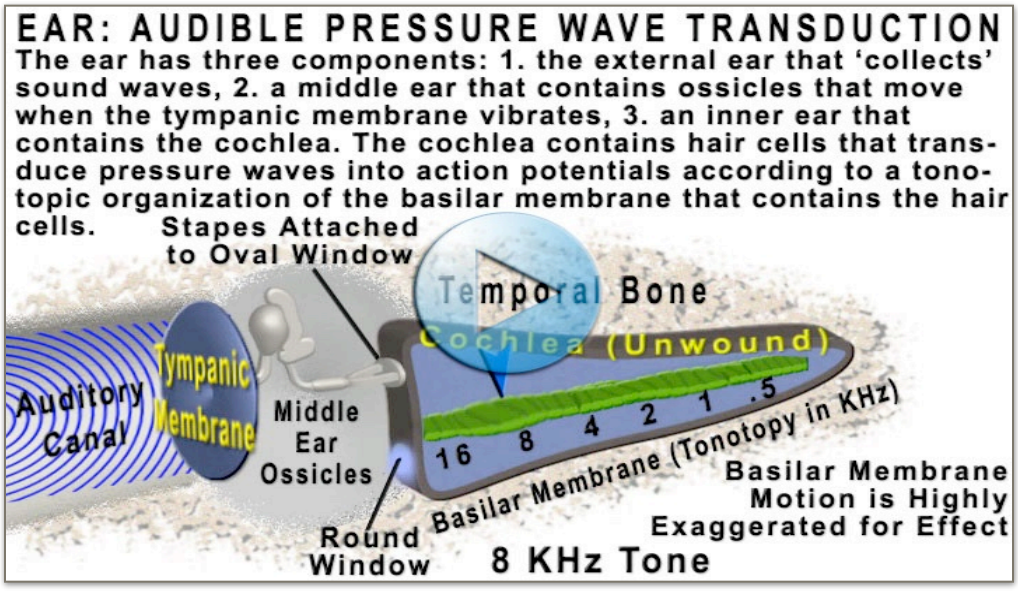


Fig 13-4. Basilar Membrane Tonotopic Organization Movie (gec). GO TO: gmomm.pitt.edu Fig13-4 _Video

Traveling waves that displace the tympanic membrane, middle ear ossicles and inner ear fluids contain frequencies that localize basilar

membrane displacements along its length. The basilar membrane's stiff, narrow base is best displaced by high frequencies in the sound's signature while the wider and more compliant apex is best displaced by lower frequency components of the sound. This tonotopic organization provides a basic anatomical coding of sound transduction at least for low intensity sounds that reach the ear. Higher frequencies tend to activate slightly broader regions at least when sound decibels are high. Thus different spiral ganglion afferent neurons will be activated according to the frequency components of the complex sounds that we listen to. The following animation illustrates this tonotopic organization of the basilar membrane for pure tones that should produce *relatively* distinct basilar membrane displacements according to the location rules stated above. Of course our ears are not accustomed to hearing such simple pure tones so one would imagine a significant portion of the basilar membrane in motion with complex sounds. This would be especially true when sounds get louder since the tonotopic frequency response tuning curves have a "U" shape where basilar membrane motion is most isolated with low decibel levels but expands as sound intensity levels rise up to an asymptotic level where the intensity now begins to cause damage and the person may experience pain as well as an uncomfortably loud sound. High decibel pure tones produce broader basilar membrane oscillations than for low decibel level tones.

INNER EAR: TUNNELS, FLUIDS, HAIRS, MEMBRANES AND ACTION POTENTIALS

The inner ear contains both vestibular and auditory components. The auditory portion is located in the cochlea and innervated by the auditory division of the eighth cranial nerve: vestibulocochlear nerve. The cochlea is a spiral organ that contains three fluid-filled chambers (tunnels).

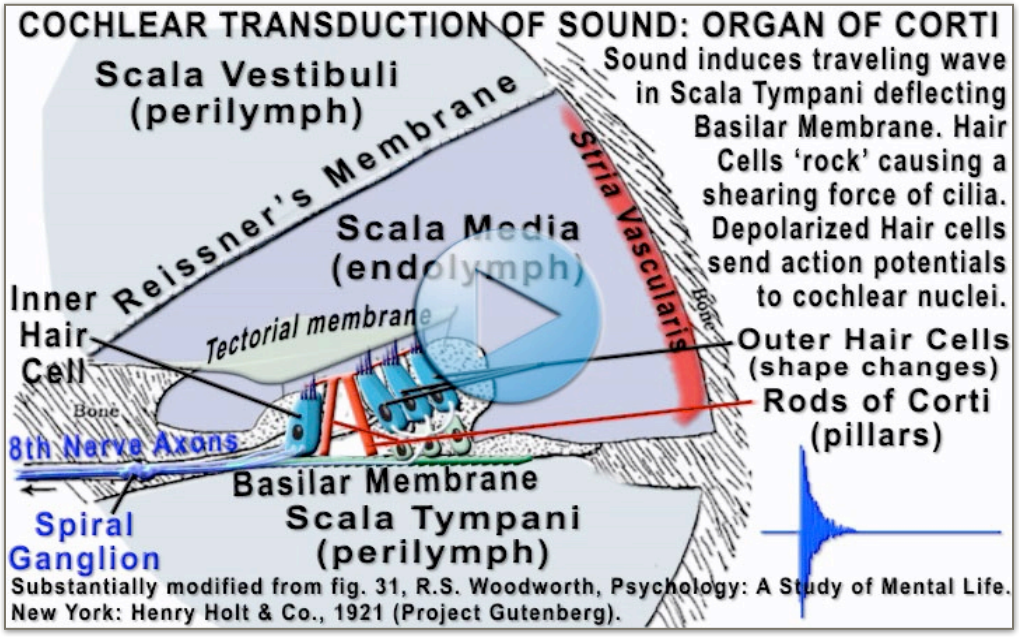


Fig 13-5. Organ of Corti: Basilar Membrane Rocks Movie (gec). GO TO: gmomm.pitt.edu Fig13-5 Video

The apparatus responsible for hearing is the Organ of Corti associated with the

basilar membrane, tectorial membrane and embedded hair cells that are mechanotransducers of traveling waves within the tunnels. These traveling waves are produced by coupling the sound transduction by way of external and middle ears into fluid motion in the tunnels. Such fluid motion perturbs the basilar membrane that tilts stereocilia of hair cells to generate action potentials in the spiral ganglion cell axons (eighth nerve auditory division). *The Organ of Corti Rocks Movie illustrates the complex motion due to traveling waves.* The vestibular component will be discussed later.

The Organ of Corti contains a single row of inner hair cells along the length of the cochlea plus three rows of outer hair cells in parallel to the inner hair cells. There are an estimated 3500 inner hair cells along the length of the human cochlea and ~12,500 outer hair cells along the same length. Despite the three fold greater number of outer hair cells it is the inner hair cells that transduce the basilar membrane motion into afferent signals representing the neural code that we interpret as sound. Since we have about a thousand-fold range of frequencies that we hear (20 Hz to 20 kHz) each of the 3500 hair cells must be responsive to more than one single pure tone frequency. Moreover, most of what we hear is not restricted to pure tones but complex sounds constructed of multiple harmonics. Many hair cells along the basilar membrane participate in sound transduction almost continuously (in a relative tonotopic fashion) for all but the softest of sounds. Each inner hair cell has ~10 afferents forming potent synapses on the hair cell body. By contrast, each outer hair cell has but a single afferent forming a synapse and more than one outer hair cell is innervated by a single afferent axon. The outer hair cells provide poor resolution *afferent* messages but are critical for hearing soft (low decibel level) sounds. It has been hypothesized that the outer hair cells act as a cochlear amplifier to increase the gain of the fluid motion that rocks the inner hair cell stereocilia by ~40dB; a substantial amplification of the traveling waves.

The outer hair cells have the capability of changing their shape: lengthening slightly when hyperpolarized and contracting slightly when depolarized. Since many of the outer hair cell stereocilia are “embedded” in the overlying tectorial membrane this change in shape may alter the flow of endolymph fluid that tilts the inner hair cell stereocilia. Moreover, the shortening and lengthening of the outer hair cell soma tends to push or pull on the basilar membrane and the reticular lamina. Such motion may boost the signal transduced by the inner hair cell stereocilia motion. The “motor” protein in the outer hair cells is named *prestin* and appears to be unusually fast-acting. When the outer hair cells are depolarized due to influx of K^+ and Ca^{++} ions through “tip-link” ion channels in the stereocilia of the outer hair cells, the prestin motor proteins shorten. Although the details regarding the mechanism responsible for the outer hair cell cochlear amplification have not yet been fully explained, there is evidence supporting the link between outer hair cell damage due to ototoxic drugs or due to outer hair cell damage following long exposure to loud environmental sounds/noise and a substantial reduction of basilar membrane motion coupled with a significant hearing loss.

COCHLEAR HAIR CELL MECHANOTRANSDUCTION

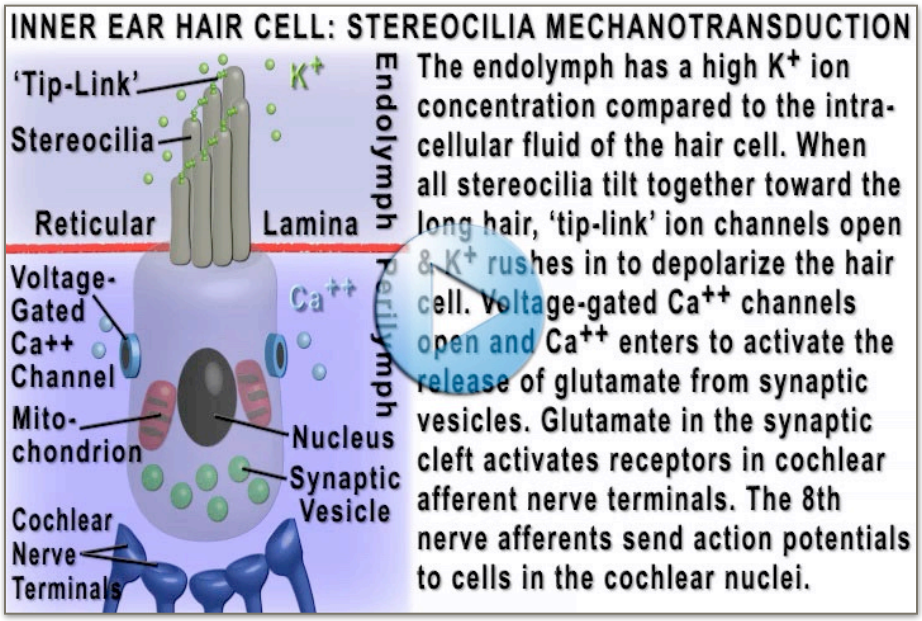
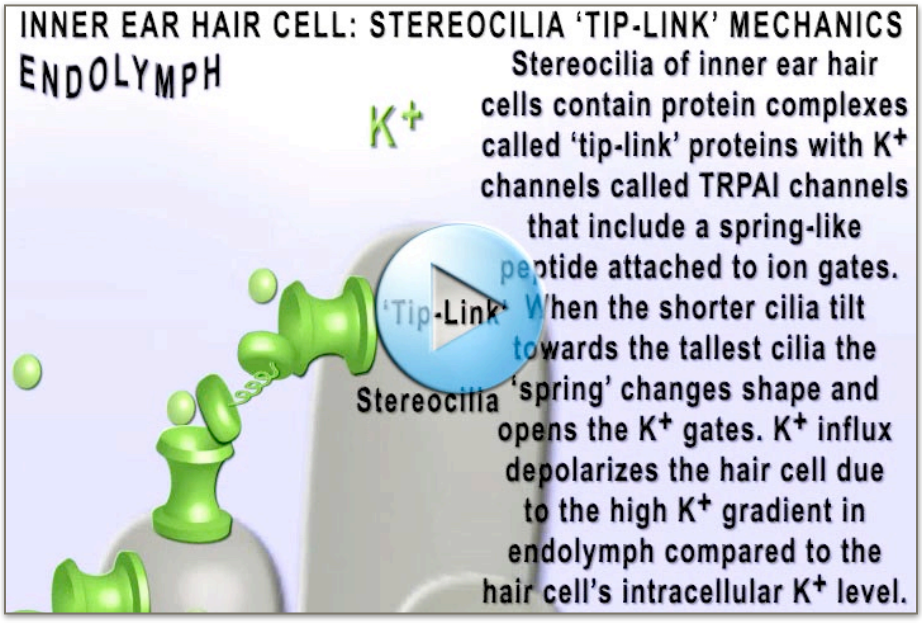


Fig 13-6. Inner Hair Cell Stereocilia Mechano-transduction (Tilt) Movie (gec). GO TO: gmomm.pitt.edu Fig13-6_Video

The hair cell in the Organ of Corti transduces traveling waves (basilar membrane rocking) and endolymph motion into stereocilia tilting. The rule is this: Tilt Towards Tall (TTT) = depolarization of hair cell and Tilt Towards Small (TTS) = hyperpolarization. The endolymph that surrounds the hair cell stereocilia has a high level of potassium compared to the intracellular concentration of K^+ within the hair cell soma. Thus it is the influx of K^+ ions (plus Ca^{++} ions) that will trigger the influx of calcium through voltage-gated Ca^{++} channels at the base of the hair cell. This activates transmitter release from the hair cell that, in turn, depolarizes auditory afferent processes that synapse on the hair cell. Action potentials in the auditory afferents travel to one of the ipsilateral cochlear nuclei to begin the central processing of auditory data.



STEREOCILIA TIP-LINK ION CHANNELS

Fig 13-7. Tip-Link Mechano-transduction in Hair Cell Stereocilia Movie (gec). GO TO: gmomm.pitt.edu Fig13-7_Video

Investigators have identified a protein complex located at the tips of the

stereocilia that are thought to provide the mechanosensitive mechanism for influx of ions when the stereocilia are tilted. These “tip-link” complexes are illustrated in the movie below. The actual mechanism contains more elements than shown in this schematic simulation.

OTOACOUSTIC EMISSIONS: ORGAN OF CORTI RETORTS

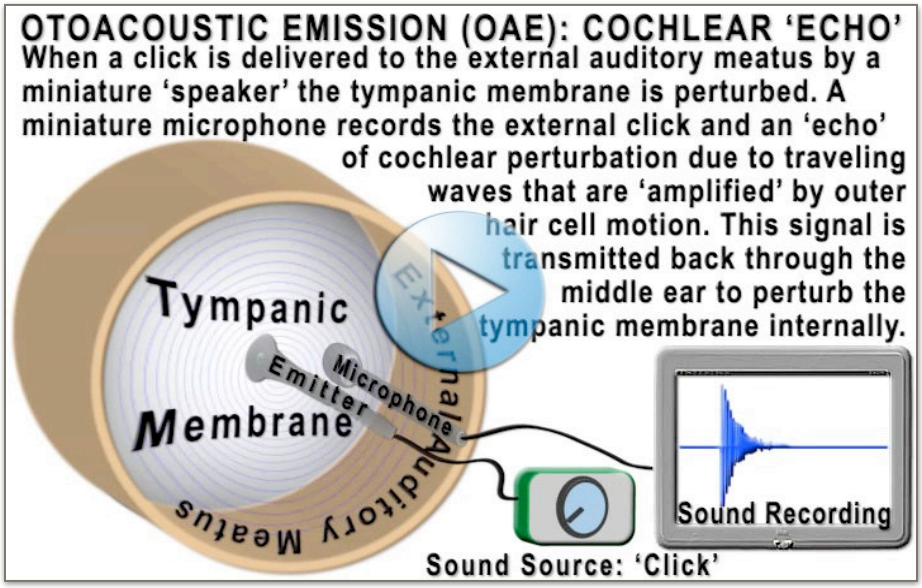


Fig 13-8. Otoacoustic Emission: Cochlear Echo Movie (gec). GO TO: gmomm.pitt.edu Fig13-8 _Video

The mechanical distortion of the Organ of Corti not only sends signals to the brain but also introduces a small echo back through the middle ear to “beat” the tympanic membrane *from the inside*. This otoacoustic generated signal depends upon a living Organ of Corti and viable outer hair cells.

Ototoxic drugs, trauma or other sources of damage particularly to outer hair cells will obliterate or significantly attenuate this internally generated “reverberation.”

The introduction of otoacoustic instrumentation in the ear canal can test for basic viability of the inner ear for individuals who are not able to be tested by way of a classic auditory hearing examination.

Other sources of internally generated signals are those associated with tinnitus. Tinnitus is described as a buzzing, humming, ringing, rushing or other abnormal consistent sound that is present even when the environment is quiet. Often this is a symptom of inner ear damage although individuals may experience this sensation after exposure to loud sound for even a short time, e.g., loud music. Tinnitus in the latter circumstance may represent a bad (inner ear) hair day. Repeated exposure to loud environments or ototoxic medications may result in outer hair cell damage that is permanent. Prolonged tinnitus is a much more serious issue that should be investigated since it is often associated with pathology of the auditory periphery. If a subject reports a spontaneous “clicking” sound this may actually be due to abnormal motion of the middle ear ossicles which should be investigated by a qualified health professional.

If this is not complicated enough for you there are known efferent axons innervating cochlear hair cells that may provide an efferent feedback to primarily the outer hair cells. It is still unclear what role the efferents have on auditory afferent transduction/ transmission of sound-induced basilar membrane motion. Some evidence suggests that activation of auditory efferents attenuates basilar membrane motion (motor gating of sensory signals via outer hair cell motility?). The cochlear efferents may also improve the ability to extract behaviorally relevant signals from noise in a complex auditory environment. The efferent axons arise primarily from cells located in the superior olive. Damage to hair cells has long been related to hearing loss due to aging or prolonged exposure to loud environments, recent research suggests a possible relationship between plastic changes in cochlear afferent and efferent endings and hearing loss.

CENTRAL AUDITORY REPRESENTATION: SHAREWARE

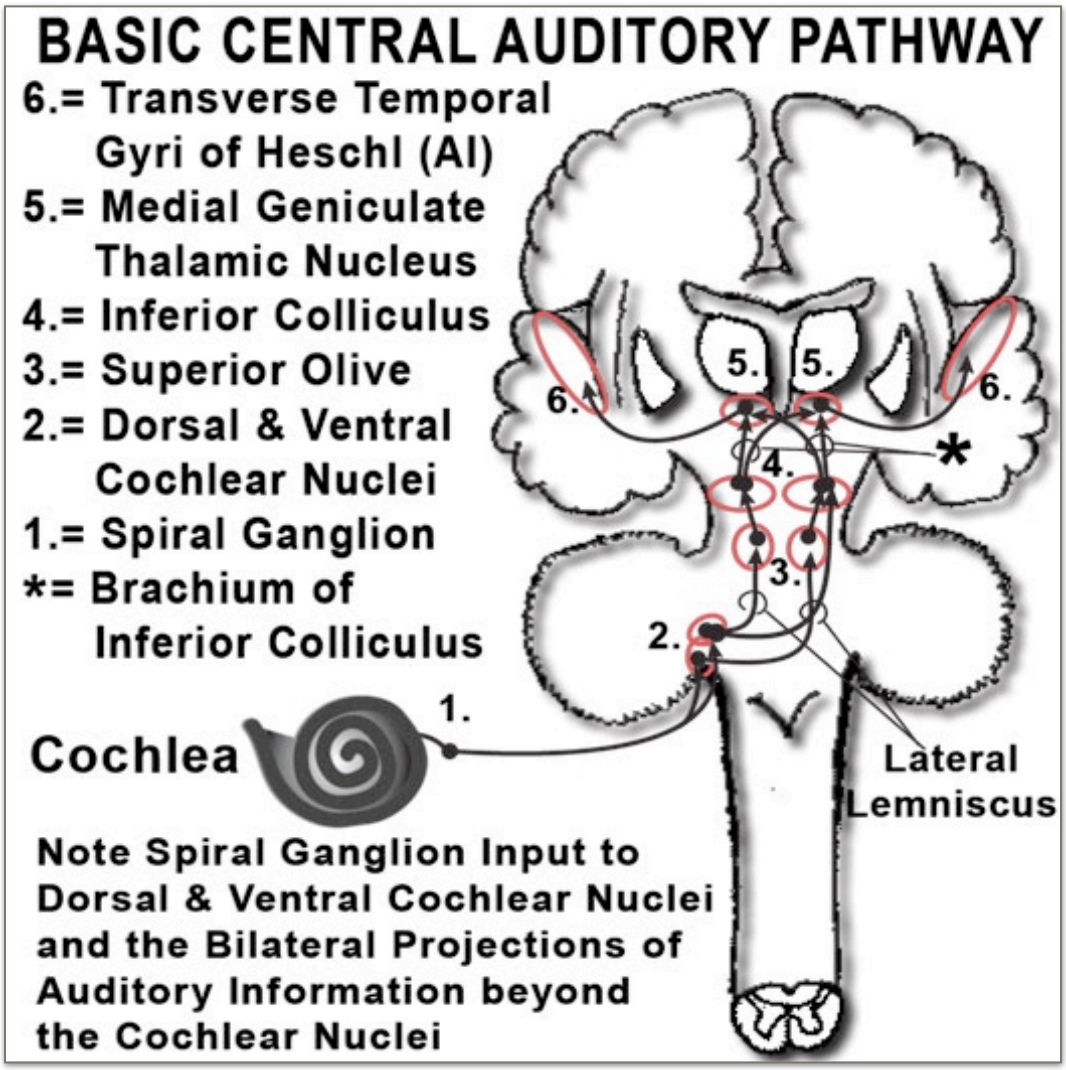


Fig 13-9. Basic Central Auditory Pathway to Primary Auditory Cortex (AI) (gec).

Auditory afferents synapse on neurons within the ipsilateral dorsal and ventral cochlear nucleus in the brainstem. All other central auditory projections from the cochlear nuclei inward up to and including the transverse temporal gyri of Heschl (primary auditory

cortex) contain a bilateral representation (neurons with binaural receptive fields). A profound unilateral deafness strongly suggests a peripheral origin for the deficit (inner ear or acoustic nerve). The following figure shows the most direct pathway from the cochlear nuclei to the transverse temporal gyri of Heschl which is the location of the primary auditory cortex (AI). Other more complex auditory connections exist that are not represented in the simplified auditory pathway.

BOTTOM-UP CENTRAL AUDITORY PROCESSING: "FUTZING" WITH BASILAR MEMBRANE SIGNALS

I am going to propose a concept that will get me into hot water with my auditory neurophysiologist colleagues. Much of the heavy lifting in bottom-up auditory processing occurs in the ear (external, middle and inner ear). The subcortical central processors of auditory information "futz" with the signals to build tonotopic contrast, distinguish where the sounds come from and assist the brain to determine whether the sounds are important to listen to. One could argue that those distinguishing features (frequency contrast, signal detection within a noisy background, sound localization & detection of behaviorally relevant salient sounds) represents ***serious*** and necessary "futzing." Most bottom-up auditory information originating from the two ears arrive at the central processing areas at slightly different times although the temporal delays between the two ears may be quite minimal. Coding of this information appears to be different depending upon the fundamental frequency components of the data. While the system can successfully phase-lock neural responses to low frequency components (up to ~3-4 kHz), higher frequency components up to 16-18 kHz for humans appear to be coded with alternative rate coding "strategies." Many synaptic potentials in the subcortical central auditory centers tend to be brief which significantly speeds up processing times. Tonotopic organization is relatively well maintained as information passes up to and within the primary auditory cortex. Phase-locking may occur at every cycle for frequencies below ~ 1 kHz or phase-locking for only a proportion of cycles for slightly higher frequencies up to ~3-4 kHz. Interaural sound intensity may differ for the two ears based upon the origin of the signal relative to placement of the two ears. The head, neck and upper body may act as a baffle that creates a "sound shadow" in different directions according to the origin of the sound relative to the person's head/neck/body for higher frequency bandwidths. Low frequency sounds that have longer wavelengths may actually "bend" around the head creating no real shadow. This intensity difference due to a "sound shadow" for higher frequencies may be sufficiently strong enough to act as an intensity code for interaural high frequency sound localization.

BRAINSTEM AUDITORY SIGNAL PROCESSING

There are two "bottom-up" mechanisms that have been suggested that allows for localization of sound at least in the horizontal plane (azimuth). One mechanism utilizes a temporal difference in arrival of sound to the two ears as a localizing signal. If a sound is directly in front of the subject the timing difference is zero. As the sound moves to the

left or right sound will now reach each ear at slightly different times. This Interaural Time Difference (ITD) signal is generated in some neurons in the Superior Olive and perhaps other brainstem auditory nuclei where very slight time differences in ipsilateral vs. contralateral inputs (<100 microseconds) facilitates best firing of ITD sensitive cells. ITD is best for lower frequency than higher frequency sounds. ITD has been demonstrated in some species that have small interaural distances (small heads) but these findings have not been replicated in other species even those with a short distance between the two ears. Several models have been proposed one of which depends upon timing of excitatory inputs from the two ears and another model suggesting that the difference in timing of fast EPSPs and IPSPs are responsible for the ITD. There is no direct evidence for ITD cells in human auditory brainstem but some psychophysical studies suggest a possibility for ITD even in big head species where ITD may be 500-600 microseconds.

The other mechanism of bottom-up sound localization involves the slight difference in intensity of sounds when directed from one side of the head. This is thought to be due to the sound shadow (baffle) due to the physical structure of the pinna, head neck and upper body. Since so many auditory brainstem neurons are binaural (other than the cochlear nuclei) matching of intensity as altered firing rate seems to be quite plausible. There is evidence that inhibitory connections from interneurons in the Nucleus of the Lateral Lemniscus (not shown in figure above) may provide the necessary modulation to enhance differences in ipsilateral versus contralateral ear inputs.

TOP-DOWN AUDITORY PROCESSING: NOW HEAR THIS!

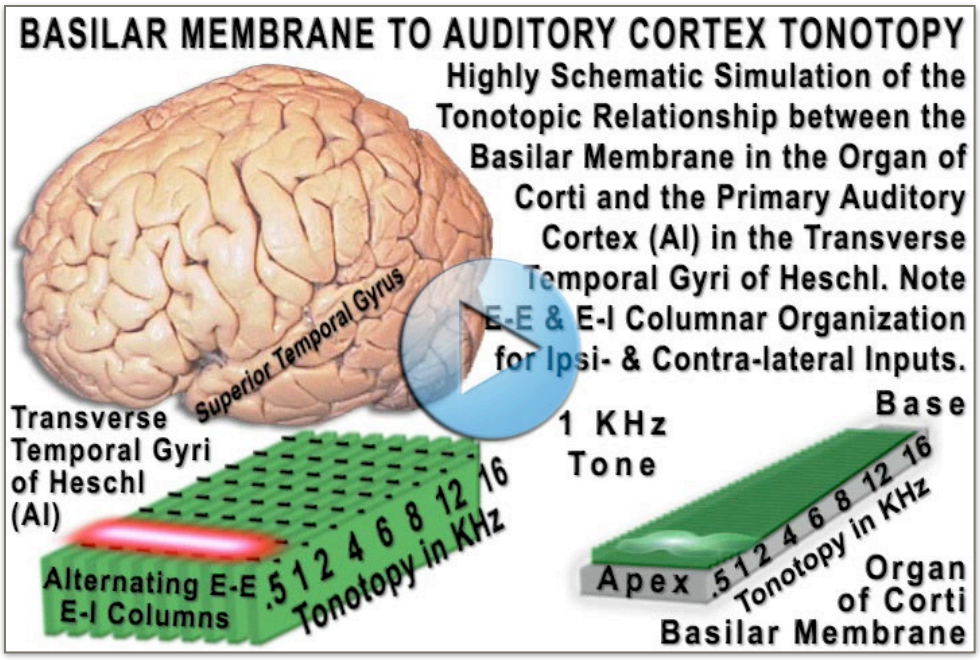


Fig 13-10. Tonotopic Representation from Basilar Membrane to Primary Auditory Cortex: A Schematic View Movie (gec). GO TO: gmomm.pitt.edu Fig13-10 Video

The other source of heavy lifting regarding sound is the top-down processing that occurs within multiple cerebral cortical areas (corticocortical or corticothalamocortical) and within

brainstem auditory neurons due to the effects of corticofugal descending influences on these initial auditory processing nuclei. Cortical auditory neurophysiologists describe a tonotopic organization within the transverse temporal gyri of Heschl along with alternating EE & EI bands of binaural neurons in auditory cortex.

EE neurons are facilitated by inputs from both ears while EI neurons are excited by one ear input but inhibited by inputs from the other ear (stereo processing). Such E-E and E-I interactions may vary by intensity in different laminae within the auditory cortex. Such variability in E-E and E-I interactions are not simulated in the schematic representation of tonotopic organization in the movie above. More complex sounds which have no pure frequency bands, e.g., “chirps”, “tweets”, “trills” and “vocalized” words may be processed by populations of auditory neurons responsive to features of the “phoneme’s” spectral content.

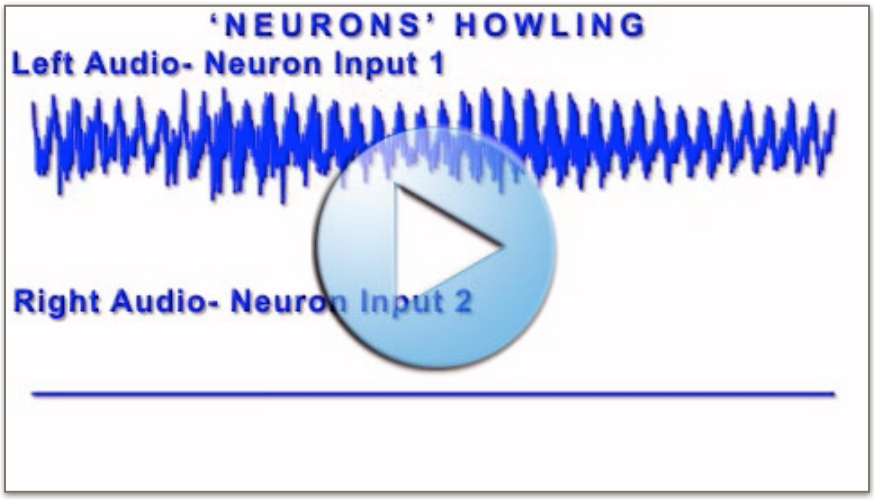


Fig 13-11. Neurons Howling Movie (gec). GO TO: gmomm.pitt.edu
Fig13-11_Video

Cortical/subcortical top-down processing helps the brain understand the intent of others (don’t talk to me with that tone of voice), communicate thoughts, ideas and feelings with others and extricate the nuances of spoken or sung words for their explicit and implicit value, e.g., music played by expert professionals that you consider to be beautifully rendered. Imagine Beethoven “hearing” the score as if it were being played by a symphonic orchestra as he placed the notes on the score: certainly his auditory brain and limbic brain areas must have been active even though his basilar membrane was not. Again, do you think that Steven King expects your auditory-related areas and limbic system to be active as you read his books even though the auditory hallmarks of terror are only imagined? The basilar membrane can transduce the real sounds but not the accompanying feelings. Corticocortical and Corticofugal modulation of brainstem centers provide top-down selectivity (fine tuning of tonotopic tuning), gain control, attentional and affective modulation of bottom-up auditory data. Listen to the song or read the lyrics (end of 1st verse) of “The Boxer” by Paul Simon released April, 1969 as a single (Simon & Garfunkel) by Columbia Records. Some individuals who have autism or age related perceptual deficits may have no such regulatory mechanism to hear only some sounds but disregard the rest. A number of studies have provided at least indirect

evidence that the central auditory tonotopy may be modified by experience or by pathology at multiple levels of the auditory system neuraxis.

Understanding spoken language or typical animal vocalizations requires not only reliable and high fidelity “bottom-up” signal processing in the listener’s ears but also a “top-down” interpretation of the complex frequency spectra and the intonation of the voiced sounds. Both of these aspects are important to understand the spoken word and the ability to recognize the particular speaker. Some voices are much better recognized and more eloquent than others. If you have stereo audio you can see and hear a particular vocalization that you would want to be able to identify and localize if hearing it in the wild: see and hear Neurons Howling Movie.

VESTIBULAR TRANSDUCTION OF HEAD/BODY MOTION ANGULAR ACCELERATION: SEMICIRCULAR CANALS

The vestibular portion of the inner ear transduces linear or angular acceleration of the head/body and provides one reference to gravity (“G” forces). The semicircular canals provide signals regarding angular acceleration in pitch, roll and yaw. The semicircular canals are filled with endolymph that after a lag transiently flows in the opposite direction to head motion.

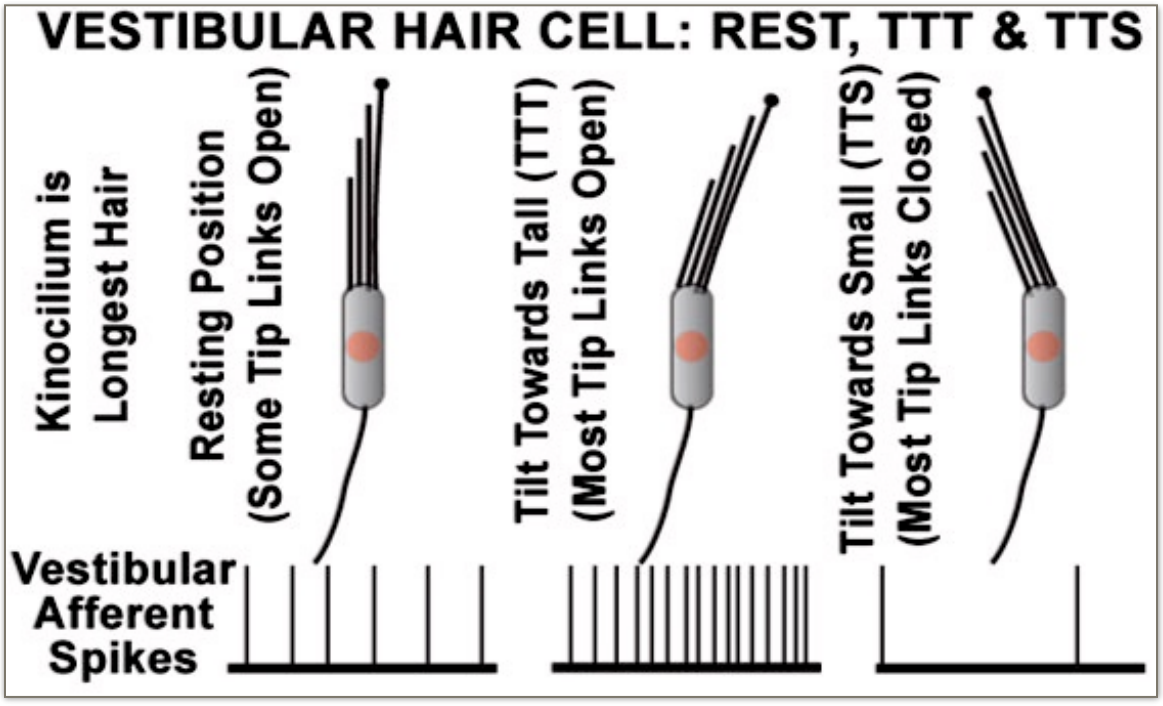


Fig 13-12. Vestibular Hair Cells of the Semicircular Canals and Otolith Organs (gec).

Within each semicircular canal hair cells similar but not identical to those in the cochlea provide the mechanotransduction when the hairs are tilted. Multiple hair cells reside within a “gelatinous” matrix called the cupula. The matrix “bends” with endolymph flow. The hairs are tilted when the cupula is displaced. The vestibular hairs have

different lengths: see Vestibular Hair Cells of the Semicircular Canals and Otolith Organs figure.

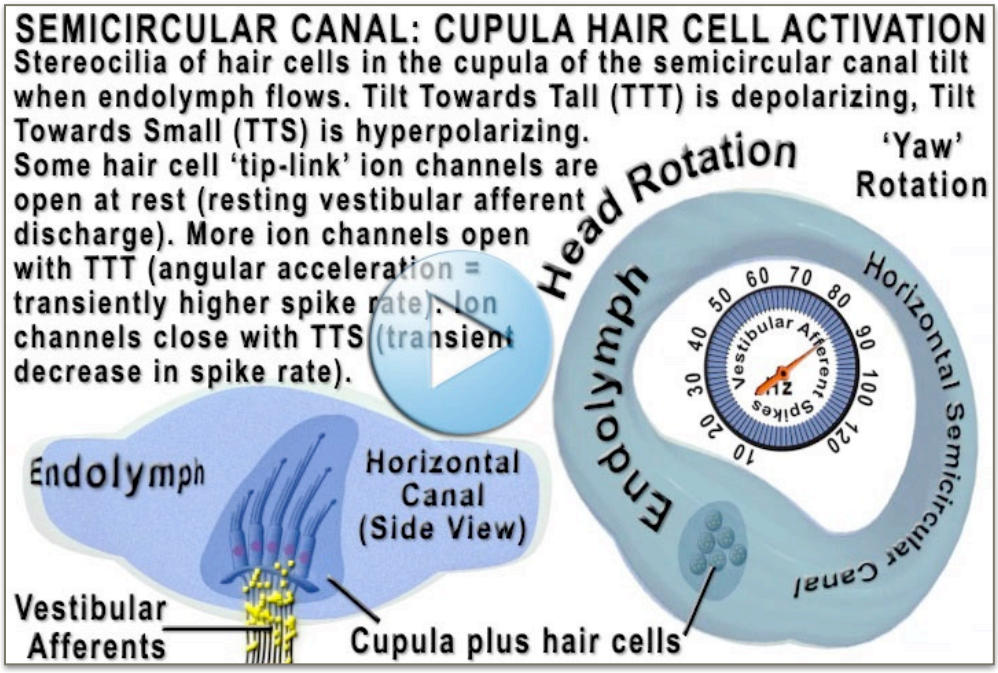


Fig 13-13. Semicircular Canal TTT Depolarization and TTS Hyper-polarization Movie (gec). GO TO: gmomm.pitt.edu Fig13-13_Video

Vestibular afferents innervate the hair cells and even when there is no head motion they provide a baseline of discharge due to the properties of tip-link protein complexes in the hair cells. The tip-link architecture for these vestibular hair cells appears to be arranged such that when the hairs are not deformed some of the tip-link channels are open allowing influx of K^+ and Ca^{++} ions. This ion influx produces a net depolarizing influence (producing a resting action potential discharge of vestibular afferents). Stereocilia for each hair cell are arranged from short to tall and a special cilium called the kinocilium is "tallest" of all. When the stereocilia of the hair cells move there is a rule as to the membrane potential fluctuation. Stereocilia Tilt Towards Tall (TTT) = increased depolarization due to more tip-link channels opening and a higher afferent discharge. Stereocilia Tilt Towards Small (TTS) = "hyperpolarizing" influence (most tip-link channels close) resulting in a decrease in vestibular afferent discharge. Thus the vestibular periphery is a source of tonic excitation to the neurons post-synaptic to this input. The vestibular system provides dynamic and static signals regarding head acceleration, head position and the relationship of the head to gravity, the head relative to "true" vertical (no head/body tilt) and the horizon. As will be discussed below the central vestibular system and the other brain areas influenced by vestibular inputs use multiple sources of information to control equilibrium, posture and eye movements (see below).

VESTIBULAR (MACULAR) OTOLITH ORGANS: SACCULE & UTRICLE

The macular portion of the vestibular peripheral sensory organs includes the utricular macula which is positioned in a primarily horizontal plane and the saccular macula that is orthogonal to the utricle and lies in a primarily vertical plane. However, the otolith organs tend to have a bend to their base structure such that activation of differently oriented macular hair cells may respond to multi-planar head motion (linear acceleration), gravitational forces and head position.

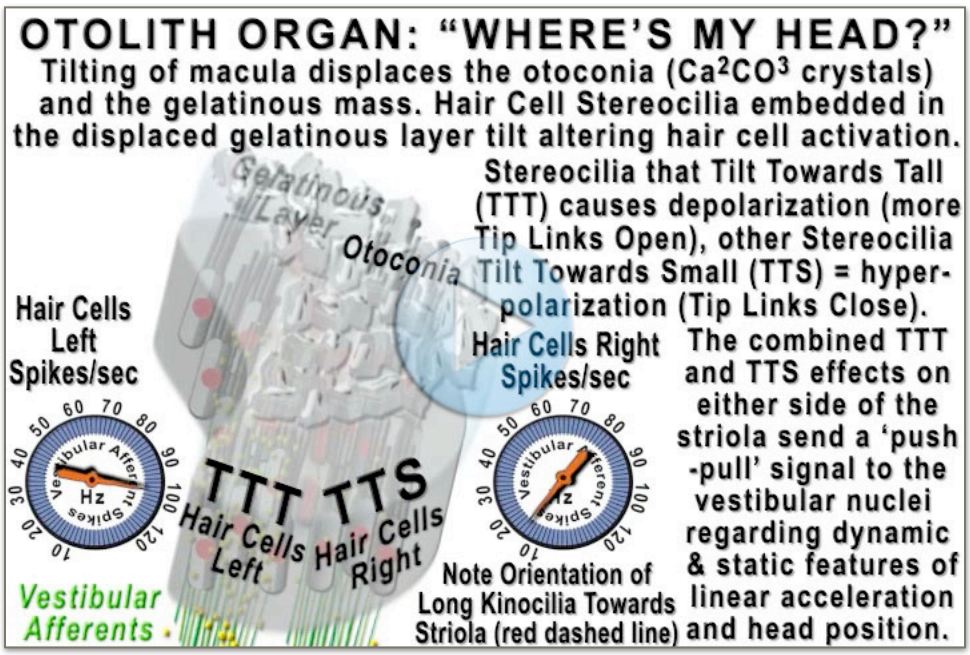


Fig 13-14. Otolith Macular Organ for Linear Acceleration and Head Position Movie (gec). GO TO: gmomm.pitt.edu Fig13-14 _Video

The hair cells of the otolith organs are similar to those located in the cupulae of the semicircular canals. There is a long kinocilium along with stereocilia of progressively shorter lengths as they get further away from the kinocilium. Like the rest of the ear from the tympanic membrane on into the cochlea and the vestibular apparatus, macular receptors are all about motion (see animation above). Endolymphatic fluid surrounds the cupulae and utricles. This fluid is continuous with the endolymph of the cochlea and disorders of endolymphatic "flow" or altered molecular/ionic composition of this fluid could result in both balance problems and hearing problems, e.g., Meniere's Disease.

VESTIBULAR NUCLEI: BASIC CONNECTIONS

Vestibular afferents provide monosynaptic excitatory inputs to virtually all portions of the ipsilateral vestibular nuclei and VIII nerve afferents provide the major source of mossy fiber excitatory input to the vestibulocerebellum: the flocculonodular lobe (flocculus and nodulus) and to portions of the midline cerebellar vermis.

The vestibular system is a phylogenetically old and highly integrated system that provides information about fundamental properties of balance and equilibrium. Such a system is highly preserved from invertebrate species that have "vestibular" organs similar to that found in the inner ear of the mammalian system. Experiments with crabs have shown that artificially substituting iron filings for calcium carbonate crystals in their

otolith organs makes them susceptible to magnetic fields that get crabs moving in unusual ways.

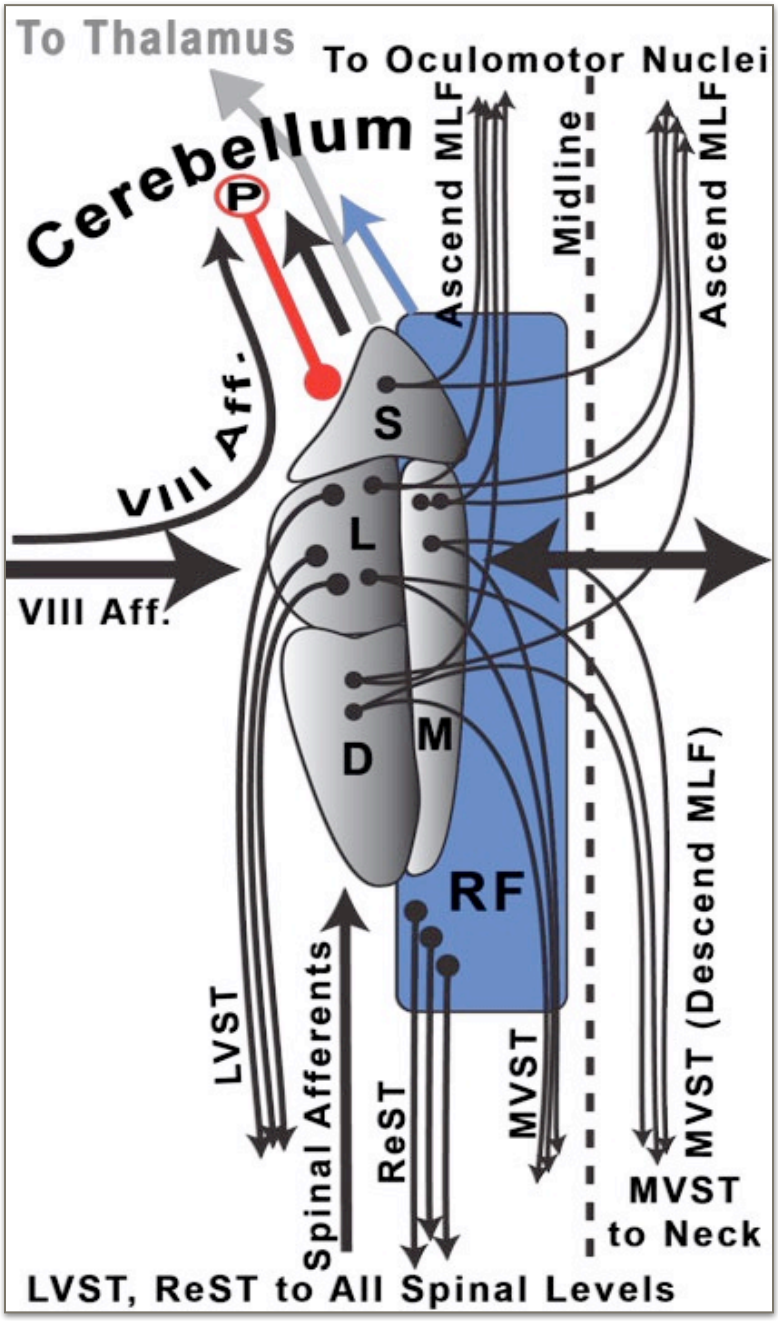


Fig 13-15. Major Connections of the Vestibular Nuclei. Key: Vestibular nuclei: D= Descending, L= Lateral, M= Medial, S= Superior Nucleus; RF= Reticular Formation; LVST = Lateral Vestibulospinal Tract; MVST= Medial Vestibulospinal Tract; MLF= Medial Longitudinal Fasciculus; VIII Aff.= Vestibular Afferents; P= Purkinje cells in Vestibulo-cerebellar Cortex; DoubleArrow = Bilateral Connections between Right and Left Vestibular Nuclei.

Indeed unless your work or recreational activities dynamically "tax" your inner ear you will be oblivious to the incredible signals generated by your vestibular organs. These receptors may only loom into awareness when their is vestibular dysfunction. Vertigo, dysequilibrium, blurred vision when moving your head and nausea with head motion all get your attention.

The Vestibular Nuclei include a Superior, Medial, Descending and Lateral Nucleus. Right and left vestibular nuclei are heavily interconnected. The major source of excitatory peripheral input comes from vestibular afferents innervating the semicircular canal cupulae and the otolith organs of the utricle and saccule. Not all subnuclei receive the same type or extent of vestibular inputs from the various semicircular canals and otolith organs (not illustrated here). Other excitatory inputs to the vestibular nuclei come from spinal sources (primarily proprioceptive input from muscle receptors and joint receptors). Much

of this proprioceptive input originates from deep cervical axial muscles and from apophyseal joints of cervical vertebrae. The deep muscles of the neck have a very high density of muscle spindles compared to other axial and limb skeletal muscles. Neck proprioceptive inputs may provide either a canceling effect as referenced to vestibular inputs or in some cases neck and vestibular inputs may be additive. Vestibular Nuclei have reciprocal connections with some reticular formation nuclei and vestibular nuclei as well as vestibular afferents provide mossy fiber inputs to the flocculonodular lobe and portions of the vermis of the cerebellum (vestibulocerebellum). The flocculonodular lobe Purkinje cells provide a powerful GABAergic inhibitory input back to the vestibular nuclei. Excitatory output from a portion of the fastigial nucleus of the cerebellum provides inputs to the vestibular nuclei and reticular formation.

Two descending vestibulospinal tracts influence the spinal cord. The lateral vestibulospinal tract (LVST) influences axial and proximal (limb girdle) segmental motor centers at all levels of the spinal cord. The LVST along with the Reticulospinal tracts (ReST) influence medial motor nuclei bilaterally at all levels of the spinal cord. The medial vestibulospinal tract (MVST) influences neck only segmental motor centers. The MVST as well as tectospinal tract axons and some ReST axons form the descending medial longitudinal fasciculus (MLF) that in conjunction with the ascending MLF provides a pathway that coordinates head and eye movements. The descending MLF targets segmental motor centers (ventral horn interneurons and motoneurons) controlling neck muscles as well as cervical propriospinal neurons that assist in coordination of neck/trunk axial muscles and limb muscles for large scale muscle synergies required for postural control.

VESTIBULAR NUCLEI: PUSH-PULL ANTAGONISM

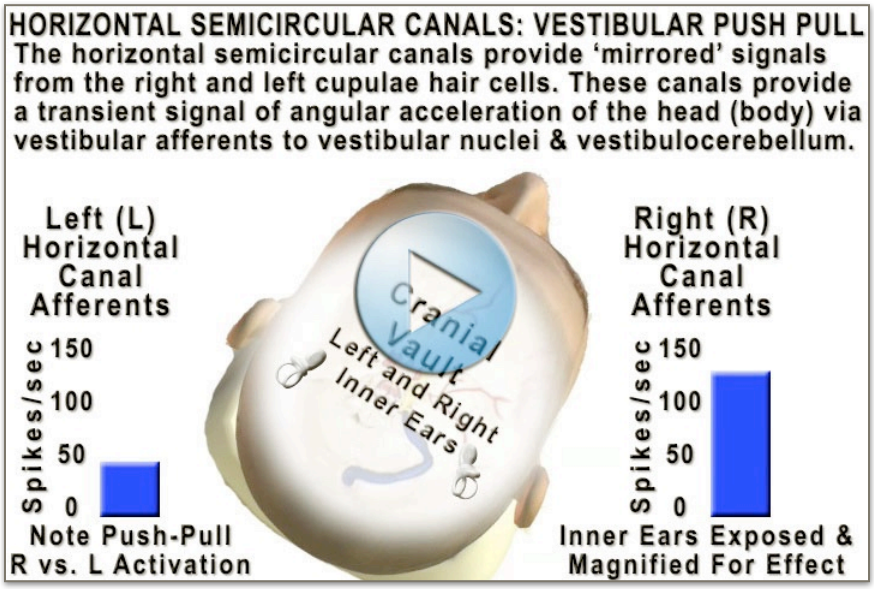


Fig 13-16. Vestibular Push-Pull Antagonism Movie (gec). GO TO: gmomm.pitt.edu *Fig13-16_Video*

Input from the semicircular canals on either side of the head tend to be antagonistic to one another. For example, head motion will increase discharge from semicircular canal vestibular afferents on one side while the other side has an ~equal decrease in discharge. Since the right and left vestibular nuclei are

interconnected with one another and are reciprocally connected with the vestibulocerebellum the two sides provide a push-pull signal of head acceleration. If this balance is disturbed the subject may experience multiple signs and symptoms of a vestibular disorder (see below). The following movie attempts to demonstrate this balanced push-pull antagonism that provides a signal regarding motion while not impairing our vision (VestibuloOcular Reflex-VOR) mechanism nor our balance/ equilibrium due to vestibular signal transients.

VESTIBULAR FUNCTION: EQUILIBRIUM, BALANCE, HEAD AND EYE MOVEMENT CONTROL

Endolymph flow in the semicircular canals and the maculae provide important cues regarding head motion and position that assist in stabilization of eye movements and postural musculature as we move. Since the head is like a bowling ball balanced on a small pedestal (atlas/axis) the ability to balance that mass while still moving the rest of the body attached to the pedestal may not be something that the vestibular system can accomplish on its own. IT (inner ear) has help. Somatosensory cues including tactile and proprioceptive information plus vision round out the sensory cues to assist and modulate information arising from the vestibular apparatus. One might imagine that in their absence (total deafferentation and no vision) that the vestibular system will be highly taxed and unable to provide the rapid responses to body/head motion that normally occurs when the three sources (vestibular/visual/somatosensory) are integrated in the intact nervous system. Vestibular inputs to Ventral and Pulvinar Thalamic Nuclei provide a source of thalamocortical vestibular influence to Area 3a Somatosensory Cortex and to other Posterior Parietal Areas. Direct vestibular afferent input to and indirect vestibular nuclei reciprocal connections with the cerebellum appear to be critical adaptive circuitry for equilibrium and dynamic postural control. One wonders whether a brain having only isolated vestibular information might alter the individual's perception of "where is my head?" Without somatosensory and visual cues, vestibular cues originating in the head might be very craniocentric in their referential data. Perhaps the isolated inner ear could persuade the brain to think that the bowling ball (head) is a bit wobbly since it now seems to be "passively" placed on its pedestal (neck) held there only by gravitational forces. Remember that non-vestibular (somatosensory and visual) cues are organized in vestibular and other brainstem nuclei that are interconnected with the cerebellum and thalamus. Even more drastic might be the illusion that the head is "detached" from any body beneath it when there is such a limited scope of knowledge from alternative cues concerning the constraints and affordances related to the environment in which it lives. A head tilt could be perceived as a very risky event if there are no non-vestibular cues to prevent the illusion that your smart bowling ball is about to fall off its pedestal. Head and body motion is typically self-actuated. Therefore the motor system has some say regarding our estimates of where our head and body are in space and how such estimates are "computed" within brain areas that integrate sensorimotor signals.

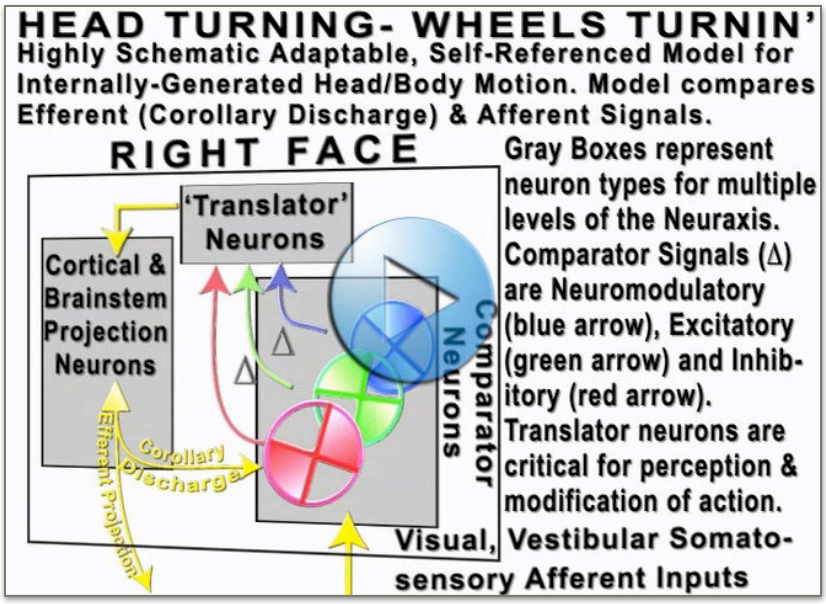


Fig 13-17. Highly Schematic Model for Self Generated Head/Body SensoriMotor Comparator Movie (gec). GO TO: gmomm.pitt.edu
Fig13-17_Video

Few studies have directly examined signal processing within the vestibular system in freely moving subjects but when this has been done the findings would suggest that any relatively linear multisensory integration due to passive head/body translations becomes quite nonlinear when the motor system evokes intrinsic self-motion cues (internal "virtual reality" model). Based upon relatively limited direct evidence, it is suggested that motor corollary discharges (re-efference) modulate and provide some level of gating of multisensory motion cues. Likely brain areas for such motor-out (top-down) versus sensory-in (bottom-up) comparisons would include: portions of the cerebellum, the cerebello-rubro-olivo-cerebellar loop, the basal ganglia, the superior colliculus, portions of the thalamus, the cerebral cortex and perhaps even the cervical long propriospinal neurons. Bernstein's hypothesized circular servo-loop nervous system organization would seem to be an ideal model for a brain that utilizes a process of matching what is expected (anticipated) with what actually ensues as we move. The error signal generated by any mismatch (which most certainly will occur) provides a learning signal for better matching on subsequent trials that have similar characteristic features. Bernstein's servo-loop hypothesis was discussed earlier and will be revisited in later chapters. A highly schematic representation of a top-down versus bottom-up comparator model is animated (Head Turning-Wheels Turnin' Movie.) Note that the "Translator," Comparator and Descending Projection Neurons may be next door neighbors in certain brain areas, e.g, cerebral cortex or superior colliculus not always anatomically isolated to separate nervous system levels.

Any lesion that 1.) interrupts one or more sensory channels, 2.) disrupts the normal flow of that information, 3.) alters the processing centers for motor-sensory matching or 4.) disrupts the "motor" corollary discharges will render the brain a "skeptic" of any sensory updates that it receives when that brain's owner moves. The "logical" result would be a tentative system that must use much greater caution in what it does (slower, guarded movements). Major errors when matching "Top-Down" and "Bottom-Up" signals results in an internal model that is ***not*** part of the normal repertoire, i.e., one based on

past experience. Lesions in the cerebellum, basal ganglia and posterior parietal cortex are known locations where such mismatching of data results in a variety of postural and movement dysfunctions. Lesions in these locations may severely tax the brain's plastic resources to compensate and regain function. The altered brain is now suddenly less sophisticated and less confident about predicting positive outcomes in a feedforward manner. ***Is there a rehabilitation specialist in the house?***

The vestibular system will be further discussed regarding its role in Posture and Locomotion in the chapter bearing that name. The relationship of the vestibular system to the cerebellum is further explored in the Cerebellum chapter. The VestibuloOcular Reflex (VOR) has been discussed in the prior chapter on Vision.

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Chapter 14

MOTOR SYSTEM: INTRODUCTION-PERIPHERAL & SPINAL

The motor system provides the neural control of the musculoskeletal system so that you may move within and manipulate your environment with some degree of grace & confidence even in the face of external perturbations. The motor system includes well-connected neural networks at the spinal, brainstem, cerebellar and cortical levels that implement and regulate motor control. Sensory & motor functions are often tightly coupled, and certain behaviors e.g., active touch, represent our nervous system's propensity to actively seek information, not just react to stimuli. Skeletal muscle provides one means to a behavioral end.

SKELETAL MUSCLE: MUSCLE FIBERS, MYOFIBRILS AND MYOFILAMENTS

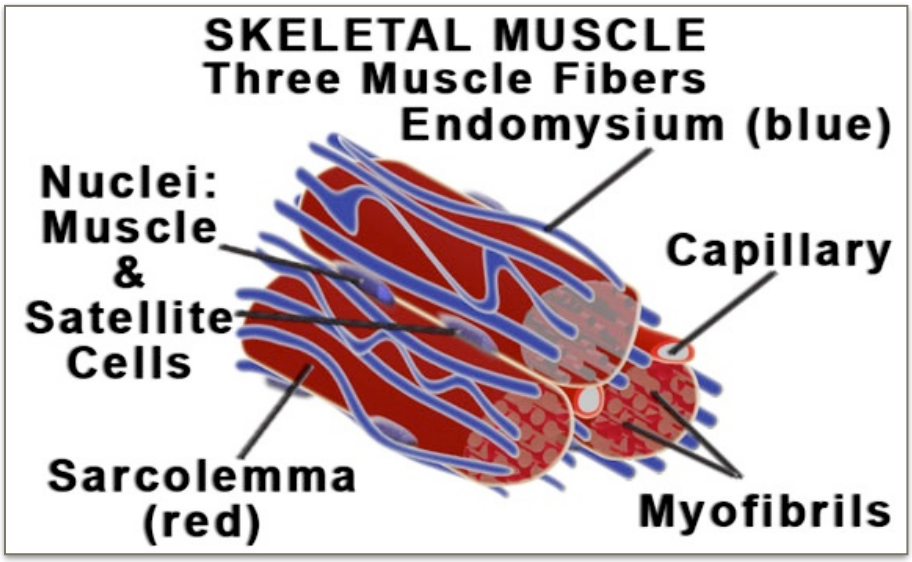


Fig 14-1. Muscle Architecture at the muscle fiber level (gec).

Muscle contains contractile and non-contractile proteins. Contractile proteins (myosin and actin) generate the tension in the muscle. Non-contractile proteins include those that provide ultrastructural integrity: epimysium, perimysium and endomysium as well as proteins that convert excitability into contraction: sarcolemma, sarcoplasmic reticulum, troponin, tropomyosin, T-tubule system. Blood supply is well developed in skeletal muscle. All contribute to skeletal muscle function. Many of the non-contractile tissues have high elasticity and thus contribute to passive tension when a muscle is lengthened (see below).

SKELETAL MUSCLE THICK AND THIN MYOFILAMENTS: CONTRACTILE PROTEINS

Muscles contain many muscle fibers that, in turn, are composed of myofibrils that have organized matrices of multiple thick and thin myofilaments. Myofilaments are parsed into serially connected sarcomeres separated by Z lines.

Myofilaments are the contractile portion of muscle where cross-bridges are formed as contraction proceeds (myosin heads protruding from the thick myofilaments transiently bind with troponin binding sites on the thin myofilaments to produce the power stroke). Myofilaments produce active tension. Sarcomeres lengthen or shorten as the muscle changes its length. Prolonged immobilization of a muscle in a shortened or lengthened position will alter length-tension curves & alter the number, length, and cross-sectional area of sarcomeres.

Skeletal muscle is mutable (plastic). Increasing use produces alterations in contractile and/or non-contractile structural and metabolic proteins within the active muscle. Therapeutic exercise that targets strength gains through progressive loading increases contractile protein density (thick & thin myofilaments). Exercise that targets muscle endurance through low load, high repetition will add metabolic proteins: increased mitochondrial numbers/size and improve microvasculature within the muscle.

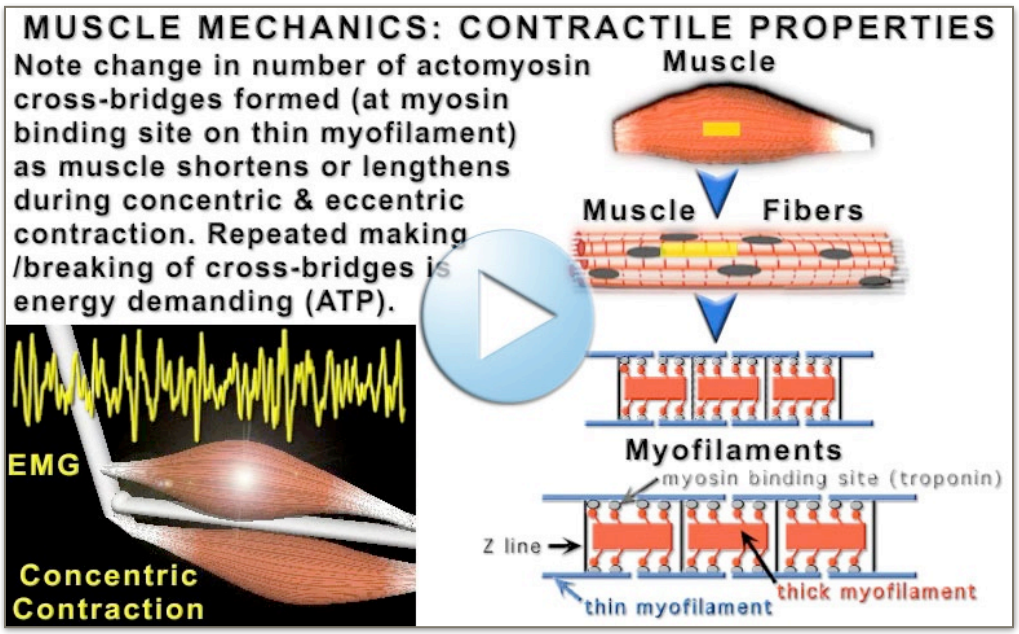


Fig 14-2. Muscle Mechanics and Length-Tension Relation-ship Movie (gec). GO TO: gmomm.pitt.edu Fig14-2_Video

At short lengths thin myofilaments overlap and relatively few binding sites are exposed (low active tension). At long lengths the thin myofilaments are so elongated that the myosin heads are out of reach of most binding sites (low active tension). The most number of binding sites occurs at a middle length (optimal length or Lo). This corresponds approximately to the resting length of the muscle. Muscle contains non-contractile elements e.g., sarcoplasmic reticulum, endomysium and other supportive tissues. Beyond the resting length these tissues provide passive tension as they are stretched. Total tension at the longer lengths is composed of active tension (which declines as the muscle elongates) and passive tension (that rises with longer length). At short lengths total tension equals active tension due only to contractile components. Total tension does not decline as steeply at long lengths since passive tension "takes up the slack" of declining active tension. These relationships between

length and tension (length-tension curve) are measured in free muscle placed in an isometric jig where the muscle is tetanized by artificial stimulation. Muscles in-situ rarely reach the shortest and longest lengths that are tested in the muscle jig (*in-vivo* working range is limited by skeletal attachments).

Immobilization of a limb typically leads to secondary changes in non-contractile proteins in joints and muscle. In addition, contractile proteins are altered secondary to long-term immobilization. Sarcomeres lengthen or shorten as the muscle changes its length. Prolonged immobilization of a muscle in a shortened or lengthened position will alter length-tension curves and alter the number, length, and cross-sectional area of sarcomeres. Actual changes depend on the muscle's architecture, e.g., fusiform vs. pennate and whether it is a unijoint or multijoint muscle.

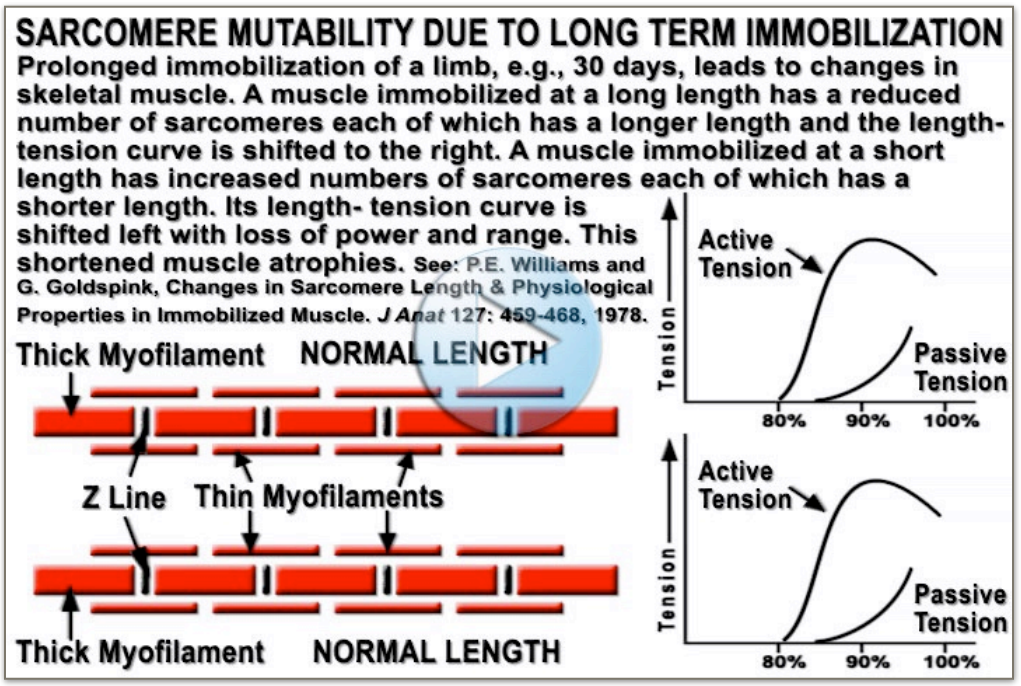


Fig 14-3. Immobilization Alterations of Muscle Physiology and Sarcomere Ultrastructure (gec). GO TO: gmomm.pitt.edu Fig14-3 Video

MUSCLE ACTION

POTENTIALS ARISE FROM ELECTRICAL ACTIVITY OF CONTRACTING MUSCLE FIBERS.

Perhaps the simplest movement is one where the agonist does most or all the work. Such a movement may be the lifting (concentric/shortening contraction) followed by the lowering (eccentric/lengthening contraction) of a load by the agonist muscle. If the agonist and antagonist cross only one joint and the muscles have no other role (e.g., for stabilization of a more proximal joint), then the antagonist muscle may be relatively silent. In reality these conditions are rarely met. Mammalian skeletal muscles are often multiarticular and simultaneously control multiple degrees of freedom in a moving limb.

This animation shows activation of gamma and alpha motor axons during lifting and lowering of a load, as well as, muscle spindle and GTO afferent discharge as the

muscle contracts and changes length. Activation is illustrated by glowing lights entering or exiting the muscle. Maximal activity occurs at the muscle's optimal length during both concentric and eccentric phases of contraction. The 'raw' Electromyogram (EMG) of the muscle (green trace) shows the waxing and waning of activity as the muscle shortens and lengthens (look and listen!). Note greater EMG for the concentric versus eccentric phase of the contraction (EMG trace = 200 msec). The dynamic Spectral Density histogram of the EMG shows the frequency distribution (3-300 Hz) of the motor unit action potentials (MUAPs) as the contraction proceeds. This is not the firing rate of individual motor units but the summed activity of all MUAPs. This partially accounts for the higher frequency components of the signal (especially when there is greater overlap of MUAP signals).

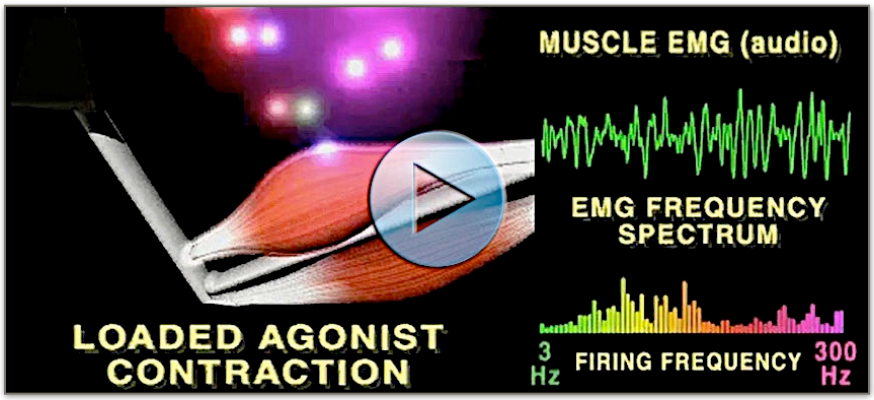


Fig 14-4. Electromyography (EMG): Electrical Activity Recorded from Contracting Muscle Movie (gec, dh). GO TO: gmomm.pitt.edu
Fig14-4_Video

MOTOR UNIT: FUNCTIONAL UNIT OF MAMMALIAN SKELETAL MUSCLE CONTRACTIONS

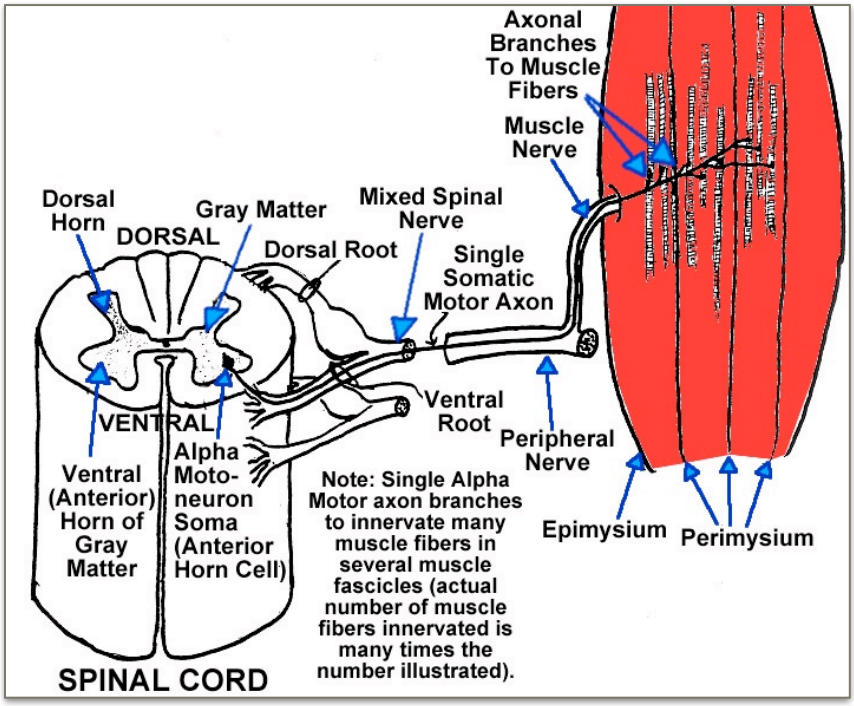
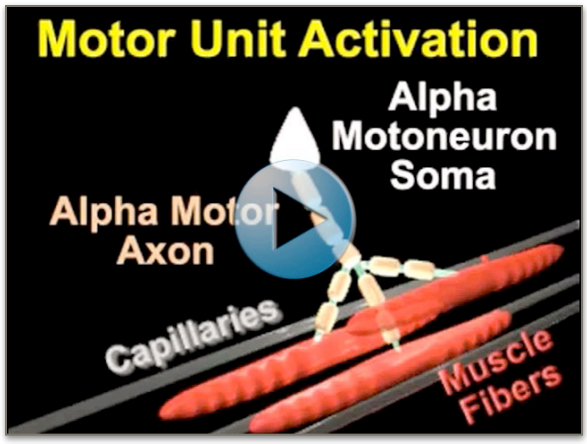


Fig 14-5A. Components of the Motor Unit (gec).

C. S. Sherrington described the alpha motoneuron (AMN) and the many muscle fibers innervated by the AMN as the motor unit. The motor unit is the functional unit of contraction in skeletal muscle. Normally, once an action potential is conducted from the axon hillock of the AMN to the muscle, all muscle fibers contacted by the axon collaterals will be activated.

Fig 14-5B. Motor Unit Activation Movie (gec). GO TO: gmomm.pitt.edu *Fig14-5_Video*



This assumes that the periphery (nerve and muscle) is intact, the neuromuscular junction is functioning normally and muscles are unfatigued. Sherrington referred to the alpha motoneuron (anterior horn cell) as the final common pathway for all movements involving skeletal muscle. Weakness may result from muscle disease, neuromuscular junction defects or Lower Motor Neuron (LMN) pathology. LMN pathology includes Motoneuron Disease, and peripheral nerve disorders (including large fiber peripheral neuropathies) that effect large alpha motor axons anywhere from the ventral root to intramuscular alpha motor axon collaterals: Motor Unit Activation Movie.

ELECTROMYOGRAPHY (EMG) RECORDING MOTOR UNITS IN ACTION

Does our nervous system control one muscle at a time? At one level (Sherrington's Final Common Pathway) our nervous system must control individual functional units (motor units) within each muscle. Ultimately, motoneurons and interneurons of the segmental motor centers (SMCs) are responsible for this crucial task. However, if our central nervous system had the responsibility of individually keeping track of each and every motor unit's firing pattern during complex movements, our heads would never fit through most doors. By contrast, our motor system is complex enough, confident enough and sophisticated enough to resist any temptation to "micromanage" actions except for rare circumstances (see below).

The motor system is a perfect example of the power of distributed control and the ability to use information to adapt, learn and improve the efficiency of muscular output as finely tuned synergistic groups. However, we CAN recruit an individual motor unit. John V. Basmajian, showed that individuals can recruit a single motor unit, in isolation, when trained to do so with Electromyographic (EMG) Biofeedback Single Motor Unit Training (SMT). Recording EMG through indwelling, fine-wire electrodes, many different muscles were trained. Using audio/visual representations of muscle activity, EMG Biofeedback has been used successfully as an auxiliary modality during motor "retraining" (muscle reeducation). Basmajian and others found that no specific talent is required for SMT. You do not have to be an athlete, scholar or musician for SMT. Actually skilled workers may require longer training periods than those with no specific skills/talents. This suggests an inherited motor control system capable of facilitating select alpha motoneurons while suppressing others within a given muscle! Play movie.

See: J.V. Basmajian, Muscles Alive: Their Functions Revealed By Electromyography. Baltimore, Williams & Wilkins, 114-130, 1974.

Fig 14-6. Single Motor Unit Electromyographic (EMG) Biofeedback Movie (gec). GO TO: gmomm.pitt.edu
Fig14-6_Video

MOTOR UNIT TYPES: SLOW TWITCH (S) AND FAST TWITCH (FF, FR)

At one time muscles were classified as being either slow (red) or fast (white). Investigations begun in the 1960s and '70s further delineated the characteristics of individual motor units. A motor unit is defined here as the alpha motoneuron, alpha motor axon, all of its branches within an anatomically defined muscle, and all the skeletal (extrafusal) muscle fibers innervated at the neuromuscular junctions (end plate zones) for those motor axon branches within the muscle. Classic studies by R.E. Burke and colleagues identified fast twitch and slow twitch motor units. Physiological, morphological, contractile and metabolic differences in motor units revealed three major types: slow twitch (S), fast twitch fatigue-resistant (FR), and fast twitch fast-fatigue (FF) in mammalian limb muscles. A fourth type called fast intermediate (FI) accounted for a minority of motor units that fall in the continuum from slow to fast. Other investigators (V.R. Edgerton & colleagues) further characterized the metabolic profiles of the motor unit types. The S motor unit is classified as SO (slow oxidative) because of its contractile properties and reliance on aerobic metabolic pathways. Likewise the FR motor unit is known as the FOG (fast oxidative-glycolytic) due to its fast contractile properties coupled to either an oxidative or a glycolytic metabolism. The FF motor unit is called FG (fast glycolytic) since this motor unit uses an anaerobic metabolic pathway exclusively. Histochemical studies of human muscle have attempted to correlate these findings with the biochemical profile of skeletal muscle fibers. Type I is associated with S (SO), type IIA with FR (FOG), and type IIB with FF (FG). These classifications are not inclusive for all striated muscle; facial muscles, deep paraspinal muscles, and extraocular muscles have motor units with contractile & metabolic profiles that may be quite different from the classic three. Each motor unit contributes to the total tension/ force produced by the anatomically defined muscle. It should be noted that the muscle

fibers within each motor unit are not typically clustered within a single muscle fascicle but are spread among several fascicles which helps to distribute the tension/force produced by each motor unit. There is some evidence that different motor unit types may be distributed in a non-random fashion, e.g., superficial vs. deep within the muscle.

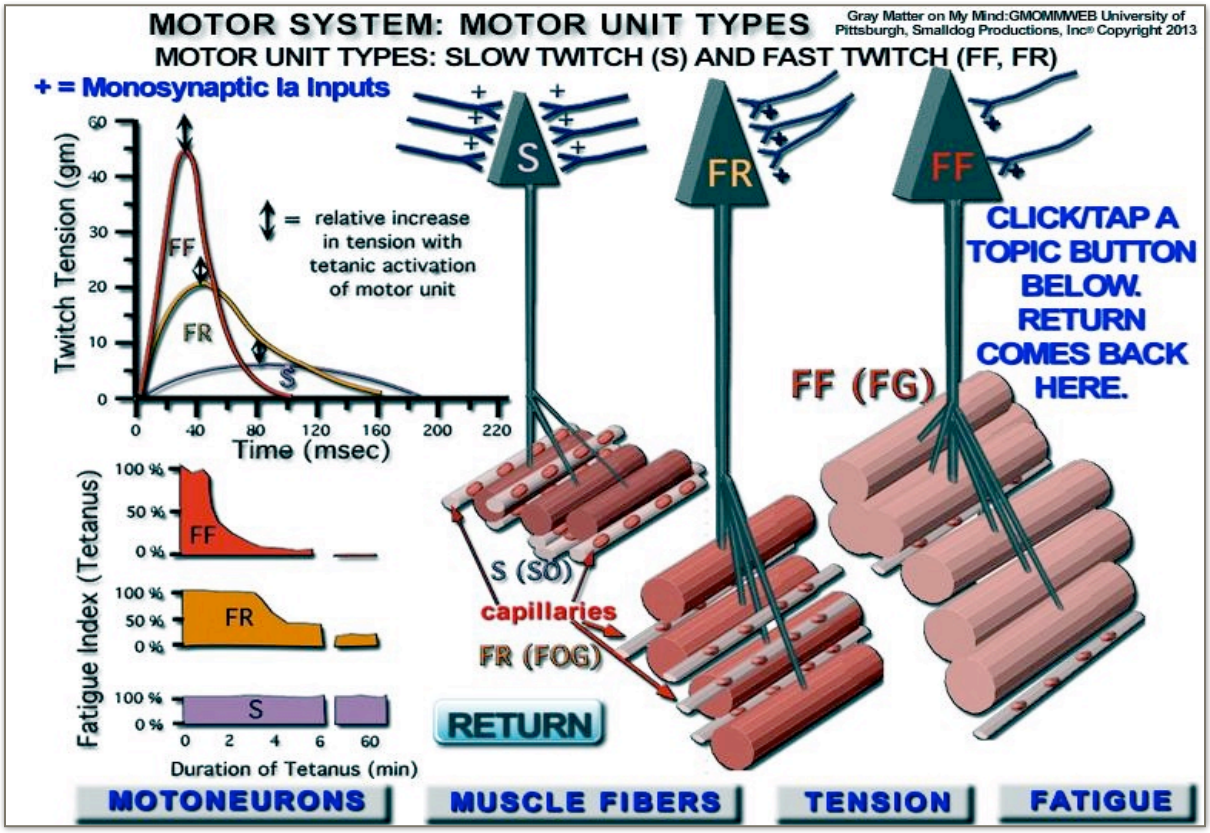


Fig 14-7. Fast Twitch and Slow Twitch Motor Unit Type Introduction Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig14-7_Interactive Media]

MOTOR UNIT TYPE CHARACTERISTICS: MOTONEURON SOMAS

The slow twitch (S) motoneuron somas are the smallest of the three alpha motoneuron types: S, FR, FF. The S motoneuron's small soma size relates to its early recruitment in motor output. According to the size principle (of Henneman) the resistive/capacitive properties of the motoneuron soma size directly influence the level of excitation needed to get the cell to fire an action potential. The smaller S motoneuron soma requires less total depolarizing input to raise its level of excitation to threshold. The larger FR and largest FF motoneurons require more depolarizing inputs to raise their level to threshold as compared to the S motoneuron. The order of recruitment for activities requiring greater levels of force is S, then FR, then FF. Other factors may also influence recruitment order. For example, the S motoneuron has a dense population of

monosynaptic Ia afferent input from muscle spindles in the agonist muscle(s). This Ia input is proportionally less to the FR and FF motoneurons (see Ia inputs). Phasic stretch to the agonist muscles will provide a strong excitatory drive to the slow twitch motor units as compared to the fast twitch motor units. On the other hand, S motoneurons have little polysynaptic FRA (flexion reflex afferent) input compared to the fast twitch motoneurons (not illustrated). The alpha motor axon is slightly smaller and slower conducting (~10-20 % slower) than axons of the fast twitch axons (but still faster than the gamma motor axons).

MOTOR UNIT TYPE CHARACTERISTICS: MUSCLE FIBERS

Compared to the fast twitch muscle fibers, the slow twitch (S) muscle fibers have a smaller cross-sectional area (less tension), have more mitochondria, and are surrounded by a richer bed of capillaries. The S motor units are called SO because their twitch properties are slow and they use oxidative metabolism only. In other words, the SO muscle fibers use an aerobic metabolic pathway exclusively. As long as the blood supply is maintained, adequate perfusion is maintained, and adequate serum glucose or fatty acids are present, these muscle fibers can continue to generate tension. These are the endurance motor units used for posture, locomotion, and most daily activities that do not require high force output. These muscle fibers are usually identified as type I fibers by histochemical staining for Myosin ATPase. S motor unit territories range from small to medium (innervation ratios of 1: 100-200) although this varies across individuals and species.

FR muscle fibers are intermediate between S and FF in their cross-sectional area, number & size of mitochondria, amount of stored glycogen, and the number of capillaries surrounding them. They are called FOG since they are Fast twitch and use either an Oxidative or Glycolytic metabolic pathway. They can go either way depending on the current circumstances. FOGs are often classified as type IIA according to histochemical profiles of their myosin ATPase staining. They are called to action as force demands increase and as tasks demand speed or rapid bursts of activity. These motor units have some resistance to fatigue but cannot sustain a maximal output for long duration activities without endurance training.

The fast twitch fast-fatigue (FF) muscle fibers are the largest in cross-sectional area. The pale FF muscle fibers have relatively few mitochondria, a sparse capillary supply, and are loaded with stored muscle glycogen (source of energy). FF are called FG since they are Fast and use only a Glycolytic metabolic pathway. They constitute the major bulk of most mixed muscles but are called into action only for limited tasks that require rapid, and transient very high force output. Type FF (FG) motor unit territories are usually large with innervation ratios of 1: 600-800 with considerable variations across muscles and species. FG are usually classified histochemically as type IIB.

MOTOR UNIT TYPE CHARACTERISTICS: TWITCH & TETANIC TENSION

The Slow twitch (S) motor unit twitch tension is low and slow. The time to peak tension is 100-120 milliseconds and the relaxation time is even longer (see twitch tension curve). The effect of tetanizing the S motor unit is to actually double the tension output (in this example from 5 to 10 units of tension). S motor units are recruited first in almost all activities that you do. As tension requirements increase the FR and finally the FF motor units are added (i.e., the S motor units are not typically disengaged with higher force muscle activation). This recruitment order from S to S+FR to S+FR+FF with increasing demands follows Henneman's size principle. There are a few documented exceptions to the size principle for motor unit recruitment. The Fast twitch fatigue-resistant (FR) motor unit's twitch tension is intermediate between that of the slow twitch (S) and the fast twitch fast-fatigue (FF) motor unit. As illustrated in the twitch tension curve, the time to peak tension is fast (< 50 milliseconds) but the relaxation time is slow (~ 100 msec). Tetanizing the FR motor unit produces only a minor proportional increase in tension. S motor units are recruited first in almost all activities that you do. As tension requirements increase the FR and finally the FF motor units are added (i.e., the S motor units are not disengaged with higher force muscle activation). The Fast twitch fast-fatigue (FF) motor unit's twitch tension is very fast and very large. The time to peak tension is <50 msec. and the duration of the relaxation time is only 50-60 msec. The amplitude of twitch tension is about ten fold that of the S motor unit and at least twice that of the FR motor unit (see twitch tension curves). Tetanizing the FF motor unit will yield relatively little benefit since there will be about a 10% increase in tension but at a high metabolic cost (see fatigue index). This increased tension due to tetanization may be worth the cost for those situations where absolute maximal force is required for very short bouts of activity. S motor units are recruited first in almost all activities that you do. As tension requirements increase the FR and finally the FF motor units are added (i.e., the S motor units are not disengaged with higher force muscle activation).

MOTOR UNIT TYPE CHARACTERISTICS: FATIGUE INDEX

Fatigue index curves are generated by stimulating an individual motor unit's alpha axon with repeated high frequency bursts of stimulation, and then comparing initial tension with subsequent tension some minutes later. The Slow twitch (S) motor unit is virtually unfatigable. Tension output is undiminished even 60 minutes after activating the motor unit with repeated fatiguing bursts of electrical stimulation. The S motor unit is used preferentially in tasks requiring low load, long duration, and relatively slow actions. They are joined by fast twitch motor units as demands increase for lifting heavier loads, and for intermittent, high speed actions. The fast twitch fatigue-resistant (FR) motor unit is capable of producing higher tension than S motor units but FR tension drops to ~50% within 5-10 minutes when maximally activated. Tension has dropped to ~10% of maximal output 60 minutes after activating the motor unit with repeated fatiguing bursts of electrical stimulation. The FR motor unit's fatigue index is intermediate between the

FF motor unit and the S motor unit type. The fast twitch fast-fatigue (FF) motor unit is capable of producing much higher tension than either the S or FR motor units but its tension drops to <50% within 1-2 minutes when maximally activated. Tension has dropped to <10% of maximal output 5-6 minutes after activating the motor unit with repeated fatiguing bursts of electrical stimulation. The FF motor units are fundamentally glycogen-depleted after short periods of intense activity.

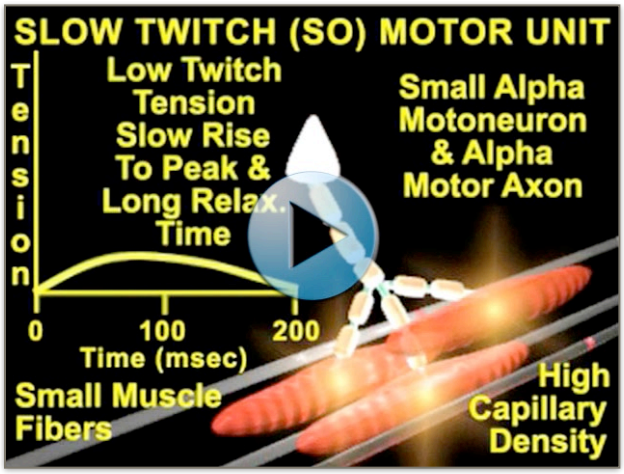


Fig 14-8. Slow Twitch Motor Unit Type Characteristics Movie (Left) (gec). GO TO: gmomm.pitt.edu *Fig14-8_Video*

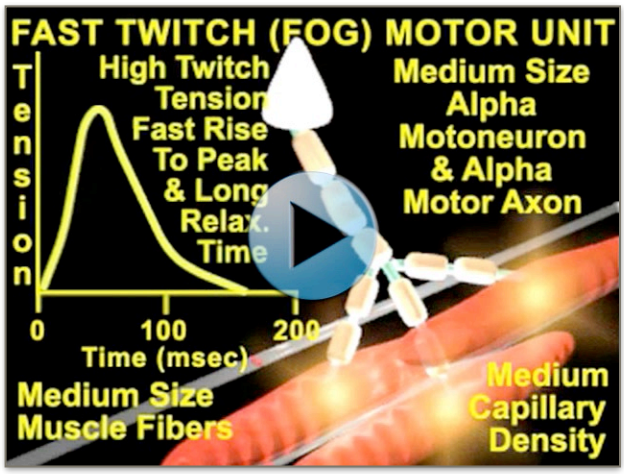


Fig 14-9. Fast Twitch, Fatigue Resistant Motor Unit Type Characteristics Movie (Right) (gec). GO TO: gmomm.pitt.edu *Fig14-9_Video*

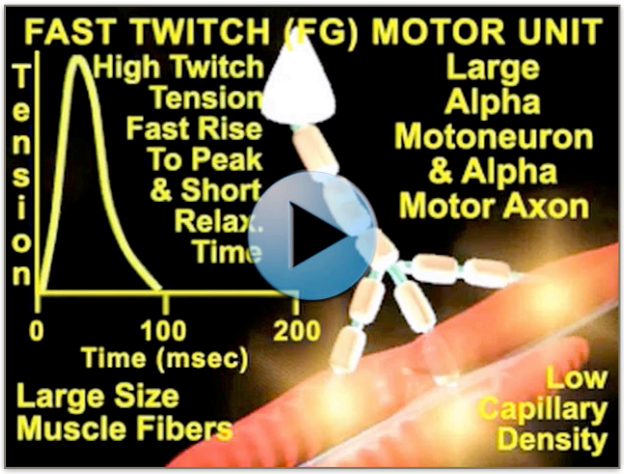


Fig 14-10. Fast Twitch, Fast Fatigue Motor Unit Type Characteristics Movie (gec). GO TO: gmomm.pitt.edu *Fig14-10_Video*

HENNEMAN'S SIZE PRINCIPLE OF MOTOR UNIT RECRUITMENT

Despite all that is known about the properties of motor units, the exact manner by which different motor unit types are recruited in simple to complex tasks has not been characterized in detail. If one uses surface electromyographic (EMG) recordings of a muscle the general level of activation can be readily appreciated but the details of firing of individual motor units is lost in the symphony of electrical activity from many motor units that produce an interference pattern of overlapping potentials on the oscilloscope screen. Indwelling

electrodes (fine wire or multiplexed needle electrodes) provide a more restricted “look” at only a few (~3-12) motor unit potentials at one time. We know that neighboring motor units do not have precise synchrony of activation, but instead have a relatively asynchronous pattern of recruitment. This means that as contraction builds towards a maximal voluntary contraction (MVC) more motor units will be recruited at a relatively fast rate of discharge (up to ~20-40 impulses per second). Even with sophisticated equipment to capture individual waveform characteristics of several motor units, eventually individual Motor Unit Action Potentials (MUAPs) will overlap one another in the recording & “contaminate” the EMG trace.

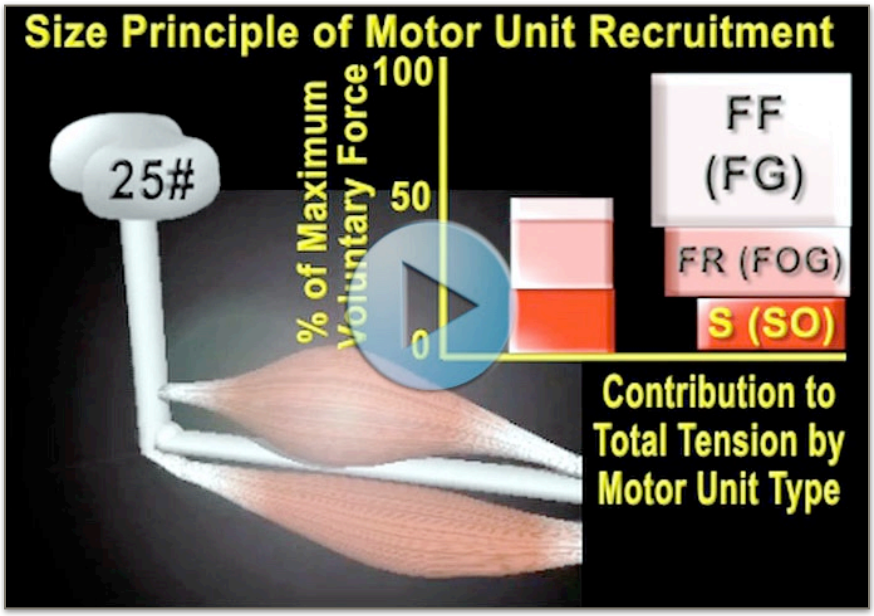


Fig 14-11. Henneman’s Size Principle Movie (gec). GO TO: gmomm. pitt.edu Fig14-11 _Video

Evidence suggests that motor unit recruitment follows the size principle of Elwood Henneman so that only S motoneurons should be active at low force ramping or steady isometric contractions. FR and FF motor units will be recruited as contraction approaches the MVC for that muscle. Fewer studies have investigated individual motor unit recruitment with fast or alternating contractions (most single motor unit studies use a ramp and hold isometric contraction).

SPINAL VENTRAL HORN NEURONS, MOTOR NUCLEI AND MOTONEURON POOL TOPOGRAPHY

The Ventral Horn contains Medial and Lateral Motor Nuclei and surrounding Integrative and Propriospinal Neurons that provide sensory-motor integration and the generation and regulation of signals that activate skeletal muscle in trunk and limbs. Each motor nucleus contains a group of local interneurons and motoneurons that collectively are sometimes called Segmental Motor Centers (SMCs). SMCs have dedicated their neuronal lives to helping you move in a smooth, controlled fashion. These SMCs are influenced by a balance of Peripheral, Spinal and Descending Pathway Inputs and they influence the Brainstem and Cerebellum. The SMCs send information about ongoing motor output to the Cerebellum by way of the Ventral Spinocerebellar Tract and to Brainstem Centers via Spinoreticular/Spinothalamic Tracts.

The Intermediate Gray of the Spinal Cord contains a network of relay neurons that connect various levels of the spinal cord; these Propriospinal Neurons provide an important pathway to coordinate activity within nearby spinal cord segments (Short Propriospinal Neurons) or among multiple levels that include limb and trunk musculature (Long Propriospinal Neurons).

There is a general topography of motoneuron pool representation within the ventral horn. Axial musculature (neck and trunk) motoneuron pools are located within the medial motor nuclei at all levels of the spinal cord. Limb musculature motoneuron pools are located within the lateral motor nuclei of the cervical enlargement (upper extremity) and the lateral motor nuclei of the lumbosacral enlargement (lower extremity). The motoneuron pool topography within the lateral motor nucleus has flexors located more dorsal than the extensors and proximal limb including girdle muscles located medial to the distal musculature (see figure).

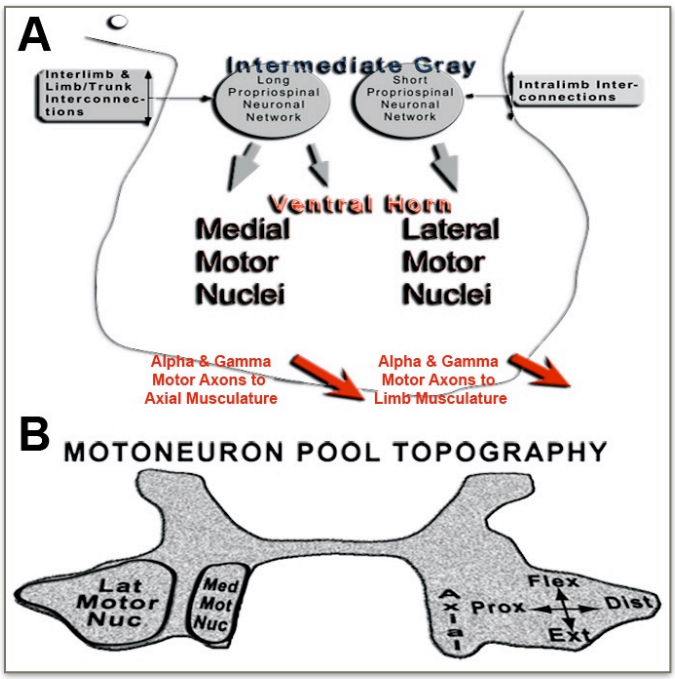
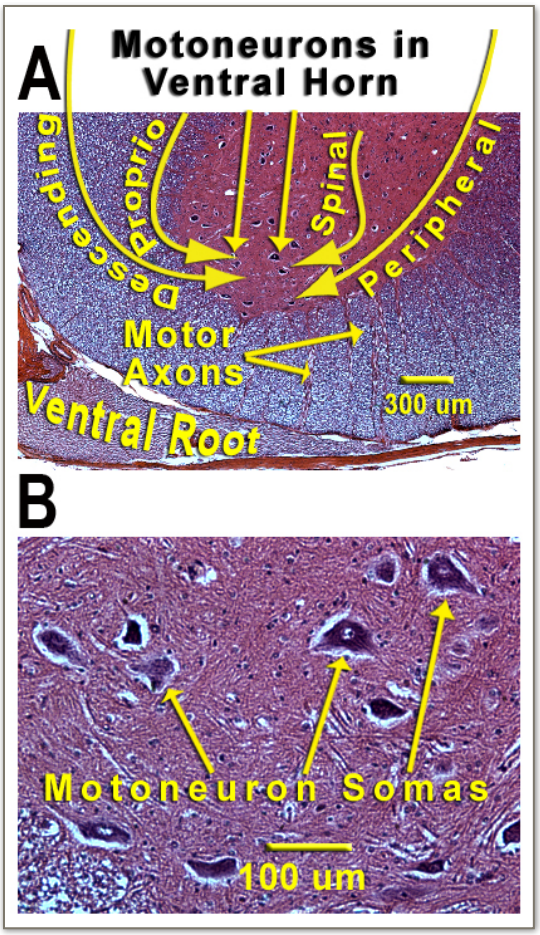


Fig 14-12. A. Medial & Lateral Motor Nuclei in the Ventral Horn of Spinal Cord , B. Motoneuron Topography within ventral horn gray: Lat Motor Nuc = Lateral Motor Nucleus, Med Mot Nuc = Medial Motor Nucleus, Prox = Proximal Limb & Girdle Musculature, Dist = Distal Limb Musculature, Flex = Flexors, Ext = Extensors (gec).

ALPHA-GAMMA COACTIVATION OF EXTRAFUSAL & INTRAFUSAL MUSCLE

Multiple sources of excitatory and inhibitory inputs impact Alpha Motoneurons (AMNs) and Gamma or Fusimotor Motoneurons (GMNs or FMNs, respectively) located in the ventral spinal motor nuclei (see figures). Some inputs (Group I Muscle Afferents to AMN and Target-Specific Descending Tracts to AMN and GMN) have a strong, focused influence on a limited pool of Motoneurons and SMC Inhibitory Interneurons.

Other influences to AMNs & GMNs provide facilitatory or suppressive influences that are broader and more susceptible to spinal & supraspinal fluctuations in excitability. Fluctuations may relate to the overall behavioral state and ongoing sensorimotor processes: rhythmic, e.g., Central Pattern Generator (CPG) or non-rhythmic, e.g., reflex, activity. Neuromodulatory pathways may provide short-lasting or long-lasting plastic changes. Note absence of monosynaptic Ia Afferent input to GMN. Alpha-



Gamma Coactivation ensures that both Extrafusal (EFM) and Intrafusal (IFM) Muscle fibers will contribute to motor control for most of our movements.

Fig 14-13A,B. A.Multiple Inputs Converge Upon Motoneurons (gec) B. Magnified View of Stained Motoneurons in the Ventral Horn of the Spinal Cord (gec).

However, there are some instances where a flexible linkage may contribute to subthreshold events for some neurons but threshold for others, e.g., GMNs require less depolarization to reach threshold. Motoneurons are influenced by target specific excitatory and inhibitory ionotropic fast conducting "kiss and run" synaptic inputs. In addition, metabotropic synaptic inputs using "stay and flirt" G-coupled Persistent Increased Conductance (PIC) Na^+ and Ca^{++} channels provide neuromodulatory influences that alter thresholds of motoneurons in a more persistent fashion. One of these inputs is a Noradrenergic (NOR) pathway that influences most areas of the brain and spinal cord in a global depolarizing fashion. Such NOR depolarization allows for individual Motoneurons (MNs) to fire at a higher rate and increased levels of NOR may also increase the pool of MNs recited with the same level of ionotropic inputs. Thus, force production will increase even though descending or local spinal inputs remade the same: a gain control mechanism at the spinal level (see Heckman, et.al., 2009 for review).

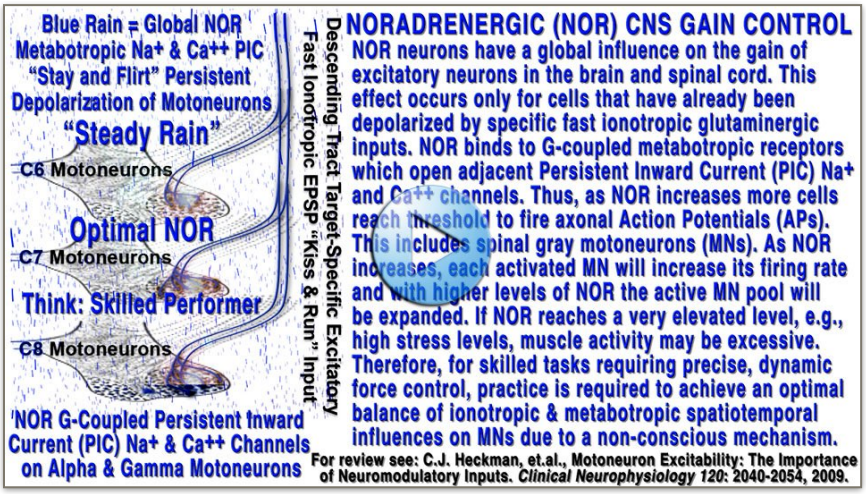


Fig 14-14. Goldilocks and the Three NORs Gain Control of Motoneuron Excitability (gec). GO TO: gmomm. pitt.edu Fig14-14_Video

ALPHA-GAMMA CO-ACTIVATION FIXED OR FLEXIBLE?

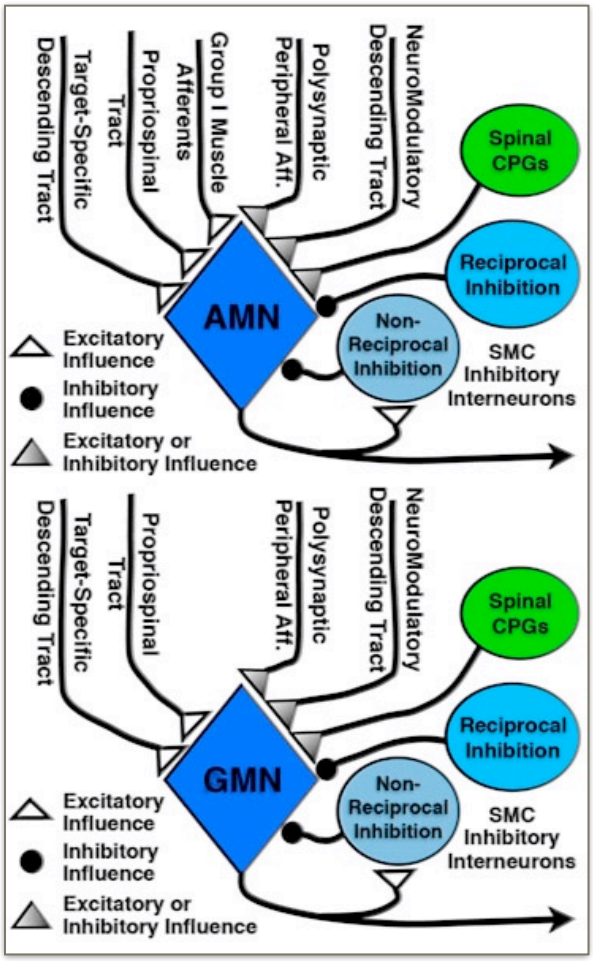


Fig 14-15. Sensory, Spinal and Supraspinal Inputs to Alpha and Gamma Motoneurons (gec).

Muscle spindle afferents and efferents are active when the muscles in which they are located are active. Dynamic Ia afferent discharge is activated also if a perturbation suddenly interferes with the progression of the contraction (see cat lift in the Interactive file below). Increasing the gamma dynamic drive increases the sensitivity to rapidly changing muscle lengths (coding the rate of change of muscle length/limb position).

Increasing the static sensitivity due to increased static gamma discharge enhances spindle sensitivity to code the actual muscle length (position cue). The nervous system can adjust dynamic and static gamma firing according to demands of the task. Note lack of gamma discharge at rest & maximal activity from both dynamic & static gamma motoneurons when task demands are high (se e cat jumping or beam walking in the Interactive file below). Actual data regarding gamma motor activity in behaving animals is sparse. Most inferences regarding gamma motoneuron activation come from indirect measure.

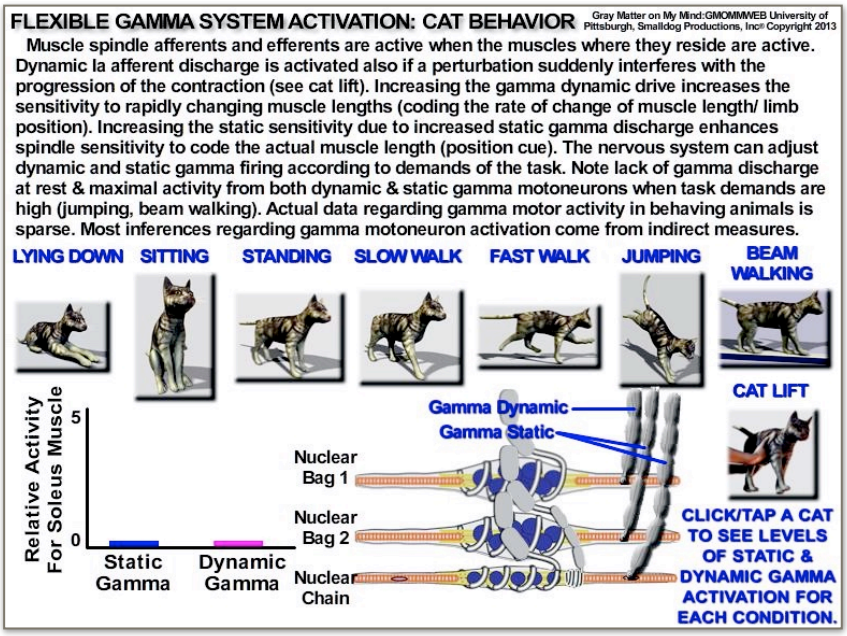


Fig 14-16. Static and Dynamic Gamma Motoneuron Activation in Behaving Animal: Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig14-16_Interactive Media]

SEGMENTAL MOTOR CENTER NEURONS: SPINAL LEVEL PRECISION CONTROL OF MUSCULATURE

The Ventral Horn Segmental Motor Center Motoneurons and Interneurons Labeled Movie identifies the interneurons and motoneurons that form the segmental motor centers in a 'generic' segment of the spinal cord. Only the Lateral Motor Nucleus is illustrated, but the Medial Motor Nucleus would have a similar configuration. Note this “virtual” representation would actually consist of pools of neurons in the real spinal cord.

Groundbreaking research by John Eccles and colleagues in the twentieth century provided the basic architecture for interneuronal motor control at the spinal level. Identification of the spinal neurons and their proposed “classical” role in motor control is demonstrated in the Interactive Flash File below. Other investigators have built upon these early findings to provide greater detail about the roles of individual classes of neurons and their networked interaction with peripheral, spinal and descending pathway influences. Select one neuron at a time to build the Segmental Motor Control (SMC) Network.

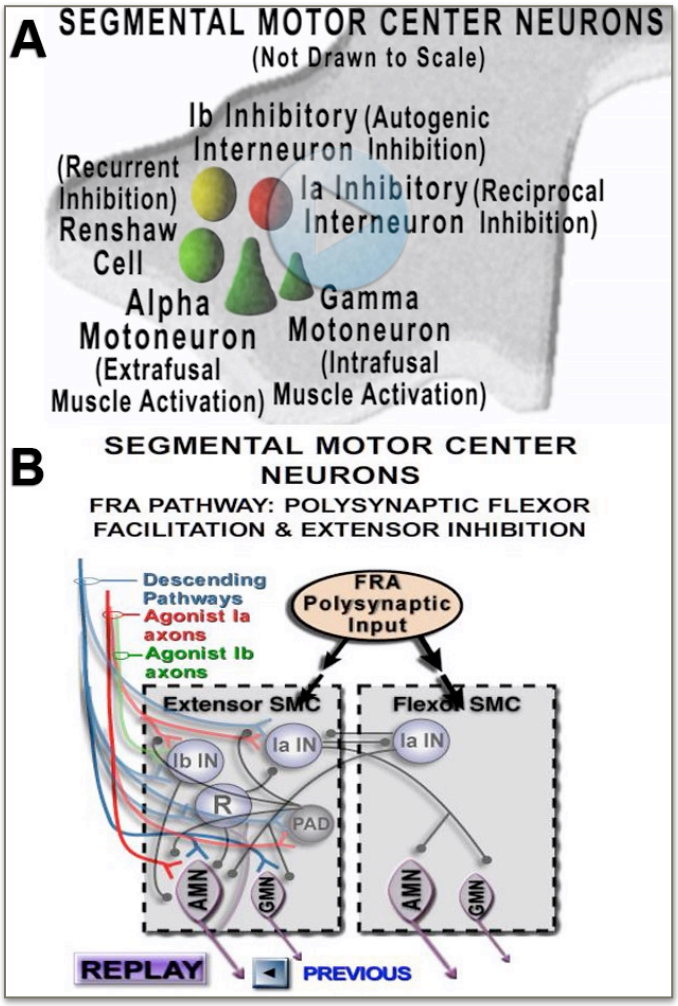


Fig 14-17A. Extensor & Flexor Segmental Motor Center Motoneurons and Interneurons Labeled Movie (gec). GO TO: gmomm.pitt.edu
Fig14-17A_Video

Fig14-17B. SMC-Interactive Media File: Build the SMC Circuitry one neuron at a time (gec). GO TO: gmomm.pitt.edu
Fig14-17B_Interactive Media

SEGMENTAL MOTOR CENTER ALPHA MOTONEURONS: FINAL COMMON PATHWAY FOR MOTOR UNIT ACTIVATION

Segmental Motor Centers (SMCs) are grouped according to anatomic/ physiologic muscle groups: Agonist vs. Antagonist. In the examples used here, Extensors are the Agonists and Flexors the Antagonists. Obviously if the task involved a concentric flexion

movement about a joint, the Flexors would be the Agonists & Extensors the Antagonists. The Alpha Motoneuron (AMN) sends an Alpha Motor Axon into the ventral root to innervate skeletal muscle. Each axon innervates a defined population of muscle fibers to form a functional unit of contraction (motor unit). These muscle fibers are known as Extrafusal Muscle Fibers (EFM) since they reside outside of the capsule of the muscle spindle. Motor Units are classified as slow-twitch or fast-twitch depending on their metabolic, histologic and electrophysiologic profiles; fast-twitch are sub-classified according to variations in these properties. The AMN is the final decision point for the nervous system to either engage or suppress contraction of the motor unit's muscle fibers; once an action potential is generated at the axon hillock of the AMN it will propagate to the muscle and cause a contraction (assuming an intact PNS, neuromuscular junction, and muscle). AMNs and GMNs are typically coactivated in most actions that we do.

SEGMENTAL MOTOR CENTER GAMMA MOTONEURONS: MODULATION OF MUSCLE SPINDLE STRETCH SENSITIVITY

The Gamma Motoneuron (GMN) is also called the Fusimotor Neuron (FMN) because it sends a Gamma Motor Axon into the ventral root to innervate specialized muscle fibers within the capsule (intrafusal) of the muscle spindle; these intrafusal muscle fibers (IFM) do not do the work of the muscle (generation of force/tension) but have an important role in adjusting the sensitivity of the stretch receptor endings within the muscle spindle. Muscle Spindles are important proprioceptive organs within skeletal muscle. GMNs come in two basic flavors: dynamic and static. Increasing activation of Dynamic GMNs increases the sensitivity of the primary receptor ending of the Nuclear Bag^1 component of the muscle spindle, thus increasing sensitivity to velocity/acceleration of muscle lengthening. Increase in discharge of Static GMNs increases sensitivity to actual (static) muscle length by increasing the sensitivity of the Primary and Secondary Receptor Endings of the Nuclear Bag^2 & Nuclear Chain Components of the Muscle Spindle. Thus information about both the rate of change of limb position, and actual limb position can be adjusted through GMN recruitment.

MONOSYNAPTIC STRETCH REFLEX: H-REFLEX IS MODULATED ACCORDING TO LEVELS OF MUSCLE ACTIVITY FOR DIFFERENT PHASES OF HUMAN GAIT

The monosynaptic stretch reflex may be activated by a tap of a muscle's tendon: Tendon Reflex (T Reflex) or the monosynaptic pathway utilized in the stretch reflex may be activated artificially by electrical stimulation of the Ia afferent axons which innervate the primary endings of muscle spindles. The electrically activated monosynaptic reflex is the Hoffmann Reflex (H Reflex); see T Reflex H Reflex Circuitry Interactive Media File.

The stretch reflex like most sensorimotor circuits in the CNS does not operate in a vacuum. Although the monosynaptic reflex circuitry is very precise and simple, it is

influenced by the level of excitability of the interneurons and motoneurons in the Segmental Motor Center (SMC) due to local spinal circuitry, peripheral afferent inputs and descending pathway influences.

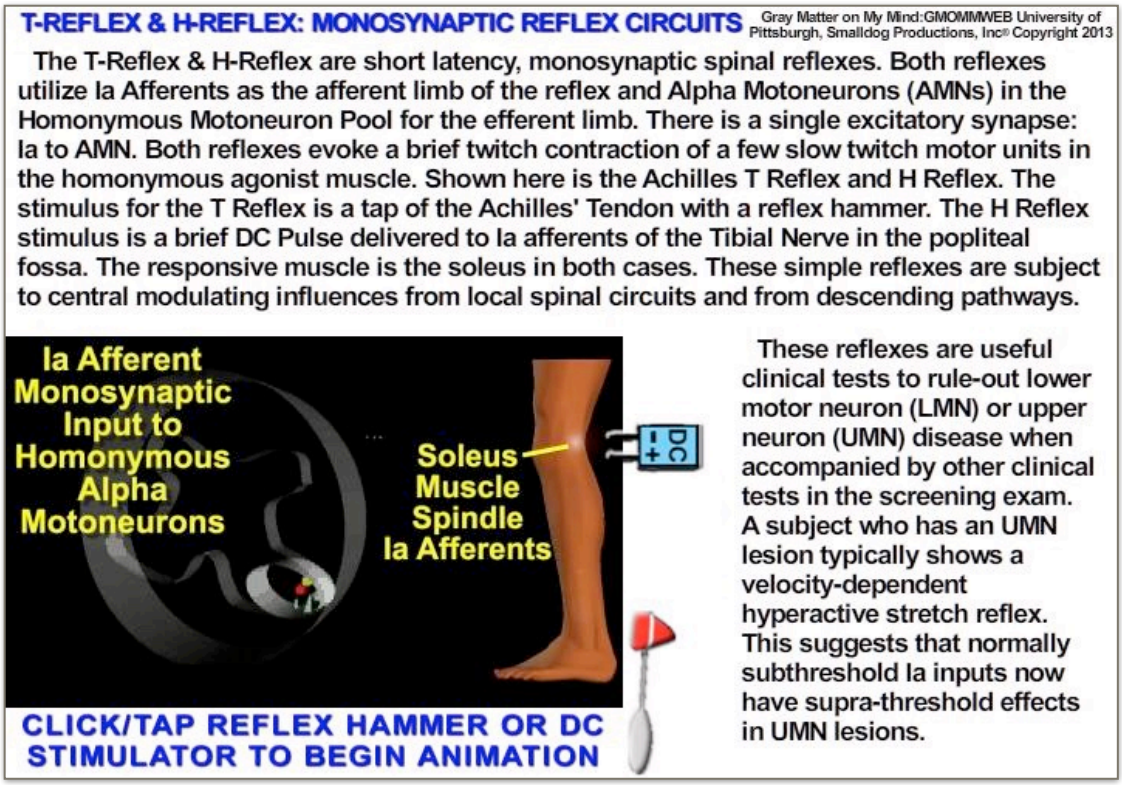


Fig 14-18. T Reflex & H Reflex Circuitry-Interactive Media File: (gec). GO TO: gmomm.pitt.edu [Fig14-18_Interactive Media]

Researchers using the H-Reflex as a monitor of stretch reflex excitability have shown how greatly the central motor system influences this simple reflex circuit in human subjects. The interactive flash file illustrates the proportional changes of motoneuron excitability related to muscle output during the gait cycle. The soleus muscle activity is high during the loaded stance phase of gait while soleus is inactive during the unloaded swing phase of bipedal locomotion

The Soleus H-Reflex amplitude is proportional to Soleus Muscle activity (integrated EMG - iEMG) when walking. This window into the excitability of SMC circuitry dramatically illustrates how important descending and spinal central drive is to even the simplest reflex circuit. No change in the M-Wave indicates that there is a consistent intensity of Stimulation to the Tibial Nerve at different points in gait cycle and therefore the altered monosynaptic H-reflex signifies an altered motoneuron excitability according to the demands of muscular output.

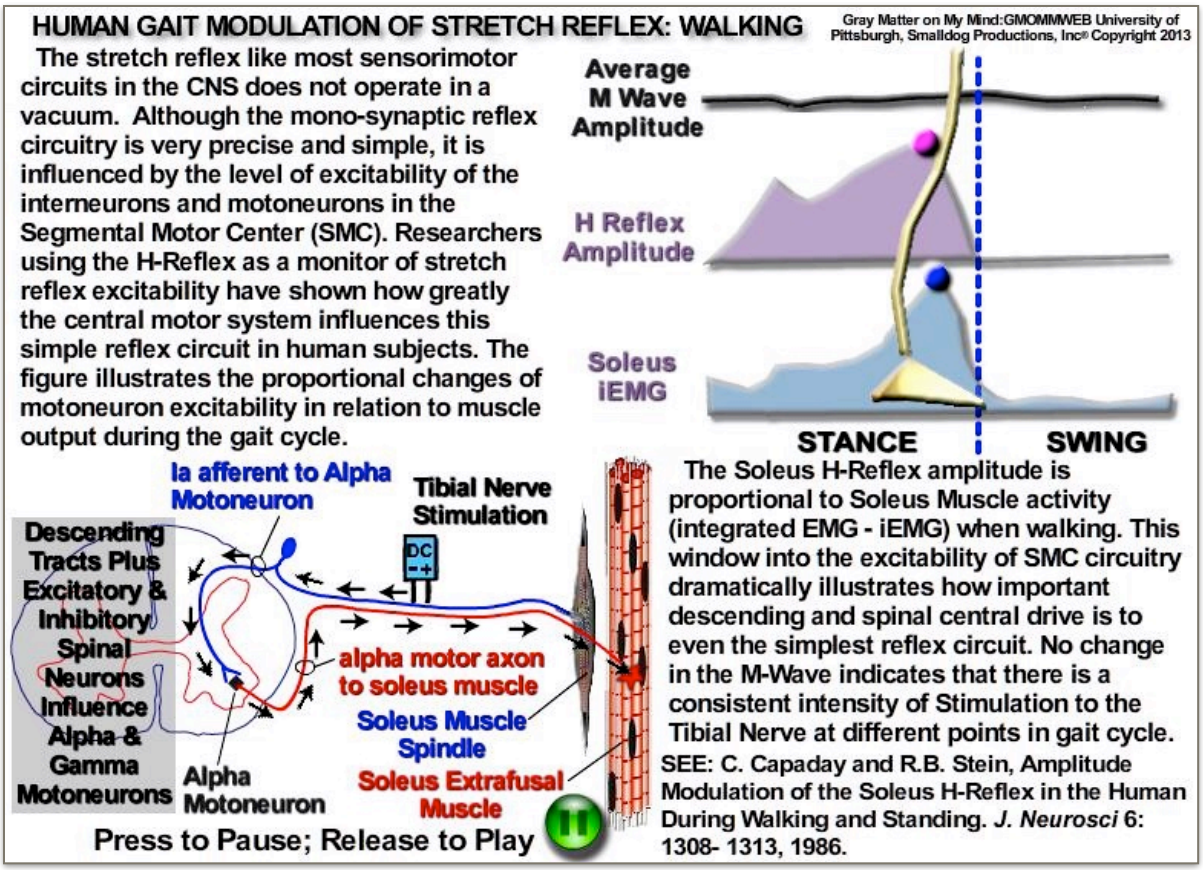


Fig 14-19. H-Reflex Modulation During Human Gait: Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig14-19_Interactive Media*

SEGMENTAL MOTOR CENTER IA INHIBITORY INTERNEURONS: RECIPROCAL INHIBITION OF ANTAGONIST MOTONEURONS

The Ia Inhibitory Interneuron (IaIN) is the local interneuron within the Segmental Motor Center (SMC) responsible for Reciprocal Inhibition of Antagonist Muscles. This interneuron was so named because of the potent monosynaptic excitatory drive from Ia axons that innervate the primary receptor endings of muscle spindles living in the agonist muscles. There are, however, other sources of excitatory drive including axons from descending pathways, Propriospinal Neurons (not illustrated), and polysynaptic spinal circuitry (see later).

The IaINs are reciprocally connected (inhibitory) between the agonist and antagonist SMCs. This Interneuron postsynaptically inhibits the AMNs, FMNs and the Ia INs located in the Antagonist SMC. The effect of this reciprocal inhibition is to suppress activation of antagonist muscles, reduce their spindle sensitivity and prevent any IaIN inhibition from the Antagonist SMC during the period of Agonist SMC Activation (Agonist Muscle Contraction). For example, when the Extensors are active, the flexors will be inactive. Lack of this IaIN Inhibitory influence would increase the probability of co-

contraction of Agonist and Antagonist Muscles (which would increase muscular/joint stiffness).

SEGMENTAL MOTOR CENTER IB INHIBITORY INTERNEURONS: NON-RECIPROCAL AUTOGENIC INHIBITION OF AGONIST AMNS

The Ib Inhibitory Interneuron (IbIN) is the local interneuron within the Segmental Motor Center (SMC) responsible for Non-Reciprocal (Autogenic) Inhibition of Agonist Muscles. This interneuron was so named because of the potent monosynaptic excitatory drive from Ib axons that innervate the Golgi Tendon Organs (GTOs) living in the agonist muscles. GTOs, located at the juncture of muscle fibers and collagen fibers of the tendon, are proprioceptors sensitive to active tension. GTOs are responsive to the static and rate of change of muscle tension developed during muscle contraction. As a group, GTOs are sensitive to the whole range of tensions within “physiological” contractions but actually shutdown if tensions exceed this limit.

There are other sources of excitatory drive to the IbIN including Ia axons, Descending Pathways, Propriospinal Neurons (not illustrated), and Polysynaptic spinal circuitry (see later). The IbINs are thought to be important in regulation of recruitment of AMNs within the Agonist SMC. This regulation may limit the rate of discharge of AMNs and limit the number of motor units active at any one time by inhibiting the “fringe” AMNs in the pool that have weak excitatory drive. This regulation may be critical in distributing the 'work load' of the AMN pool to reduce the possibility of premature fatigue and increase the likelihood that motor units will be activated in an asynchronous fashion (smoother building of tension).

SEGMENTAL MOTOR CENTER RENSHAW CELLS: NON-RECIPROCAL RECURRENT INHIBITION OF AGONIST AMNS

The Renshaw Cell (R) is the local interneuron within the SMC responsible for Recurrent Inhibition of Agonist and Disinhibition of Antagonist Muscles. Recurrent Inhibition was named because of its potent source of monosynaptic excitation from recurrent collaterals of Alpha Motor Axons. There are other sources of excitatory drive to the Renshaw Cell including Descending Pathways, Propriospinal Neurons (not illustrated), and Polysynaptic spinal circuitry (see later). The Disinhibition of Antagonist SMCs occurs by Renshaw Cell Inhibition of the Ia Inhibitory Interneuron (reduction of reciprocal inhibition). Like the IbINs, R Cells are thought to be important in regulating recruitment of AMNs within the Agonist SMC. R cells may limit the rate of discharge of AMNs and the number of motor units active at any one time by inhibiting the “fringe” AMNs in the pool that have weak excitatory drive. This regulation may be critical in distributing the “work load” of the AMN pool to reduce the possibility of premature fatigue and increase the likelihood that motor units will be activated in an appropriate fashion (smoother building of tension).

In addition, R Cells may assist in the switching between Agonist and Antagonist Activation by reducing Reciprocal Inhibition as phasic excitatory drive of the Agonist SMC decreases and the Antagonist SMC increases (e.g., locomotion), or this disinhibition could facilitate a cocontraction of Agonists and Antagonists during tonic excitatory drive to both SMCs (reducing reciprocal inhibition in both centers).

SEGMENTAL MOTOR CENTER PAD INTERNEURONS: PRESYNAPTIC INHIBITION OF IA & IB AFFERENTS - GABA-B

The PAD Interneuron is a neuron that provides axoaxonic synapses on Group I afferents as those afferents synapse upon other Interneurons and on Motoneurons within the Segmental Motor Center (SMC). PAD refers to Primary Afferent Depolarization, one mechanism by which the PAD Neuron depolarizes the Group I afferent axon terminals, thus reducing the extent of transmitter released from these excitatory afferent terminals. This form of presynaptic inhibition selectively reduces the influence of Muscle Receptors (Primary Spindle Endings and Golgi Tendon Organs) while allowing other inputs (e.g., Descending Pathways, Propriospinal Neurons, FRA Inputs) full access to the SMC Circuitry. The PAD Inter-neuron axons are thought to release GABA as a neurotransmitter that binds to GABA-$_B$ receptors on the Group I afferent axon terminals. These receptors appear to be able to bind a GABA-$_B$ Chemical Agonist (Baclofen™). Thus, Baclofen™ used therapeutically should increase this presynaptic inhibition of Ia and Ib Afferents at the Spinal Cord Level (with other possible effects elsewhere in the CNS).

SEGMENTAL MOTOR CENTER FRA PATHWAY: POLYSYNAPTIC FLEXOR FACILITATION & EXTENSOR INHIBITION

The FRA Polysynaptic Input within the Segmental Motor Center (SMC) represents multiple interneurons interconnected within a network that influences the Interneurons and Motoneurons within both Agonist and Antagonist SMCs across many spinal cord segments. Due to the extensive convergence, divergence of connectivity activated by a variety of peripheral and central sources, the “functional influence” of this pathway varies according to overall states of activity in SMCs and other centers in the CNS. The pathway is so named because of the grouping of afferents, and their effect in the isolated spinal cord preparation. FRAs (Flexion Reflex Afferents) refer to a group of afferents in the muscle nerves (Groups II-IV in Agonist and Antagonist muscles) and A Beta-C fiber afferents in Cutaneous Nerves. In the isolated spinal cord, input from a widespread area of the skin, joints or other deep muscle receptors (excluding Ia and Ib axons) produces a stereotypic facilitation of flexor muscles and inhibition of extensor muscles. The most potent source of FRA input is from nociceptors. Strong FRA input will dominate SMC activation in the isolated spinal cord. Effects of weaker FRA input may vary according to the state of spinal cord activity in the intact system. For example, non-noxious FRA input will facilitate flexors and inhibit extensors in a non-weight bearing

limb but may actually have the exact opposite effects in a load-bearing limb. This 'reflex reversal' may be a mechanism by which a broad range of sensory receptors dynamically adjust the overall pattern of motoneuron activity. FRA input effects may be less predictable for transition states, e.g., during swing to stance or vice-versa.

SEGMENTAL MOTOR CENTER MOTONEURONS AND INTERNEURONS SPATIOTEMPORAL SUMMATION ANIMATION

The Ventral Horn Segmental Motor Center Spatiotemporal Summation Movie that follows the Ventral Horn Segmental Motor Center Label Movie illustrates the effect of a short burst of impulses (shown as small red spheres) simulating a number of axons from a single or from multiple sources, e.g., Ia afferents from muscle spindles, & lateral corticospinal tract axons onto a pool of Alpha Motoneurons.

Note the increasing depolarization (increased intensity of glow) as the impulses summate. Many motoneurons are activated at subthreshold levels; only two motoneurons have sufficient depolarization to produce action potentials (small blue spheres). The actual circumstance that might apply to this scenario could be stretch of the homonymous muscle (activating the monosynaptic Ia stretch reflex) as an individual volitionally activates the agonist muscle (via the monosynaptic input of lateral corticospinal tract axons). However, it is improbable that recruitment is this restricted for most normal daily activities since actions are often superimposed on postural control of the moving body part. Even if recruitment patterns occur in the awake person in an externally stabilized limb, there is subthreshold “background” depolarization of many interneurons and motoneurons. The red input spheres show a “packet” of activation that, in reality, would be somewhat spread over multiple sites as the axon branches to form multiple synaptic contacts with the dendritic tree, and/or soma of multiple interneurons and motoneurons across multiple spinal cord segments. Activation of SMC interneurons, and Propriospinal Neurons provides a greater sphere of influence even with this extraordinary capacity to consciously isolate muscle action. The “virtual” activation shown in this animation is, therefore, an oversimplification of reality.

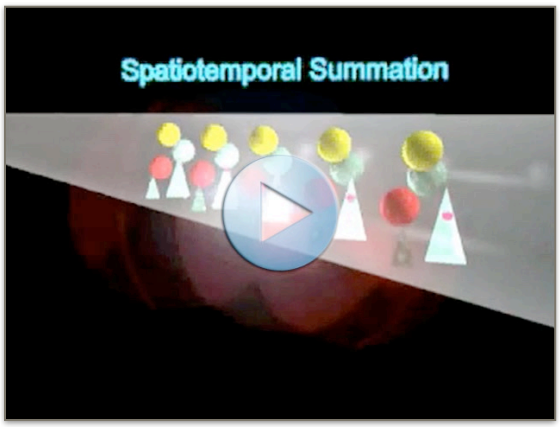


Fig 14-20. Ventral Horn Segmental Motor Center Spatiotemporal Summation Movie (gec). GO TO: gmomm.pitt.edu *Fig14-20_Video*

PROPRIOSPINAL NEURONS PROVIDE INTERSEGMENTAL COMMUNICATION WITHIN THE SPINAL CORD.

The propriospinal tract is an almost continuous band of axons immediately surrounding the

gray matter (see thin orange fill surrounding gray matter in figure below). This tract provides a major source of intersegmental connectivity within the spinal cord.

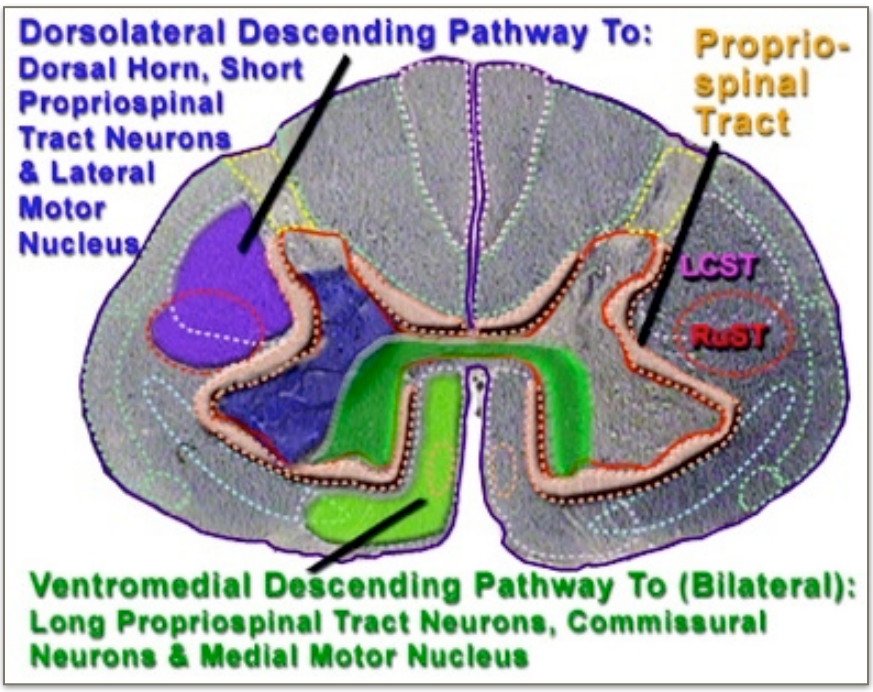


Fig 14-21. Dorsolateral, Ventromedial Descending Pathways & Propriospinal Tract (gec).

Propriospinal Neurons are scattered throughout the intermediate gray. Some cells in the dorsal and ventral horn may also contribute axons to ascend or descend in this tract.

A special group of these neurons found at the third and fourth cervical levels are thought to be a major source of intersegmental coordination for upper extremity actions that require synergistic cooperation from many muscles. A similar group of propriospinal neurons in the lumbosacral cord may have a like function for synergistic lower extremity actions. They are influenced by converging inputs from descending pathways, peripheral inputs, and spinal interneurons. Long propriospinal neurons send their axons over many segments at multiple levels of the cord. These long-range connections may be important for “whole body” integration since bilateral influences are common for these projections (interlimb and limb-trunk coordination). Short propriospinal neurons tend to restrict connectivity unilaterally and within that specific level of the cord (intralimb coordination)

DESCENDING PATHWAYS HAVE ENORMOUS INFLUENCE ON SEGMENTAL MOTOR CENTER MOTONEURONS AND INTERNEURONS

THE DORSOLATERAL DESCENDING PATHWAY

The dorsolateral Descending Pathway is a functional grouping of tracts located in the lateral funiculus. The two major tracts in this pathway are the lateral corticospinal tract (LCST) and the rubrospinal tract (RuST); reticulospinal tract axons in the dorsolateral funiculus (DLF) are also located in this pathway. The major spinal gray matter targets for the LCST and the RuST are motoneurons and interneurons in the

lateral motor nucleus of the ventral horn, and short propriospinal neurons in the intermediate gray. The LCST has a significant input to neurons in the substantia gelatinosa and nucleus proprius of the dorsal horn as well as collateral branches to dorsal column nuclei as these axons descend in the medullary pyramid. This pathway projects to all levels but the majority of axons terminate in the cervical cord. This pathway is critical for fine motor control of the extremities, especially for reaching and grasping with the upper extremity, well-regulated foot placement, and modulation of somatosensory inputs by the LCST and the DLF. Active touch, in particular, requires cooperation of the ascending dorsal column medial lemniscus tract and the descending LCST. The DLF has an important role in modulation of peripheral sensory input, autonomic function and spinal reflexes.

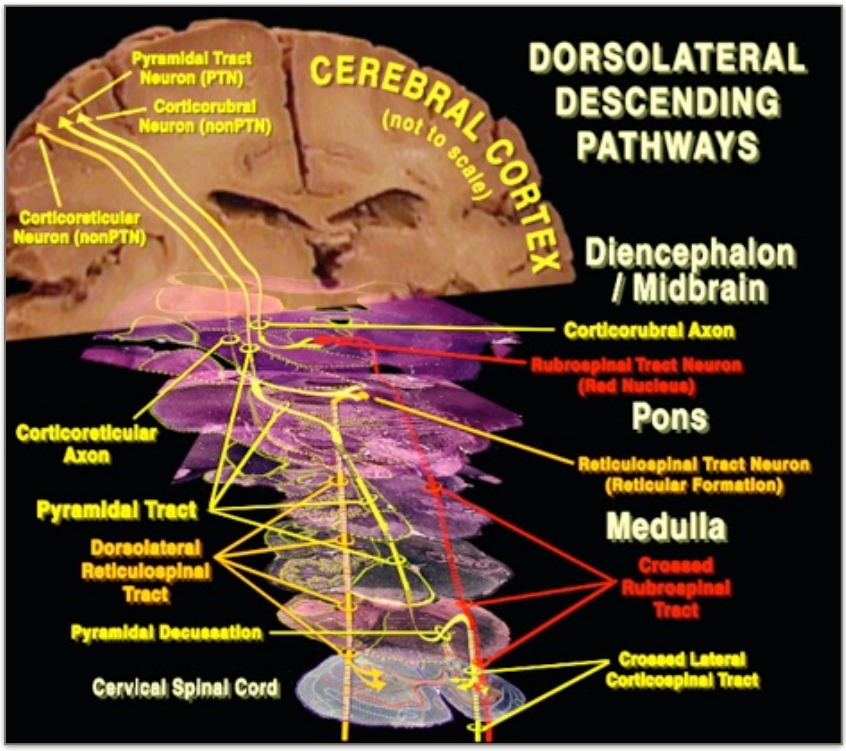


Fig 14-22. Dorsolateral Descending Pathway Mapped on Brain and Spinal Cord (gec). GO TO: gmomm.pitt.edu Fig14-22_Video

THE VENTROMEDIAL DESCENDING PATHWAY

The Ventromedial Descending Pathway represents a number of tracts located in the Anterior (Ventral) funiculus. The tracts include: Reticulospinal Tracts originating from Reticular Formation Nuclei in the pons and medulla, Vestibulospinal Tracts originating in the Vestibular Nuclei, the Anterior Corticospinal Tract (crossed and uncrossed fibers) originating from Pyramidal Tract Neurons (PTNs) in the Cerebral Cortex, and the Tectospinal Tract (cervical cord only) originating in neurons in and around the Superior Colliculus of the midbrain. Together these tracts influence Segmental Motor Center Interneurons and Motoneurons in the Medial Motor Nucleus and some Segmental Motor Center neurons in the medial aspect of the Lateral Motor Nucleus where the limb girdle muscles are represented. These tracts influence Long Propriospinal Tract Neurons that interconnect many segments across more than one level of the cord; and to a limited extent Short Propriospinal Tract Neurons. These Ventromedial Descending Pathway

tracts influence Commissural Interneurons located close to the midline in the spinal gray and thus effect bilateral actions of the trunk/neck and limb girdle muscles. This pathway provides descending postural and balance control, eye/neck coordination for visuomotor tasks, and regulation of “gross” motor activities requiring a high degree of synergistic muscle activity such as locomotion, lifting, and mobilization/stabilization of axial musculature for all types of “fine” and “gross” actions.

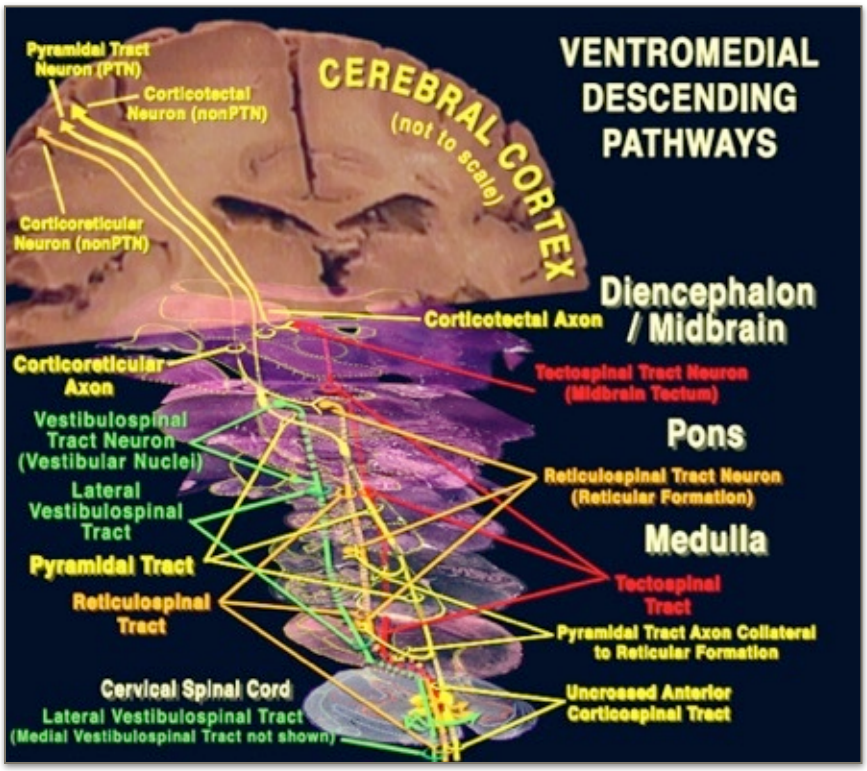


Fig 14-23. Ventromedial Descending Pathway Mapped on Brain and Spinal Cord (gec). GO TO: gmomm.pitt.edu Fig14-23_Video

SPINAL NETWORKS FOR NEURAL CONTROL OF LOCOMOTION (STEPPING)

Normal gait requires rhythmic, propulsive movements of the legs superimposed upon dynamic postural control of the body; one might describe walking as graceful falls followed by agile recovery of balance. Current concepts regarding the neural basis of locomotion include spinal central pattern generators (CPGs), brainstem locomotor regions, cortical and subcortical motor areas, propriospinal tracts, descending pathways to initiate gait & energize spinal centers, and tactile & proprioceptive sensory inputs that modulate the discharge of sensorimotor centers including spinal CPGs.

Normal human gait is characterized by reciprocal leg motion coupled to motion of the head, trunk and often the upper extremities. Although the basic pattern of forward progression is stereotypical, one's overall “body language” may change according to mood, urgency, terrain, anxiety, fatigue, etc (see figures). Gait patterns must be rapidly altered when one changes direction, steps to avoid an obstacle, or alters the gait pattern, e.g., walk to run.

Locomotion means different things to different people. For some it is a convenient way to transport their brain from one place to another, for others it is a vital component

of every day work, while others use walking, jogging, running or other forms of wheeled locomotion for recreation, stress reduction or neuroprotection. For some, all locomotion depends critically on wheeled mobility. Here we consider basic bipedal gait and the spinal neural mechanisms believed to be important for coordinated locomotion.

Locomotor research suggests that spinal CPGs use reciprocal inhibitory connections to generate the stepping pattern characteristic of gait. Although the actual neurons responsible for pattern generation have yet to be isolated, evidence suggests that a distributed network of CPGs links hip to knee to ankle.

Fig 14-24. Neural Control of Locomotion: The Basics of Rhythm Movie (gec, jec). GO TO: gmomm.pitt.edu Fig14-24 Video

A half-center linkage of flexors and extensors has been hypothesized (since the early 1900s by Graham Brown) to account for patterning within a limb. It is suggested that the two networks (F & E) are reciprocally inhibitory. Spinal stepping CPGs are thought to be powered by Brainstem Locomotor Regions that tonically drive the CPG and associated spinal networks. Such networks provide coordinated multilimb and trunk movement patterns characteristic of normal gait Theories regarding spinal CPGs have existed for a century. T. Graham Brown described such a mechanism in the early 1900s. Brown, a contemporary of C. S. Sherrington showed that a spinal animal suspended over a treadmill would step. Stepping persisted even if a limb was deafferented. This lead to a hypothesis of central pattern generation by reciprocally inhibitory “half-centers” for agonist/antagonist muscles (T.G. Brown, 1914).

Renewed interest in CPGs was kindled again in the middle of the twentieth century when Graham Brown's experiments were duplicated. This spark ignited a fire in the belly of a number of neurophysiologists to search for the elusive CPG. Champions of this research in vertebrates include: S. Grillner, H. Forrsberg, K.G. Pearson, C. Perret, A. Lundberg, G.N. Orlovsky, M.L. Shik, O. Andersson and others. CPGs require rhythm. They do not require specific sensory input to drive the pattern but such peripheral input may have significant modulatory effects on the CPG (see Sensory Feedback). Spinal CPGs are influenced by Propriospinal Neurons that provide in intralimb and interlimb coordination and limb-trunk coordination. CPGs are “driven” by descending pathways that may not contain specific pattern instructions but do control the stepping network activation. Actual linkages of half-centers for proximal to distal muscles & right to left limbs is still unknown (see references). There is limited evidence that spinal CPGs can

be reactivated following complete spinal cord transection in humans, although researchers are attempting this therapeutic intervention.

Segmental Motor Centers (SMCs) are busy places from head to tail during locomotion. Not only are they being accessed by the spinal CPGs but also by circuitry that controls posture. SMCs keep you upright and body parts coordinated while you get from here to there. All this and you can worry about your weekend or your "portfolio" while your brainstem and spinal cord do their work with nary an email to your cognitive self (till you stumble-that tends to get your attention). Try to imagine concentrating on each muscle coupling at every joint on both sides, all the while keeping your head off the turf. The brainstem and spinal portions of your neuraxis are the ultimate multitaskers! Now what were you saying about the lowly spinal neuraxis? Both SMCs and CPGs provide information about ongoing motor events (efferent feedback) to the Cerebellum via the Ventral Spinocerebellar Tract (VSCT) and to Reticular Formation Nuclei (including Locomotor Regions) via a Spinoreticular Pathway.

Sensory feedback from cutaneous and proprioceptive inputs go to all levels. Sensory input while not required to generate the stepping pattern has significant influence on the motor output. Investigators have revealed an important interaction among CPGs and reflexive circuitry. For example, cutaneous input to the foot during the swing phase of gait facilitates flexors, but the same input to the weight-bearing limb may have no effect or actually produce a "reflex-reversal." The cutaneous input facilitates extensors in the reversal response. Phase-dependent input from receptors signaling limb position (especially from proximal limb proprioceptors: hip joint and hip muscle receptors) assists the transition between swing and stance. Thus somatosensory inputs may extend stance or abbreviate the swing phase of gait. Peripheral inputs relayed to the cerebellum by way of the Dorsal SpinoCerebellar Tract (DSCT) is an important source of information that is compared to efferent feedback relayed by the Ventral SpinoCerebellar Tract (VSCT). In addition, a SpinoOlivary Tract provides segmental feedback that may be integrated with RubroOlivary input. Such comparative data are sent to the cerebellum by way of Climbing Fibers.

SEGMENTAL MOTOR CENTERS (SMCS) IN ACTION: AGONIST-ANTAGONIST INTERACTIONS DURING COMMON FUNCTIONAL TASKS

One of the most direct, noninvasive measures of Segmental Motor Center (SMC) activity is surface electrode electromyographic (EMG) recordings of muscles during performance of a task. Unfortunately, in the past, many laboratory studies of upper extremity motor control utilized tasks that restricted motion to a single joint and/or single plane of motion. While these tasks simplify the experimental design, they may not reflect more "natural," functional tasks used in our daily lives.

The implications for modeling motor control by SMCs and other motor centers in "simple" unijoint tasks may not generalize to more complex free motion tasks that require considerable coordination of effort among multiple axial and limb muscles, e.g. see Bernstein, 1967; Gribble, et.al., 2003; Latash, 2018. Complex actions requiring synergistic control of many muscles and joints (multiple degrees of freedom) have recently been incorporated into biomechanical and neurophysiological studies (e.g., reaching and grasping). Studies of human and non-human subjects have called into question the validity of some of the original theories based on older techniques that reduced motion to its least common denominator. For example, recent studies suggest that synchronous activation of motor units within the same or synergistic distal hand musculature may occur for the dominant but not for the non-dominant hand, see Fuglevand, 2011. Descending pathways, in particular the Lateral CorticoSpinal Tract (LCST), provide a critical input to recruit SMC neurons for volitional actions to accomplish our goals (see LCST to SMC Activation Movie).

Fig 14-25. LCST to SMC Activation Movie. Large & Small Pyramids = Alpha & Gamma Motoneurons, respectively. Red Spheres = Ia Inhibitory Interneurons. Blue beams = LCST Input to Agonist SMC. Red Beams = Reciprocal Inhibition of Antagonist SMC Neurons. Shower of Small Particles = Nonspecific Modulatory Influences on SMC (gec). GO TO: gmomm.pitt.edu Fig14-25 _Video

The following section will examine some of these concepts by showing movies and surface EMG recordings of muscles used in common functional tasks. The relationships seen in motor unit output will be related to proposed SMC activation with simple animations of spinal cord activation patterns.

These examples are not meant to be anything but an introduction into the complex integration of neural networks at the output stage of the motor system. Each example shows the raw EMG of the Biceps & Triceps, or Anterior Deltoid & Lumbar Paraspinal Muscles using surface electrode recordings. The EMG is synchronized to the video and selected still frames are shown with the corresponding EMG segment marked. If you have stereo speakers you can hear the EMG of the Triceps or Deltoid in the right speaker and the Biceps or Paraspinals in the left. Animations of SMC activity follow several EMG movies.

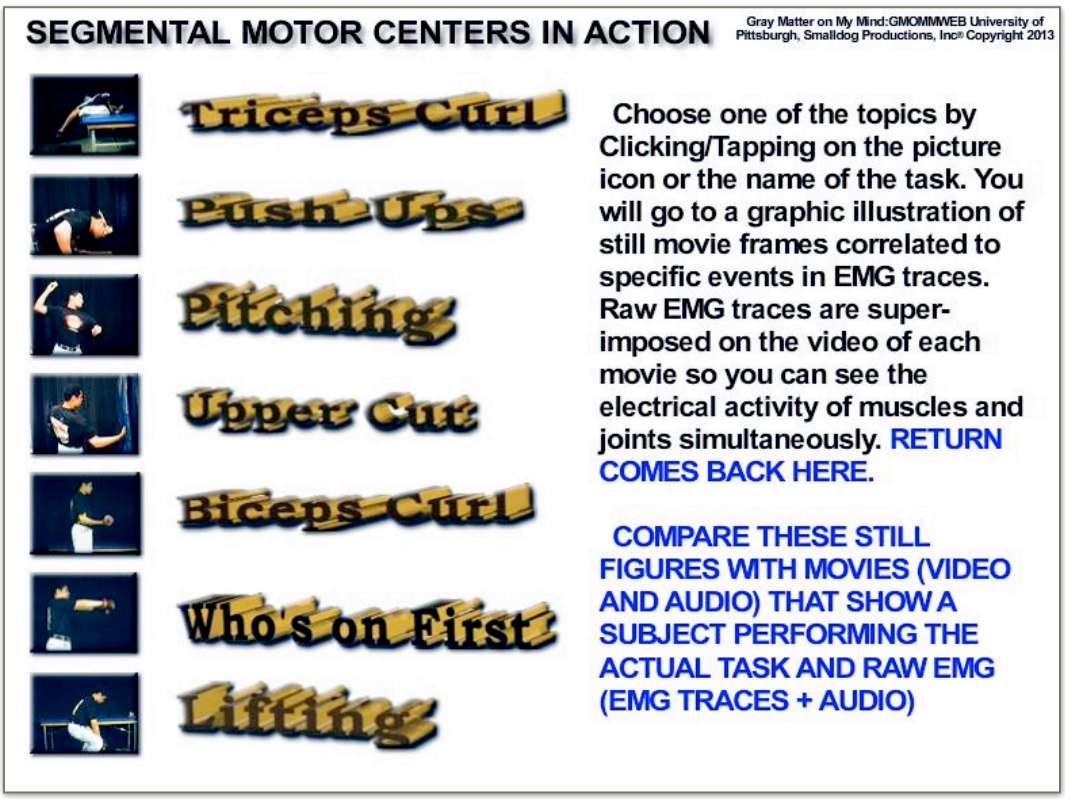


Fig 14-26. Segmental Motor Centers In Action Interactive Media File. See the correlation of EMG and biometrics for motion for a number of common daily tasks or exercises. Movies relating EMG to motion are shown below. GO TO: gmomm.pitt.edu *Fig14-26_Interactive Media*

SEGMENTAL MOTOR CENTERS IN ACTION: TRICEPS CURL

The Triceps Brachii is the major extensor muscle group for the elbow. When performing a relatively simple task such as the triceps curl demonstrated here, the triceps muscles are the agonists for elbow extension. However, they do not work alone. The biceps (and other elbow flexors) are concurrently active, and the arm must be stabilized by a host of shoulder girdle muscles. Even with slow actions that have minimal degrees of freedom, SMCs of agonists and antagonists have complex interactions. Simple reciprocal inhibition of the antagonist (biceps and other elbow flexors in this case) does not accompany agonist (triceps) contraction, e.g. see Gribble, et.al., 2003; Latash, 2018.

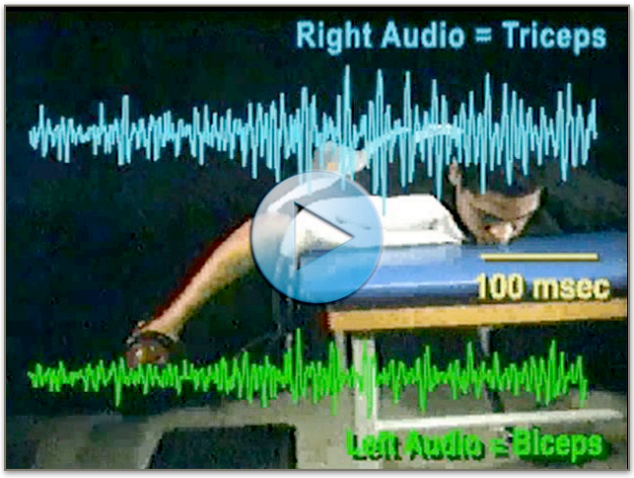


Fig 14-27. SMCs in Action: Triceps Curl Movie (gec, jec). GO TO: gmomm.pitt.edu Fig14-27_Video

Likewise, the level of EMG at any one specific angle during this exercise is not constant. Notice the much greater level of EMG during the concentric (shortening) phase of the triceps as the load is lifted against gravity.

SEGMENTAL MOTOR CENTERS IN ACTION: BICEPS CURL

The Biceps Brachii is one of three major elbow flexor muscles (Brachioradialis and Brachialis are additional elbow flexors). Since the biceps functions to not only flex the elbow but also flex the shoulder and supinate the forearm, its recruitment is determined by the total requirements of the task.

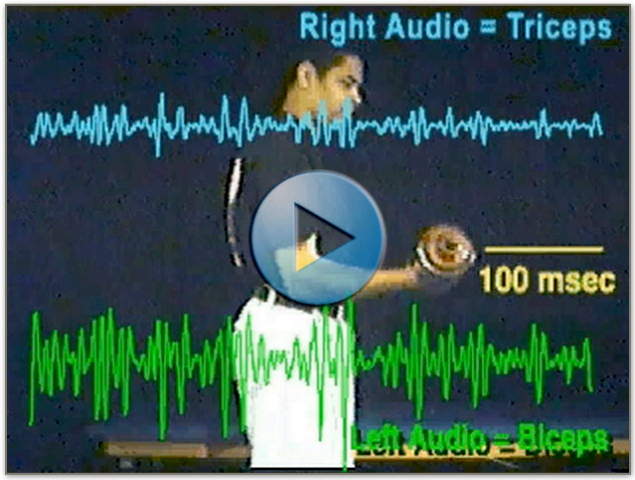


Fig 14-28. SMCs In Action: Biceps Curl Movie: Supination (gec, jec). GO TO: gmomm.pitt.edu *Fig14-28_Video*

The examples here show the biceps is a strongly activated when lifting a weight with the forearm supinated but relatively suppressed when the forearm is pronated. Therefore, these three elbow flexor muscles are not automatically coactivated as synergists for all tasks. The CNS cannot rely upon a single stereotypical pattern for all actions involving limbs that have multiple degrees of freedom of motion.

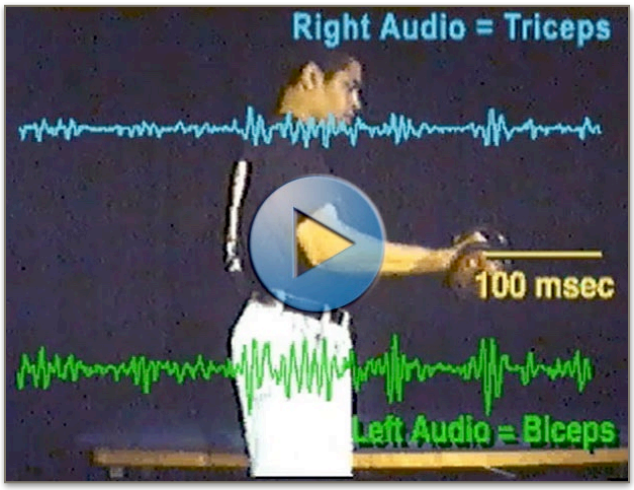


Fig 14-29. SMCs in Action: Biceps Curl: Pronation (gec, jec). GO TO: gmomm.pitt.edu *Fig14-29_Video*

The SMCs In Action Biceps Curl Movies for Supination and Pronation movies show a dramatic difference in recruitment of the biceps in elbow flexion depending on the position of the forearm (supinated versus pronated). Remember biceps have a role as a supinator and when forearm is pronated may be relatively inhibited by reciprocal inhibition segmental motor center interneurons (Ia IN). Additionally, altered patterns of descending control signals from the cerebral cortex may alter synaptic excitatory drive to supinators vs. pronators depending upon the task demands of the particular muscle: its role as agonist, synergist, stabilizer, or as antagonist, e.g., see Griffin, Hoffman and Strick, 2015.

Since the biceps supinates the forearm as well as flexes the elbow, the position of the hand when lifting the weight (palm up vs. palm down) is critical to how the different elbow flexors contribute to the motion. When lifting the weight with the palm down (forearm pronated) the pronators must reciprocally inhibit the supinator muscle and the biceps even though the biceps is a strong elbow flexor. Thus, some muscles may be synergistic agonists for some motions but not for others. Since the elbow flexor SMCs all exist in the same levels of the spinal cord, anatomical location of these motor nuclei does not determine their functional contribution to complex limb movements. Compare the supination vs. pronation movies.

SEGMENTAL MOTOR CENTERS IN ACTION: PUSHUPS

The biceps and triceps have actions at the elbow and shoulder (flexion & extension, respectively at each location). The biceps, in addition, is a supinator of the forearm. Note the relative level of activation of these muscles as the body is lowered and then raised against the force of gravity. Remember that the control includes not only the movement of the elbow and shoulder but also stabilizing the hand on the surface. This stabilization incorporates wrist and forearm activity, and stabilization of the scapula by powerful muscles acting at the "scapulothoracic joint." At full elbow extension the elbow may be "locked" by a combination of shoulder and forearm rotation, requiring little elbow extensor muscle activity to sustain this posture. A loss of the ability to volitionally activate the seventh and eighth cervical SMCs will make this task impossible.

A Pushup is one example of a slow, controlled change in posture using upper extremity musculature. It consists of a "gravity-assist" component where the triceps control the descent using an eccentric (lengthening) contraction (see light gray ramp in figure), followed by a concentric (shortening) "gravity-resist" contraction of the triceps to raise the body against gravity (dark gray ramp in figure).

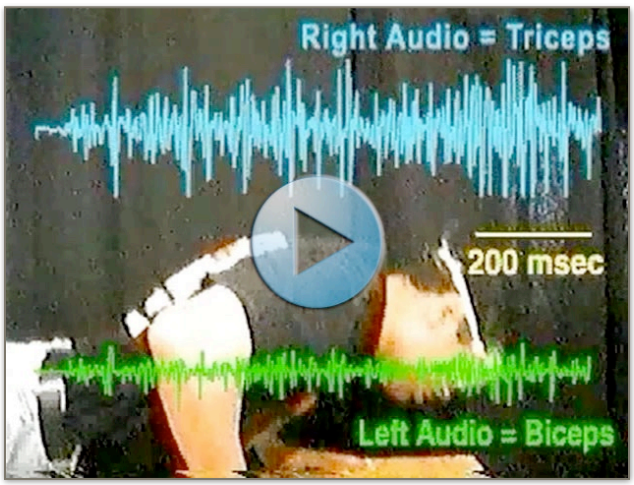


Fig 14-30. SMCs In Action: Pushups Movie. Note: Protective goggles are not required for this task; we forgot to remove the goggles after finishing the previous task-hammering a nail (gec, jec). GO TO: gmomm.pitt.edu *Fig14-30_Video*
Note the difference in EMG output for the different phases. The antagonist biceps muscles are relatively inactive but are not silent. Remembering that portions of both the triceps and biceps act at the elbow and shoulder (glenohumeral joint), how might the biceps contribute to this functional activity?

SEGMENTAL MOTOR CENTERS IN ACTION: FLEXOR & EXTENSOR ACTIVATION

The following animation shows Motoneurons & Interneurons that comprise the Segmental Motor Centers (SMCs) for the Cervical 5-8 (C5-C8) levels of the Spinal Cord. The Flexor and Extensor SMCs are separated so they are more easily identifiable. The animation illustrates the summed activity levels of the SMC neurons related to the changes in EMG for the Biceps (C5-6), and the Triceps (C7-8) when doing a pushup. Obviously, more SMCs would be active in the actual spinal cord since many other muscles are active when one does this functional task. This “virtual” slow-motion SMC animation illustrates the difference in activation of the triceps SMC during the eccentric versus concentric phase of a pushup, and the small contribution of the biceps SMC to this task.

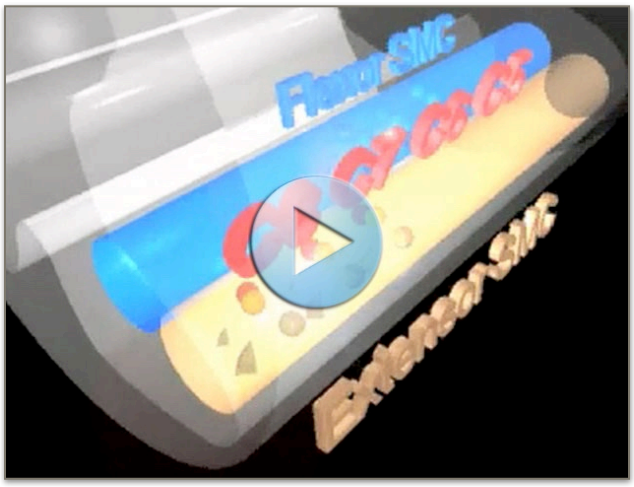


Fig 14-31. Segmental Motor Centers Animation of Neuronal Activation for Triceps & Biceps for Pushup (gec). GO TO: gmomm.pitt.edu Fig14-31_Video

SEGMENTAL MOTOR CENTERS IN ACTION: PUNCHING

Punching by a professional is an example of a "skilled ballistic" movement, one which requires a high force and an expected impact on an object. For non professionals, this fast action includes an initial 'launching" of the fist "guiding" the hand to a target and then controlling the "impact" at least to the extent of protecting the integrity of the hand's soft tissues and skeletal infrastructure.

Note rapid bursts of the biceps and triceps. The initial biceps "agonist burst" followed by a silent period and then a second "agonist burst" is typical of a fast continuous movement. A triceps "antagonist burst" occurring during the biceps' silent period is another feature of fast continuous movements. Note the stronger correlation of these bursts in later punches that were more forceful than earlier ones. A professional's movement is faster and typically includes only a single agonist burst followed by an antagonist burst for punches where one’s impact on the target is controlled (self-terminated ballistic). Punches that use only one agonist burst (no antagonist burst) is a non self-terminated ballistic movement. Punching is a skilled task requiring synergistic activation of axial and limb muscles. Initially, trunk and arm are extending and rotating to

take maximum advantage of the viscoelastic properties of soft tissues and provide a proper lever arm to store elastic energy to assist in the launching of the hand forward.

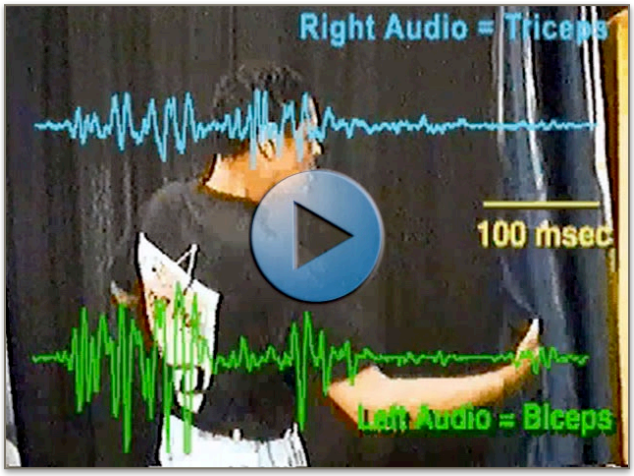


Fig 14-32. Segmental Motor Centers In Action: Punching (Nonprofessional) Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig14-32_Video*

The forward motion of the punch is a fast/ballistic motion with an initial burst from the biceps (and a number of shoulder muscles) as the arm is launched. A second burst from the biceps occurs at impact with the surface. The triceps is most active in mid-swing as it helps to "guide" the hand to the target; a continuous movement with a triphasic EMG pattern.

Punching by a professional boxer might show a more pronounced bursting pattern or possibly even a ballistic biphasic biceps/triceps pattern if the target is taken to be within the interior of the mat (target) rather than its surface (self-terminating ballistic motion). Punches that use only one agonist burst (no antagonist burst) is a non self-terminated ballistic movement. Such fast continuous or ballistic movements are thought to be feedforward "programmed" movements

SEGMENTAL MOTOR CENTERS IN ACTION: FLEXOR & EXTENSOR ACTIVATION FOR PUNCHING

The segmental motor center animation below shows Motoneurons & Interneurons that comprise the Segmental Motor Centers (SMCs) for the Cervical 5-8 (C5-C8) levels of the Spinal Cord.

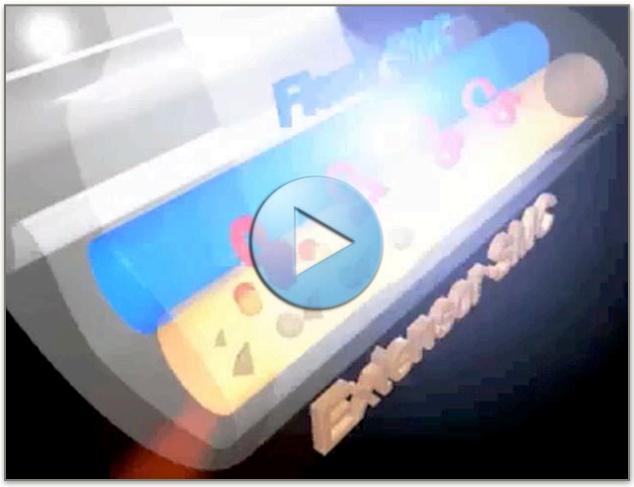


Fig 14-33. Segmental Motor Centers Animation for Triceps & Biceps for Punching Neuronal Activation Movie (gec). GO TO: gmomm.pitt.edu *Fig14-33_Video*

The Flexor and Extensor SMCs are separated so they are more easily identifiable. The animation illustrates the summed activity levels of the SMC neurons related to the changes in EMG for the Biceps (C5-6), and the Triceps (C7-8).

Obviously, more SMCs would be active in the actual spinal cord since many other muscles are active when one does this functional task. This “virtual” slow-motion SMC animation illustrates the difference in activation of the biceps and triceps SMCs during the initial setting of the limb for the punch (biceps>triceps) and then the triphasic activation during the ballistic forward motion of the arm. Note that the “launch” and “impact” phases are dominated by the biceps in this “uppercut,” while the triceps is most active in mid-swing (guide) prior to fist contact with the mat. A professional boxer might hit the target differently (endpoint = the interior rather than the surface). In that case the burst pattern might be more pronounced or possibly even biphasic (ballistic).

SEGMENTAL MOTOR CENTERS IN ACTION: PITCHING

Throwing is a skilled task requiring synergistic activation of axial and limb muscles. During the “wind-up” the trunk and arm are extending and rotating to take maximum advantage of the viscoelastic properties of soft tissues and provide a proper lever arm to store elastic energy to assist in the launching of the hand forward (delivery). This transition between the “wind-up” and the “delivery” is marked by a silent period for both elbow flexors and extensors. Forward motion of the arm is a fast/ballistic motion with an initial burst from the triceps (and a number of shoulder muscles), an intermediate burst from the biceps and then a second burst from the triceps as the ball leaves the hand.

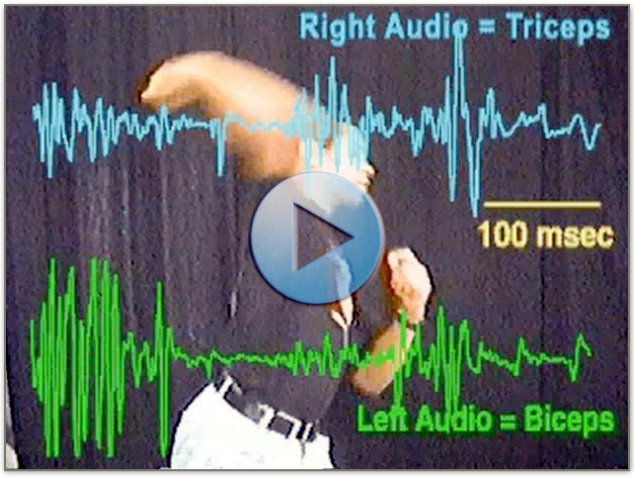


Fig 14-34. Segmental Motor Centers In Action: Pitching (Nonprofessional) (gec, jec). GO TO: gmomm.pitt.edu Fig14-34 _Video

This triphasic (Agonist-Antagonist-Agonist) EMG pattern is typical for fast continuous programmed movements.The follow-through shows little activity in either elbow muscle group. Pitching by professional ballplayers has been further subdivided into other stages in the entire action series. One can see, even pitching by a nonprofessional, involves rotator cuff muscles of the glenohumeral joint as critical to throwing a ball (overhand).

The spinal cord animation for pitching shows Motoneurons and Interneurons that comprise the Segmental Motor Centers (SMCs) for the Cervical 5-8 (C5-C8) levels of the Spinal Cord. The Flexor and Extensor SMCs are separated so they are more easily identifiable. The animation illustrates the summed activity levels of the SMC neurons related to the changes in EMG for the Biceps (C5-6), and the Triceps (C7-8).

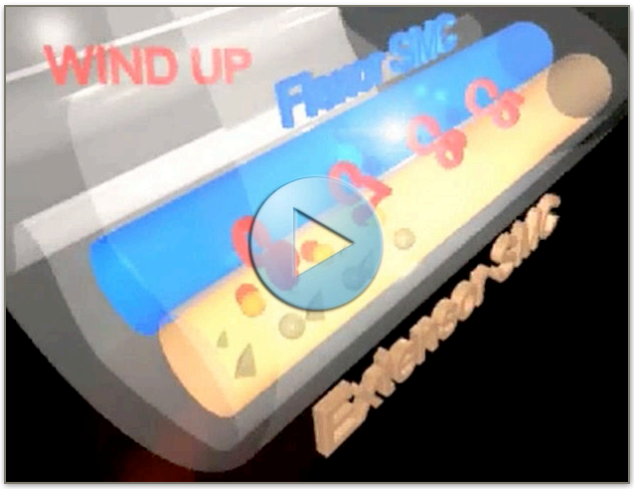


Fig 14-35. Segmental Motor Centers Animation for Triceps & Biceps for Pitching Neuronal Activation Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig14-35_Video*

Obviously, more SMCs would be active in the actual spinal cord since many other muscles are active when one does this functional task. This "virtual" slow-motion SMC animation illustrates the initial activation of the biceps >> triceps SMCs during the "wind up" of the limb followed by a silent period, and then the triphasic activation during the ballistic forward motion of the arm. The "delivery" is characterized by an initial triceps burst, a biceps burst, and then a second burst in the triceps. This triphasic EMG pattern is typical for ballistic motions. In the case of pitching it is the rapid motion of the arm that propels the hand (and ball) forward in the "delivery." A professional pitcher might show an even more pronounced triphasic or even a biphasic ballistic pattern when delivering the pitch. The biphasic pattern at the elbow would consist of a triceps burst followed by a biceps burst during the delivery.

SEGMENTAL MOTOR CENTERS IN ACTION: LIFTING-MOBILITY BUILT ON STABILITY

Who's on first? The following movie shows an individual lifting weights applied to both wrists. EMG electrodes are recording activity in the Anterior Deltoid and the Lumbar Paraspinal Muscles. Lifts are done rapidly and slowly. Notice the motion of the trunk as well as the arms.

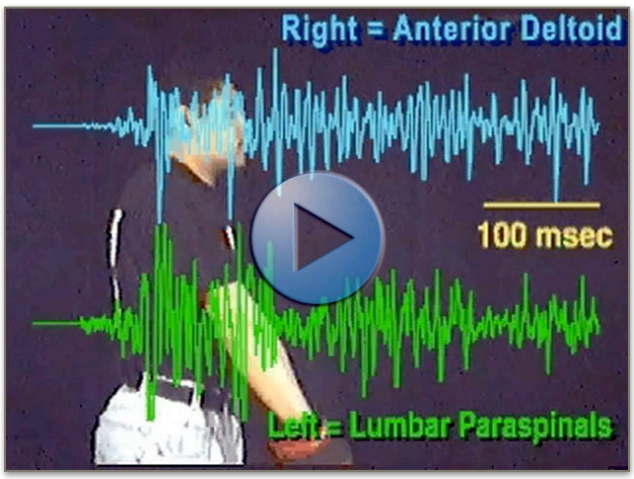


Fig 14-36. Segmental Motor Centers In Action: Lifting-Center of Mass Perturbation Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig14-36_Video*

For both rapid and slow lifts the onset of activity in the Lumbar Paraspinal Muscles slightly precedes the onset of Deltoid EMG. The activity in both muscles shows two bursts when lifting rapidly (see upper traces in the diagram of EMG activity in the two muscles). Note that the second burst in the Deltoid occurs before that in the Paraspinals, and appears to correlate with the control of the weight as the arm reaches a horizontal position.

The Paraspinals increase activity slightly later as the arm is being lowered. This “bursting” is not present in slow lifts (see lower traces). In both cases the motor control centers must initially anticipate perturbation of the body's center of mass and send feedforward signals to postural muscles just before the signals to initiate arm motion. As the weight is moving the Paraspinals make adjustments to control the center of mass. The brain cannot ignore the biomechanical demands of moving in our environment.

The thick green horizontal bar at the initial portion of the right hand EMG traces mark the portion of this trace that is expanded (in time) in the left hand traces. The thin vertical green lines in the left traces indicate the onset of EMG for the lifting task.

SEGMENTAL MOTOR CENTERS IN ACTION: LIFTING-FOR BETTER OR WORSE

The following two movies show a dramatic difference in recruitment of the lumbar paraspinal and anterior deltoid muscles with two different methods of lifting a weight from a low surface and placing it on a higher one.

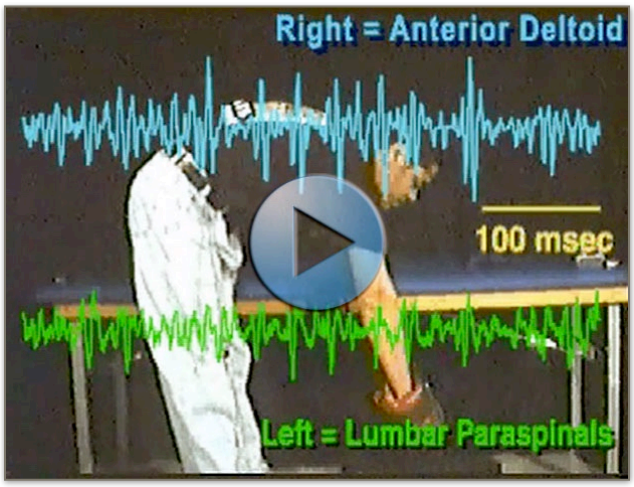


Fig 14-37. Segmental Motor Centers In Action: Lifting For Worse Movie (left)-Note Loading of Spine far from subject’s center of mass (gec, jec). GO TO: gmomm.pitt.edu *Fig14-37_Video*

The best method keeps the object close to one's center of mass, and uses strong lower extremity muscles to bend and lift (see Lifting For Better Movie).

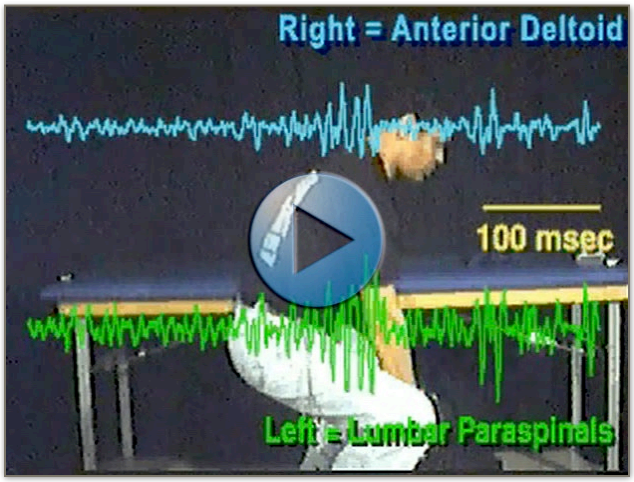


Fig 14-38. Segmental Motor Centers In Action: Lifting For Better Movie-Note Loading of Spine close to subject’s center of mass (gec, jec). GO TO: gmomm.pitt.edu *Fig14-38_Video*

The second method displaces one's center of mass forward while bending at the waist and lifting with outstretched arms (see Lifting For Worse Movie). If you were required to do this task repeatedly day after day which method would you prefer? Remember bigger muscular output is not always better

when EMG reflects high levels of stress to vulnerable soft tissues.

Control of posture by the motor control centers must take into account those constraints of a spine supporting an erect body mass. The utilization of paraspinal and abdominal muscles in quadrupeds may be quite different from ours, so also might be the required neurophysiology of the SMCs controlling axial muscles in four-legged versus two-legged species.

SEGMENTAL MOTOR CENTERS IN ACTION: PREDICTIVE VS. REACTIVE RESPONSE TO PERTURBATION

The ability to maintain a posture despite an unexpected perturbation relies on use of feedback sensory data to make adjustments of musculature in response to the external forces that disturb current conditions. We are wired to consciously or subconsciously attend to sensory information that might predict such disturbances. We use those data to anticipate an expected displacement of the whole body or body segment so adjustments are made in a predictive manner. Catching a heavy ball dropped into the hand without any information about the time of drop or its path to the hand requires a reactive response based solely on feedback from somatosensory receptors in the perturbed arm/hand.

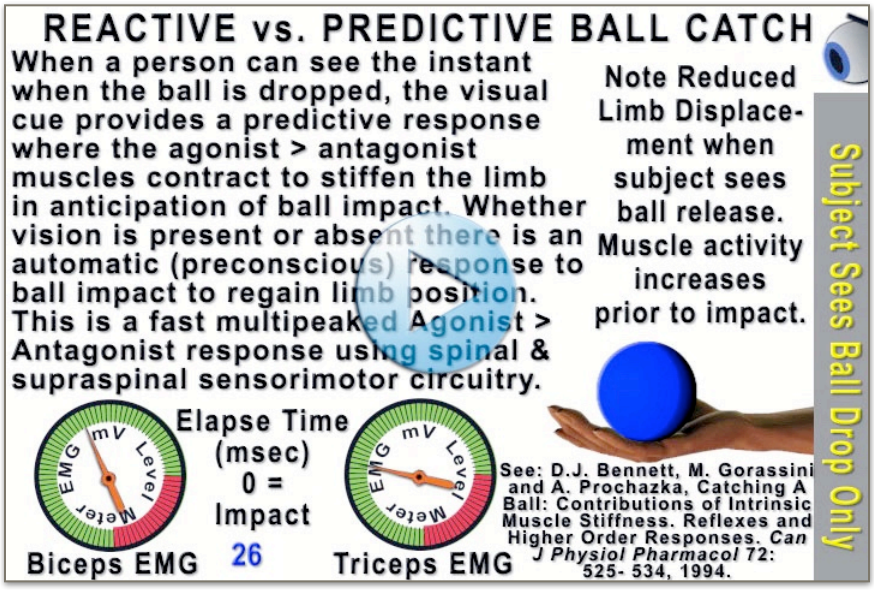


Fig 14-39. Segmental Motor Centers In Action: Catching A Ball Movie: Advantages of Predictive Vision (gec) GO TO: gmomm.pitt.edu Fig14-39_Video

If we know when the ball is dropped even without information about its path allows for expectation of ball-hand contact based upon our previous knowledge about gravity, and velocity of ball motion based upon that physics. We then stiffen the arm by cocontracting the arm (elbow) muscles in anticipation of the ball contact. We thus add a predictive component to decrease the amount of displacement of the hand when the ball hits the hand. Seeing the expected source of near-future perturbation allows for both a predictive and a reactive component.

SEGMENTAL MOTOR CENTERS IN ACTION: REAL VS. FICTIVE WHISKING - LIMITATIONS OF STIMULUS-INDUCED MUSCLE ACTIVATION (NEUROMUSCULAR ELECTRICAL STIMULATION)

Skeletal muscle may be activated by either spinal motoneurons sensing action potentials to the motor units or the muscle may be activated by electrically stimulating the motor axons in the muscle's nerve supply. The former is characterized by a relatively asynchronous motor unit (MU) recruitment according to Henneman's size principle (slow-twitch MU recruited before fast twitch MU). The latter artificial muscle nerve activation by electrical pulses produces synchronous activity within the lowest threshold axons innervating the fast twitch motor units.

Fig 14-40. Segmental Motor Centers In Action: Real & Fictive Whisking Movie - Limitations of Neuro-muscular Electrical Stimulation (gec). GO TO: gmomm.pitt.edu Fig14-40_Video

Thus motor unit recruitment using electrical stimulation of motor axons tends to activate the same motor units with each burst of stimuli resulting in a brisk contraction. Although ramping of the amplitude of stimuli may simulate a smoother recruitment such artificial involuntary contractions are not as smooth as the volitional asynchronous recruitment according to the size principle of motor unit recruitment. The Fictive Whisking Movie illustrates this difference between volitional and electrically induced contractions of fast-twitch motor units of the intrinsic sling muscles within the mystacial pad of the rat face.

CLINICAL NEUROMUSCULAR PATHOLOGY: WEAKNESS

Weakness is one of the most common problems associated with sensorimotor disorders. Weakness may be easily quantified using a manual muscle test for each

muscle group in some disorders but quite inscrutable for others. Functional weakness is often poorly quantifiable by routine clinical strength tests. On the other hand, functional deficits are quite obvious to the patient and to the trained eye of the clinician. The difficulty is often one of adequately documenting changes in these deficits using tests that are sensitive, and reliable. Weakness may be described as fatigue, heaviness, clumsiness, slowness, numbness, or even a decrement in performance in highly practiced, skilled activities. True weakness (a loss of volitional muscle force/tension) may be non-neurological, e.g., loss of muscle mass and strength due to disuse.

Many systemic diseases including those that result in poor nutrition may effect the ability to generate sufficient energy to do the work required during daily activities. Inadequate perfusion of peripheral nerve and muscle may lead to weakness.

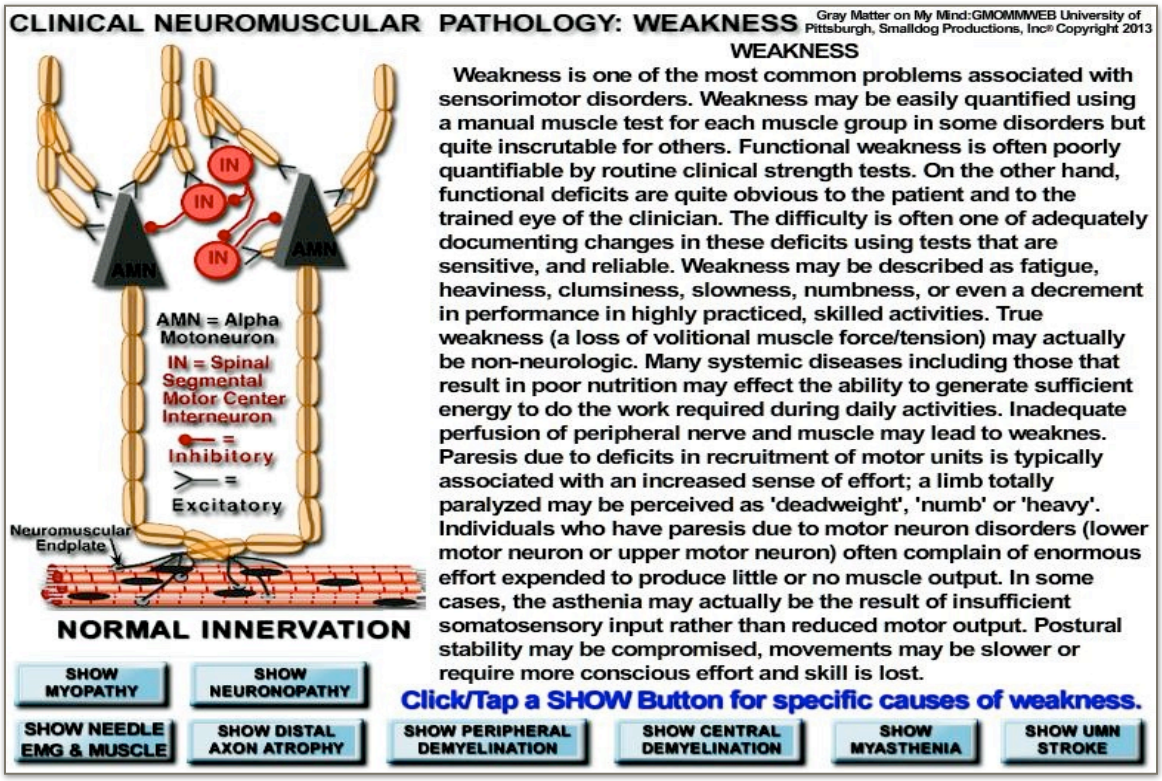


Fig 14-41. Clinical Weakness, EMG Needle Exam & Muscle Biopsy Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig14-41_Interactive Media]

Paresis due to deficits in recruitment of motor units is typically associated with an increased sense of effort; a limb totally paralyzed may be perceived as “deadweight,” “numb,” or “heavy.” Individuals who have paresis due to motor neuron disorders (lower motor neuron or upper motor neuron) often complain of enormous effort expended to produce little or no muscle output. In some cases, this asthenia may actually be the result of insufficient somatosensory input rather than reduced motor output. Postural

stability may be compromised, movements may be slower or require more conscious effort and skill may be reduced.

CLINICAL NEUROMUSCULAR PATHOLOGY: PERIPHERAL NERVE INJURY-CHROMATOLYSIS & WALLERIAN DEGENERATION

Peripheral Nerve Injury (PNI) resulting from trauma to a nerve results in a series of axonal and neuronal reactions. An initial degeneration of the axon and myelin distal to the injury is accompanied by a central chromatolysis of the cell bodies in the dorsal root ganglion and motoneurons in the ventral horn. The soma swells, the nucleus becomes eccentric in its location and the Nissl substance (chromatin-endoplasmic reticulum and ribosomes) is dispersed. The cell body is gearing up for repair and an increase in protein production associated with regeneration. Astrocytes surrounding the motoneuron may react and interpose glial extensions between presynaptic and postsynaptic membranes effectively removing many synaptic inputs. A classic series of events occurs distal to the injury in peripheral nerves. Schwann cells proliferate, macrophages invade, axonal membranes disintegrate and myelin is removed and decomposed into myelin "ovoids". The membrane "debris" is removed by the macrophages with the assistance of proliferated Schwann cells. The Schwann cells arrange themselves to form a growth tube for the regenerating axons. The growth tubes are called Bands of Bungner. The severed axons send out multiple axonal sprouts. If one of these sprouts finds its way into the Band of Bungner it will grow towards its target (sensory receptor or muscle fiber). As the one sprout grows within this "tunnel" any remaining axonal sprouts are normally retracted. All of this "mechanical" activity is accompanied by chemical responses including altered levels of neurotrophins, cell adhesion molecules and other chemical guidance cues for regenerating axons.

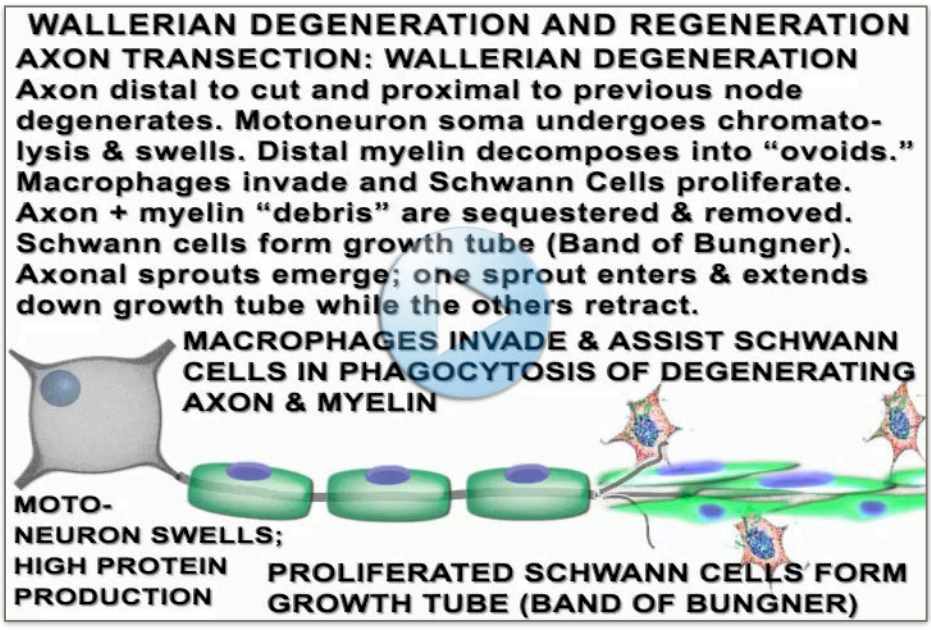


Fig 14-42. Wallerian Degeneration and Regeneration Following Axon Transection Movie (gec). Large File Be Patient. GO TO:gmomm.pitt.edu Fig14-42_Video

When/if the axon reinnervates a sensory or motor target the Schwann cells remyelinate the axon as it increases

its diameter: for review see Burnett & Zager, 2004; Fu & Gordon, 1997; Lee & Wolfe, 2000; Navarro, et.al., 2007; Terenghi, 1999. These steps are illustrated in the Wallerian Degeneration and Regeneration movie.

A number of review articles describe the levels of PNI according to two common classification systems (see references). Seddon's (1943) classification includes neuropraxia, axonotmesis and neurotmesis while Sunderland's (1952a,b) classification of first, second, third, fourth and fifth degree injuries is more detailed. Recovery is more extensive when perineurium is intact, e.g., Seddon's neuropraxia or axonotmesis or Sunderland's first or second degree injuries. Interruption of perineurium and epineurium (Seddon's neurotmesis or Sunderland's fourth-fifth degree injuries) have a poorer prognosis for full or even partial recovery of function even with microsurgical repair.

Results of recent studies in rodents suggest that regeneration may be enhanced by a single one hour period of stimulation of the proximal stump of the transected nerve following microsurgical repair. The most common stimulus pattern is a 0.1 msec pulse waveform (cathode proximal to anode) delivered at 20 Hz (20 pulses per sec). The effect may be due to enhanced up-regulation of neurotrophins (Neurotropin 4/5 and BDNF) expressed by the neurons and/or Schwann cells. The stimulation promotes enhanced regrowth of both peripheral sensory (dorsal root ganglion cells) & motor neurons: see Al-Majed, et.al., 2004; Brushart, et.al., 2002, 2005; Geremia, et.al., 2007; Gordon, et.al., 2008.

CLINICAL NEUROMUSCULAR PATHOLOGY: MYOPATHY-PRIMARY MUSCLE DISEASE

Myopathies are diseases of skeletal muscle that attack muscle fibers. Many primary muscle diseases are inherited, and are progressive (Muscular Dystrophies or MD). The muscle weakness begins early in childhood for most forms of MD. Cardiac myopathy may accompany skeletal muscle degeneration. Degeneration of the contractile proteins results in a reduced ability to generate force. Motor units have a reduced innervation ratio and to generate tension the individual must increase recruitment by firing more motor units at a higher rate of discharge. Clinical Electromyographic Needle Exams reveal small amplitude, polyphasic potentials (myopathic potentials). Electromyographers report an early interference pattern (motor unit potentials overlap long before a maximal volitional effort is reached). A myopathic early interference pattern revels overlapping small amplitude polyphasic motor unit potentials typical of primary muscle disease.

Normally an interference pattern is seen only when maximal effort is requested and normal motor units with larger amplitude fill the screen. Nerve Conduction is normal in primary muscle disease.

There are no sensory deficits, no evidence of central motor or other brain dysfunction. Most types of primary muscle disease involve proximal > distal

musculature. Reduced power in shoulder and hip girdle muscles and axial muscles make reaching, transfers, standing and walking a challenge that eventually becomes disabling. Weakness typically spreads to more distal muscles.

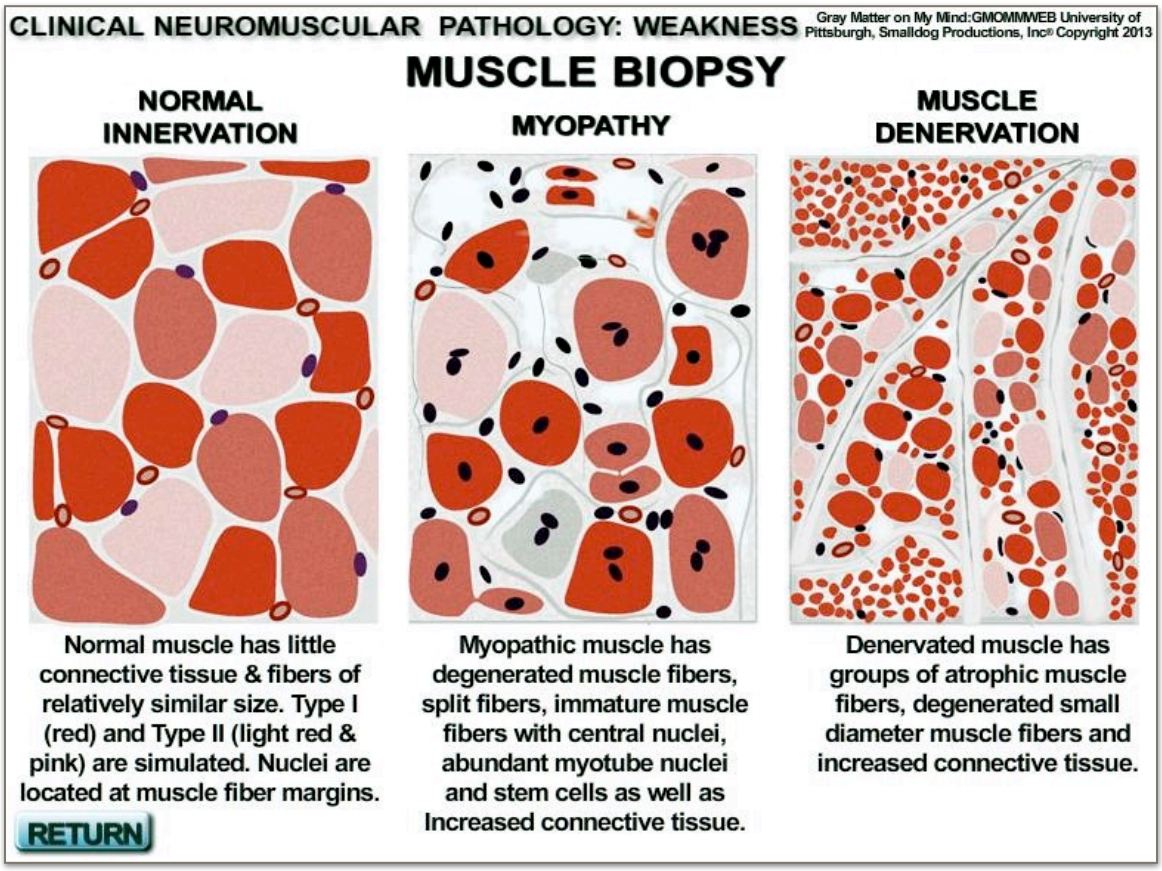


Fig 14-43. Muscle Biopsy Simulations of Normal, Myopathic and Denervated Muscle (gec). GO TO: gmomm.pitt.edu *Fig14-43_Interactive Media*

A waddling gait, lordotic standing posture, and difficulty in rising from a recumbent position are characteristic of the Duchenne and other forms of muscular dystrophy. Clinical examination typically includes a test for loss of muscle power in rising from a lying position on the floor. Individuals with proximal weakness tend to “climb-up” upon themselves to rise to a standing position (often called a Gower's sign).

Despite the severe weakness in the affected muscles, those muscles may actually appear to be well developed (pseudohypertrophy). The involved muscles have an increase in connective tissue, evidence of immature multinucleated muscle fibers, split muscle fibers and fibrotic replacement of degenerated muscle fibers. Late in the disease, muscle biopsies may reveal a high percentage of “fat” that has replaced the lost muscle tissue.

CLINICAL NEUROMUSCULAR PATHOLOGY: NEURONOPATHY-MOTONEURON DISEASE

Neuronopathies are diseases of the motor neuron. Lower Motor Neuron (LMN) Disorders have a classic constellation of signs and symptoms. A LMN Disorder is characterized by a flaccid paresis or paralysis with no sensory system involvement. Severe atrophy of the muscle is due to denervation of the involved motor unit's muscle fibers. Deep Tendon Reflexes are hypoactive or absent for the involved muscles.

Clinical Electromyographic Needle Exam reveals electrical signs of denervation including abnormal potentials at rest (fibrillation potentials, positive sharp waves, and fasciculation potentials). Requests for volitional contraction shows that Motor Unit Recruitment is abnormal (reduced number of motor units that fire at a higher rate than normal). Motor unit potentials that survive in incomplete lesions are abnormal (polyphasic and giant potentials). The surviving motor unit axons sprout new axon collaterals within the muscle to "rescue" denervated muscle fibers; this results in an expanded motor unit territory for surviving motor units. Missing in a true Anterior Horn Cell (LMN) Disease are the pathological reflexes typical of an Upper Motor Neuron Disorder. Abnormal synergies are absent, though the individual may substitute remaining muscles to create actions to accomplish the task at hand. Weakness can be quantified with a manual muscle test that isolates specific muscles or muscle groups. The individual has no difficulty in isolating specific muscle actions but those affected muscles will be weak (reduced force production). Diseases of the spinal cord may show a combined Upper Motor Neuron and Lower Motor Neuron Syndrome due to involvement of the descending tracts and ventral horn gray, respectively. Amyotrophic Lateral Sclerosis (ALS) shows a combined UMN/LMN disease process. ALS typically involves motor nuclei within the brainstem that may affect speech, swallowing, tongue movements, and facial expressions. The extraocular muscles are often sparred at least until late in the course of this fatal disease.

CLINICAL NEUROMUSCULAR PATHOLOGY: AXONAL DEGENERATION-PERIPHERAL NEUROPATHY

Peripheral Neuropathies are diseases of the peripheral nervous system axons anywhere from the roots to distal axonal branches in the periphery. Distal axonal degeneration results in denervation of muscle fibers and sensory receptors in the periphery. Both sensory and motor axons may be affected but some neuropathies have a predilection for one or the other. Axonal degeneration is accompanied by a reactive change in the motoneuron soma: chromatolysis. The soma swells and the RNA machinery gears up for axonal regeneration. Motor Nerve Conduction Studies may be normal until many axons are involved. Sensory Nerve Conduction may show reduced amplitudes of evoked potentials early, or no evoked response if many axons are involved. This process is usually seen in the distal most segments and may progress proximally (dying-back phenomenon).A dying-back is thought to be related to poor

health of the distal segments due to poor axonal transport and/or poor perfusion in the distal limb. Sensory changes associated with large fiber conduction (e.g., discriminative touch, proprioception) or small fiber (pain & temperature) may be found, as well as, reduced or absent deep tendon reflexes for involved musculature.

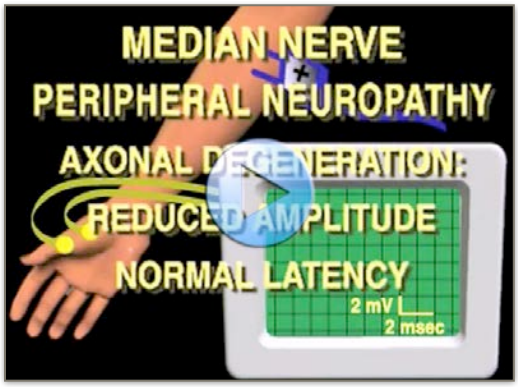


Fig 14-44. Abnormal Clinical Motor Nerve Conduction Exam Movie; Evidence of Denervation (gec). GO TO: gmomm.pitt.edu *Fig14-44_Video*

Electrical signs of muscle denervation are typically found in the clinical EMG needle exam (fibrillation potentials and positive sharp waves). Abnormal Motor Unit Potentials may be seen especially if denervated fibers are "rescued" by surviving axon branches. Weakness may be variable depending on the stage and severity of nerve involvement.

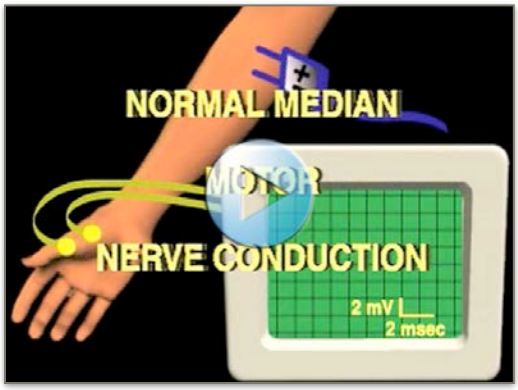


Fig 14-45. Normal Clinical Motor Nerve Conduction Exam Movie. No Evidence of Denervation or Demyelination (gec). GO TO: gmomm.pitt.edu *Fig14-45_Video*

Early muscle fatigue may be the most significant functional problem that may or may not be revealed by a routine manual muscle exam. Polyneuropathies are often distal and symmetric. Examples include diabetic, alcoholic, or toxic polyneuropathies that show distal muscle weakness and atrophy, and a distal "stocking-glove" pattern of sensory loss. There are many variations to these patterns of involvement, e.g., small fiber versus large fiber disease. Some investigators have suggested that the nerves are sick and therefore more susceptible to a second insult such as pressure or ischemia.

CLINICAL NEUROMUSCULAR PATHOLOGY: SEGMENTAL DEMYELINATION-PERIPHERAL NEUROPATHY

Peripheral Neuropathies are diseases of the peripheral nervous system axons anywhere from the roots to distal axonal branches in the periphery. Segmental Demyelinating Diseases result in loss of myelin and possibly impairment or destruction of the Schwann Cells responsible for myelinating these axons. Both sensory and motor axons may be affected but some neuropathies have a predilection for one type versus another. Loss of myelin results in focal slowing of nerve conduction, or, if severe, a focal conduction block may be present. Nerve Conduction Studies may reveal such deficits if

the test includes the involved segment of nerve. This process may be multisegmental and severe such as Acute Guillian Barre Syndrome, or the lesion may be localized to a single site of nerve compression or ischemia, e.g., Mild, Acute Carpal Tunnel Syndrome or nerve root compression. Some demyelinating diseases progress to axonal degeneration with resultant denervation of involved motor units. Sensory changes associated with large fiber conduction (e.g., discriminative touch, vibration sense, proprioception) may be found, as well as, reduced or absent deep tendon reflexes for involved musculature.

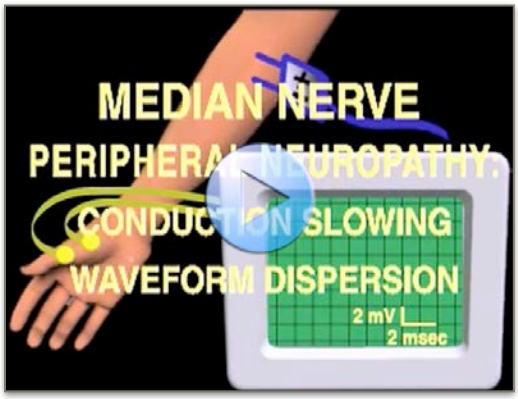


Fig 14-46. Abnormal Clinical Motor Nerve Conduction Exam Movie. Evidence of Demyelination (gec). GO TO: gmomm.pitt.edu
Fig14-46_Video

Frank electrical signs of muscle denervation may be absent in the clinical EMG needle exam unless a secondary axonal degeneration is present. Weakness may be a labile finding depending on the stage and severity of nerve involvement. Early muscle fatigue may be the most significant functional problem that may or may not be revealed by a routine manual muscle exam. Polyneuropathies are often distal and symmetric. Examples include diabetic, alcoholic, or toxic polyneuropathies that show distal muscle weakness and atrophy, and a distal "stocking-glove" pattern of sensory loss. On the other hand, a spinal nerve root entrapment due, for example, to a herniated disc will show a radiating/ radicular pattern associated with the appropriate dermatomal and myotomal reference.

There may be a rapid onset of symptoms or there may be a more gradual functional loss depending on the severity of the radicular pressure.

There are many variations to these patterns of involvement, e.g., small fiber versus large fiber disease. Some investigators have suggested that the nerves are sick and therefore are more susceptible to a second insult such as pressure or ischemia.

CLINICAL NEUROMUSCULAR PATHOLOGY: MYASTHENIA

Myasthenia Gravis and Myasthenic Syndrome are diseases of the neuromuscular junction. Myasthenia Gravis is an autoimmune disorder of the Acetylcholine (ACh) Receptors. A reduced number of ACh receptor sites are found at the motor endplate of involved skeletal muscles. Muscles innervated by somatic peripheral and Cranial nerves may show premature fatigue to repetitive nerve stimulation. Single stimuli may reveal no electrophysiological abnormalities but stimulation with rapid trains shows a decrementing evoked motor response. This amplitude reduction may be reversed by rapid-acting Anticholinesterase drugs (e.g., Neostigmine).

These drugs prolong the action of ACh by reducing the breakdown of ACh by Cholinesterase in the synaptic cleft. Single-fiber Electromyography shows a telltale increase in 'jitter' in single motor unit recruitment. Normally, the single motor unit will have a consistent latency as seen on the EMG screen (little or no jitter). Myasthenic motor units have a greater variability in the synaptic junction delay seen as an increase in jitter. Individuals may experience increased fatigue as the day wears on but others may have acute episodes of weakness upon rising, before their first medication of the day. Individuals who have Myasthenia Gravis may have Thymus Gland Tumors. Thymectomy improves their symptoms. Anticholinesterase drugs are routinely prescribed for these patients.

A second type of Myasthenia is Myasthenic Syndrome. This is often associated with Oat cell Carcinoma of the lung. Myasthenic Syndrome typically shows an incrementing evoked motor response to repetitive nerve stimulation. Repeated activation of the motor end plate allows greater accumulation of ACh. The problem is not with a reduced ACh receptor population (it may actually have a compensatory increase) but a deficit in ACh release at the neuromuscular junction. The single-fiber EMG studies of Myasthenic Syndrome show an increase “jitter” as in muscles affected by Myasthenia Gravis.

LOWER MOTOR NEURON (LMN) SYNDROME: POSITIVE AND NEGATIVE SIGNS OF PERIPHERAL NERVE DISORDERS

A lower motor neuron (LMN) pathology has a constellation of signs and symptoms resulting from loss of alpha motoneuron innervation of its motor unit. For example, a lesion of the alpha motoneuron cell body or its axon typically produces a “classic” LMN disorder. Damage to ventral horn gray in the spinal cord or motor axons in the peripheral nerve will result in a LMN Syndrome that includes the following signs and symptoms; the actual pattern depends on extent and location of the actual peripheral nervous system lesion. The LMN disorder includes both 'positive' and 'negative' sequelae.

LMN “Positive” Signs and Symptoms: Flaccidity, Hyporeflexia or Areflexia (decreased or absent deep tendon reflexes, no clonus, no abnormal mass reflexes), Down-going (negative) Babinski and negative Hoffmann Sign (upper extremity). Electromyographic (EMG) needle exam of denervated muscle reveals abnormal potentials at rest (fibrillation potentials, positive sharp waves, & possibly fasciculation potentials).

LMN “Negative” Signs and Symptoms: paresis/paralysis, loss of motor power, reduced number of motor units that can be recruited, altered motor unit territory, presence of clinical & electrophysiological evidence of muscle denervation. Nerve conduction studies may reveal evidence of peripheral motor denervation: Reduced motor evoked potential amplitude or waveform area. Request for volitional activation reveals reduced interference pattern (inadequate motor unit summation on maximal

contraction), and often abnormal motor unit potentials (size, shape & phases) in the EMG needle exam of denervated muscle.

LOWER MOTOR NEURON (LMN) SYNDROME: "FLACCID" PARESIS

Neural control of voluntary movement requires cooperation of many motor control centers located at all levels of the nervous system. Here we are concentrating on the descending pathways that synapse upon the segmental motor centers (SMCs) in the spinal cord, and the alpha motoneurons that provide the neural link to skeletal muscles in the periphery. Damage to the former results in an upper motor neuron (UMN) Syndrome, damage to the latter, a lower motor neuron (LMN) Syndrome.

Fig 14-47. Lower Motor Neuron Weakness Movie: Manual Muscle Test reveals reduced contraction strength but good isolation/fractionation (weak contraction limited to target muscle group) (gec, jec). GO TO: gmomm.pitt.edu *Fig14-47_Video*

Damage to the long tracts does not result in degeneration of motoneurons in the SMCs. However, a total transection of the spinal cord does isolate the spinal circuitry below the level of the lesion causing altered motor output with loss of volitional control. Incomplete or unilateral lesions result in varying forms of functional weakness and loss of dexterity. Damage to spinal motoneurons compromises one's ability to recruit sufficient muscle activity to engage the affected body region in many functional activities (reduced capacity to recruit motor units).

Fig 14-48. Normal Strength Manual Muscle Test: Motor System Produces Maximal Voluntary Contraction. Compare to LMN Weakness Movie above (gec, jec). GO TO: gmomm.pitt.edu
Fig14-48_Video

The Lower Motor Neuron Weakness Movie above shows an example of "flaccid" paresis due to a LMN disorder. The movement is restricted to the appropriate muscles (normal fractionation). However, dorsiflexors are weak. The foot cannot be lifted fully against gravity and the examiner easily pushes the foot down with no resistance offered by the weak dorsiflexors.

This screening suggests that during gait there will be foot-drop that may be compensated by excessive flexion of hip/knee during swing or a circumduction of the limb to clear the foot during swing. A “foot-slap” would be expected at footstrike since the dorsiflexors cannot eccentrically control the heel-to-toe transition as weight is borne on the limb. Such a LMN weakness of distal muscles could be due to a peripheral neuropathy, e.g., diabetic neuropathy or a peroneal nerve pressure neuropathy. Compare this LMN Weakness Movie with the Normal Strength Test Movie that follows.

CLINICAL ELECTROPHYSIOLOGY: EMG NEEDLE EXAM

Clinical Electrophysiology of the Peripheral Nervous System (PNS) typically includes Nerve Conduction and Electromyographic (EMG) Studies. An EMG Needle Exam uses indwelling electrodes to record extracellular skeletal muscle activity.

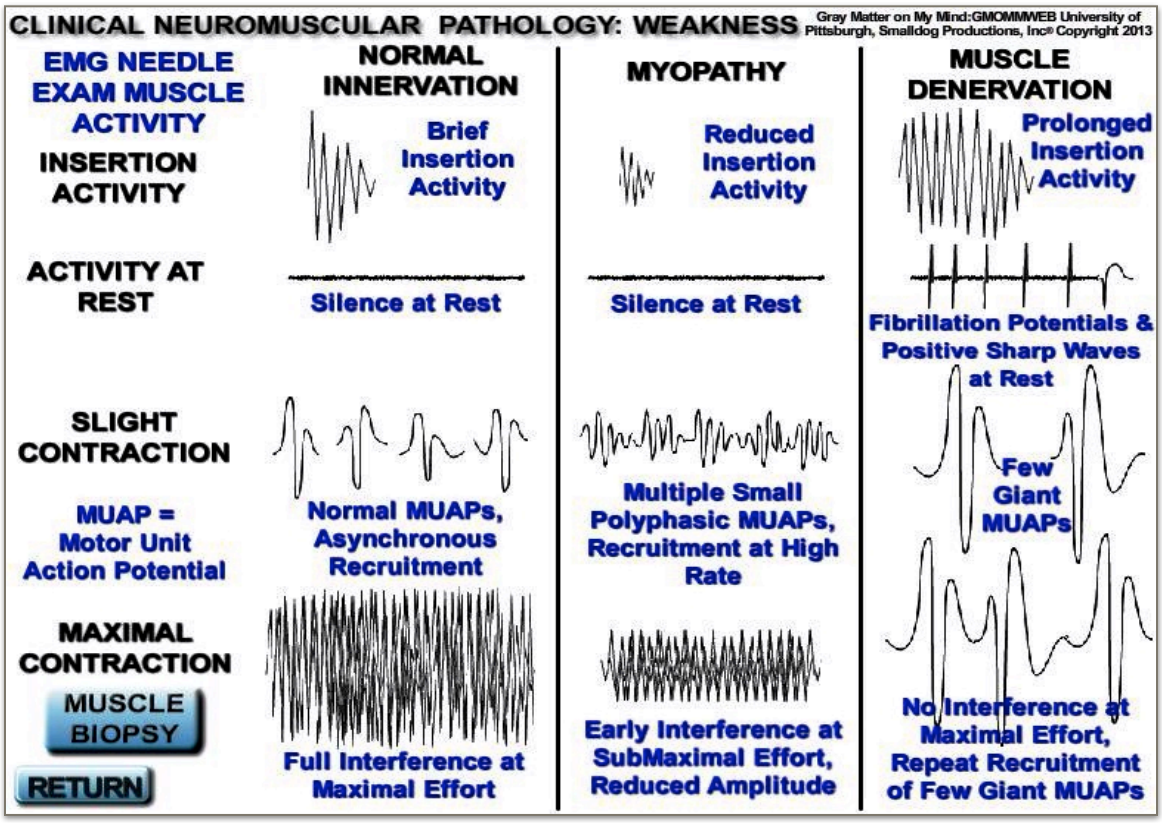


Fig 14-49. EMG Needle Exam: Intact, Myopathic & Denervated Muscle (gec). GO TO: gmomm.pitt.edu *Fig14-49_Interactive Media*

Activity is assessed upon needle entry (insertion activity), at rest (no muscle contraction), and during submaximal and finally maximal volitional isometric contraction. The EMG needle exam is used to disclose the location and severity of suspected lower motor neuron involvement or to rule out an upper motor neuron syndrome or other causes of weakness. Muscles may be selected according to peripheral nerve or root

level innervation. Both extremity and back muscles may be examined. Some muscles innervated by cranial nerves may be examined by experienced electromyographers. The examiner looks (at an oscilloscope trace) and listens (to an audio monitor of EMG) for electrical signs of PNS denervation and/or re-innervation.

The EMG needle exam of a denervated muscle shows a prolonged period of insertional activity that outlasts the actual movement of the needle. The sarcolemma is hyper-irritable. This is followed by fibrillation potentials at rest; an important sign of denervation. At submaximal muscle contraction few MUAPs are seen; these abnormal motor units are large amplitude polyphasic "giant" potentials suggesting re-innervation of denervated muscle fibers rescued by surviving motor axons. At maximal (weak) contraction, the same MUAPs are seen at higher rates of discharge; one sees incomplete interference pattern typical of a muscle that has few surviving motor units.

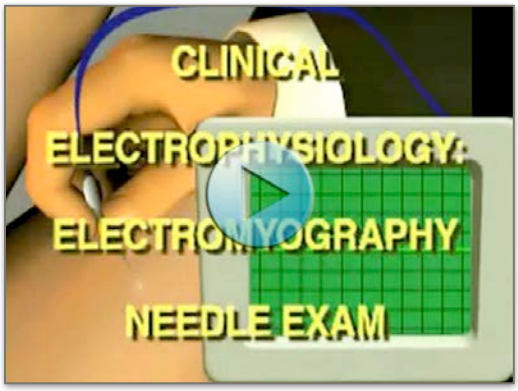


Fig 14-50. Normal EMG Needle Exam: Motor Innervation Intact Movie (gec). GO TO: gmomm. pitt.edu *Fig14-50_Video*

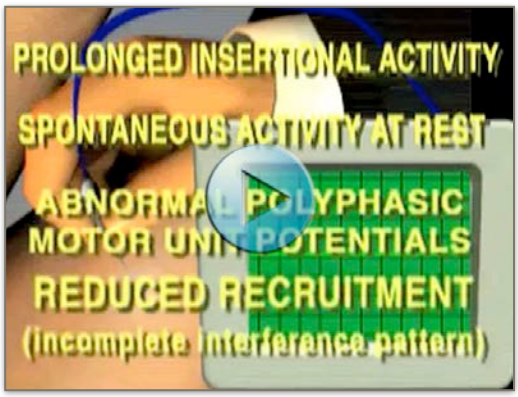


Fig 14-51. L M N Needle Exam Movie: Electrical Signs of Muscle Denervation (gec). GO TO: gmomm.pitt.edu *Fig14-51_Video*

These movies simulate the sights and sounds an electromyographer would experience with a person who has an intact nervous system & one who has muscle denervation due to a peripheral nerve lesion.

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Chapter 15

POSTURE AND LOCOMOTION: THE BASICS

POSTURE INTRODUCTION: A TRUE BALANCING ACT

Posture, balance and equilibrium are deep-seated, fully integrated bodily functions and have been since our ancestors climbed onto *terra firma*. Integration of these functions involves a multilevel, distributed sensorimotor system. The default mode of operation appears to be anticipatory rather than reactive but both feedforward and feedback modes of operation are utilized at a preconscious level. Unless sufficiently perturbed, or such a disturbance is unanticipated, normal adults use proactive, predictive control measures that seem to be transparent to the individual and to most observers. This "grace" in the face of evolving environmental challenges appears deceptively simple. It is not. Many sensorimotor nervous system disorders show abnormal posture/balance control. Vestibular disorders in particular remind the individual of a sensory input that normally works "*incognito*" (in the background). Sensory input vital to normal function includes: 1. somatosensation (tactile from support surface and proprioceptive from axial & limb muscle and joint receptors), 2. visual input regarding the horizon and optic flow as we move, and 3. vestibular input from the inner ear (labyrinthine semicircular canals as angular accelerometers plus otolith organs that inform us about linear accelerations of our head).

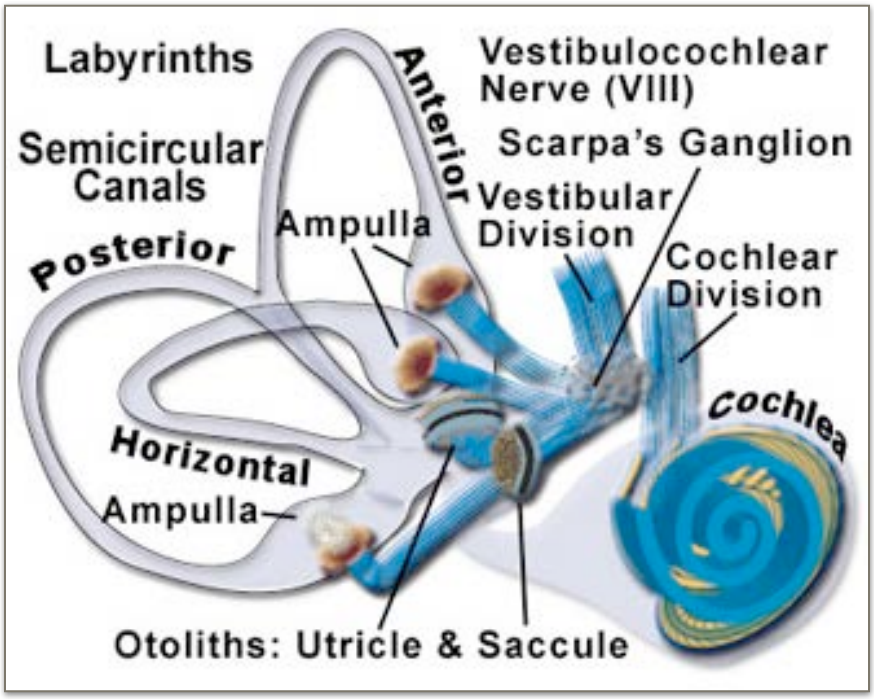

Fig 15-1. Vestibular Labyrinths, Their Innervation and Relationship to Cochlea (gec).

Typically, all three sensory modalities are integrated at multiple sites: spinal & brainstem centers, cerebellum and cerebral cortex. Most young adults use somatosensory cues for most postural/balancing chores (light or dark environment). Individuals with peripheral sensory disorders and many older adults tend to gravitate towards a greater reliance on visual cues.

The vestibular system acts as a final arbitrator if other cues are either missing, inappropriate or confound one another. It is the duty of the vestibular receptors and their central connections to keep our heads off the turf when all other sensory cues fail.

SENSORIMOTOR CONTROL OF POSTURE IS A DISTRIBUTED PROCESS

"Stand up straight, don't slouch." That is one way to describe posture. However, there is more to postural control than good biomechanics. Neural control of posture requires interactions among distributed sensorimotor centers from spinal to supratentorial levels. Posture includes stabilizing limb, trunk and head muscle contractions so that we do not succumb to gravity, lose control of our sensory inputs (visual, vestibular and somatosensory) or find ourselves unable to complete motor tasks in the face of internal or external perturbations. Therefore, control of our upright posture (balance) is but one of many tasks of the postural control system. Some neuroscientists have hypothesized that our motor system contains two parallel control subsystems; one for posture and the other for movement.

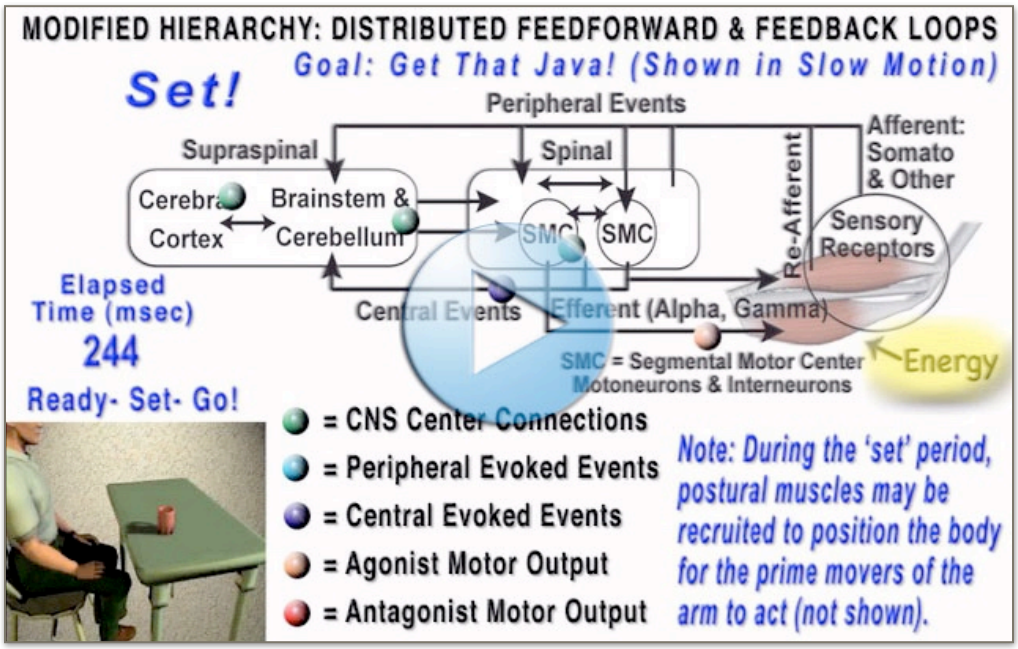

Fig 15-2. Modified Hierarchy: Distributed Movement and Postural Control Movie (gec). GO TO: gmomm.pitt.edu Fig15-2_Video

Based on evidence from lesion studies and recordings in awake subjects, the dorsolateral descending pathway appears to be necessary for fractionated distal limb movements and the ventromedial descending pathway necessary for postural control and locomotion. The only permanent deficit in primates appears to be the loss of fractionated finger movements & no persistent postural abnormalities following a lesion of dorsolateral pathways. Bilateral lesions of ventromedial descending pathways results in severe deficits in postural control and locomotion but sparing of distal limb dexterity if the limb is externally stabilized. Sparing of one ventral funiculus saves postural control and locomotion.

STABILIZATION OF CENTER OF MASS FOR PREDICTIVE VS. REACTIVE PERTURBATION OF STANDING POSTURE

WHO'S ON FIRST? When you lift an object in front of your body your center of gravity shifts forward. To keep you from falling forward your postural muscles must compensate. Is this done in a feedback or feedforward mode? This example shows that the lumbar paraspinal muscles are recruited early, just before the onset of the Anterior Deltoid EMG. Therefore, while the Deltoid may be the “prime mover” for the task of lifting the arm, it is not recruited alone, nor is it recruited first in the entire task (including feedforward postural adjustments). Brain and spinal motor centers send signals to neurons or muscles responsible for action (actuators). In addition, corollary discharges from these motor areas are sent to integrative areas that may correlate these motor signals with sensory data to anticipate or react to perturbations, e.g. portions of posterior parietal cortex, thalamus and cerebellum. On the other hand, as illustrated in the movie below not all postural muscle activations can be predictive since external conditions can unexpectedly perturb our center of mass requiring a reactive response.

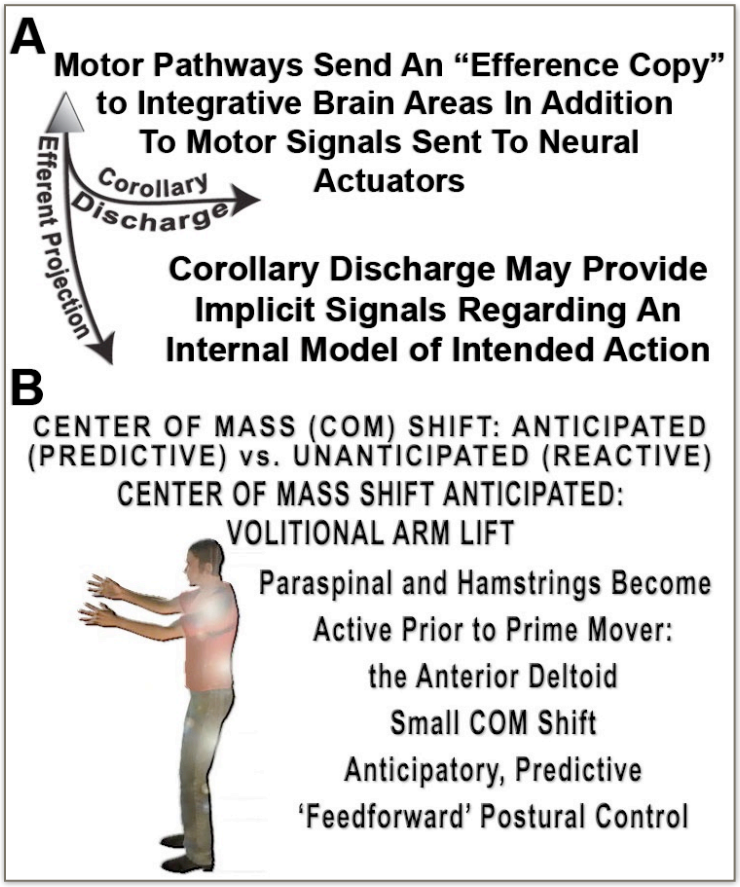

Fig 15-3. Panel A: Efferent Copy, Panel B: Predictive and Reactive Postural Adjustments of Center of Mass Perturbation (gec). GO TO: gmomm.pitt.edu Fig15-3_Video

The following figure and movie shows an individual lifting weights applied to both wrists. EMG electrodes are recording activity in the Anterior Deltoid and the Lumbar Paraspinal Muscles.

Lifts are done rapidly and slowly. Notice the motion of the trunk as well as the arm. For both rapid and slow lifts the onset of activity in the Lumbar Paraspinal Muscles slightly precedes the onset of Deltoid EMG. The activity in both muscles shows two bursts when lifting rapidly (see upper traces in the diagram of EMG activity in the two muscles). Note that the second burst in the Deltoid occurs before that in the Paraspinals, and appears to correlate with the control of the weight as the arm reaches a horizontal position. The Paraspinals increase activity slightly later as the arm is being lowered.

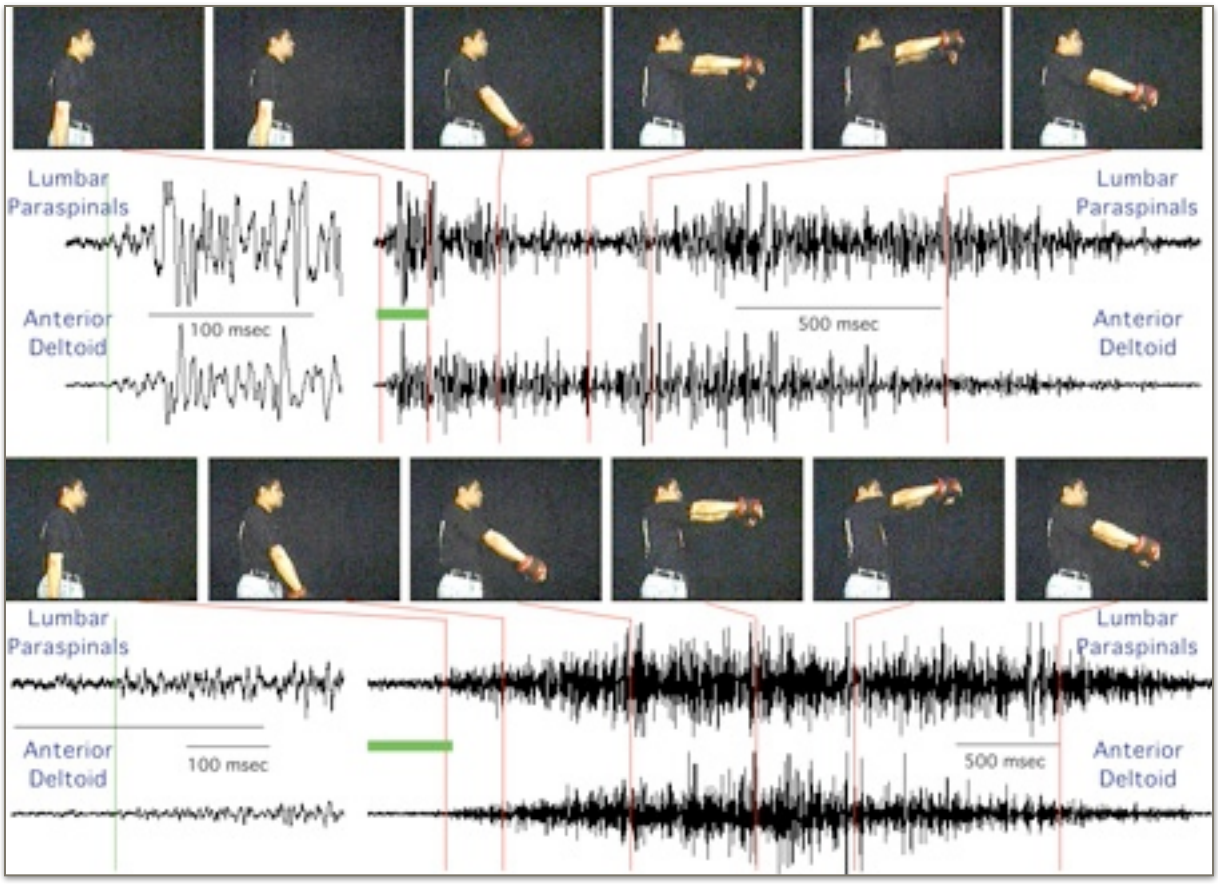

Fig 15-4. Paraspinals On First! The thick green horizontal bar at the initial portion of the right hand EMG traces mark the portion of this trace that is expanded (in time) in the left hand traces. The thin vertical green lines in the left traces indicate the onset of EMG for the lifting task (gec, jec).

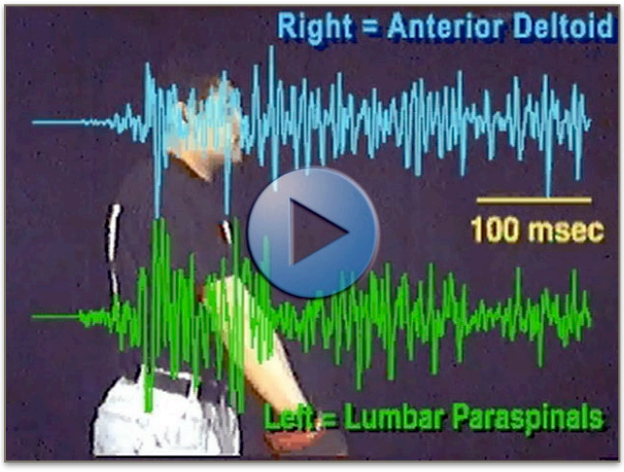

Fig 15-5. Who's On First: The movie (gec, jec). GO TO: gmomm.pitt.edu
Fig15-5_Video

This "bursting" is not as evident in slow lifts (see lower traces). In both cases the motor control centers must initially anticipate perturbation of the body's center of mass and send feedforward signals to postural muscles just before the signals to initiate arm motion. As the weight is moving the Paraspinals make adjustments to control the center of mass. The brain cannot ignore the biomechanical demands of moving in our environment.

ROMBERG: SENSORY OR CEREBELLAR ATAXIA?

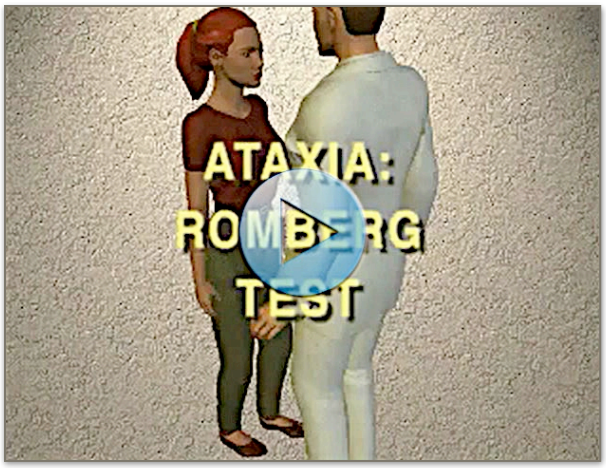

Fig 15-6A. Positive Romberg Testing Sensory Ataxia Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig15-6A_Video*

The Romberg Test is a simple test of balance (station). The subject stands with feet together: first with eyes open and then with eyes closed. A *positive Romberg* test is one where the subject must step to regain balance with eyes closed but not with eyes open. It is a test for *sensory ataxia*. Individuals who have sensory medial lemniscal and/or spinocerebellar long tract signs, and proprioceptive deficits of the lower extremities typically have a positive Romberg. Just an increase in sway with the eyes closed condition is not a positive finding. Placing the person in a Tandem Romberg position increases the challenge and may reveal more subtle sensory ataxic deficits. An individual cannot get into the feet together stance (eyes open) without losing her balance. She has a negative Romberg but a positive test for balance deficits (sway) due to a central sensorimotor postural disorder such as is found with cerebellar or vestibular disease. Without visual and somatic cues, the vestibular system cannot detect or compensate for the small slow drifts in the center of mass that lead to the imbalance when eyes are closed.

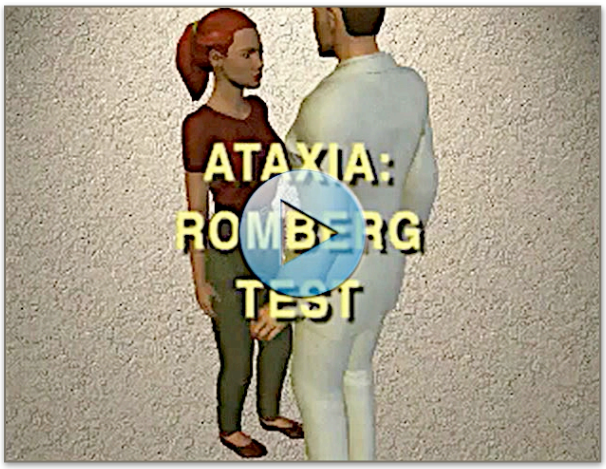

Fig 15-6B. Negative Romberg Cerebellar Ataxia Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig15-6B_Video*

P O S T U R O G R A P H Y INTRODUCTION

In the early 1970s, Lewis M. Nashner, while at MIT, developed a system to perturb standing posture of human subjects in a controlled manner. This began a series of experiments by Nashner, M. Woollacott, A. Shumway-Cook, F. Horak and others that have spanned many decades. Posturography testing has been used to investigate hypotheses regarding the neural basis of postural control, and balance deficits due to sensorimotor disorders in children and adults. These studies also have inspired other novel approaches to the study of motor control. The posturography device consists of a force platform(s) that can be rotated (up or down), or translated in an anterior or posterior direction. The subject's motion (sway) is measured as well as EMG from selected trunk and lower limb muscles. Typically, the first order of business for our

balance control system is to keep our heads off the ground. Second, is the addition of some articulated “viscoelasticity” so that we are not held in a rigid, statuesque pose. Third, we must be able to rapidly & efficiently adjust to perturbation of our centers of mass imposed by our own movement or due to anticipated or unexpected external events. Evidence suggests that our ability to walk (bipedal locomotion) must wait for maturation of postural control. Gravity may be either a constraint or an affordance to our sensorimotor system. Environmental conditions influence dynamic balance control.

POSTUROGRAPHY: ADAPTATION TO REPEATED ANKLE ROTATIONS

An upward rotation of the platform tends to displace the subject posteriorly if the posterior leg muscles respond to the ankle rotation (triceps surae stretch response?). Response latencies to the stimulus are ~90-120 msec (long loop response). Typically monosynaptic short latency responses (~30-35 msec) to the muscle stretch are suppressed over several trials. However, any response from the stretched muscles will be destabilizing and will increase the subject's sway. Normal subjects rapidly adapt to the rotational perturbation such that within 3-5 trials the destabilizing muscle responses are attenuated.

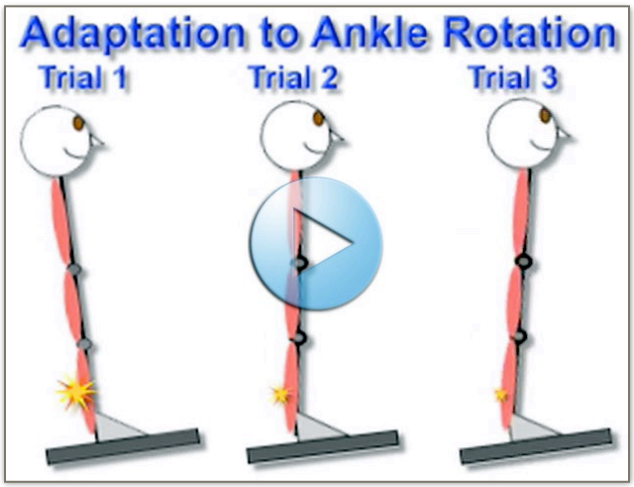

Fig 15-7. Posturography: Adaptation to Repeated Ankle Dorsiflexion (gec). GO TO: gmomm.pitt.edu *Fig15-7_Video*

These adaptive, automatic postural adjustments are taken as evidence that the postural responses do not employ simple feedback pathways; nor are they typical volitional reaction time responses (~200-250 msec latency). Adaptation to ankle rotations may be abnormal when certain pathologies are present. For example, subjects who have certain types of cerebellar lesions may be unable to adapt to these or other perturbation protocols even with many repetitions.

POSTUROGRAPHY: ANKLE STRATEGY & LITTLE ANKLE JERK

A posterior translation of the platform displaces the subject's center of mass (COM) anteriorly. If the motion is not too fast or too far to displace the COM beyond the subject's base of support (BOS) a so-called "in-place" ankle strategy is used to regain an upright stance. The posterior leg muscles (triceps surae, hamstrings) and hip/trunk extensors respond to the perturbation. Response latencies are ~90-120 msec (long loop response). Short latency responses (~30-35 msec) are typically suppressed. There is a

typical distal to proximal temporal sequencing of muscle activation. The response pattern has been called an inverted-pendular kinematic response (see references). These adaptive, automatic postural adjustments are taken as evidence that postural responses do not employ simple reflex pathways; nor are they typical volitional reaction time responses (~200 msec latency). Based on several experimental studies, the ankle strategy is said to employ somatosensory > visual > vestibular cues for rapid efficient balance control in young adults. Spatial and/or temporal errors may occur with some pathologies, or in other age groups.

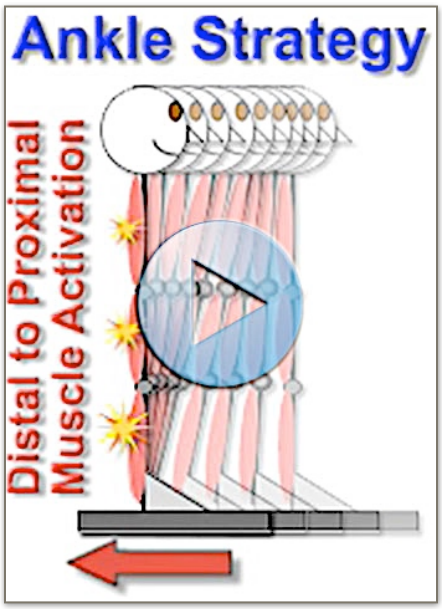

Fig 15-8. Posturography: Ankle Strategy for Postural Adjustment to Horizontal Platform Translation Movie (gec). GO TO: gmomm.pitt.edu *Fig15-8_Video*

POSTUROGRAPHY: HIP STRATEGY & BEAM JERK

A posterior translation of the platform displaces the subject's center of mass (COM) anteriorly. If the base of support (BOS) is reduced by standing on a narrow beam, the subject normally responds with a so-called "in-place" hip strategy to regain an upright stance. There is considerable body and head motion with anterior leg muscles (pretibial muscles, quadriceps) and hip/trunk flexors responding initially to the perturbation. Response latencies are typically equivalent to those for an ankle strategy (~90-120 msec).

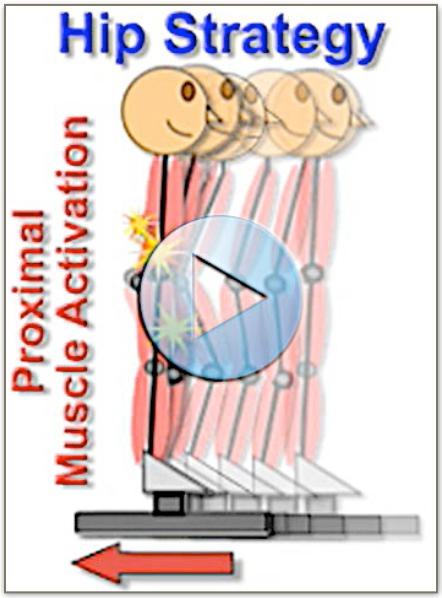

Fig 15-9. Posturography: Hip Strategy for Postural Adjustment to Horizontal Platform Translation When Standing on Beam Movie (gec). GO TO: gmomm.pitt.edu *Fig15-9_Video*

There is a typical proximal to distal or simultaneous temporal sequencing of muscle activation. Later compensatory responses may follow. These adaptive, automatic postural adjustments are taken as evidence that the postural responses do not employ simple reflex pathways; nor are they typical volitional reaction time responses (~200 msec latency). Based on several experimental studies, the hip strategy is said to involve the vestibular system to a greater extent than the ankle strategy (where full foot contact can provide adequate torque).

POSTUROGRAPHY: STEP STRATEGY FOR BIG JERK

A posterior translation of the platform displaces the subject's center of mass (COM) anteriorly. If the motion is fast enough or far enough to displace the COM beyond the subject's base of support (BOS) a so-called "stepping" strategy is used to regain an upright stance. Many neck, trunk, and limb muscles respond to the perturbation as the subject steps to extend the BOS. The head and body move to reestablish a new BOS. A significant delay in a subject's response latency is likely to cause a fall. Individuals who have pathologies that delay response initiation, especially those related to balance control, are at risk. Parkinson's Disease, Stroke or other Upper Motor Neuron Pathologies often causes such postural control abnormalities.

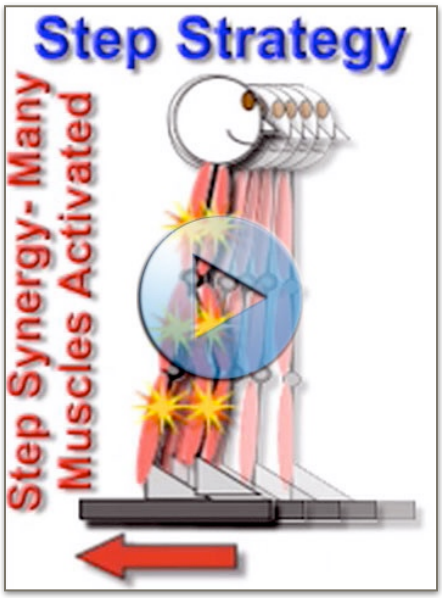

Fig 15-10. Posturography: Step Strategy for Postural Adjustment to Horizontal Platform Translation When Center of Mass is Displaced Beyond Base of Support Movie (gec). GO TO: gmomm.pitt.edu Fig15-10 _Video

POSTUROGRAPHY: SWAY REFERENCED JERK & SENSORY DEPRIVATION

To challenge the postural control system, somatosensory and/or visual cues may be manipulated. Either one or both of these cues may be referenced to the subject's sway. This is accomplished by rotating the platform anteriorly as the Center of Mass (COM) moves forward (somatosensory cue disruption), and/or rotating the visual surround proportional to the subject's sway.

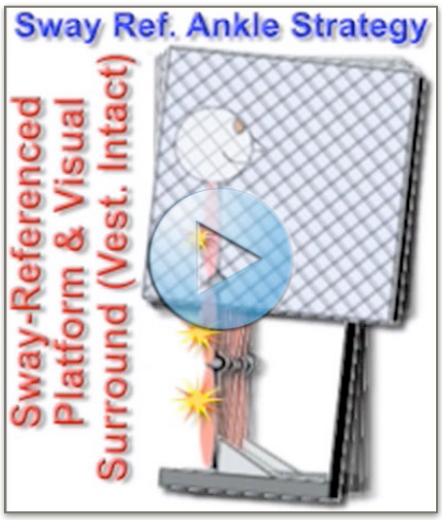

Fig 15-11. Posturography: Strategy for Postural Adjustment to Horizontal Platform Translation When Referenced to Postural Sway (Distorted Somatosensory and Visual Cues) (gec). GO TO: gmomm.pitt.edu Fig15-11_Video

Non-perturbed sway in this "referenced" condition tends to produce a positive feedback loop. Such manipulations tend to be disorienting but normal adult subjects, while increasing their sway, do not lose their balance. This is thought to be due to an intact vestibular system that acts as the final arbitrator (as referenced to earth) to keep the head off the floor. Responses tend to be slightly delayed (~180 msec).

Very young children or adults who have certain types of vestibular disorders or other CNS postural abnormalities may fall when challenged with this paradigm unless protected (harness).

The Vestibular System is the final arbitrator in balance control. When visual and/or somatosensory inputs are lost or provide inadequate or conflicting information, the vestibular apparatus provides control of balance in normal but not vestibular-loss subjects. Acute vestibular pathologies frequently produce profound disability. Fortunately treatment and time often reduce these signs, symptoms and impairments.

LABYRINTHS: PUSH-PULL SEMICIRCULAR CANALS AND OTOLITHS' GRAVITAS

Vestibular input from the inner ear (labyrinthine semicircular canals: angular accelerometers plus otolith organs that inform us about linear accelerations of our head & gravity) provide information for equilibrium, balance and postural control. Vestibular Goals include (tongue in cheek and with the able contributions of a talented supporting cast- e.g, cerebellum, somatosensory system, visual system, postural support motor system):

1. Keep my head off the turf unless I intend to gently place it there.

2. Keep my eyes on the prize as it walks, runs, flies, floats or motors along my horizon.

3. Let me steadily “walk the walk and talk the talk” with friends as we tool down a busy sidewalk.

4. Let the observer imagine the grace of a (name your favorite athlete or performer) NOT that of Larry, Moe and Curly as I perform my actions and gestures.

5. Let me not be the one who provokes a loud speaker “Clean up on aisle 5” as I do my shopping.

6. Keep my back steady and let my arms and legs be easy-going: NO “stiff” demeanor.

7. If it is not too much to ask, let the only thing that rings be freedom NOT my head.

Vestibular Labyrinthine Push-Pull Mechanism for Balance Movie shows the input from the right and left ampulla hair cells of the horizontal semicircular canals & the subsequent transient alteration in discharge of the eighth nerve afferents that, in turn, project to their respect vestibular nuclei. Animation shows a person rotating her head to the right. Keep an eye on the bar in the balance meter (bottom center). Play movie more than once to catch all the action; VOR = Vestibulo-Ocular Reflex.

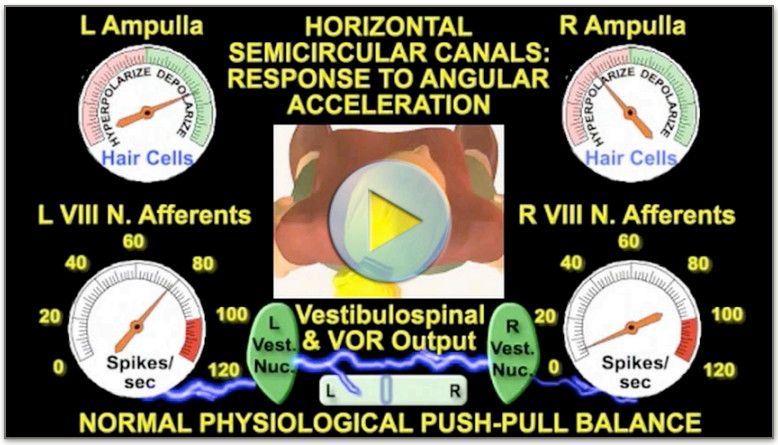

Fig 15-12. Vestibular Labyrinthine Push-Pull Mechanism for Balance Movie (gec). GO TO: gmomm.pitt.edu
Fig15-12_Video

VESTIBULOPATHY: DIZZINESS, DISEQUILIBRIUM, VERTIGO, NYSTAGMUS

Lesions of the peripheral or central vestibular system can be severely disabling. The vestibular system has such an important role in control of eye movements, head and neck movements, gaze control, balance, equilibrium, and posture that lesions tend to affect multiple areas of daily function. In addition, as most of us are aware, the vestibular system has a significant input to brainstem centers related to visceral function. Fortunately, the vestibular system is plastic and most individuals compensate for vestibular loss to some degree (thanks, in large part, to an adaptive vestibulocerebellar influence). Nevertheless, busy environments tend to be disruptive and/or anxiety-provoking events for the compensated individual; these environments may trigger avoidance behaviors for uncompensated individuals. Falls (balance and equilibrium disorders), a stiff neck (avoidance of head motion especially when body is in motion) and impaired visuomotor function (impaired visual-vestibular coordination) may be serious complications. Vestibular rehabilitation may improve function and reduce the disabling effects of these impairments.

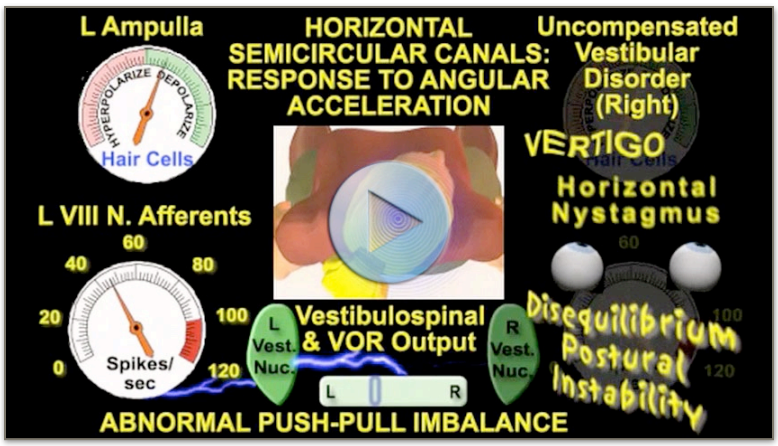

Fig 15-13. Vestibulopathy: Abnormal Push-Pull Mechanism for Balance Movie (gec). GO TO: gmomm.pitt.edu
Fig15-13_Video

Movie shows the result of a right peripheral vestibular lesion in an uncompensated individual. Note the signs & symptoms and think about how disruptive they will be to normal function. Watch movie more than once to see all the action associated with an imbalanced push-pull vestibular system. Signs, symptoms & deficits may vary across individuals who have a

vestibulopathy according to lesion site, time after insult, & individual reactions to somatic and visceral disturbances.

LOCOMOTION

LOCOMOTION INTRODUCTION

Normal gait requires rhythmic, propulsive movements of the legs superimposed upon dynamic postural control of the body; one might describe walking as graceful falls followed by agile recovery of balance. Current concepts regarding the neural basis of locomotion include spinal central pattern generators (CPGs), brainstem locomotor regions, cortical and subcortical motor areas, propriospinal tracts, descending pathways to initiate gait & energize spinal centers, and tactile & proprioceptive sensory inputs that modulate the discharge of sensorimotor centers including spinal CPGs.

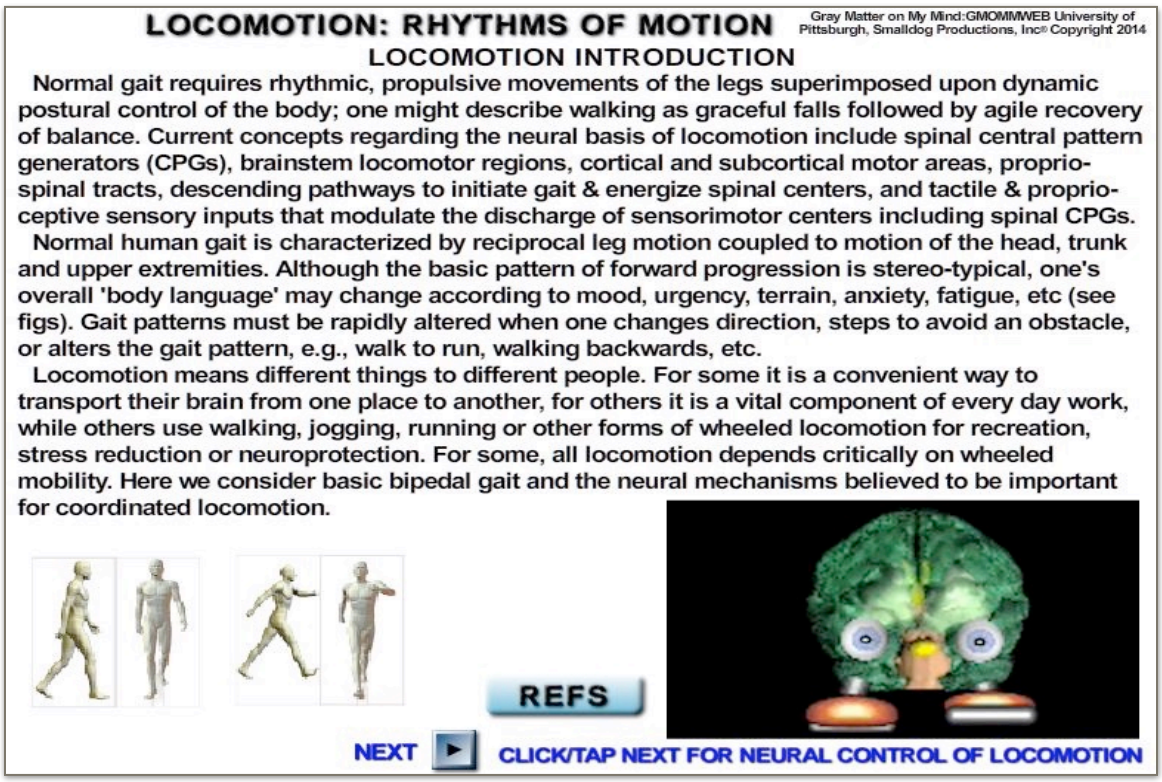

Fig 15-14. Locomotion Interactive Media File (gec). GO TO: gmomm.pitt.edu
Fig15-14_Interactive Media

Normal human gait is characterized by reciprocal leg motion coupled to motion of the head, trunk and upper extremities (see movie). Although the basic pattern of forward progression is stereotypical, one's overall “body language” may change according to mood, urgency, terrain, anxiety, fatigue, etc. Gait patterns must be rapidly altered when one changes direction, steps to avoid an obstacle, or alters the gait pattern, e.g., walk to run.

Locomotion means different things to different people. For some it is a convenient way to transport their brain from one place to another, for others it is a vital component of every day work, while others use walking, jogging, running or other forms of wheeled locomotion for recreation, stress reduction and/or neuroprotection. For some, all locomotion depends critically on wheeled mobility. Here we consider basic bipedal gait and the neural mechanisms believed to be important for coordinated locomotion.

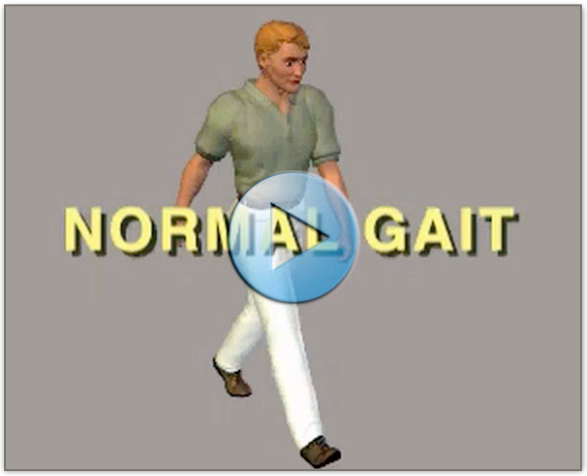

Fig 15-15. Human Bipedal Walking Movie (gec, jec). GO TO: gmomm.pitt.edu
Fig15-15_Video

NEURAL CONTROL OF LOCOMOTION INTRODUCTION

Normal gait requires rhythmic, propulsive movements of the legs superimposed upon dynamic postural control of the body; one might describe walking as graceful falls followed by agile recovery of balance. Current concepts regarding the neural basis of locomotion include spinal central pattern generators (CPGs), brainstem locomotor regions, cortical and subcortical motor areas, propriospinal tracts, descending pathways to initiate gait & energize spinal centers, and tactile & proprioceptive sensory inputs that modulate the discharge of sensorimotor centers including spinal CPGs.

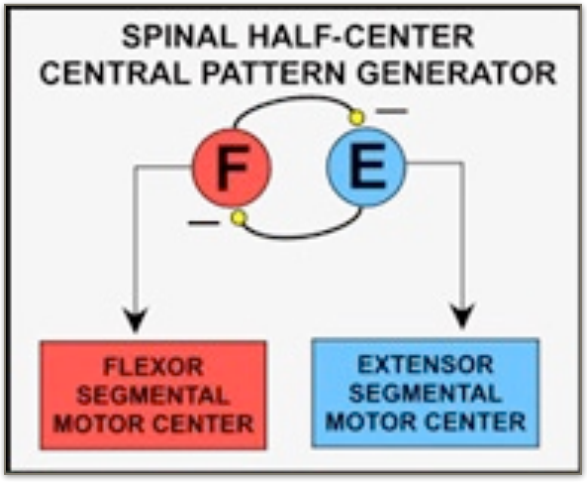

Fig 15-16. Spinal Central Pattern Generator For Stepping: Half-Center Hypothesis (gec).

Locomotor research suggests that spinal CPGs utilize reciprocal inhibitory connections to generate the stepping pattern characteristic of gait. Although the actual neurons responsible for pattern generation have yet to be isolated, evidence suggests that a distributed network of CPGs links hip to knee to ankle. A half-center linkage of flexors and extensors (F & E) has been hypothesized (since the early 1900s by Graham Brown) to account for patterning within a limb. It is suggested that the two networks (F & E) are reciprocally inhibitory. Spinal stepping CPGs are thought to be powered by Brainstem Locomotor Regions that tonically drive the CPG and associated spinal networks. Such networks provide coordinated multilimb and trunk movement patterns characteristic of normal gait.

DISTRIBUTED CONTROL OF LOCOMOTION

Research on the mammalian neural control of locomotion at the single neuron recording level has been implemented primarily with quadrupeds.

Such evidence may translate to human bipedal locomotion but perhaps with significant neural control modifications for integrating the tenuous bipedal (two-footed) posture perturbed on a regular basis by forward, backwards or even sideways progressive translation of our center of mass beyond our base-of-support.

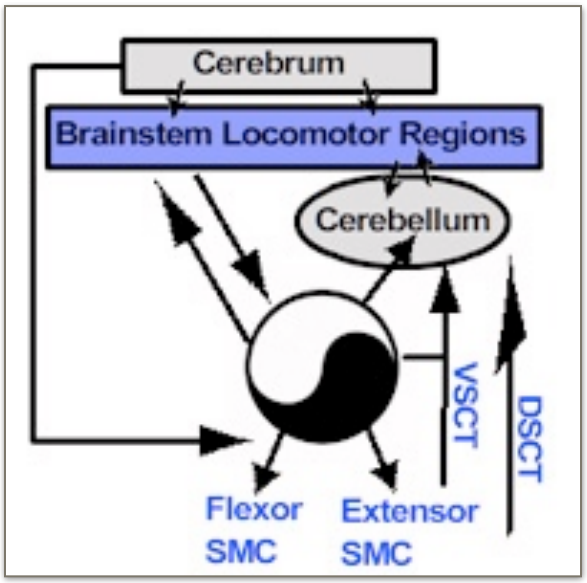

Fig 15-17. Fundamental Central Circuitry for Neural Control of Locomotion (Yin-Yang = Spinal CPGs); Peripheral Sensory Inputs to CPGs Not Illustrated (gec).

SPINAL CENTRAL PATTERN GENERATORS

Theories regarding spinal CPGs have existed for a century. T. Graham Brown described such a mechanism in the early 1900s. Brown, a contemporary of C. S. Sherrington showed that a spinal animal suspended over a treadmill would step. Stepping persisted even if a limb was deafferented. This lead to a hypothesis of central pattern generation by reciprocally inhibitory "half-centers" for agonist/antagonist muscles (T.G. Brown, 1911). Renewed interest in CPGs was kindled again in the middle of the twentieth century when Graham Brown's experiments were duplicated. This spark ignited a fire in the belly of a number of neurophysiologists to search for the elusive CPG. Champions of this research in vertebrates include: S. Grillner, H. Forrsberg, K.G. Pearson, C. Perret, A. Lundberg, G.N. Orlovsky, M.L. Shik, O. Andersson and others. CPGs require rhythm. They do not require specific sensory input to drive the pattern but such peripheral input may have significant modulatory effects on the CPG (see Sensory Feedback). Spinal CPGs are influenced by Propriospinal Neurons that provide in intra- limb and inter-limb coordination and limb-trunk coordination. CPGs are "driven" by descending pathways that may not contain specific pattern instructions but do control the stepping network activation. Actual linkages of half-centers for proximal to distal muscles & right to left limbs is still unknown (see references). There is little evidence that spinal CPGs can be reactivated following complete spinal cord transection in humans.

BRAINSTEM LOCOMOTOR REGIONS

Brainstem Locomotor Regions (BLRs) include the Subthalamic Locomotor Region (SLR), Mesencephalic Locomotor Region (MLR) and a Pontine Locomotor Region

(PLR) as described by M.L. Shik, G.N. Orlovsky and F.V. Severin (see Shik and Orlovsky, 1976). These Russian investigators showed in cats that stimulation of these brainstem regions can induce locomotor patterns that shift from a slow to a fast walk, to a trot, to a gallup as the intensity (not rate) of stimulation increases. The PLR probably corresponds to reticulospinal tract projections from reticular formation neurons to spinal CPGs and Propriospinal Neurons (especially C3-C4 levels). BLRs are thought to influence force not the timing of stepping patterns.

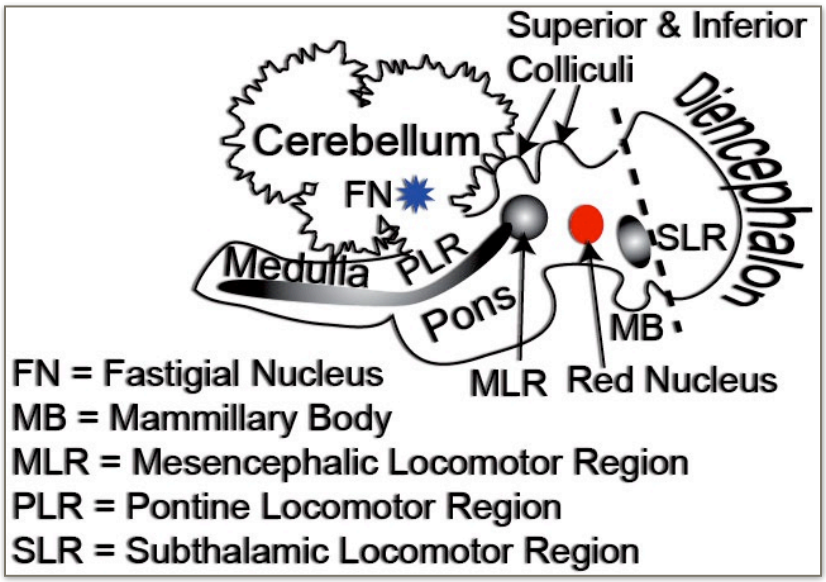

Fig 15-18. Brainstem Locomotor Regions and Associated Structures Movie. Dashed Line = level of brainstem transection for BLR research as described in text (gec).

The MLR corresponds to a midbrain site that includes portions of the caudal Cuneiform Nucleus, Locus Coeruleus, Periaqueductal Gray & the Pedunculo-pontine Nucleus. The SLR is located at the level of the Subthalamic Nucleus (and nearby fiber tracts).

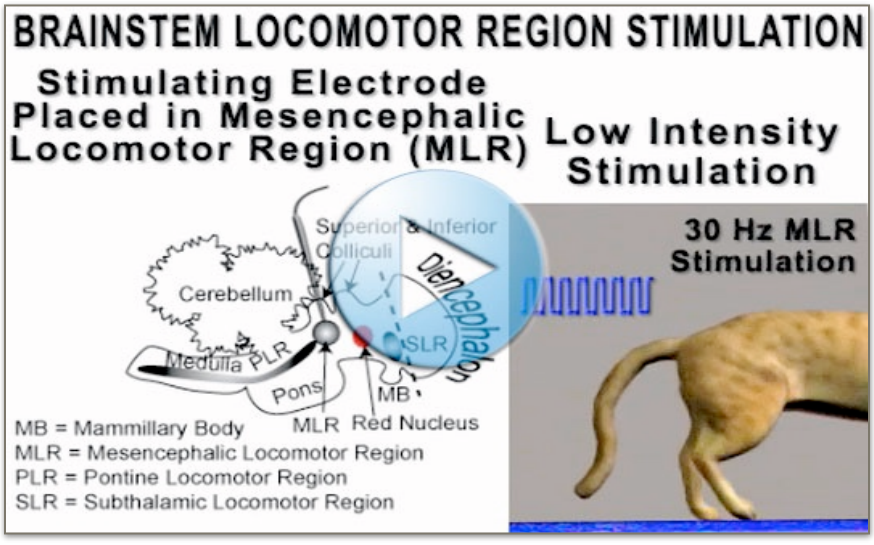

Fig 15-19. Brainstem Locomotor Region Stimulation Movie (gec). GO TO: gmomm.pitt.edu
Fig15-19_Video

These BLRs are interconnected with the Cerebellum that coordinates the rhythm (cerebellar removal causes ataxia but not a loss of rhythmic stepping). A separate locomotor region has been suggested to reside deep within the midline cerebellum in the neighborhood of the Fastigial Nuclei. The PLR may represent the white matter pathways responsible for connecting the other SLRs to the spinal cord CPGs. The BLRs are influenced by

Corticobulbar pathways (from cerebral cortex) and by limbic and non-limbic Basal Ganglia. There is only limited indirect evidence for spinal CPGs and BLRs in primates; furthermore, stepping in spinal primates appears to require at least partial sparing of one ventrolateral or ventromedial descending pathway.

SPINAL SEGMENTAL MOTOR CENTER INTERNEURONS AND MOTONEURONS: MOTOR OUTPUT

Segmental Motor Centers (SMCs) are busy places from head to tail during locomotion. Not only are they being accessed by the spinal CPGs but also by circuitry that controls posture. SMCs keep you upright and body parts coordinated while you get from here to there. All this and you can worry about your weekend or your 'portfolio' while your brainstem and spinal cord do their work with nary an email to your cognitive self (till you stumble-that tends to get your attention). Try to imagine concentrating on each muscle coupling at every joint on both sides, all the while keeping your head off the turf. The brainstem and spinal portions of your neuraxis are the ultimate “multitaskers!” Now what were you saying about the lowly spinal neuraxis? Both SMCs and CPGs provide information about ongoing motor events (efferent feedback) to the Cerebellum by way of the Ventral Spinocerebellar Tract (VSCT) and to Reticular Formation Nuclei (including Locomotor Regions) by way of a Spinoreticular Pathway.

SPINAL SEGMENTAL MOTOR CENTER ALPHA AND GAMMA MOTONEURONS: GAIT MODULATION OF EXCITABILITY

The stretch reflex like most sensorimotor circuits in the CNS does not operate in a vacuum. Although the monosynaptic reflex circuitry is very precise and simple, it is influenced by the level of excitability of the interneurons and motoneurons in the Segmental Motor Center (SMC). Researchers using the H-Reflex as a monitor of stretch reflex excitability have shown how greatly the central motor system influences this simple reflex circuit in human subjects.

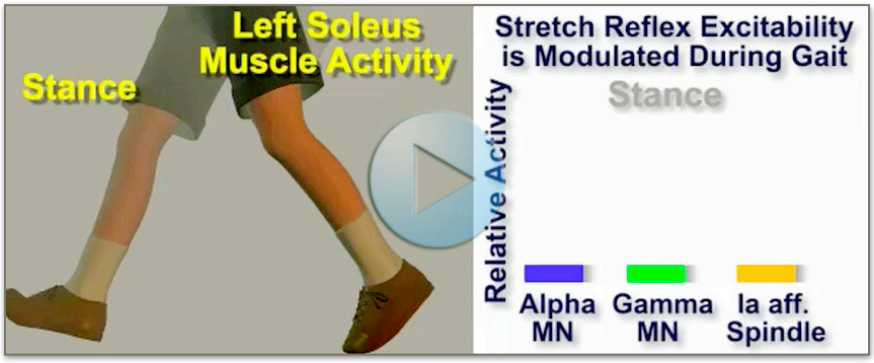

Fig 15-20. Motoneuron Excitability Modulation During Gait (gec). GO TO :gmomm.pitt.edu
Fig15-20_Video

The Motoneuron Excitability Modulation During Gait movie illustrates the proportional changes of alpha & gamma motoneuron excitability in relation to muscle output during the gait cycle. The amplitude of the Soleus H-Reflex due to Ia afferent input from the muscle spindle is proportional to Soleus Muscle activity when walking. This window into the

excitability of SMC circuitry dramatically illustrates how important descending and spinal central drive is to even the simplest reflex circuit.

Running is not simply walking at a high speed either from a biomechanical or from a neurophysiological perspective. When investigators compared subjects walking or running at various speeds they found differences in the H Reflex for the soleus muscle. The soleus H Reflex is modulated in proportion to the measured EMG as the gait cycle proceeds when walking. An increase in Alpha Motoneuron (AMN) excitability & EMG occurs in-phase during the loading of the limb when walking, but the amplitude of the soleus H Reflex rises dramatically hundreds of milliseconds prior to heel strike when subjects run. Soleus EMG on the other hand remains low until the foot hits the ground: an increase in Ia afferent facilitation of soleus AMNs (increased gamma motoneuron activity?) appears to lead that of EMG output in running humans. Soleus AMNs may be actively inhibited to prevent premature firing during the gait cycle when running; central influences converge on AMNs to maintain subthreshold depolarization.

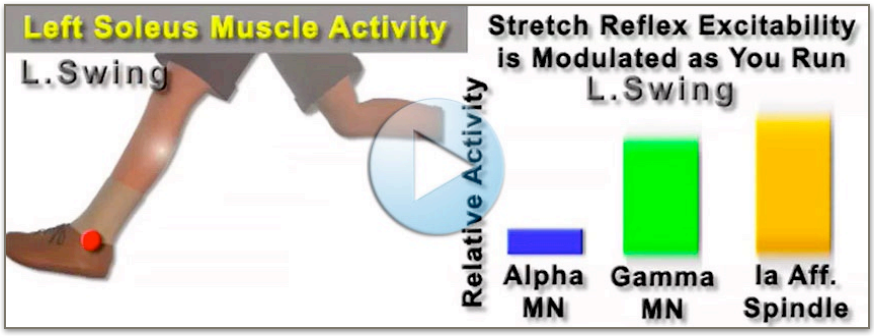

Fig 15-21. Motoneuron Excitability Modulation During Running (gec). GO TO: gmomm.pitt.edu Fig15-21_Video

Inhibition of soleus AMNs prior to heel strike may be due to presynaptic inhibition of Group I afferents (PAD IN), reciprocal inhibition by Ia Inhibitory Interneurons (the Anterior Tibialis Muscle has a peak of activity just prior to heel strike), or more complex interactions of spinal CPG, reflex & SMC circuitry and descending influences.

PROPRIOSPINAL NEURONS AND COORDINATED LOCOMOTION

Propriospinal Neurons are scattered throughout the intermediate gray. Some cells in the dorsal and ventral horn may also contribute axons to ascend or descend in this tract. A special group of these neurons found at the third and fourth cervical levels are thought to be a major source of intersegmental coordination for actions that require synergistic cooperation from many muscles (e.g., locomotion, reaching). A similar group of propriospinal neurons in the lumbosacral cord may have a similar role in coordination of lower extremity functions. They are influenced by converging inputs from descending pathways, peripheral inputs & spinal interneurons. Long propriospinal neurons send their axons over many segments at multiple levels of the cord. These connections may be important for “whole body” integration since bilateral influences are common for these projections (interlimb and limb-trunk coordination). Short propriospinal neurons

tend to restrict connectivity unilaterally and within that specific level of the cord (intralimb coordination). The propriospinal tract is an almost continuous band of axons immediately surrounding the gray matter. This tract provides a major source of intersegmental connectivity within the spinal cord.

CEREBELLUM AND COORDINATED POSTURE AND LOCOMOTION

The cerebellum is important in coordination of synergistic movements including locomotion and postural adjustments that must accompany gait. Rhythmic output from locomotor centers continues even after removal of the cerebellum. However, gait becomes ataxic and stiffness regulation (tone) may be disturbed. The anterior lobe of the cerebellum appears to be particularly important in gait. Note that the cerebellum is in a strategic location that has reciprocal connections with brainstem postural control centers, brainstem locomotor regions, and the cerebral cortex. In addition, the cerebellum receives peripheral (afferent) feedback via the dorsal spinocerebellar tract and central (efferent) feedback from spinal CPGs and SMCs via the Ventral SpinoCerebellar Tract (VSCT). Sensory and motor feedback are said to be compared with signals from motor generator centers in the brainstem and cerebral cortex. An error signal is derived, and error corrections are made through cerebellar circuitry which includes climbing fiber inpt from the Inferior Olive. The cerebellum has little direct impact on spinal centers but does influence centers that project to the spinal cord by way of the ventromedial and the dorsolateral descending pathways.

PERIPHERAL SENSORY INPUTS MODULATE LOCOMOTOR PATTERN

Sensory feedback from cutaneous and proprioceptive inputs go to all levels. Sensory input while not required to generate the stepping pattern has significant influence on the motor output. Investigators have revealed an important interaction among CPGs and reflexive circuitry. For example, cutaneous input to the foot during the swing phase of gait facilitates flexors, but the same input to the weight-bearing limb may have no effect or actually produce a “reflex-reversal.” The cutaneous input facilitates extensors in the reversal response. Phase-dependent input from receptors signaling limb position (especially from proximal limb proprioceptors: hip joint and hip muscle receptors) assists the transition between swing and stance. Thus somatosensory inputs may extend stance or abbreviate the swing phase of gait. Peripheral inputs relayed to the cerebellum by way of the Dorsal SpinoCerebellar Tract (DSCT) is an important source of information that is compared to efferent feedback relayed by the Ventral SpinoCerebellar Tract (VSCT). In addition, a SpinoOlivary Tract provides segmental feedback that may be integrated with RubroOlivary input. Such comparative data are sent to the cerebellum by way of Climbing Fibers.

CEREBRAL CORTEX AND BASAL GANGLIA: ROLES IN ADAPTIVE LOCOMOTION

Decorticate quadrupeds are capable of ambulation and a number of other stereotypical synergistic movement patterns but have difficulty in challenging environments e.g., where foot placement is critical. Goal-directed locomotion is lost if the cortex and basal ganglia are disconnected from lower brainstem. These supratentorial structures access postural and locomotor spinal centers by way of descending brainstem tracts and corticospinal tracts. The pathways synapse on segmental motor center motoneurons and interneurons, interneurons that are suspected to be part of CPG networks, and propriospinal neurons that in-turn coordinate intralimb, interlimb & limb-trunk actions. It has been suggested that cortical control of reaching and locomotion have similarities in pathways to the C3-C4 propriospinal neurons. These neurons provide synergistic motor control. The importance of cortical control lies with precise positioning & manipulation of the distal limb: foot or hand (see A.P. Georgopoulos and S. Grillner, 1989). Both limbic and non-limbic portions of basal ganglia circuitry are thought to be important components in initiation/regulation of gait. Animal studies suggest that multiple brain areas provide more or less input to control of gait depending on the behavioral context, e.g., escape behavior vs. walking on a narrow beam.

LOCOMOTION NEURAL CONTROL: REFLEX VS. CPG MODELS

Two schools of thought regarding neural control of locomotion emerged from early work with reduced animal nervous systems: end of the nineteenth continuing well into the twentieth century. One model hypothesizes that stepping is the result of chaining reflexes together to produce repeatable patterns of movement (e.g., stepping). This model is supported by work done primarily with spinalized or decerebrate cats and deafferented monkeys. C.S. Sherrington and his collaborators described, in detail, stretch reflexes, flexion & crossed extension reflexes and more complex reflexes that together could form the neural basis of stepping and quadrupedal gait. This model suggests that stimuli applied to cutaneous, muscle & joint receptors evoke complex, reproducible, multijoint actions that resemble stepping movements. Sherrington's research supports the hypothesis that sensory input is both necessary and sufficient to evoke patterned motor responses in the lesioned and presumably in the intact animal.

A second school of thought emerged from work done in multiple laboratories across international boundaries in mid to late twentieth century. This model hypothesizes that stepping and locomotion are generated by intrinsic central pattern generators (CPGs) that generate the complex neural patterns necessary and sufficient for locomotion. The CPG model states that sensory input is neither necessary nor sufficient to generate stepping patterns; rather such extrinsic input modulates the basic pattern to make it adaptable to changing environmental circumstances. This work reproduced and then

advanced the findings of T. Graham-Brown a contemporary of Sherrington. Graham-Brown demonstrated that a decerebrate cat would step for a short time following a complete thoracic spinal cord transection. Graham-Brown then added a complete deafferentation of both hindlimbs and reported that the cats would still step despite the loss of this sensory input to the isolated spinal cord. These experiments were confirmed later by twentieth century neurophysiologists and thus was born the CPG model. Russian investigators demonstrated that following a high brainstem decerebration (that preserves all posterior fossa and caudal diencephalic structures) animals would recover postural control and locomotor activity post-lesion. They then described brainstem locomotor regions that activate spinal CPGs.

NEURAL CONTROL OF LOCOMOTION: GAIT MOVIES

The following animations show some of the relationships among spinal CPGs (rhythm generator & mutually inhibitory pattern generators), peripheral sensory input, descending locomotor drive from the brain & motoneurons that drive muscles for gait.

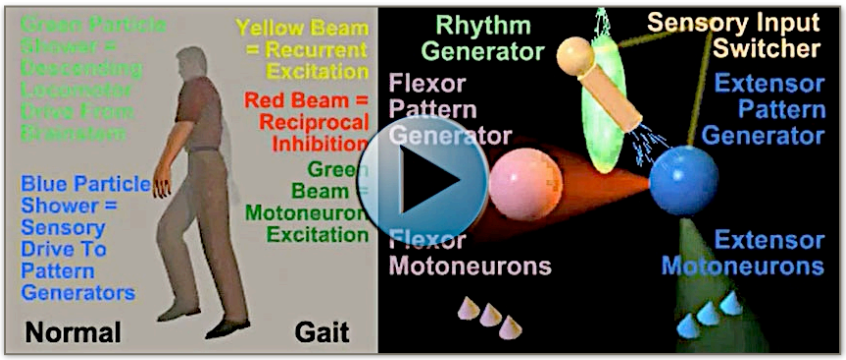

Fig 15-22. Walking at Usual Speed Movie (gec). GO TO: gmomm.pitt.edu
Fig15-22_Video

Action is shown in slow motion so you can follow the sequence of events. Note the greater sensory and descending drive when gait speed is increased (Fast Walk Movie). Flexor & Extensor Pattern Generators are reciprocally inhibitory (half center hypothesis, see red beam).

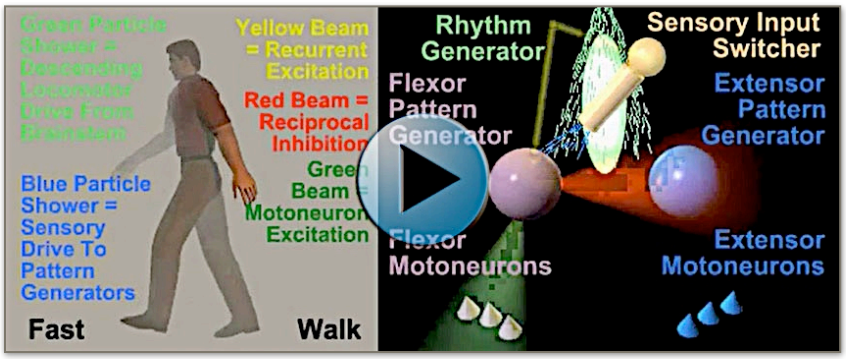

Fig 15-23. Walking Fast Movie (gec). GO TO: gmomm.pitt.edu
Fig15-23_Video

Walking in the snow provides a more challenging environment for gait. Postural control as well as the rhythmic locomotor output may require greater attention. Footfalls in the snow may not be as predictable as on a firm, level walking surface and greater effort must be expended during the swing phase of gait. Visual input and other cerebral influences (orange

shower of particles to pattern generators) may be more important to control exact foot placement (compare Normal Walk versus Walk In Snow Movies).

Fig 15-24. Walking In Snow Movie (gec). GO TO: gmomm.pitt.edu
Fig15-24_Video

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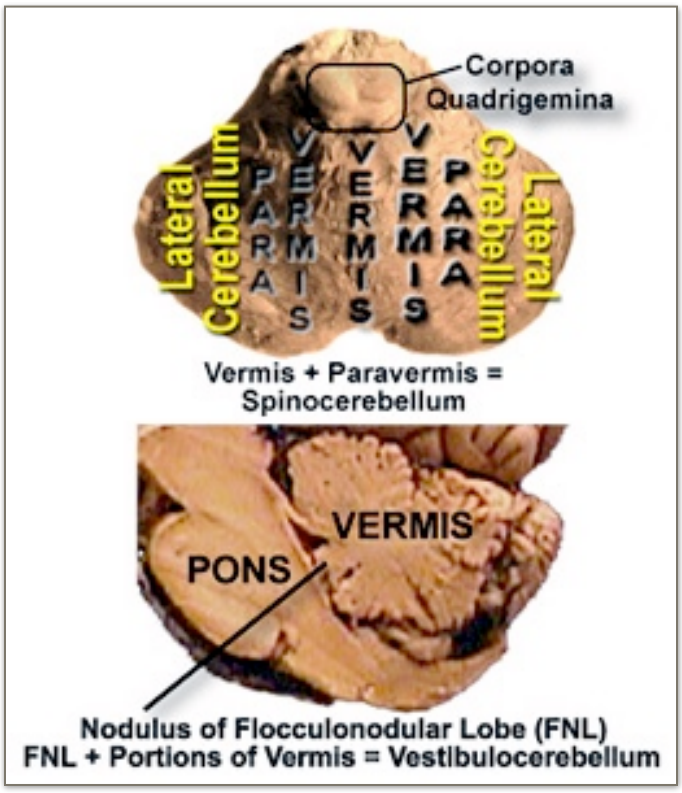
Chapter 16

CEREBELLUM

CEREBELLUM: DIVISIONS, CIRCUITS & DYSFUNCTION

The Cerebellum (little brain) is the major space-occupying structure in the posterior fossa of the cranial vault. Some neuroscientists claim the cerebellum is the location of half or more of the total neurons in the brain. Most of these cells are the very small, abundant granule cells in the cerebellar cortex.



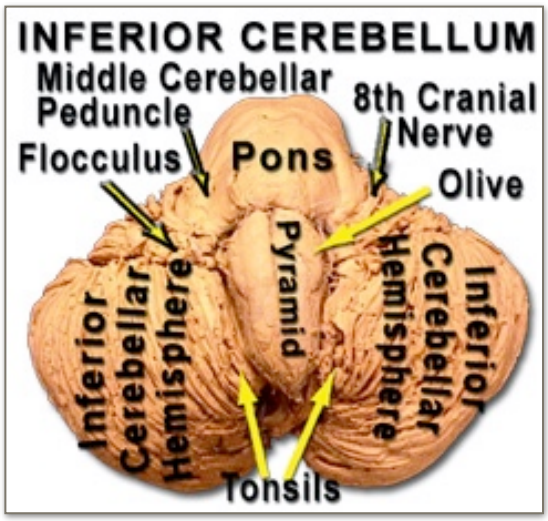


Fig 16-1ABC. Superior (Top Left), Medial (Bottom Left) and Inferior (Top Right) Views of Cerebellum (gec).

In the past, cerebellar function has been described, in a word, as coordination. The Cerebellum has been divided into the FLOCCULONODULAR LOBE, a MEDIAN PORTION (VERMIS), a RIGHT & LEFT PARAMEDIAN PORTION (PARAVERMIS) in the ANTERIOR LOBE, and a RIGHT & LEFT LATERAL CEREBELLUM in the POSTERIOR LOBE that is much expanded in higher primates. There are three classical functional divisions: the Vestibulocerebellum, Spinocerebellum, and Cerebrocerebellum. These 3 functional divisions are related to the major source of input to each. Inputs to the cerebellum, with one notable exception, are collectively referred to as mossy fiber input. Mossy fiber inputs may come from Vestibular Afferents or from Nuclei in the Brainstem or Spinal Cord. Input from the Inferior Olivary Complex is called Climbing Fiber Input. While the Cerebellum has little direct effect on the motor circuitry of the spinal cord, its impact is

significant, via its influence on Cortical & Subcortical Motor Centers in the Brain that do project to Spinal Motor Centers.

Sensorimotor control includes structures at all levels of the nervous system (control) as well as the peripheral musculature that is the motor for our actions. Although traditionally these structures have been arranged in a hierarchical order from cerebrum to muscles, findings from many studies suggest a more distributed control such that decisions and implementation occur at many levels amongst neural assemblies that are reciprocally connected. This section is devoted to cerebellar structure, function, and dysfunction.

The Cerebellum (little brain) accounts for only ~10% of the total higher primate brain volume yet estimates suggest it contains more than half of all neurons in the brain. The Human Cerebellum has expanded as has the Human Cerebrum. The two are extensively linked for implementing skilled actions and implicit 'thoughts' to form internal models of success that are, at once, highly efficient and beautiful to behold. The Cerebellum has been implicated in Implicit Motor and Non-motor Learning and Climbing Fiber Input seems to be particularly important in this regard e.g. see Ito, 2008, 2012; Schmahmann, 1991; Strick, et.al., 2009; Thach, 1998.

CEREBELLAR CIRCUITRY NEURONS

The cerebellum shows high levels of activity in studies that use histochemical metabolic markers or imaging techniques to reveal brain function. This includes neurons in the deep nuclei and in the cortex. All cells in the cerebellum, with two exceptions, are inhibitory neurons. Only the cells of the nuclei and one interneuron type (Granule Cells) in the cerebellar cortex are excitatory. The module of interneurons and Purkinje Cell Projection Neurons is found consistently from one area of cerebellar cortex to the next. The cerebellar cortex has three layers. The deepest layer contains the excitatory Granule Cells and an inhibitory interneuron called the Golgi Cell. Granule Cell axons vertically ascend to the surface of the cerebellar cortex where they bifurcate to form axons that spread horizontally along the folia. These axons are called parallel fibers (since adjacent Granule Cells send axonal projections that are parallel with one another). The parallel axons excite dendritic arbors of Purkinje Cells living beneath these parallel fibers. This set of Purkinje Cells forms an "on-beam." The Purkinje Neuron somas are located in the middle Purkinje Layer. The upper layer, the Molecular layer, contains two inhibitory interneurons: the Stellate Cell and the Basket Cell. These interneurons inhibit Purkinje Cells adjacent to those excited within the "on-beam." These adjacent Purkinje Cells form an "off-beam" on either side of the "on-beam." The "on-beam" Purkinje Neurons provide potent inhibition of the deep cerebellar nucleus cells postsynaptic to them. The deep nuclear cells postsynaptic to the "off-beam" are disinhibited. Thus the ON BEAM-OFF BEAM antagonism provides a dynamic "tuning" of deep nuclear cell discharge. Since these deep cells are excited by mossy fiber input they rarely are silent but their firing *patterns* are adjusted exquisitely by Purkinje Cell

influences. Granule cells are likewise excited by mossy fiber input but are modulated by Golgi Cell inputs. Golgi cells have complex synaptic profiles (called glomeruli) with the connections between mossy fibers, themselves, and granule cells. Golgi Cell dendrites are excited by the parallel fibers so they have a recurrent inhibitory action on Granule Cells, much like the Renshaw Cell influence on motoneurons in spinal Segmental Motor Centers. Climbing fibers project from cells in the Inferior Olivary Complex to synapse directly on Purkinje Cells and the Stellate/Basket Cell Complex. Climbing fiber inputs produce powerful effects on the Purkinje Cells. Unlike mossy fiber input, climbing fibers fire at very low rates only under certain circumstances will firing increase. Climbing fibers are activated when there are changes in the "motor program" and adjustments must be made. Climbing fiber input may provide an important mechanism to reset the cerebellar circuitry when learning is taking place (induction of Long Term Depression or LTD), e.g. see Boyden, et.al., 2004; Carey, 2013; Ito, 2002a,b; Ito, et.al., 1982; Raymond, et.al., 1996; Shadmehr, et.al., 2010; Yang & Lisberger, 2014.

MOSSY FIBER INPUT, DEEP CEREBELLAR NUCLEUS AND CEREBELLAR CORTEX EXCITATORY GRANULE CELLS

Illustrated in this figure are six Granule cells (Gr) that send their axons to the surface of the Cerebellar Cortex. At the surface the Granule Cell axons bifurcate to form parallel fibers. Mossy fiber input excites the Granule cell dendrites and the Deep Cerebellar Nucleus (DCN). The group of Granule cells and their parallel fibers form a functional unit or module that combined with other modules produces a local network called the "on-beam."

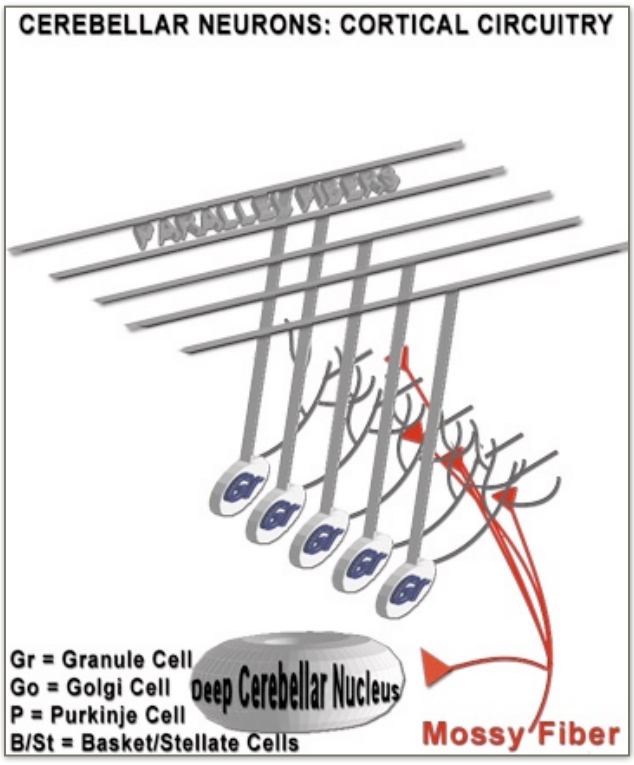


Fig 16-2. Mossy Fibers, Deep Cerebellar Nucleus and Cerebellar Cortical Granule Cells (gec). The Interactive Media File lets you build the Cerebellar Microcircuit in stages. GO TO: gmomm.pitt.edu

Fig16-2 Interactive Media

CEREBELLAR CORTEX INHIBITORY GOLGI CELL

The next illustration shows the effect of adding the Golgi Inhibitory (GABAergic) Interneuron to the Cerebellar Circuitry. Golgi cells are excited by the mossy fibers & perhaps parallel fibers. Golgi cell axons form complex synapses with Granule cell dendrites and mossy fiber axons. The Golgi Cell may act to

recurrently inhibit the Granule Cells. This recurrent inhibition is similar to the Renshaw Cell's inhibition of Motoneurons in the spinal Segmental Motor Center, that limits discharge of the motoneurons. Thus Golgi Cells tend to limit Granule Cell Activity.

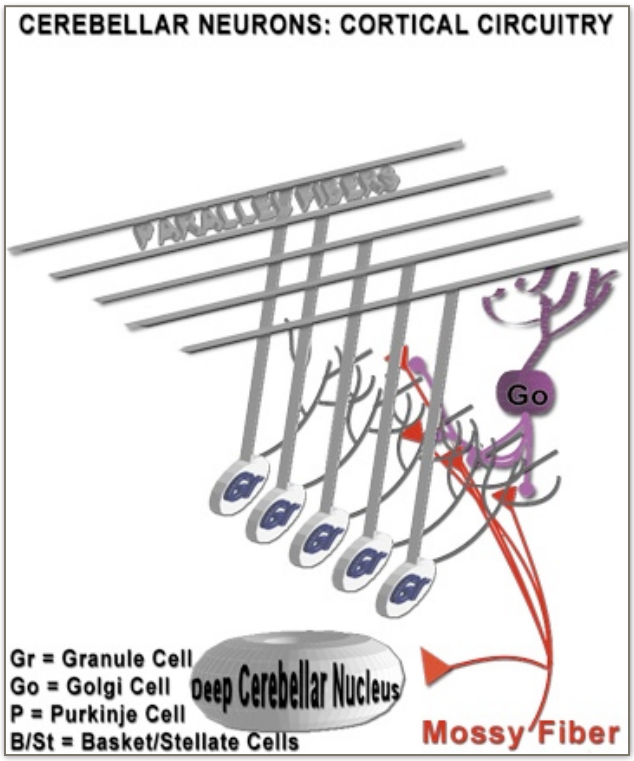


Fig 16-3. Cerebellar Cortex: Golgi Inhibitory Cell (gec).

CEREBELLAR CORTEX PURKINJE CELLS: GABA PROJECTION CELL

The next illustration shows the Purkinje Cells, the sole output neuron of the Cerebellar Cortex. Purkinje Cells provide a powerful inhibition of the Deep Cerebellar Nucleus (DCN) Neurons. Purkinje cells are excited by a group of parallel fibers, forming an “on-beam” for inhibition of DCN cells. The output of the Purkinje Cells (and therefore of the Cerebellar Cortex) provides a mechanism to modulate the discharge pattern of the postsynaptic DCN cells; these nuclear cells are rarely silent since they are driven by mossy fiber inputs. It is the Purkinje Cells that provide precise regulation of firing that is critical for the timing inherent in coordinated movements. While the “on-beam” Purkinje Cells provide GABAergic inhibition of DCN Neurons Inhibitory Interneurons (Stellate & Basket Cells) within this “on-beam” inhibit Purkinje Cells in neighboring modules. These adjacent Purkinje Cells form “off-beams” that surround the “on-beam” module. DCN cells postsynaptic to the “off-beam” modules are disinhibited. Thus a contrast is built that improves the acuity of DCN Neuron discharges.

ON-BEAM OFF-BEAM LATERAL INHIBITION BY GABA BASKET AND STELLATE CELLS

The illustrated Basket/Stellate Interneurons are actually two different cell types combined here to simplify the diagram. These two GABAergic interneurons are excited by the same parallel fibers that excite the Purkinje Neurons in the “on-beam” module.

Basket cell axons extend into adjacent modules (that have inputs from other Parallel Fibers) to inhibit the Purkinje Neurons in those surrounding modules. This surround effect produced by the Basket Cell Inhibitory Interneurons accounts for the “off-beam” properties. It should be clear now that Neurons in the Cerebellum are very busy

modulating firing patterns of Cerebellar Cortical and DCN neurons: ON Beam P cell inhibition plus OFF Beam P cell disinhibition of deep cerebellar nuclear or vestibular nuclei neurons.

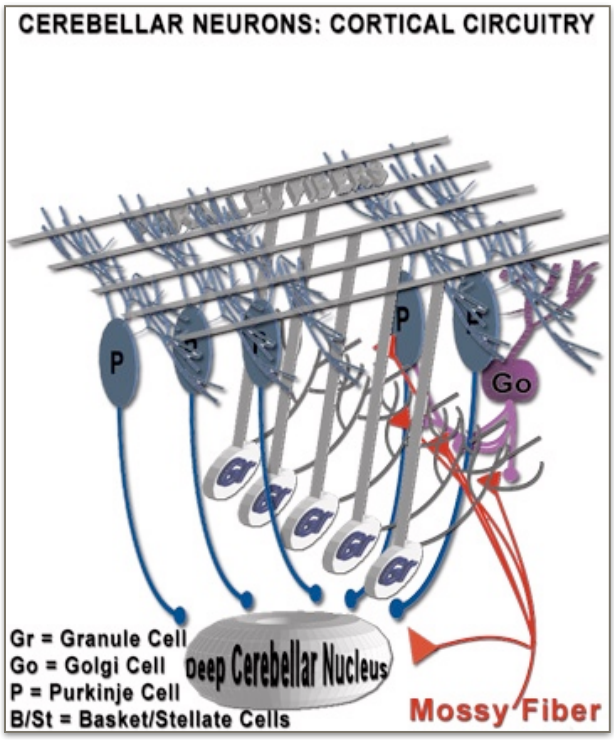


Fig 16-4. Cerebellar Cortex Purkinje Cells: GABAergic Projection Cells that Inhibit Deep Cerebellar Nucleus Cells (gec).

The On Beam OFF Beam antagonism will provide a more distinct contrast between those deep cerebellar output neurons that are suppressed while nearby cells whose firing is facilitated (disinhibited): a spatiotemporal contrast that presumably enhances the precision of sensorimotor processing within the "downstream" targets of deep cerebellar neuronal projections.

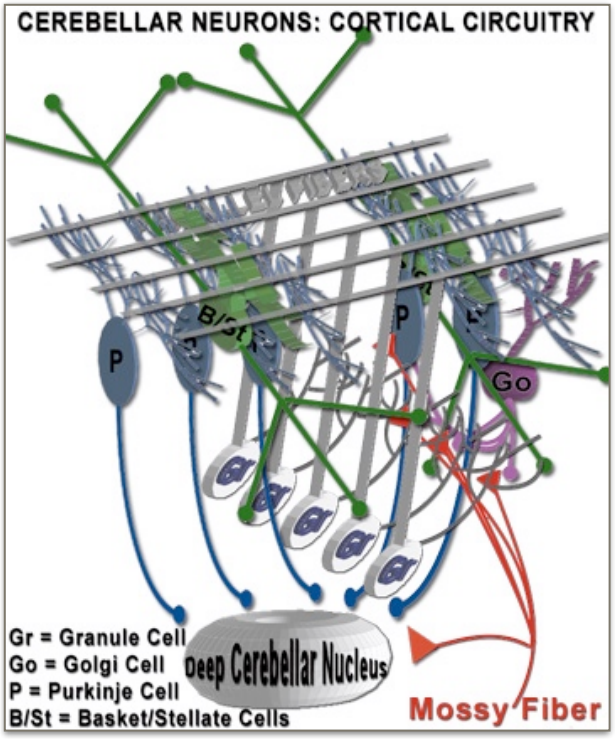


Fig 16-5. GABAergic Basket and Stellate Cells for ON-Beam OFF-Beam Lateral Inhibition Antagonism (gec).

CLIMBING FIBER INPUT TO MODULATE PURKINJE CELL FIRING

Climbing fibers (CFs) are a special type of input to the Cerebellar Cortex from cells in the Inferior Olivary Complex. Unlike Mossy Fibers, CFs are active only under certain conditions. Climbing fiber input to Purkinje Cells is readily observed as a distinct "complex" spike generated in these neurons. Parallel fiber input (due to mossy fibers),

on the other hand, produces “simple” spikes in Purkinje Cells. Climbing Fibers provide a mechanism to reset the Cortical Circuitry when adaptations are required during error correction and when motor learning is in progress. A recent study suggests that the duration of the complex spike (number of spikelets in the waveform) is related to learning, see Yang and Lisberger, 2014. The Inferior Olive is in a good position to carry out these tasks. There are inputs to the Inferior Olive from the Cerebral Cortex, the Red Nucleus, and the Spinal Cord (SpinoOlivary Tract). A Cerebello-rubro-olivary loop may be a critical path to update the Cerebellum as conditions change.

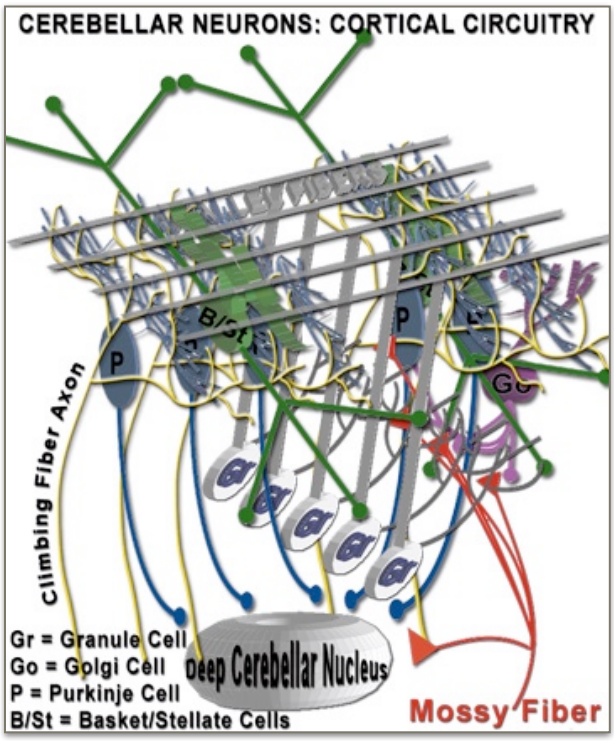


Fig 16-6. Climbing Fiber Input to Purkinje Cells from Inferior Olivary Neurons (gec).

SIMPLIFIED CEREBELLAR CORTEX CIRCUIT MODULE + MOSSY FIBER & CLIMBING FIBER INPUTS: THE MOVIE

All cells in the cerebellar cortex with one exception, are inhibitory (I) neurons. Only Granule Cells are Excitatory (E). A module of E & I interneurons + Purkinje Cell Projection Neurons is repeated across the cerebellar cortex. Cerebellar cortex has three layers. The deepest layer contains the excitatory Granule Cells and an inhibitory interneuron called the Golgi Cell both of which are activated by Mossy Fiber inputs.

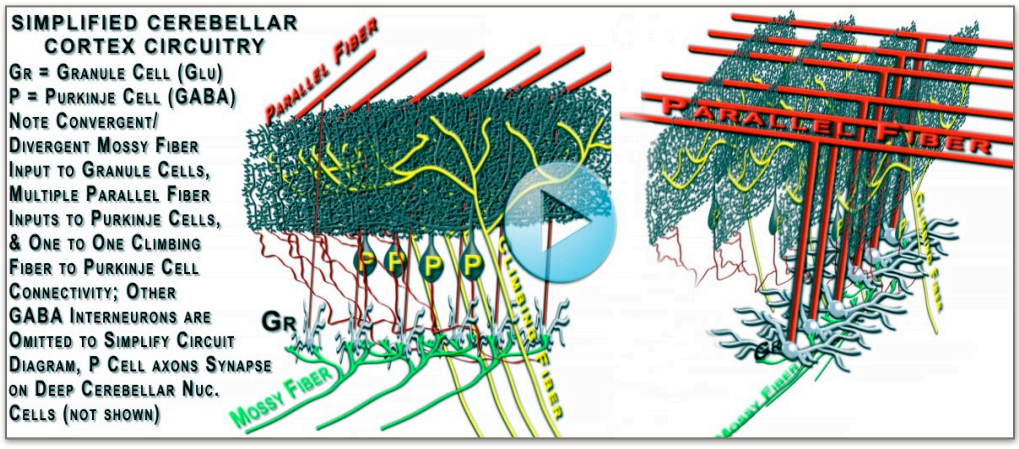


Fig 16-7. Simplified 3D Cerebellar Cortex Circuitry Movie (gec). GO TO: gmomm.pitt.edu

Fig 16-7 Video

Granule Cell axons vertically ascend to the surface of the cerebellar cortex where they bifurcate to form axons that spread horizontally along the folia. These axons are called parallel fibers

(see Figure). Parallel fibers excite dendritic arbors of Purkinje Cells living beneath these axons. Climbing fibers (CFs) project from Inferior Olivary Complex cells to synapse directly on Purkinje Cells and the Stellate/Basket Cell I Cell Complex. CF inputs have strong 1:1 effects on the Purkinje Cells. Unlike mossy fiber input, CFs fire only under certain circumstances.

CEREBELLAR MODULAR STRUCTURE-FUNCTION RELATIONSHIPS: ON BEAM OFF-BEAM ANTAGONISM

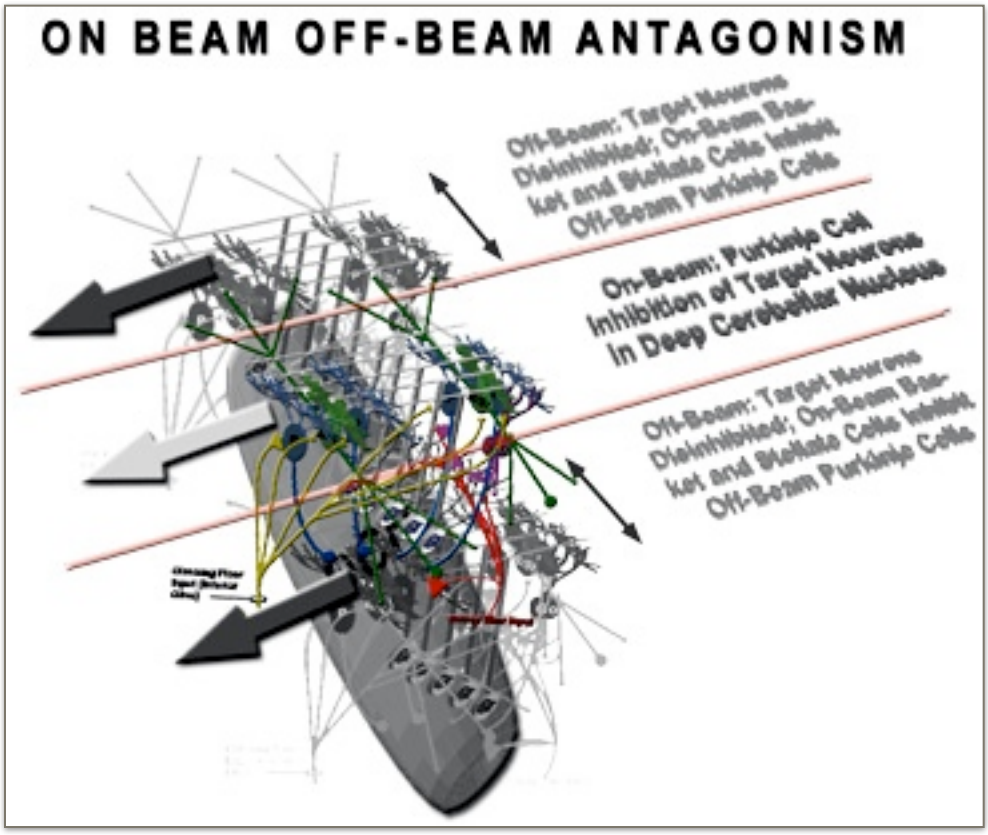


Fig 16-8. ON-BEAM OFF BEAM Antagonism Diagram (gec).

The circuit module shown here is actually repeated along the parallel red lines representing the boundaries of the on-beam. The effect of this module is to inhibit Deep Cerebellar Nucleus (DCN) cells post-synaptic to the Purkinje cells within the module. These DCN cells will be silenced (light gray arrow). The Stellate & Basket Inhibitory Interneurons located in this module extend their axons (green lines) into adjacent modules juxtaposed to the on-beam, i.e., to create surrounding off-beams (dark gray arrows). The effect of this lateral inhibitory influence is to provide an on-beam/off-beam contrast. The inhibition of off-beam modules results in a disinhibition of the DCN cells postsynaptic to them. Thus, a powerful inhibition/disinhibition contrast in the DCN allows for precise, dynamic control of cerebellar output to other motor centers. The Cerebellar Cortical On-Beam Off-Beam Modular Interactions Movie illustrates the On-Beam Off Beam Antagonism within the cerebellar cortex modules.

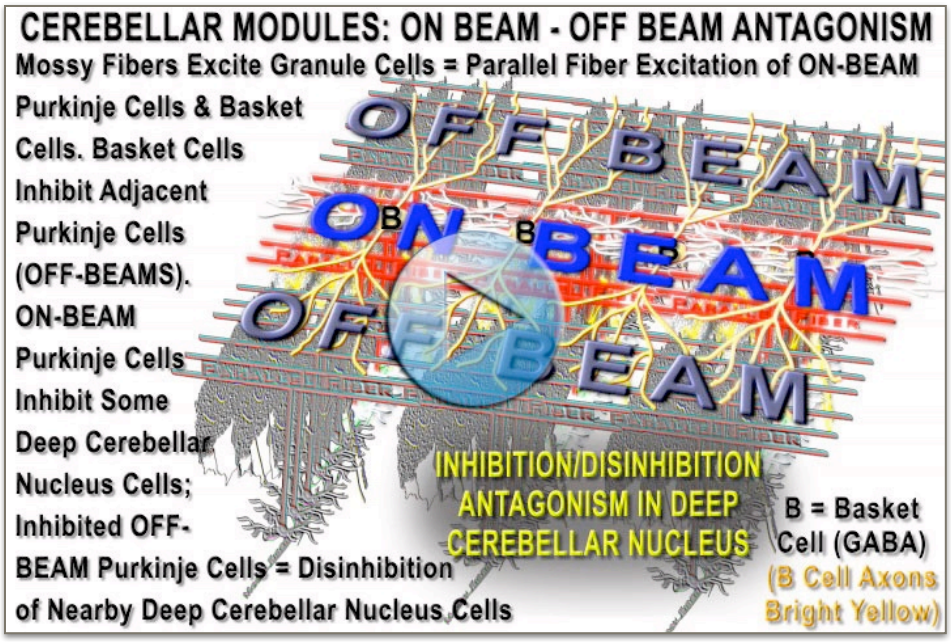


Fig 16-9. Cerebellar Cortical On-Beam Off-Beam Modular Interactions Movie (gec). GO TO: gmomm.pitt.edu *Fig16-9_Video*

CEREBELLAR STRUCTURAL/FUNCTIONAL SUBDIVISIONS

D = Dentate Nucleus: Deep Cerebellar Nucleus (DCN)
F = Fastigial Nucleus: Deep Cerebellar Nucleus (DCN)
G+E = Globose & Emboliform {Interposed} Deep Cerebellar Nuclei (DCN)
IO = Inferior Olive
LCST = Lateral Corticospinal Tract
(P) = Cerebellar Cortex Purkinje Cells;
○— = (inhibitory synapse)
ReST = Reticulospinal Tracts
Ret. Form. = Reticular Formation Nuclei (Brainstem)
RN = Red Nucleus
RST = Rubrospinal Tract
VCST = Ventral Corticospinal Tract
VII = Vestibular Afferents
VL = Ventral Lateral Nucleus (Thalamus)
VN = Vestibular Nuclei
VST = Vestibulospinal Tracts

Fig 16-10. Key for Structural/ Functional Cerebellar Subdivision Circuitry Diagrams shown below and in the Linked Interactive Flash File (gec). GO TO: gmomm.pitt.edu

Fig16-10_Interactive Media

This key is provided for the "wiring" diagrams of the Vestibulo-cerebellum, Spinocerebellum and Cerebro-cerebellum that follow. The Interactive Flash File provides a progressive layering of the three subdivisions of the cerebellum.

VESTIBULOCEREBELLUM

The Vestibulocerebellum is comprised of the Flocculonodular Lobe (FNL) and a portion of the Vermis of the Cerebellum. The major mossy fiber inputs arise from Vestibular Afferents, Vestibular Nuclei Projections, and from Tectal Inputs. The Flocculonodular Lobe has no Deep Cerebellar Nucleus to which it projects its Cerebellar Output. Instead, FNL Purkinje Cells project their axons directly to the Vestibular Nuclei (a major source of inhibitory control of these nuclei). Purkinje cells in the Vermis inhibit

cells in the Fastigial Nucleus (the deep cerebellar nucleus postsynaptic to the Vermis). The Fastigial Nucleus projects to the Vestibular Nuclei, portions of the Reticular Formation, and Tectum. The Vestibulocerebellum is important in control of eye movements; control of neck, trunk and limb girdle muscles involved in balance & postural control of head, neck, and body. The "Archicerebellum" is also involved in coordination of gait. This circuitry is critical for the Vestibuloocular Reflex (which allows you to have a stable visual gaze despite head motion).

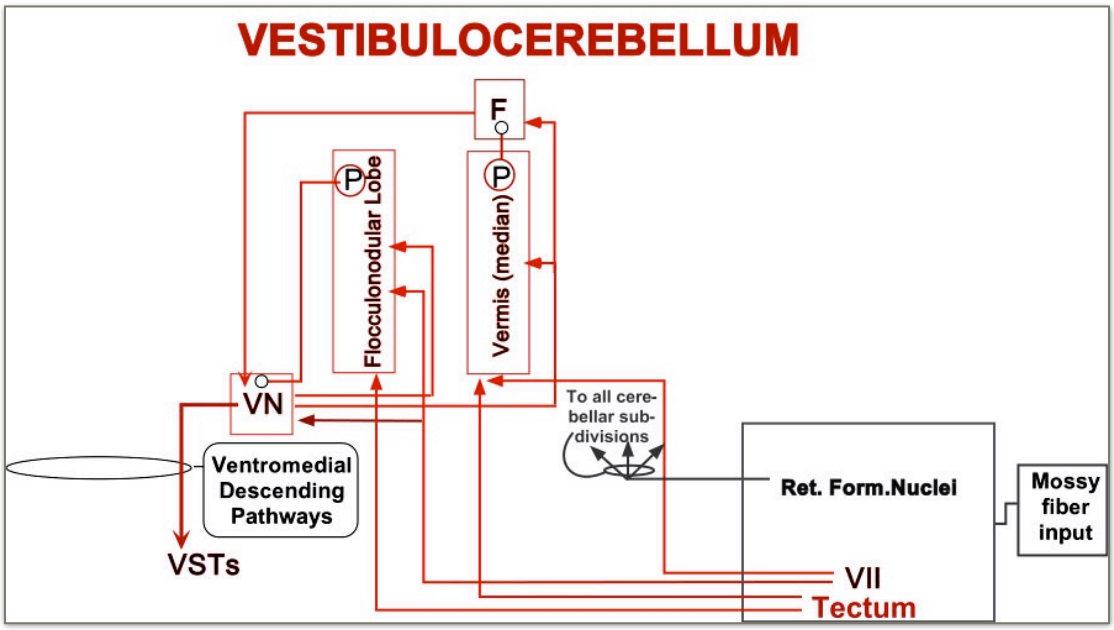


Fig 16-11. Vestibulocerebellum: Flocculonodular Lobe and Portion of Vermis (gec).

SPINOCEREBELLUM

The Spinocerebellum is composed of the Vermis and the right or left Paravermis. The Paravermal (paramedian) portion of the Cerebellar Hemisphere exists between the Lateral Hemisphere and the Median Portion (Vermis) of the Cerebellum. The major mossy fiber inputs arise from the Spinocerebellar Tracts; Dorsal Spinocerebellar Tract (DSCT), the Ventral Spinocerebellar Tract (VSCT) and the Cuneocerebellar Tract (CCT). Mossy fibers input also arises from portions of the Reticular Formation, and the Pontine Nuclei (see Cerebrocerebellum). The DSCT arises from projection neurons in the Dorsal Nucleus of Clarke (see Ascending Pathways). The DSCT provides proprioceptive feedback information from lower extremity & trunk. This Peripheral Feedback is combined with VSCT feedback about ongoing SMC motor output.

It has been suggested that information to the Spinocerebellum about efferent and re-afferent activity provides the basis for "on-line" error detection (and correction). This information may be used as "Knowledge of Results" (KR) about the movement from individual and repeated trials of a task. This KR may be critical in learning and refining the "acuity" of skilled tasks. The output from the Spinocerebellum is channeled through

3 Deep Cerebellar Nuclei. The Purkinje Cells in the Vermis inhibit cells in the Fastigial Nucleus. The Purkinje Neurons in the Paravermis inhibit two Interposed Nuclei (Globose and Emboliform Nuclei). The three deep cerebellar nuclei influence both the Ventromedial and the Dorsolateral Descending Pathways. The Fastigial Nucleus projects to the Vestibular Nuclei, and the Reticular Formation. The Interposed Nuclei project to the Red Nucleus, portions of the Reticular Formation and to Motor Areas of Cerebral Cortex by way of the Ventrolateral (VL) Thalamic Nucleus.

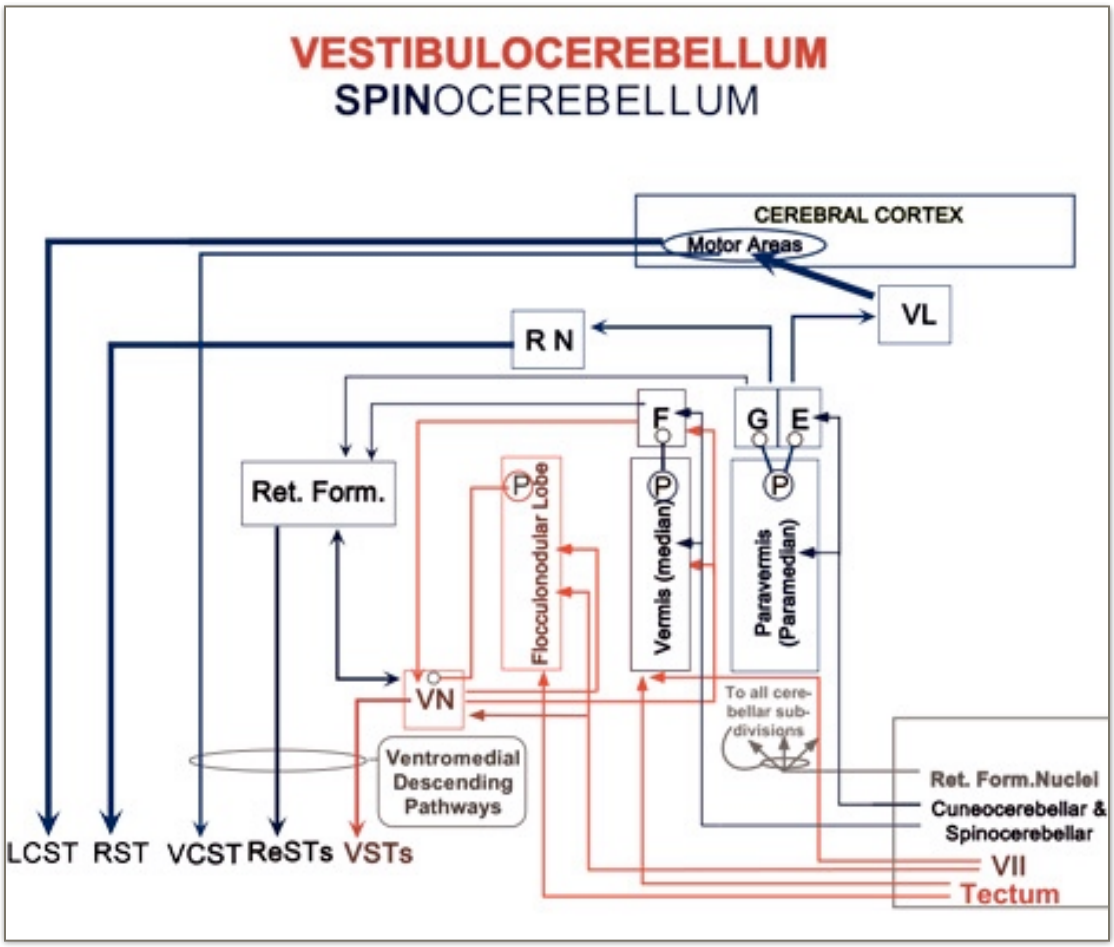


Fig 16-12. Spinocerebellum: Median and Paramedian Cerebellum (gec).

Thus, the axial muscles (bilaterally) and the limb muscles ipsilateral to the activated Cerebellar Hemisphere are influenced by the Spinocerebellum. Lesions of the Paramedian Cerebellum produce the classical signs of cerebellar ataxia in limbs ipsilaterally while lesion along the midline (median cerebellum-vermis) produce truncal ataxia and head-body ataxia.

CEREBROCEREBELLUM

The Cerebrocerebellum is composed of the right and left Lateral Cerebellum. The major mossy fiber inputs arise from the Pontine Nuclei with minor inputs from the Spinocerebellar Tracts; Dorsal Spinocerebellar Tract (DSCT), the Ventral

Spinocerebellar Tract (VSCT) and the Cuneocerebellar Tract (CCT). The output from the Cerebrocerebellum is channeled through the Dentate Deep Cerebellar Nucleus. The Dentate Nucleus influences primarily the Dorsolateral Descending Pathways. The Dentate Nucleus projects to the Red Nucleus, and to Motor Areas of the Cerebral Cortex by way of the Ventrolateral (VL) Thalamic Nucleus. Thus, the Corticospinal and Rubrospinal Tracts provide the major output to spinal levels. There is evidence that some neurons in Dentate Nucleus (and Lateral Cerebellar Cortex) are activated prior to neurons in the Primary Motor Cortex during 'volitional' movements.

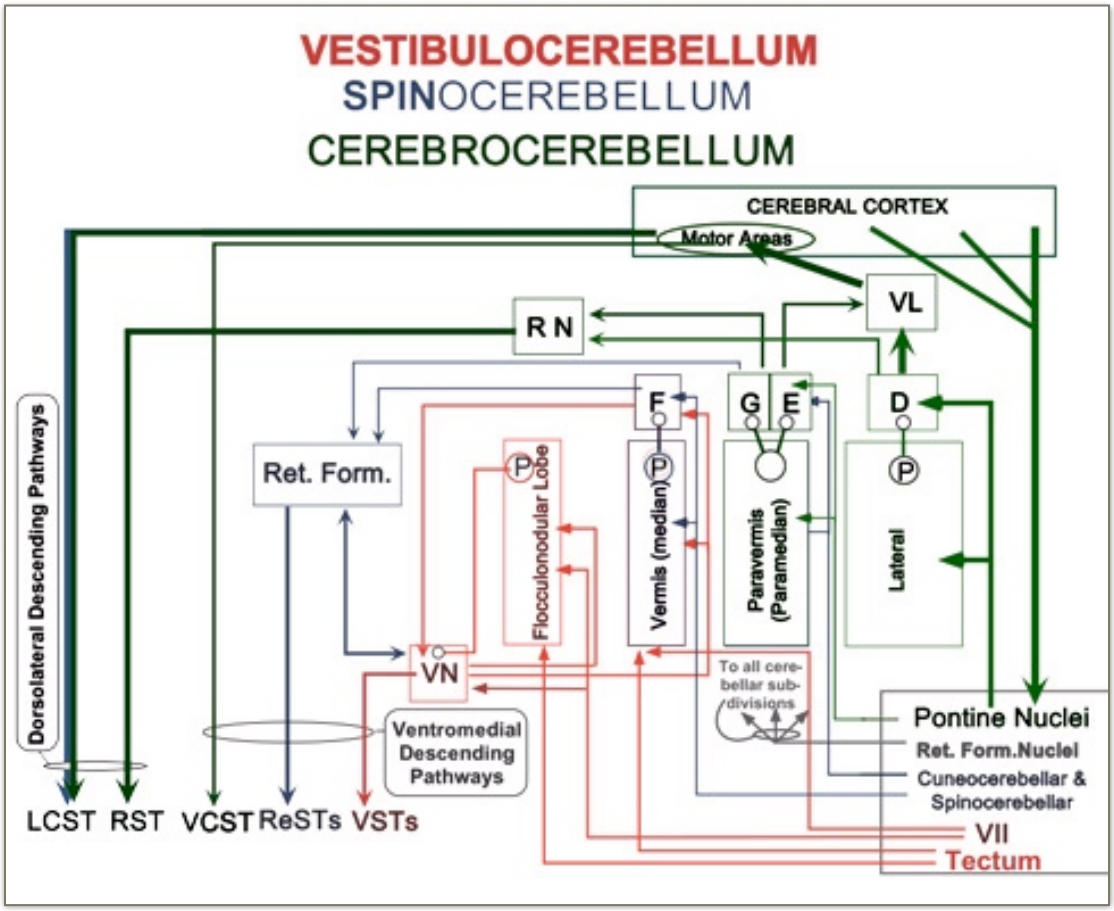


Fig 16-13. Cerebrocerebellum: Lateral Cerebellar Hemisphere (gec).

The role of the Lateral Cerebellum in the initiation of movements “generated” in Human Cerebral Hemispheres is suggested by recent brain imaging studies. The Cerebellum may have a key role in Sensorimotor tasks such as active touch where sensory input and motor output are intertwined as a reciprocating unit of processing. Some of these studies suggest a more “cognitive” role for the Lateral Cerebellum than was previously demonstrated in animal studies. Lesions of the Lateral cerebellum may show mild or no deficits when the standard battery of tests for cerebellar function are performed. Indeed, the decrement in performance of highly skilled, well-practiced tasks may be appreciated by the subject long before clinical evidence of involvement is

manifested. Motor “memories” may suffer and subtle changes may be seen in increased errors, and a slowing of action as the individual relies upon feedback in tasks that previously were so over-learned that they were automatic. The Lateral Cerebellum certainly has appropriate connections with prefrontal cerebral cortical areas to account for high levels of Cerebellar Activation in complex tasks. Functional connectivity MRI (fcMRI) in human subjects suggests that there is a substantial relationship between the cerebral association areas forming cerebral cortical networks and functional connections with a map of these networks in the contralateral cerebellar hemisphere. The movie below demonstrates this relationship and suggests a gradient for actions and cognition within the cerebral and cerebellar maps. Recent theories suggest that the lateral cerebellar cortex plays a major role in implicit processing of not only what we do but what we think: the “little brain” improves upon the precision and efficiency in the neural events responsible for the most highly skilled motoric and non-motoric cognitive expressions of our humanity.

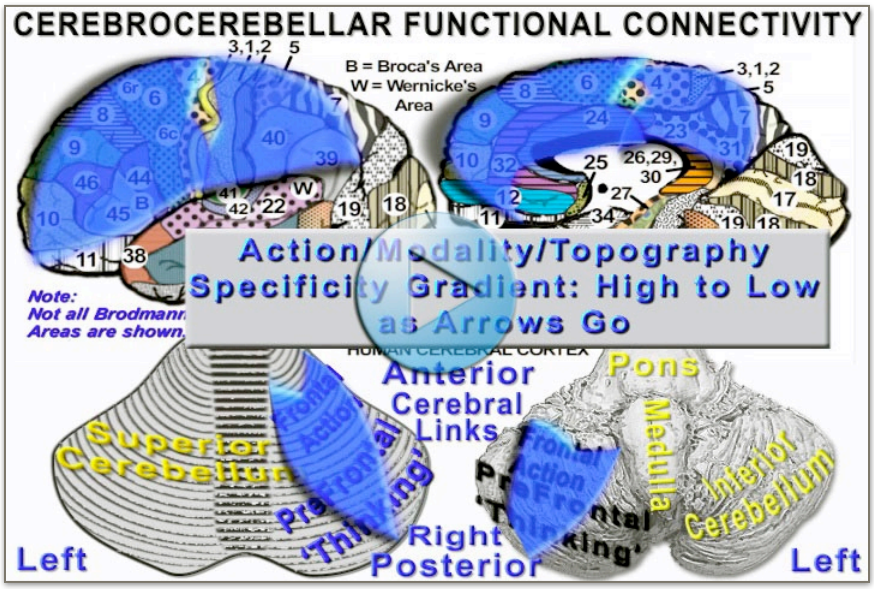


Fig 16-14. Cerebro-Cerebellar Connections and Action versus Cognitive Gradients Movie (gec). GO TO: gmomm.pitt.edu
Fig16-14_Video

INFERIOR OLIVE, CLIMBING FIBERS AND PURKINJE CELL COMPLEX SPIKES

Climbing fibers are a special type of input to the Cerebellar Cortex from cells in the Inferior Olivary Complex. Unlike Mossy Fibers, Climbing Fibers are active only under certain conditions. Climbing fiber input to Purkinje Cells is readily observed as a distinct complex spike generated in these neurons. Mossy fiber input relayed through cerebellar circuitry, on the other hand, produces simple spikes due to parallel fiber synapses on Purkinje cells.

It has been suggested that Climbing Fibers provide a mechanism to reset the Cortical Circuitry when adaptations are required during error correction and when motor learning is in progress. Recent evidence suggests that increased complexity of the complex spike (in form of increased spike duration due to more ‘spikelets’ in the waveform) is related to LTD strength and learning (see, Yang and Lisberger, 2014).

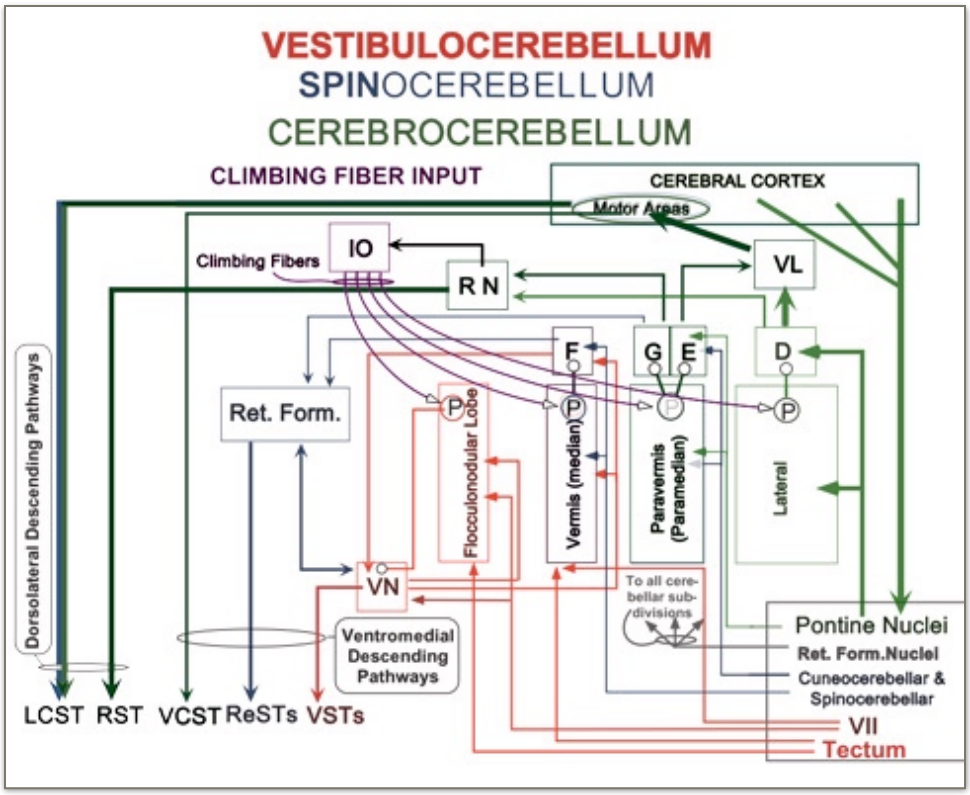


Fig 16-15. Inferior Olive-Climbing Fiber Input to All Cerebellar Subdivisions (gec).

The Inferior Olive is in a good position to carry out these tasks. There are inputs to the Inferior Olive from the Cerebral Cortex, the Red Nucleus, and the Spinal Cord (SpinoOlivary Tract). A Cerebello-rubro-olivary Loop may be a critical pathway for updating the Cerebellum as conditions change. The influence of the climbing fibers from the inferior olive is a good example of sparse spike coding. Even when inferior olive neurons are highly active during adaptation/motor learning climbing fiber discharge has a low discharge rate.

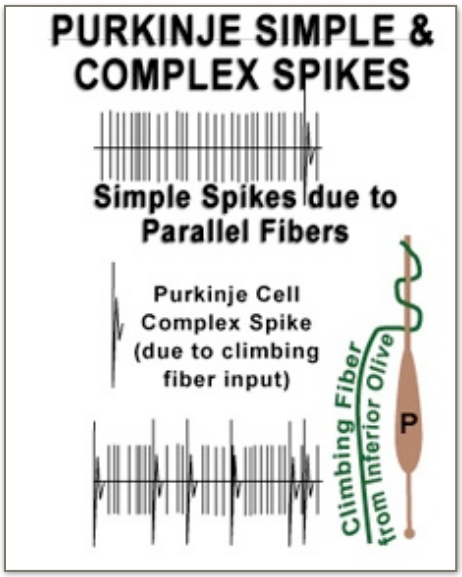


Fig 16-16. Purkinje cell Simple and Complex Spikes. Note increased Complex Spikes in lower trace suggesting that the Purkinje cell is undergoing an adaptive change in firing pattern (performance adaptation & motor learning?) (gec).

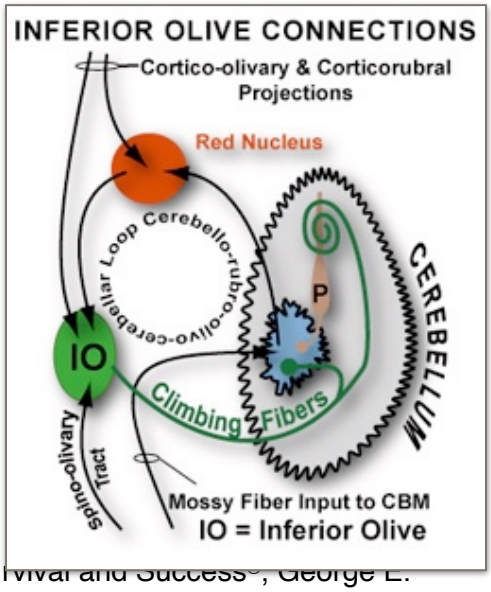


Fig 16-17. Cerebello-Rubro-Olivo-Cerebellar Loop. A recurrent pathway for cerebellar plasticity? (gec).

VENTRAL SPINOCEREBELLAR &

VENTRAL SPTH 3D MOVIE

The Ventral Spinocerebellar Tract (VSCT) provides an 'efferent' copy of ongoing motor events from the lower trunk and lower extremity to the cerebellum. There are a number of neurons in the intermediate and ventral gray that project their axons into the contralateral > ipsilateral VSCT. These neurons are influenced by afferent proprioceptive and tactile inputs and by collaterals from propriospinal neurons and interneurons in the segmental motor centers of the ventral horn. Many of the crossed axons cross back in the brainstem (i.e., its effect is as a bilateral pathway). This pathway is active during ongoing motor output and will remain active even if peripheral afferent input is removed. This crossed tract sends axons by way of the superior cerebellar peduncle to portions of both ipsilateral and contralateral cerebellar cortex and deep cerebellar nuclei. An equivalent pathway for the upper trunk, neck, and upper extremity is associated with the cuneocerebellar tract.

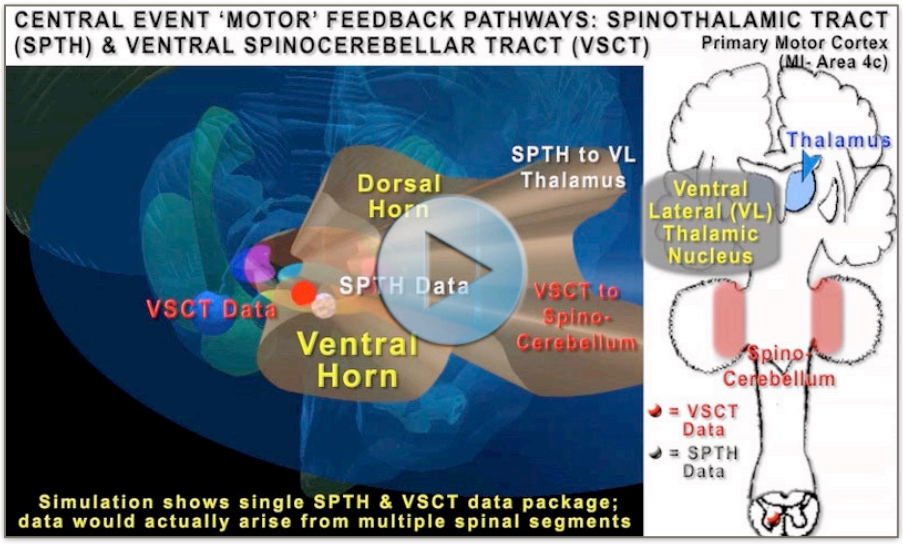


Fig 16-18. Ventral Spinocerebellar Tract and Ventral Spinothalamic Tract: Central (Sensori-motor) Feedback 3D Movie (gec). GO TO: gmomm.pitt.edu
Fig16-18_Video

The Spinothalamic Tract (SPTH) is implicated in conducting pain, temperature and some touch information to the brain. SPTH arises from Spinothalamic tract neurons located in the spinal gray. While most SPTH cells are located in the dorsal horn some SPTH neurons are residents of the intermediate & ventral horn gray. Ventral SPTH neurons are likely to relay information regarding what is going out of the spinal cord to effectors rather than what is coming into the spinal gray from afferent receptors. SPTH thalamocortical targets are multiple and not restricted to primary sensory areas. Both limbic and non-limbic areas are influenced by SPTH. The classic Spinothalamic Tract (SPTH) arising from dorsal horn SPTH neurons is implicated in pain, temperature and some touch information while more ventral SPTH cells may provide signals regarding an efferent (motor) outputs.

CEREBELLAR FUNCTIONS ©

The classic function associated with the cerebellum is motor coordination However, it is evident from recent anatomical tracing studies, functional imaging and more

sophisticated testing of cerebellar patients that non-motor functions most certainly engage the expanded mammalian cerebellum. Some investigators say the human cerebellum has greater connectivity with “cognitive” prefrontal cerebral cortex than with motor cortices (see references). Indeed, M. Ito insists the cerebellum is a critical structure within the brain for human behaviors requiring implicit memory (see Ito, 2011).

The cerebellum has been implicated in both a feedback “reactive” model and a forward internal “predictive” model of sensorimotor control. Cerebellar circuitry may be ideal to perform error detection and contribute to error correction to optimally adapt ongoing motor events and/or match forward error prediction signals with sensory feedback signals of error. Recent research suggests that individual Purkinje cells may contribute to both processes; altered Purkinje cell simple spike discharge associated with an internal predictive model followed by an altered discharge associated with subsequent sensory feedback (see Popa, Hewitt and Ebner, 2012). Thus cerebellar circuitry may be ideal for contributing significantly to both models of sensorimotor control even within a given target-directed event. In addition, the effect of climbing fiber input from the inferior olive has been implicated in the role of Purkinje cell complex spike firing modulation associated with modulation of sensorimotor function when adaptation and/or motor learning is taking place, see references.

CEREBELLAR FUNCTIONAL SUBDIVISIONS: OVERVIEW

FUNCTIONAL SUBDIVISION	VESTIBULO-CEREBELLUM	MEDIAN SPINO-CEREBELLUM	PARAMEDIAN SPINO-CEREBELLUM	CEREBRO-CEREBELLUM
MAJOR MOSSY FIBER INPUTS	VESTIBULAR AFF., VEST NUC, RF NUC, TECTUM	DSCT, VSCT, CCT, VEST NUC, RF NUC, TECTUM	DSCT, VSCT, CCT, RED NUC, RF NUC, PONTINE NUCLEI	PONTINE NUCLEI, RED NUC
DEEP CEREBELLAR NUCLEUS OUTPUT	VESTIBULAR NUCLEI (NO DEEP CBR NUCLEUS)	FASTIGIAL NUCLEUS	INTERPOSED NUCLEI: GLOBOSE & EMBOLIFORM	DENTATE NUCLEUS

FUNCTIONAL SUBDIVISION	VESTIBULO-CEREBELLUM	MEDIAN SPINO-CEREBELLUM	PARAMEDIAN SPINO-CEREBELLUM	CEREBRO-CEREBELLUM
OUTPUT VIA DEEP CEREBELLAR NUCLEI TO POSTERIOR FOSSA & SUPRA-TENTORIAL BRAINSTEM	VESTIBULAR NUCLEI, EYE MOVEMENT CENTERS VENTRO-MEDIAL DESCENDING PATHWAY	VESTIBULAR NUCLEI, TECTUM, VENTRO-MEDIAL DESCENDING PATHWAY	RED NUC, VL + VENT TIER THAL NUC, VENTRO-MEDIAL & DORSO-LATERAL DESCENDING PATHWAYS	RED NUC, VL & HO ASSOC THAL NUCLEI, INTRINSIC INTEGRATIVE & DORSO-LATERAL DESCENDING PATHWAYS
SUMMARY LIST OF PROPOSED FUNCTIONS FOR EACH FUNCTIONAL SUBDIVISION	HEAD, NECK, EYE CO-ORDINATION, BALANCE, EQUILIBRIUM, POSTURE CONTROL ERROR DETECT & CORRECT	POSTURE: WHOLE BODY SYNERGY, LOCOMOTION SPEECH, ERROR DETECT & CORRECT	SINGLE LIMB SYNERGY, PRECISE LIMB MOVE & HOLD, LIMB STABILIZE, ERROR DETECT & CORRECT	SKILL PRECISION: ACQUIRE, RETAIN, PERFECT; IMPLICIT CONTROL: COGNITIVE & COMPLEX ACTION SEQUENCES

Fig 16-19. Cerebellar Subdivisions: Functional Relationship Summary Table Key: CCT = Cuneocerebellar Tract, DSCT = Dorsal Spinocerebellar Tract, HO ASSOC = Higher Order Associative Thalamic Nuclei, RF Nuc = Reticular Formation Nuclei, VL = Ventral Lateral Thalamic Nucleus, VSCT = Ventral Spinocerebellar Tract (gec).

The following list is an overview of proposed motor and non-motor functions for which the cerebellar circuitry is well placed to either implement or modulate in a highly precise fashion.

• COORDINATION OF METRICS OF MOVEMENT AND POSTURE: DIRECTION, VELOCITY, TIMING, RATE OF CHANGE OF TORQUE

• ERROR DETECTION/CORRECTION (PREDICTIVE “FORWARD” & REACTIVE “FEEDBACK” MODES)

• CURRENT CONTROL: ongoing process of comparison between internal models of intended action to actual events. Includes peripheral afferent feedback from somatosensory, vestibular & visual receptors in the periphery plus central efferent

feedback from segmental motor centers by way of the ventral spinocerebellar tract, as well as, feedforward signals of motor intention from cerebral motor & 'association' areas to the cerebellum by way of pontine nuclei.

• KNOWLEDGE OF RESULTS (KR): utilization of feedback regarding performance to adjust output over a number of repetitions (practice effects and learning)

• SYNERGY: PRECISE CONTROL OF AGONIST, SYNERGIST, AND ANTAGONIST MUSCLES FOR THE CONCURRENT AND/OR SEQUENTIAL ORDERING OF MUSCLE CONTRACTIONS IN PATTERNED MOVEMENTS AND POSTURAL ADJUSTMENTS (Grouping to reduce degrees of freedom to be controlled)

• INITIATION AND REGULATION OF "AUTOMATIC" AND "VOLITIONAL" PROGRAMMED MOTOR OUTPUT UTILIZED IN SKILLED SENSORIMOTOR TASKS

• ASSIST OTHER CEREBRAL MOTOR & ASSOCIATIVE AREAS BY ADDING SPATIOTEMPORAL PRECISION TO THE PLANNING AND PREPROGRAMMING OF COMPLEX, SKILLED SENSORIMOTOR BEHAVIORS and COGNITIVE TASKS

• FORM/ADJUST IMPLICIT INTERNAL MODELS OF LEARNED BEHAVIORS AND "THOUGHTS": MAKING MOTOR & COGNITIVE BEHAVIORS LOOK GOOD!

• ADJUSTMENT OF MOTOR GAIN AND REGULATION OF MUSCLE STIFFNESS

CEREBELLAR DYSFUNCTION

A classical picture of cerebellar dysfunction comes from the study of posterior fossa head wounds of soldiers injured in WWI. Cerebellar lesion signs and symptoms were systematically documented by Sir Gordon Holmes, an Irish Neurologist in the British Armed Forces. G. Holmes used observation, and simple instrumentation to document the acute and subacute effects of posterior fossa lesions that involved the cerebellum. While some of the details have been questioned by more recent studies that precisely localize the lesion, there is general agreement for the broad strokes of Holmes' portrait of cerebellar deficits (see below). Collectively the deficits are called Cerebellar Ataxia. The location of the lesion determines the site of deficits. A lesion of the midline produces (bilateral) truncal ataxia and typically includes vestibular and eye movement defects. If the anterior lobe is involved an ataxic gait is obvious. A lesion of the paramedian cerebellum produces an ipsilateral limb ataxia. A dysarthric speech pattern (scanning speech) may develop with a bilateral lesion. A lesion restricted to the most lateral portion of the cerebellar hemisphere in the posterior lobe may produce few typical cerebellar signs but does result in a deterioration of skilled movements and discriminative cognitive processes. These deficits are obvious to the subject if not to the clinician. Often the screening clinical exam uses tests that are insensitive to the more subtle clumsiness recognized by the subject. The skilled actor must now slow down and consciously attend to formerly automatic tasks as errors creep into performance. Holmes and more recent investigators point out that if the lesion is restricted

superficially to the cerebellar cortex one can expect greater recovery than if the lesion includes the deep cerebellar nuclei: see Thach, 1987

SUMMARY OF HOLMES' OBSERVATIONS (CLASSIC SIGNS & SYMPTOMS OF CEREBELLAR DYSFUNCTION)

The following is a list that approximates G. Holmes' list from the early 1900s: see G. Holmes, 1939.

- Delays in initiation of movement (slow reaction time) and delays in termination of movements (rebound test)
- Delays in rapidly alternating movements (dysdiadochokinesia)
- Movement errors: direction, velocity and range (dysmetria)
- Errors in Joint Synergy (dyssynergia)
- Hypotonia (pendular deep tendon reflex) and asthenia (functional weakness despite normal strength using manual muscle test)
- Intention tremor (~ 3-5 Hz)

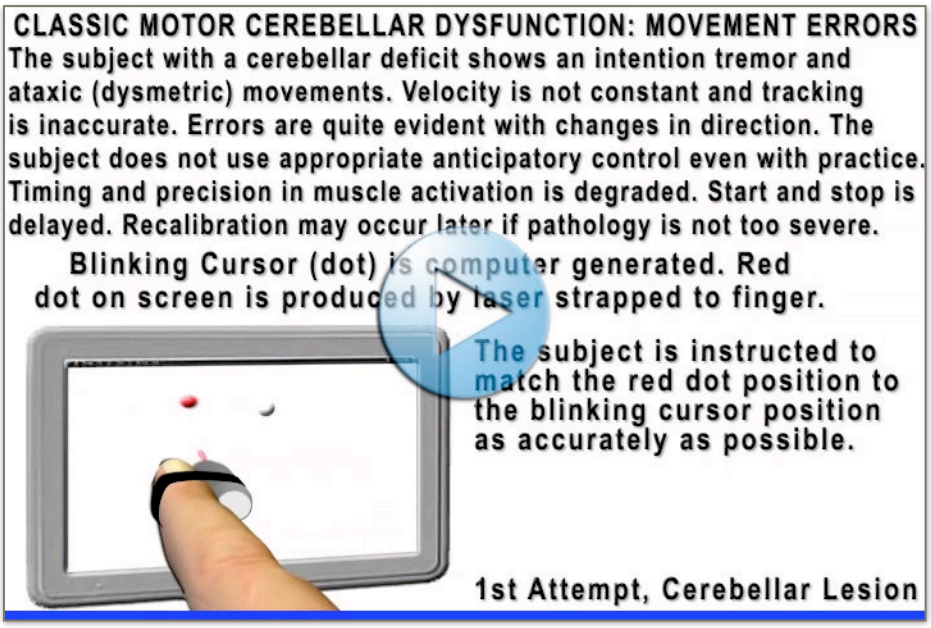


Fig 16-20. Cerebellar Dysfunction: Tracking Errors Movie (gec). GO TO: gmomm.pitt.edu Fig16-20_Video

Many of the hallmarks of cerebellar ataxia are illustrated in the movies below. Timing errors contribute to delays in initiation and termination of movement, to deficits when changing direction of movement, to poor control of velocity (dysmetria) and timing problems contribute to a poor ability to coordinate muscle coupling in multijoint movements (dyssynergia).

Fig 16-21. Sensory Ataxia Movie. Movement errors occur when visual cues are removed but not when visual cues persist (gec, jec). GO TO: gmomm.pitt.edu Fig16-21_Video

Dysmetria and dyssynergia may be revealed by a relatively simple clinical test. The individual is asked to rapidly but accurately reach for the examiner's outstretched finger then to his own nose-back to the examiner's finger, etc., in a cyclical fashion. The test is first done with the eyes open. After a number of cycles, the subject is asked to close his eyes and continue the task. Two different simulations are shown. SENSORY ATAXIA Movie shows involvement of ascending pathways responsible for proprioception. The subject does fine with eyes open but not when visual cues are removed.

The CEREBELLAR ATAXIA Movie shows the effects of a cerebellar lesion. The subject has the most errors as the target is approached with eyes open and eyes closed. Removal of the visual input has no substantial effect on the ataxia. Intention Tremor is most obvious as the Cerebellar subject's finger nears the target. The lower extremity equivalent is the heel-to-shin test where the subject places one heel on her opposite shin distally and then precisely moves the heel along the shin up to the knee and back down towards the ankle. Obviously, other lesions could produce movement errors including brainstem lesions so this test alone is not pathognomonic for sensory or cerebellar disorders.

Fig 16-22. Cerebellar Ataxia Movie. Movement errors occur when visual cues are removed AND when visual cues persist (gec, jec). GO TO: gmomm.pitt.edu Fig16-22_Video

The Rebound Test (Phenomenon) is a simple test of the ability to rapidly halt (check) a movement following an unexpected perturbation. The examiner asks the subject to produce a forceful holding contraction of an agonist muscle group and then, without warning, quickly removes the load. Normally, one ceases contraction of the agonist and activates the antagonist muscles (rebound) quickly enough to minimize motion of the tested joint. This requires rapid force adjustments to an external perturbation. Individuals who have ataxia due to cerebellar lesions typically have significant delays in initiation and cessation of movements and they fail this test. However absence of ataxia does not rule-out cerebellar lesions. An individual with a lesion restricted to the most lateral

portion of a cerebellar hemisphere may have few or no signs of ataxia. Sensory ataxic individuals may or may not show an abnormal rebound phenomenon.

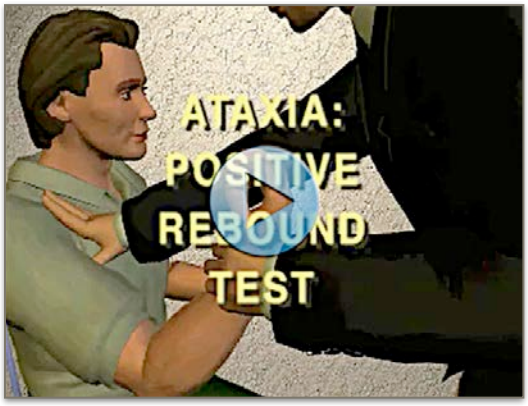


Fig 16-23. Positive Rebound Movie. Subject is unable to check loaded agonist contraction by rapid contraction of antagonists (gec, jec). GO TO: gmomm.pitt.edu Fig16-23_Video

If afferent pathways to the cerebellum are involved, inadequate control of muscle metrics will often be evident in clinical tests of coordination e.g., Friedreich's Ataxia, MS. The examiner must protect the subject from harm when performing these tests. The elbow flexors and extensors are tested in this animation. Other muscle groups may examined. A more sophisticated version of this ataxia test uses posturography equipment that precisely and unexpectedly perturbs one's standing balance under differing conditions, e.g., eyes open/closed. The device measures the resultant sway and corrective responses to the perturbation.

Fig 16-24. Dysdiadochokinesia Movie: Inability to perform rapidly alternating movements (gec, jec). GO TO: gmomm.pitt.edu Fig16-24_Video

Dysdiadochokinesia is the inability to sustain rapidly alternating movements. It represents one form of dysmetria with errors in velocity, range and direction of movements. The animation illustrates a unilateral deficit on the right side. This would be consistent with a right-sided cerebellar lesion or possibly a lesion involving the ascending proprioceptive pathway for the right upper extremity (right dorsal column-> lateral cuneate nucleus-> spinocerebellum. The individual in this simulation shows incomplete alternation between supination and pronation with loss of range, and slow inconsistent velocity of motion. Obviously, other lesions could produce movement errors including brainstem, basal ganglia, or cerebral lesions so this test alone is not pathognomonic for cerebellar disorders.

Normal gait requires rhythmic, propulsive movements of the legs superimposed upon dynamic postural control of the body; graceful “falls” followed by agile recovery of balance. Ataxic gait due to cerebellar or sensory lesions is characterized by its inconsistencies in rhythm, foot placement, stride lengths, control of the center of mass (swaying), and by a relatively clumsy control of postural support. Stance tends to be wide-based. Stopping, starting, and changing directions all represent significant

challenges to ataxic walkers, and high anxiety for their health care personnel & family members. Predicting the exact placement of the next footfall is akin to playing the lottery. For the sensory ataxic patient, closing the eyes may make walking impossible. Without visual and somatic cues, the vestibular system may be unable to compensate for the sudden changes in the center of mass that lead to postural instability with eyes closed. Some people who have uncompensated vestibular disorders may hold their heads abnormally still when moving and may become intolerably dizzy if they must turn their heads while walking, or look in some direction other than straight ahead while performing ordinary activities of daily living. Ambulation in environments flooded with rapidly changing visual scenery, near proximity to crowds of people and high environmental "noise" may be especially challenging; no mall shopping trips! Many events that are normally taken in stride at work or play become potential sources of anxiety to trigger symptoms or cause instability including falls.

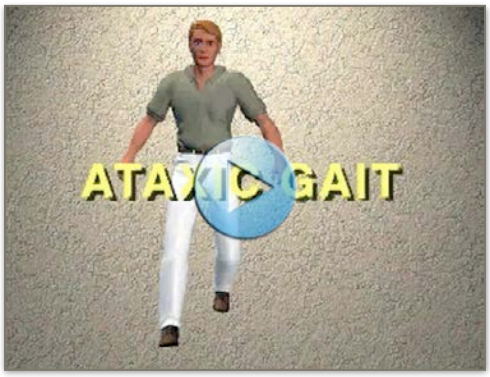


Fig 16-25. Ataxic Gait Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig16-25_Video*

CEREBELLAR ROLE IN LEARNING, ADAPTATION & PLASTICITY

Learning, memory and synaptic plasticity are buddies. Learning in the psychomotor domain requires cooperation among sensorimotor areas at many, perhaps all, nervous system levels. The cerebellum has been implicated in motor learning and in perfecting performance of skilled actions. Skill may mean different things to different people, but a conservative definition would likely include: a goal for the task, "cognitive" and sensorimotor neural components, practice, motivation and some level of talent to improve/perfect performance over time. Motor learning infers brain change. Here the discussion is limited to the role of the cerebellum and to some proposed mechanisms responsible for improved performance and motor learning. Past theories often limited cerebellar contributions to the motor aspect (executing the "will"). Subsequently, anatomical, electrophysiological and brain imaging studies suggest a broader role for the cerebellum in the decision-making process of signing the "will"; a cerebellar role in feedforward and feedback control. Studies suggest that the inferior olive and its climbing fiber input to Purkinje (P) cells are particularly important. Neuroscientists have investigated the role of long-term depression (LTD) as one critical element in P cell "training." LTD is most often found when P cells fire both simple spikes and complex spikes. Simple spikes in P cells are due to mossy fiber-parallel fiber activation. Complex spikes in P cells are due to climbing fiber input from the inferior olive. The molecular machinery behind LTD is complex so one might expect both chemical and "electrical" mechanisms to be at work.

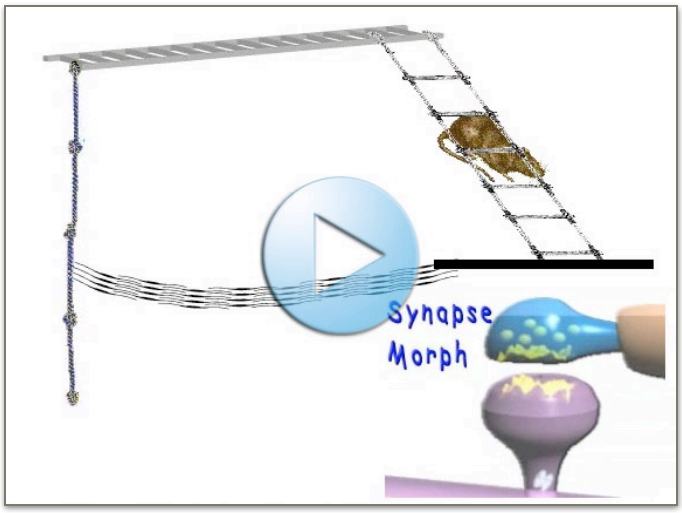


Fig 16-26. Acrobatic Rat Movie. Novel Skill Exercise and Synaptic Plasticity (gec). GO TO: gmomm.pitt.edu *Fig16-26_Video*

RATS TRAINED TO PERFORM NOVEL, ENGAGING & CHALLENGING ACROBATIC SKILL TASKS SHOW SYNAPTOGENESIS AND SYNAPTIC GROWTH WITHIN PORTIONS OF THE MOTOR SYSTEM (MOTOR CORTEX AND CEREBELLAR CORTEX IN RATS). MODIFIED SYNAPTIC PROFILES MAY PERSIST FOR WEEKS OR LONGER FOLLOWING TRAINING.

Certain cerebellar lesions and lesions of the inferior olive may disrupt the normal recalibration of motor output when conditions for a task are altered, e.g, use of prism glasses to alter a visuomotor task. Interestingly, subjects who trained with & without prism glasses for 6 weeks were able to store two "programs," one for each condition. Rats taught to perform an 'acrobatic' set of tasks (skill learning) have more synapses per neuron for cerebellar cortical P cells but not for cells in deep cerebellar or vestibular nuclei. Synaptic changes were reported for both parallel fiber and climbing fiber input to P cells. Control rats that performed "aerobic" tasks for an equivalent period of time had no such synaptic plasticity. The synaptic changes due to the "skill" training were persistent for some time after training had ceased (at least 1 month).

Fig 16-27. Dart Throwing With & Without Prism Glasses: Intact Inferior Olive (IO) Movie (gec). GO TO: gmomm.pitt.edu *Fig16-27_Video*

Throwing an object to precisely hit a target is a skilled sensorimotor task that typically improves in accuracy with practice. Tom Thach & colleagues have shown that portions of the cerebellum AND the inferior olive must function normally for this task to be both successful and adaptable. Use of prism glasses in human subjects alters the gaze-centered targeting of dart throws. Intact subjects adapt throws after donning the prism glasses within a single session (see INTACT IO Movie). Subjects who practice with & without the prism glasses over many weeks learn 2 eye-hand calibrations; throws are accurate immediately after

donning or doffing the glasses. Persons with certain cerebellar disorders or those with inferior olive degeneration make no such recalibration (see IO Degeneration Movie).

Fig 16-28. Dart Throwing With & Without Prism Glasses: Inferior Olive (IO) Degeneration Movie (gec). GO TO: gmomm.pitt.edu Fig16-28 _Video

By localizing the site of cerebellar lesions in humans or by inactivating small regions of the cerebellum in monkeys, (using small injections of a GABA antagonist [muscimol]), Thach and colleagues have suggested that mossy fibers from the contralateral pontine nuclei and climbing fibers from the contralateral inferior olive are critical for this adaptation (learning) despite minimal or absent limb ataxia. Learned adaptations appear to be predictive (feedforward > feedback) and nontransferable since even practice cannot provide instant adaptation for target location shifts due to prism glasses that refract at a different angle.

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Chapter 17

BASAL GANGLIA

BASAL GANGLIA (BG) are Deep Forebrain & Midbrain Structures reciprocally connected with the Cerebral Cortex & Brainstem. Like the cerebellum the basal ganglia access the motor and other cortical areas but do not project axons to the spinal cord to directly activate segmental motor output neuronal networks. Nevertheless, the basal ganglia as a "side-loop" structure is a subcortical center for "value-added" control of cognitive, limbic and motor behaviors. Basal Ganglia structures include: 1. Lentiform (Lenticular) Nucleus which contains the globus pallidus and the putamen, 2. caudate nucleus, 3. substantia nigra, 4. ventral tegmental area (limbic) and 5. subthalamic nucleus. Some anatomists included the amygdala (limbic) in the past.

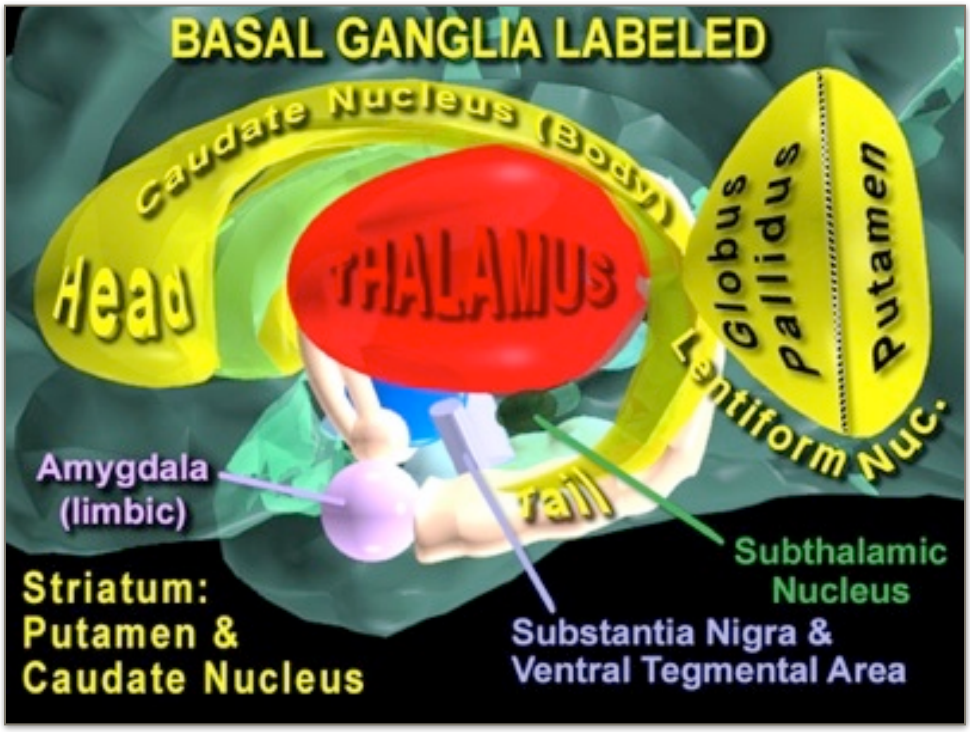

Fig 17-1. Gray Matter Structures included in the Basal Ganglia: Striatum (Putamen and Caudate Nucleus), Globus Pallidus, Subthalamic Nucleus, Substantia Nigra and Ventral Tegmental Area (gec). GO TO: gmomm.pitt.edu *Fig17-1_Video*

The basal ganglia have been subdivided into subcircuits. A basic connectivity within each of three functional subcircuits is illustrated in an interactive flash file that builds each circuit in stages. More detailed "circuit diagrams" follow in later static figures.

GENERIC BASAL GANGLIA CIRCUITRY

The basal ganglia as a group is a powerhouse of biochemistry.

Multiple neurotransmitters are involved in loops that provide intrinsic connectivity within BG and those loops that link the BG to the cerebral cortex and non-BG brainstem structures.

As the Generic Basal Ganglia Circuitry figure illustrates, GABA plays a major role producing both inhibition and disinhibition as control components within the BG circuitry. It has been proposed that a direct pathway facilitates behavior (e.g., action choices) while an indirect pathway suppresses behavior: see Basal Ganglia Subcircuits Introduction Interactive Flash file. The direct and indirect pathways are not subdivided in the Generic BG Circuitry figure below.

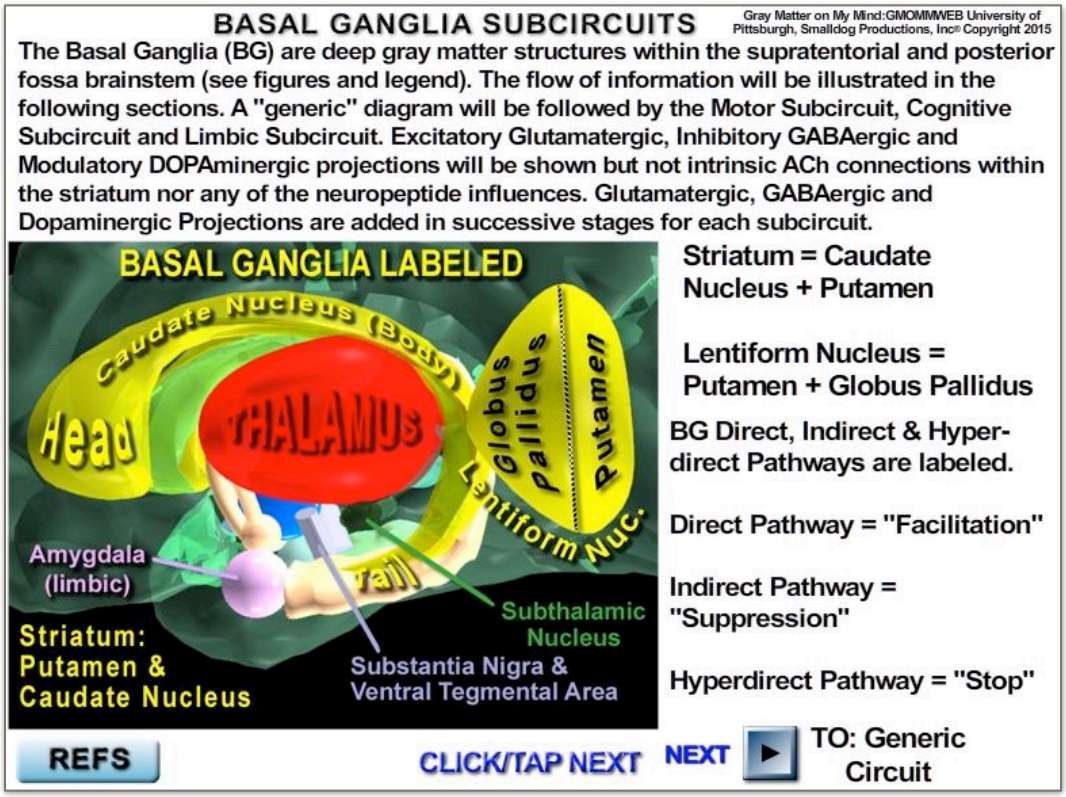

Fig 17-2. Basal Ganglia Subcircuits Introduction-Interactive Media file (gec). GO TO: gmomm.pitt.edu

Fig17-2 Interactive Media

Note that the major source of excitatory input to BG circuitry comes from the cerebral cortex directly as glutamatergic corticostriatal or thalamostriatal input or indirectly by way of cerebral cortical activation of the subthalamic nucleus (STN) that, in turn, excites pallidal and nigral structures. The hyperdirect pathway via the STN is suggested to be a pathway to halt ongoing behavior or assist in the selective facilitation of one amongst many potential behaviors (see below).

Although the primate BG output does target some brainstem structures extrinsic to the BG such as the Pedunculopontine nucleus (PPN) and Pontine Nuclei, the major output inhibits select thalamic nuclei which provide excitatory thalamocortical drive to “closed loop” cerebral cortical targets of BG circuits (see below). The Subthalamic Nucleus and the Cerebral Cortex project to the Pontine Nuclei which is the major source of excitatory mossy fiber drive to the granule cells in the lateral cerebellar cortex. In turn, the dentate nucleus of the lateral cerebellum projects to the striatum and globus pallidus. Dopaminergic neuromodulatory inputs regulate neuronal activity in the striatum

and the subthalamic nucleus. Dopaminergic cells are located in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) for the limbic subdivision (see below). The dopaminergic input to BG and cerebral cortex is thought to be associated with reward.

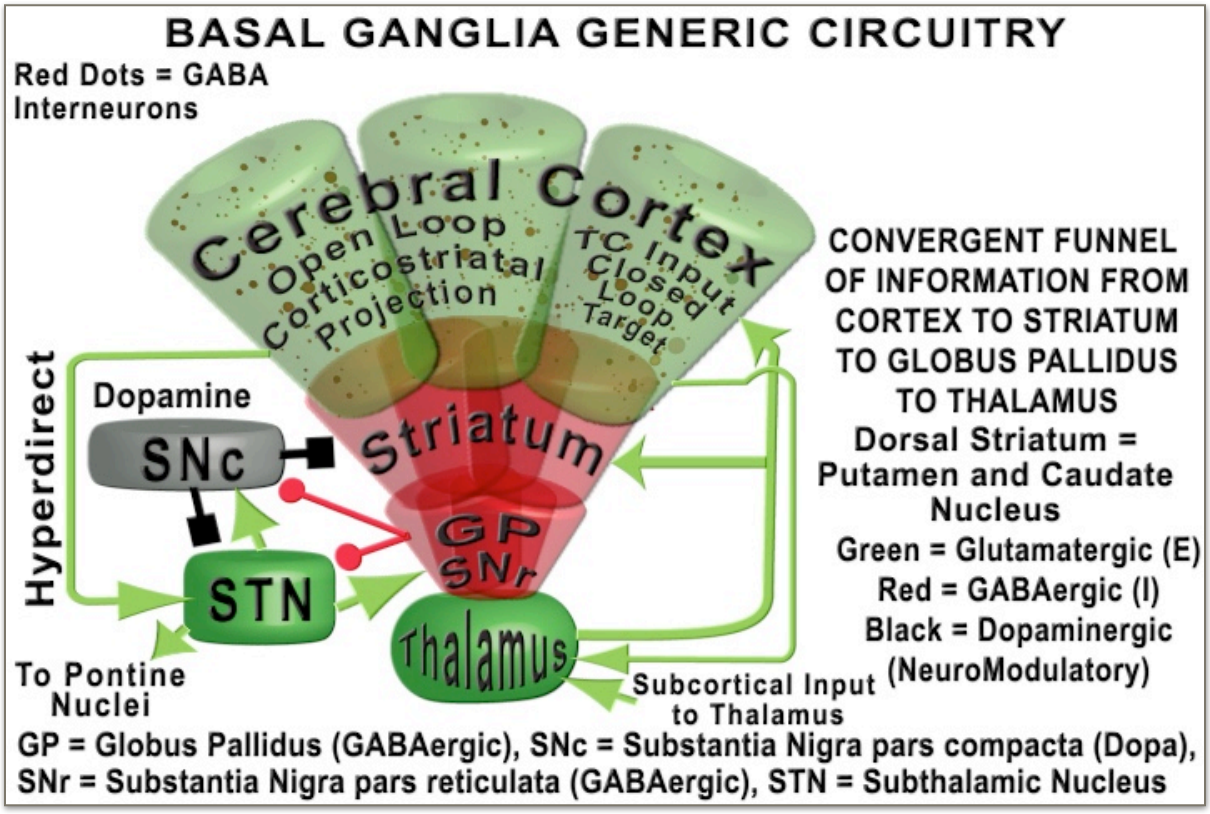

Fig 17-3. Generic Basal Ganglia Circuitry with main excitatory, inhibitory and modulatory connections identified (gec).

BASAL GANGLIA STRUCTURE/FUNCTION SUBDIVISIONS

Basal Ganglia functional subdivisions are based upon differences in corticostriatal inputs, cortical sources for open loop and closed loop connections, thalamic nuclei utilized for thalamocortical output to closed loop targets and proposed functional contributions to basal ganglia circuitry. These circuits typically operate in parallel to control reward-based learned behaviors. Note the progressive “funneling” of data that presumably has greater coalescence of information from cortex to globus pallidus.

BASAL GANGLIA MOTOR CIRCUIT

The Motor Subdivision of the Basal Ganglia (BG) includes Corticostriatal input to the Putamen from the Posterior Parietal Cortex (PPC), Primary Somatosensory Cortex (SI), Primary Motor Cortex (MI), Lateral Premotor Cortex and the SupplementaryMotor Area (SMA). The major thalamic nuclei as outputs of this circuit are the Ventral Lateral (VL) & Ventral Anterior (VA) Nuclei which project to the closed loop cortical targets (SMA, MI and Lateral Premotor Areas). Dysfunction of the Motor Subdivision is thought to be the

major contributor to motor disorders seen in BG Diseases. BG has important loop connections with both cortical and brainstem motor areas; its influence on segmental motor centers is transmitted via Dorsolateral & Ventromedial Descending Pathways.

Basal Ganglia are utilized in the planning & execution of action sequences for skilled motor tasks. The Cerebellum and many Cerebral Cortical Areas participate in planning, programming and execution of sensorimotor behaviors. Cerebellar afferents and Spinothalamic Tract afferents innervate a portion of VL that is largely non-overlapping with VL cells influenced by BG. Cerebral Cortical Areas driven by VL have direct access to the Segmental Motor Centers: Lateral Corticospinal Tract in Dorsolateral Descending Pathway and the Ventral Corticospinal Tract in the Ventromedial Descending Pathway. Basal Ganglia and Cerebellum have projections to Reticular Formation Nuclei that influence spinal cord by way of the Ventromedial Descending Pathway.

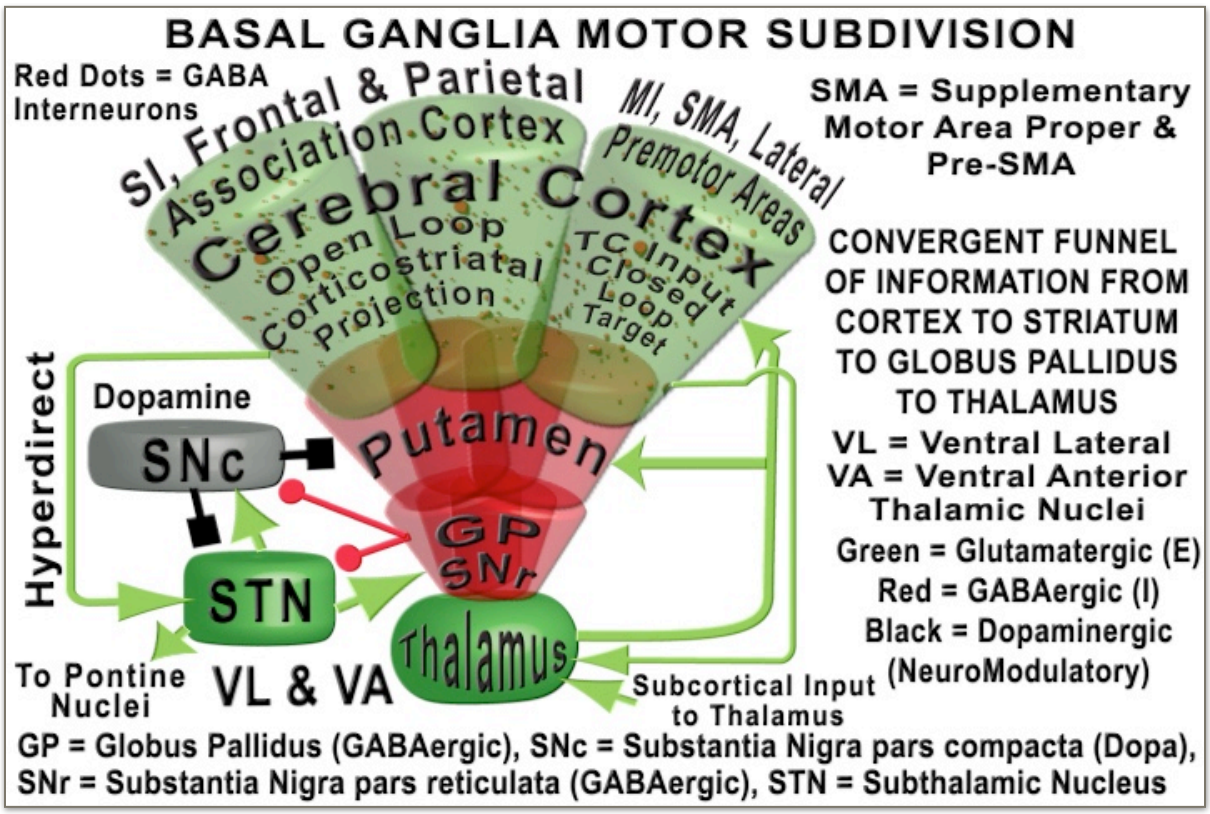

Fig 17-4. Motor Subdivision of Basal Ganglia (gec).

BASAL GANGLIA COGNITIVE CIRCUIT

The Cognitive Subdivision of the Basal Ganglia (BG) includes Corticostriatal input to the Caudate Nucleus from the Frontal and Parietal Association Areas of the neocortex. The major thalamic nucleus as output of this circuit is the Dorsomedian (DM) Nucleus which projects to the closed loop cortical targets in Dorsolateral and Ventrolateral Prefrontal Cortex (Lateral PFC). PFC Pyramidal neurons have abundant opportunities

for synaptic inputs: basal dendritic trees & spinous processes are more abundant than in primary areas or posterior association areas.

Opportunity for synaptic plasticity should be significant and synaptic convergence may offer some “immunity” to functional loss in “non-limbic” BG PFC areas until late in the course of certain neurodegenerative disorders.

PFC is massively connected with posterior parieto-occipito-temporal and some limbic association cortex. PFC is critically involved in: 1. temporal organization of behavior over periods ranging seconds to years, 2. suppression of inappropriate behaviors according to internal & external constraints including societal norms; 3. executive functions including judgement-based decision-making. Judgements take into account: risk-assessment, need, external & internal constraints to achieving a reward, energy conservation and individual personality “traits” based on one's personal history and a life-span “wiring/rewiring” across expansive regions of the brain influencing PFC.

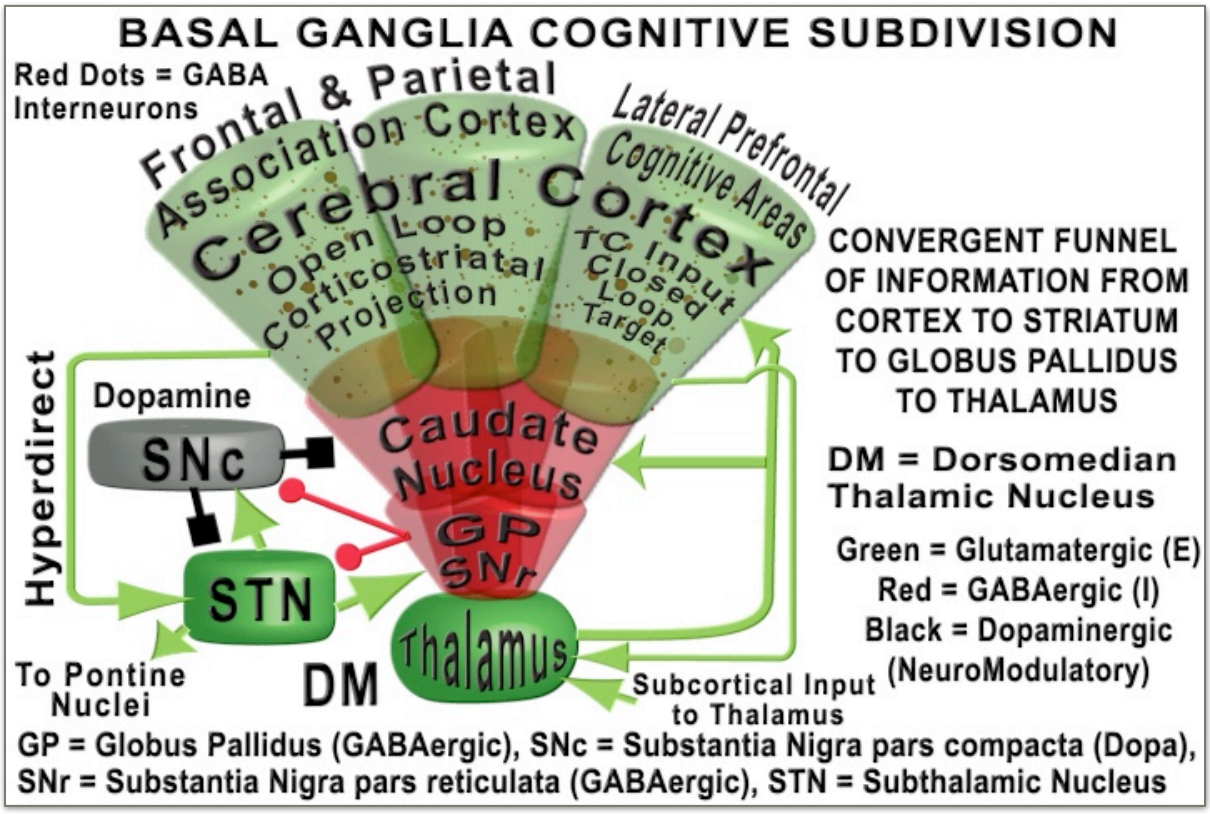

Fig 17-5. Cognitive Subdivision of Basal Ganglia (gec).

BASAL GANGLIA LIMBIC CIRCUIT

The limbic circuit of the Basal Ganglia includes structures not previously described for the motor or cognitive circuits. A specific portion of the Striatum called the Ventral Striatum (VS) is located anteriorly where the Striatum joins with the Globus Pallidus (GP). VS includes the Nucleus Accumbens. VS receives not only cortical input but subcortical input from the Amygdala and from the Ventral Tegmental Area (VTA).

Amygdala is heavily connected with limbic forebrain. VTA contains DOPA neurons similar to those in the Substantia Nigra (SNc). The Ventral Striatum projects to a portion of GP called the Ventral Pallidum (VP). VP projects to the Dorsomedian Nucleus (DM) of the Thalamus. DM, in turn, projects to the closed loop cortical targets of this circuit: the Cingulate Motor Areas and other portions of the Anterior Cingulate Cortex (ACC) and the Medial OrbitoFrontal Cortex (MOFC).

VP & VTA have reciprocal connections with the Subthalamic Nucleus. The proposed functions of this limbic subdivision of the Basal Ganglia are still speculative but include functions typical of the limbic system. This circuit may be a critical component of the neural substrate for control of the motivational and affective nature of our behaviors. It may add some "flavor" to our actions. Goal directed behavior is driven by reward expectation & risk assessment. Through Subthalamic Nucleus and Anterior Cingulate Area closed loop connections, this circuit has access to brainstem and spinal motor centers. The Amygdala provides a link to our deepest emotions and drives.

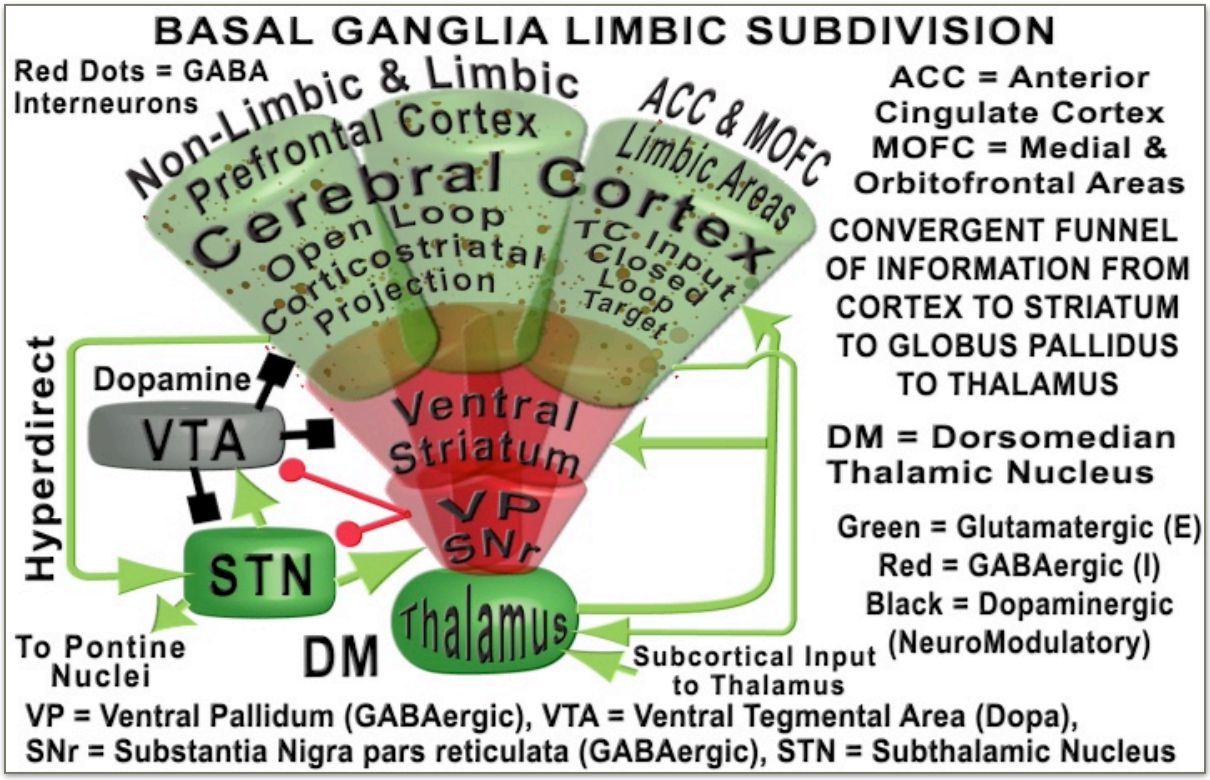

Fig 17-6. Limbic Subdivision of Basal Ganglia (gec).

It has been hypothesized that a direct pathway within the basal ganglia is responsible for facilitating behavior while the indirect pathway suppresses behavior. While there is not a consensus regarding these functions a recent study in mice shows a correlate of this direct versus indirect distinction. Optogenetic techniques allow the experimenter to target a channelrhodopsin to Dopamine D1 expressing striatal neurons (direct pathway) or channelrhodopsin to Dopamine D2 receptors (indirect pathway).

When light pulses activate the opsin-expressing D1 striatal neurons the mice seem to increase activity that leads to "reward." Alternatively, when the opsin-expressing D2 striatal neurons are light-activated the mouse freezes (all movement ceases). While it is uncertain what circuitry is actually engaged by such light stimuli, the activation pattern seems to fit with the hypothesized roles of the direct versus indirect pathway. In particular, freezing is a disabling feature of Parkinson's Disease where dopamine levels are significantly reduced in the striatum (see below and A. V. Kravitz, et.al., 2010).

CAUDATE NUCLEUS & ACTION SELECTION: HEADS OR TAILS?

Basal ganglia are implicated in reward based selection of high value behavior. Recent evidence suggests a differential role for the head vs. tail portion of the Caudate Nucleus in assessment of reward value according to current circumstances and past-experience. Based on reward-value selection of oculomotor saccades in monkeys, Hikosaka, et.al., 2014 propose a role for the head of the caudate nucleus in reward value selection based on short term (working) memory. The head of the caudate nucleus has substantial connections with prefrontal cortex where neurons provide the neural basis for good working memory. Such reward selection is flexible according to fluctuations in prevailing circumstances. By contrast, the tail of the caudate nucleus in the medial temporal lobe is well positioned to access long term memory of prior value rewarded behavior to guide action selection in a more automatic fashion. The body between the head and tail of the caudate nucleus may provide a transition between these two ends of the reward selection spectrum. There is more to a reward-behavior relationship than heads or tails; behavior requires a body.

BASAL GANGLIA FUNCTIONS © *

• **The "automatized" production of learned motor plans. Can this be habit-forming?**

• **Consolidation of motor programs into efficient goal directed motor plans.**

• **Implementation of simultaneous and/or sequential motor programs according to the behavioral context (assumes prior motor learning):**

i) memory guided (I did drive myself home .. didn't I?)

ii) self initiated (I control the rhythm and the pace, self-imposed goals)

iii) externally cued (perception/action coupling, deadlines)

iv) delayed motor set (temporal organization of behavior)

• **Making motor choices (Spatiotemporal Organization in Action-Perception Cycle):**

i) switching between motor plans and integrating motor strategies

ii) incorporating perception, judgment, drive, memory, affect, and external conditions into a plan of action (Requires Evaluation of Performance)

• Driving Action or Inaction - To do or not to do? That is the question! (Reward-Based?)

i) Is the action worth the effort? Do Now?.. Later?.. Never?

ii) Will the action satisfy a short- or long-term need? (What's in it for me?)

iii) Is the action acceptable according to homeostatic and/or societal norms; if not, what are the risks if the action proceeds?

iv) When must I suppress action for self-preservation or for the good of others (according to self/institutional moral codes)?

• Motor Energizer: revving up the neural engine, changing gears:

i) setting levels of kinetic activity (often reward based)

ii) stiffness regulation

iii) preparatory set (Get Ready… Get Set…)

• Selective Facilitation: focusing attentional & intentional resources on a particular behavior:

i) adjusting rhythms of BG and targeted neural centers (internal > external cues)

ii) regulation of quantitative > qualitative aspects of behavior

* Copyright GEC 1990 (revised 2006, 2011, 2014)

This list above could appear to be rather pretentious, suggesting that the basal ganglia control virtually everything that a thinking brain might do. The following (tongue-in-cheek) disclosure should put any BG delusions of grandeur in their rightful place.

> **BASAL GANGLIA ACCEPTANCE SPEECH (PRESENTED BY CAUDATE AT THE "BRAIN AREA OF THE DECADE" AWARD CEREMONY)***
>
> We the Basal Ganglia, hereafter known as BG, provide the following limited liability divulgence of our success (and all the little people that made this award possible-stakeholders take note):
>
> 1. BG would be a mere mass of sparks and chaotic lightning storms without the critical support of the cerebral cortex. We give a special "shout out" to our frontal lobes (primates).
>
> 2. BG sends out a special "thumbs up" to our producers-Amygdala, Hippocampus, PFC, ACC, and Mother Nature for keeping us on our toes and pushing us to new heights.

3. BG thanks the thalamus for dissemination of our work to all the most influential actors (that just happen to vote for this award)-"high-fives" for the Ventral Tier, Dorsomedian and Centromedian Nuclei.

4. BG expresses its special gratitude for our director, D. O. Hebb for his insight into this adventure, the "time & space" for us to bond as a special group and for the cooperative framework in which we could learn & grow as a family while working/playing together.

5. Special thanks to our main pharmaceutical sponsors: GABA, ACh, Glutamate, the Neuroactive Peptide family and of course Dopamine.

6. Finally, we thank, Oscillatory and her STN-GPi Gamma Band, for the wonderful score whose punctuated "funky" rhythms set a perfect backdrop for our performance (now available on iTunes).

Following BG's acceptance speech there is polite applause from the crowd with a collective murmur of unspoken resignation-

"Yeah, you look like a genius when you have unfettered access to the right people!"

*Tongue in Cheek Discourse (2018); even neuroscientists are permitted to have a sense of humor! For the quips to actually be humorous the author assumes that the reader is familiar with some basic principles of neuroscience and that you do not expect the author to be a professional stand-up comedian.

BASAL GANGLIA: PROCEDURAL LEARNING INTRODUCTION

Modern concepts of motor control & motor learning emphasis the distributed neural basis for procedural (implicit) learning. It has been suggested that the Cerebral Cortex is particularly well-suited for "unsupervised" learning since it has "privileged access" to multiple sources of information (relatively "raw" data and highly processed data). The Cerebellum is critical for "supervised" learning with the suggestion that both mossy fiber and climbing fiber inputs have supervisory roles. The Basal Ganglia (BG) are suggested to be particularly well-suited for "reinforcement" learning due, in part, to direct access to Dopamine reward signals from the Substantia Nigra and Ventral Tegmental Area in the midbrain, see: Doya, 2000. Clinical and experimental data suggest that BG are involved in both the mental (cognitive) processes that organize behavior for goal-directed motor actions (signing the will) and the implementation of motor plans (execution of the will). BG are critical for making motor choices, temporally organizing behavior over multiple time frames, and linking rewards to our decision to act. Most of these behaviors involve skilled actions that become habitual and occur with little conscious effort expended on the exquisite details of the complex events that unfold as the motor plan achieves its goal. As good citizens of a brain heterarchy, BG may alter their role in procedural

learning from one of “exploration” during initial learning to one of “exploitation” as insight into the requirements for the task ensues and errors decline. Improvement in skill infers learning: an enduring change in behavior/performance. Accuracy, agility and efficiency should improve. Goals should be met with expected rewards obtained. Other metrics such as speed and adaptability may also change if they represent critical aspects of the task. As performance improves, our brain may not be working harder just more efficiently. Some cells increase firing at just the right time while others stifle small talk to suppress irrelevant “noise.” Local & global coalitions are formed and optimized. Select neurons maintain discharge to sequence events. Entropy is reduced. The burden of control shifts within the cortex and among cortical & subcortical gray as learning continues. Rapid BG learning may precede cortical changes. There is still debate regarding the role of the basal ganglia in well-learned behaviors. One theory suggests that as one enters an over-learning phase that the neural programs that are responsible for the skill are “outsourced” to subcortical structures such as the basal ganglia and the cerebellum. A contrary theory suggests that although the basal ganglia and cerebellum contribute to the early learning phase once a skill is well-learned the “programs” reside in cerebral cortical networks. It may be that the “motor program” (if it exists!) is found in no one location and includes deep nuclei such as deep cerebellar nuclei, subthalamic nucleus and pedunculopontine nucleus.

STRIATUM: NEURAL CORRELATES OF T-MAZE IMPLICIT (PROCEDURAL) LEARNING

Researchers who have recorded activity within the dorsal striatum (Caudate Nucleus & Putamen) provide evidence that Basal Ganglia (BG) are involved in initial learning (***exploration***) and refinement (***exploitation***) of motor behavior. The striatum and the subthalamic nucleus are in key positions for linking glutamatergic cortical drive with nigrostriatal Dopaminergic (DOPA) modulatory (reward) influences from Dopamine cells in the Substantia Nigra (SNc). Output from GABAergic striatal projection neurons provide a major source of input to Globus Pallidus and SNr. The striatum may link sensory, motor, cognitive and reinforcement signals to facilitate motor choices: “ choose the best from the rest.” Striatal cells may alter firing to “lead,” “follow” or “get out of the way” to implement goal directed motor plans.

Firing patterns of task related Striatal neurons appear to be altered as an animal's behavior evolves over different stages of learning. Rats learn to make a choice while running a T maze for a chocolate reward. Open the flash file to do the task. You should be able to figure out the behavior within 4 trials.

Rats take longer to learn this task since: 1. Rats have a different view of the maze and cannot see the location of the reward AND 2. although the striatum represents a proportionally large area of the rat brain, the entire rat brain is about the size of the distal phalanx of your little finger. Watch the virtual task (START TRIAL). Four trials show all options that are possible for this T-Maze task. Actual trial choice is randomized

for ~40 trials per day. Fast learners achieve >75% proficiency within two to three days. Next you will see how striatal neurons alter their firing pattern during different phases of the task and see changes that occur as the animal becomes "over-trained." Interestingly, on average, neither the Task-Responsive nor the Task-Unresponsive cell population shows any difference in mean discharge properties whether a trial was correct or incorrect as might be expected for tactical control. Thus, these striatal cells seem to be interested in the whole strategic plan to reap a reward (goal directed behavior) or progressively "mark" specific time points in the temporal sequence from Start to Finish (see EXPERT Neurons). As learning ensues, many task-responsive neurons become more phasic & restrict firing to specific events along the timeline. Task-unresponsive cells "get out of the way" (their activity is suppressed). Firing becomes more restricted even after performance has peaked: evidence for subtle improvement in brain efficiency with over-learning. Entropy in striatal neuron firing is reduced with learning. Striatal neurons do not seem to be interested in details of altering muscular output as performance improves or selecting the most appropriate muscle synergies to run the maze correctly. Such details may be organized in other brain areas, e.g., the Cerebellum and/or Cerebral Cortical Areas? See T.D. Barnes, et.al., 2005.

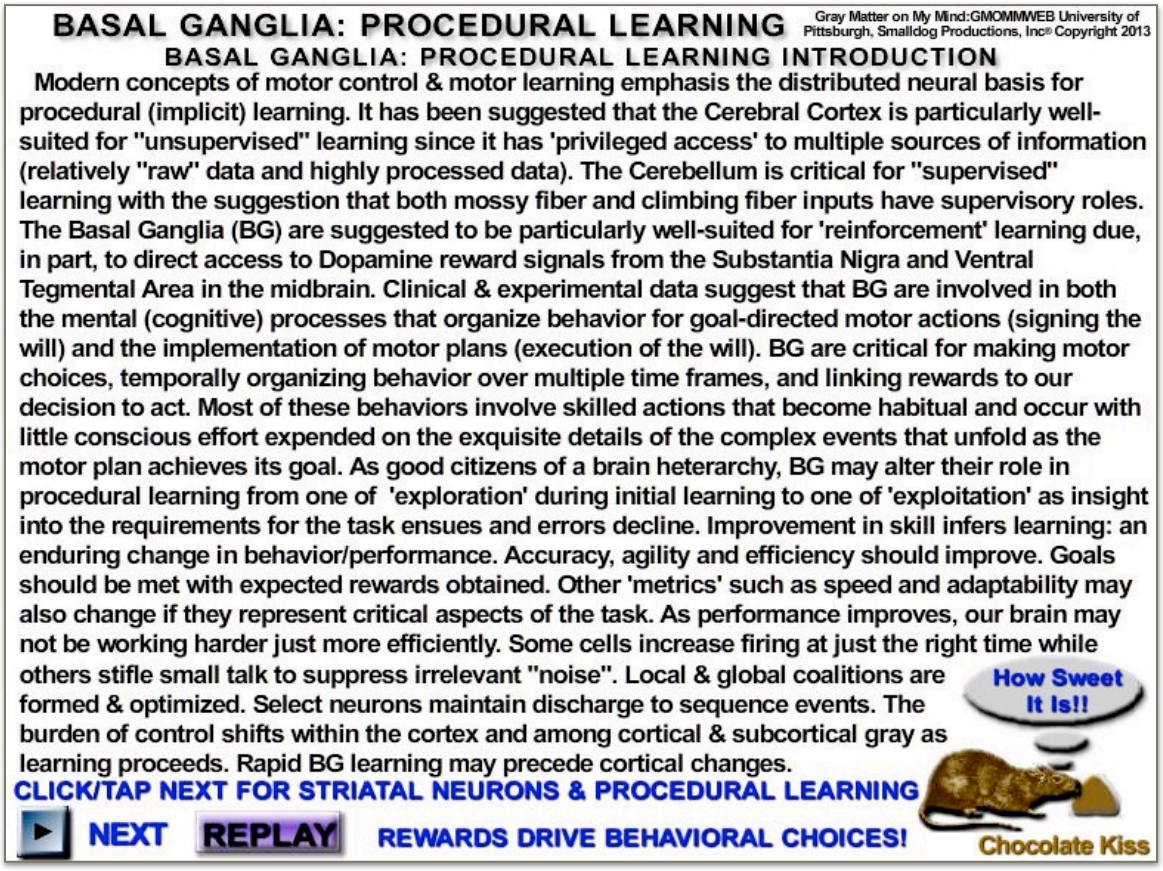

Fig 17-7. Implicit Procedural Learning and Striatal Neuron Activity Interactive Media File. gec). GO TO: gmomm.pitt.edu [Fig17-7_Interactive Media]

IDIOPATHIC PARKINSON'S DISEASE (IPD): DOPAMINE LOSS IN BASAL GANGLIA

1. Parkinson's Disease (PD) is caused by a progressive loss of dopamine (DOPA) neurons in Substantia Nigra pars compacta (SNc). This results in a loss of nigrostriatal DOPA levels and reduced DOPA in the Subthalamic Nucleus. The Motor System appears to be able to partially compensate for DOPA loss until ~50-60% of SNc DOPA neurons are lost and/or ~70-80% reduction in DOPA levels within the striatum (see below). During this early phase of DOPA loss there may be no overt motor signs of PD despite hyperactive SUB, GPi and SNr. Early theories suggested a hypoactive GPe but recent data question this concept. These changes result in excessive inhibition of the pedunculopontine nucleus (PPN) and thalamic neurons and a reduced thalamocortical drive even before clinical deficits are obvious. Thereafter, motor impairments emerge and progressively worsen (over varying time spans) in individuals correctly diagnosed with PD. Motor impairments include lead-pipe (plastic) or cogwheel rigidity, bradykinesia (poverty of movement), gait and postural deficits, resting tremor (& possibly action tremor) and periods of akinesia.

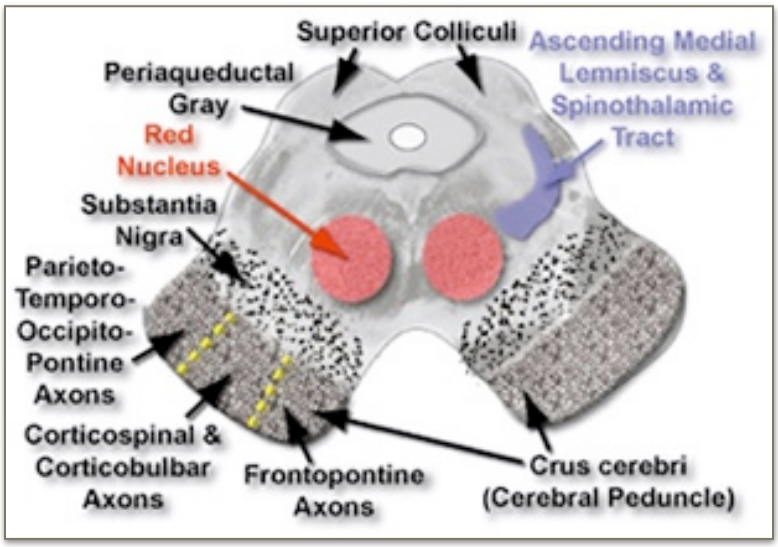

Fig 17-8. Midbrain and Substantia Nigra in Cerebral Peduncles (gec).

2. Drugs containing L-Dopa (precursor of DOPA) have been a major tool for treatment of symptomology. These drugs have no known effect on the course of the disease. Recent medical management protocols use other pharmaceutical agents including various DOPA agonists, time-released L-Dopa, and non-DOPA target drugs. Early use of L-Dopa may promote increased incidence of dyskinesia as tolerance builds and increasing drug dosage is required. All have side-effects.

3. There is an intense interest in DOPA agonists & neurotrophins that may be therapeutic in PD. Some D2 agonists are used early before L-DOPA is begun or in conjunction with L-DOPA in later stages of the disease. There is great interest in biochemicals that may be neuroprotective for this and other progressive degenerative CNS pathologies.

4. Most striatal neurons are GABAergic. The striatum contains fewer Cholinergic interneurons that modulate the many GABA neurons and are influenced by DOPA

and Glutamate inputs. The role of these ACh neurons in striatal function is poorly understood. Some PD drugs target these ACh neurons. The striatum appears to be a virtual “alphabet soup” of neurotransmitters that are part of a biochemical laboratory within the matrix & striosome compartments of the striatum. Chemical imbalances and inappropriate chemical reactions lead to devastating clinical consequences when the normal buffering systems fail.

5. Early theories attempted to explain why clinical signs of Parkinson’s Disease are not evident until ~80-90% of DOPA is lost in the Putamen. It was suggested that compensatory plasticity in DOPA within the nigrostriatal pathway maintains normal function until a critical number of Dopamine neurons die within the Substantia Nigra (signs of PD become apparent only after 50-60% of Dopaminergic neurons are lost in the Substantia Nigra, pars compacta. DOPA efficacy is thought to be up-regulated and/or there are compensatory changes in the DOPA receptors.

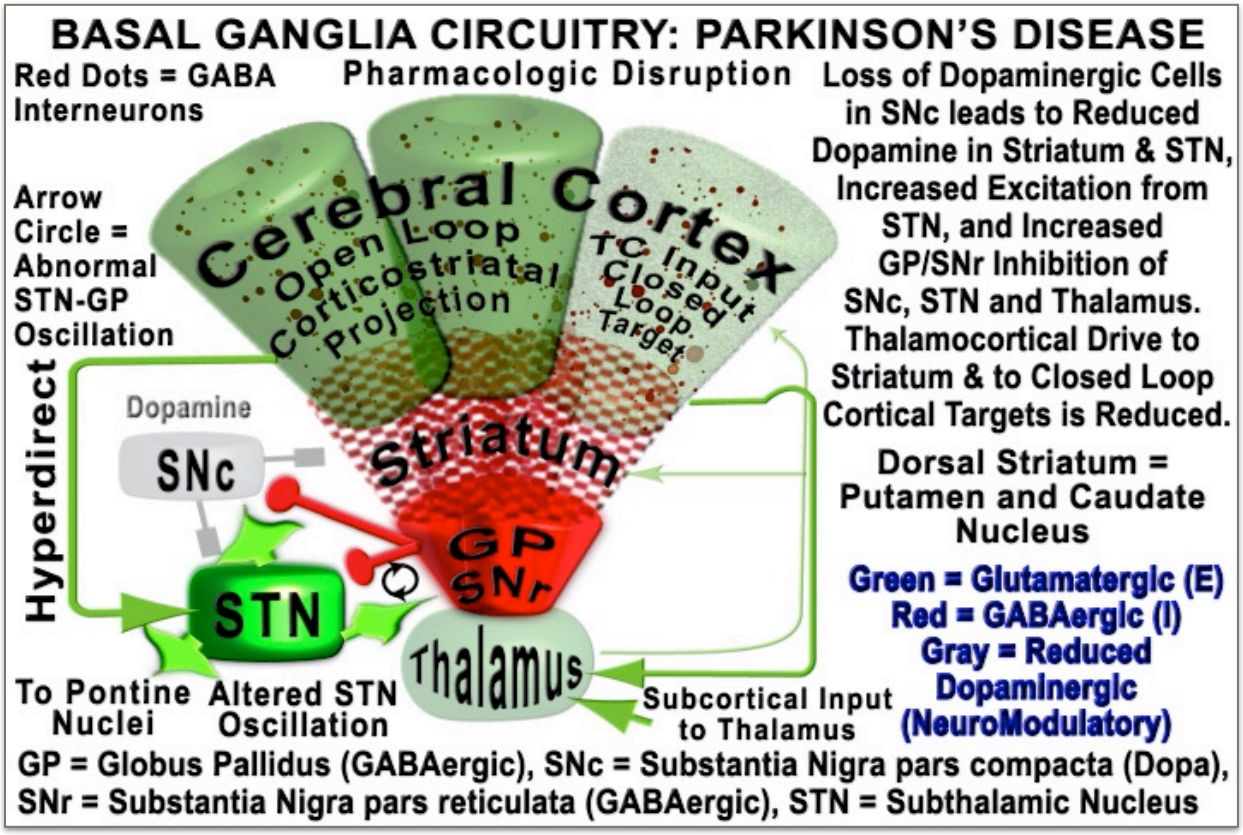

Fig 17-9. Effects of Dopamine Loss Producing BG Circuit Imbalance. Compare to Intact BG Circuit in figures above. Note increased STN excitatory drive and most significantly excessive inhibition of the thalamus resulting in reduced thalamocortical drive to closed loop cerebral cortical targets in BG circuitry (gec).

6. Recent studies question the role of DOPA compensation as a complete explanation for preclinical maintenance of motor function in Parkinson’s Disease.

Other motor circuitry within a distributed motor system may contribute to this compensation. These compensatory changes may be due in part, to changes in STN function due to a loss of DOPA as a regulatory neurotransmitter in the STN and/or changes in motor circuitry extrinsic to the basal ganglia. Corticocortical circuits may adapt to reduced thalamocortical drive and the cerebrocerebellar loop may take up the slack for an impoverished basal ganglia loop. When compensatory mechanisms fail, impoverished thalamic drive can no longer sustain SMA activity. When compensatory mechanisms fail Parkinson's symptoms become quite apparent to the clinician and the patient. Pharmacologic Intervention often attenuates these signs and symptoms early in PD. Increasing drug doses later in the disease process may induce idiopathic side effects and effectiveness of the pharmacologic intervention wanes. Play the Dopamine and SMA Movie.

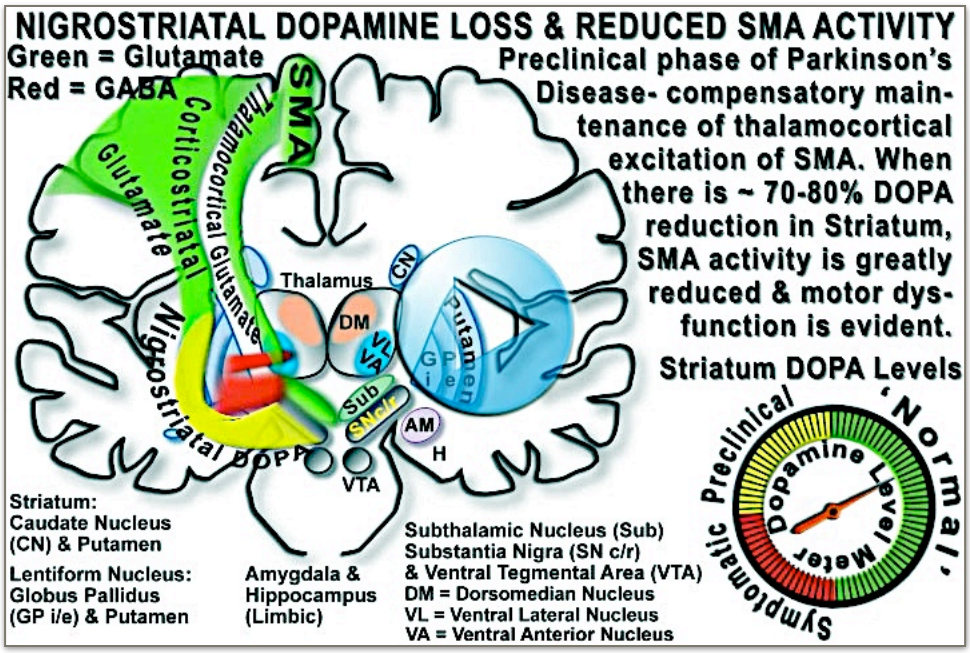

Fig 17-10. Dopamine and SMA Movie: Dopamine Reduction in Parkinson's Disease related to Motor Dysfunction and Reduction in Activity within the Supplementary Motor Area (SMA). The actual compensatory mechanisms are incompletely understood and are surely to be more complex and interactive than shown here (gec). GO TO: gmomm.pitt.edu [Fig17-10_Video]

PD CARDINAL SIGNS: RESTING TREMOR, RIGIDITY, AND POVERTY OF MOVEMENT (BRADYKINESIA, AKINESIA)

Tremor is a sign of instability in motor control loops within the nervous system. Physiological tremor is present in virtually all our actions and tends to be invisible to the naked eye except in some individuals whose tremor becomes visible when the system becomes overloaded, e.g., when anxious, or fatigued.

These non pathological tremors may be found in a variety of muscles with a frequency of ~8-12 Hertz (Hz), although distal muscles may tremor at an even higher

rate. Pathological tremors are seen in certain CNS lesions. There are a variety of tremors described by neurologists some of which are found almost exclusively in certain disease states. A resting (postural) tremor is one of the hallmarks of Parkinson's Disease (PD). The tremor exists when the body part is “at rest” but disappears or is greatly attenuated when movement begins. Resting tremor is a low frequency (~4-5 Hz) alternating activation of agonist and antagonist muscles. Motor units tend to fire synchronously, rather than being activated with the typical staggered, asynchronous recruitment order.

Fig 17-11. Resting Tremor and Bradykinesia in Parkinson’s Disease Movie (gec). GO TO: gmomm.pitt.edu *Fig17-11_Video*

Resting tremor disappears when the person is totally recumbent and relaxed or sleeping. An Action Tremor may be seen in later stages of PD. The resting tremor and bradykinesia or akinesia (poverty of movement) are compounded by a lead-pipe (plastic) or cog-wheeling rigidity.

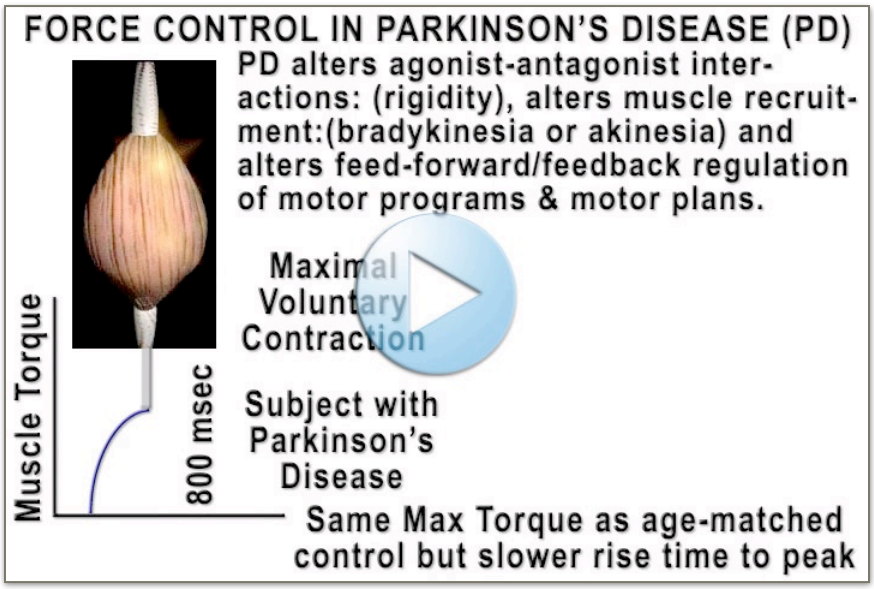

Fig 17-12. Altered Force Control in Parkinson’s Disease Movie. GO TO: gmomm.pitt.edu
Fig17-12_Video

Individuals with Parkinson’s Disease tend to move slowly (bradykinesia). The level of force production by many PD patients is often comparable to aged-matched controls. However, force curves show that movement time is increased for PD subjects compared to force curves for elderly control subjects. Rise and fall times to and from peak torque are slower than normal (see movie below). Part of this slowing may be due to a motor control problem regarding altered motor unit recruitment and part may be due to the increased stiffness (rigidity) characteristic of PD. Reaction times are slow in many but certainly not all PD subjects. Compared to age-matched subjects, many individuals who have PD have increased difficulty in motor

control when neural resources must be shared while attempting to simultaneously do two different tasks (dual tasking).

BASAL GANGLIA DOPAMINERGIC-DEPENDENT OSCILLATIONS

Coherent oscillations within portions of the motor system may provide one mechanism to "sign the will" in volitional motor activity. SMA neurons may be bound by gamma frequency (30-70+ Hz) coincident firing during motor set prior to movement onset in visuomotor tasks. Motor learning (skill) may enhance brain rhythms (gamma oscillations) important in higher brain functions (cognition, perception & volition). Recent data from subjects with Parkinson's Disease who are undergoing implantation of deep brain electrodes for treatment of motor deficits (deep brain stimulation or DBS) suggest that the subthalamic nucleus and the internal portion of the globus pallidus may have temporally coherent activation patterns when the individual is ON medication (L-Dopa) that are missing or much attenuated when OFF medication.

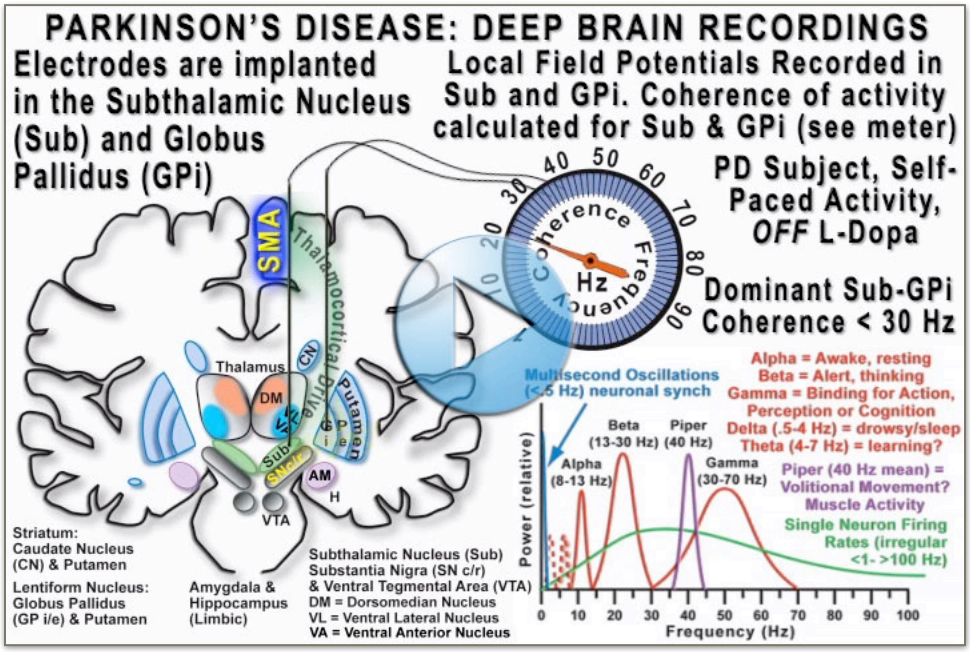

Fig 17-13. Deep Brain Basal Ganglia Recordings in Parkinson Subjects Movie (gec). GO TO: gmomm.pitt.edu Fig17-13 Video

These ON medication oscillations have a strong coherence at frequencies between ~70-80 Hz. When OFF medication these fast rhythms are replaced by weaker patterns at frequencies < 30 Hz. Based on these and other studies of individuals with PD plus studies of intact and "Parkinsonian" monkeys, a number of investigators have suggested that a DOPA-dependent activity pattern within the basal ganglia may provide a substrate that energizes thalamocortical drive to motor cortical areas for externally paced or self-paced willed movements. This hypothesis has not yet been fully tested but provides an intriguing glimpse 'behind the scenes' into possible neural mechanisms that support our will to be done: see Deep Brain Basal Ganglia Recordings in Parkinson Subjects Movie.

HUNTINGTON'S DISEASE (HD)

Huntington's Disease (Huntington's Chorea) is a progressive degenerative disease of the forebrain. Significant atrophy of the Caudate Nucleus and the Lentiform Nuclei are associated with characteristic incessant, involuntary choreiform movements. HD is an inherited (autosomal dominant) disease that involves a mutation of chromosome 4. The defect is thought to be responsible for an excitotoxic process associated with an NMDA receptor. Typically, neuronal degeneration begins in the striatum (caudate nucleus and putamen). Over time, degeneration extends to the globus pallidus, portions of the thalamus, and frontal cortex. Dementia and additional motor disorders accompany the chorea in later stages of the disease. There is no cure and various pharmacologic interventions have in some cases reduced some of the motor problems early in the disease but fail to prevent progression of the disease. L-Dopa has been used as a provocative test for suspected subclinical cases of HD and dopamine antagonists have been used therapeutically. Therefore, the same drug, L-Dopa, that helps Parkinson's patients, exacerbates the symptoms in Huntington's Disease. Involuntary Movement Disorders (PD & HD) show how a delicate balance exists in the neurochemistry of the basal ganglia. This balance exists among Glutamate, GABA, ACh, DOPA and a number of neuroactive peptides.

HEMIBALLISM: LESION OF SUBTHALAMIC NUCLEUS

A lesion of the subthalamic nucleus (STN) produces a distinct neurological disorder: hemiballism. The involuntary flinging movements are seen in the contralateral extremities. The disruption of voluntary control is limited to the involved (contralateral) side producing a stark contrast to the normal movements on the uninvolved side. This disorder is usually produced by a stroke involving the deep penetrating branches of the posterior cerebral artery that feed the STN. If you were a skeptic before, this lesion will make you a believer in the concept of lateralization of function in the CNS. Since the STN has such a central position in the basal ganglia circuitry, one might imagine the significant disconnection of motor control circuitry. In addition, the STN is a site that in experimental animal studies shows the capacity to generate or trigger rhythmic activity. It is heavily interconnected with other brainstem centers that produce rhythmic motor output (e.g., locomotion), has a significant cerebral cortical input and projects to the pontine nuclei, the major source of mossy fiber input to the lateral cerebellum.

CONVERGENCE OF SPTH, CEREBELLAR & BASAL GANGLIA INFLUENCES ON THALAMUS

The Spinothalamic Tract (SPTH) is implicated in conducting pain, temperature and some touch information to the brain. SPTH arises from Spinothalamic tract neurons located in the spinal gray. While most of these cells appear to be located in the dorsal horn, some SPTH neurons are residents of the intermediate and even ventral horn gray. SPTH thalamocortical targets are multiple and not restricted to first order thalamic nuclei and primary sensory areas. Both limbic and non-limbic thalamic and cortical areas are

influenced by SPTH. SI, MI, Somatosensory Parietal Opercular Areas (SII, PV), Insula and Anterior Cingulate Areas have SPTH inputs. Some SPTH neurons are influenced by descending corticospinal axons from frontal or parietal Pyramidal Tract Neurons (PTNs). Taken together, SPTH and Corticospinal Tracts use spinal neurons (interneurons, motoneurons and propriospinal neurons) in multiple lamina to wire us for survival and possibly for success.

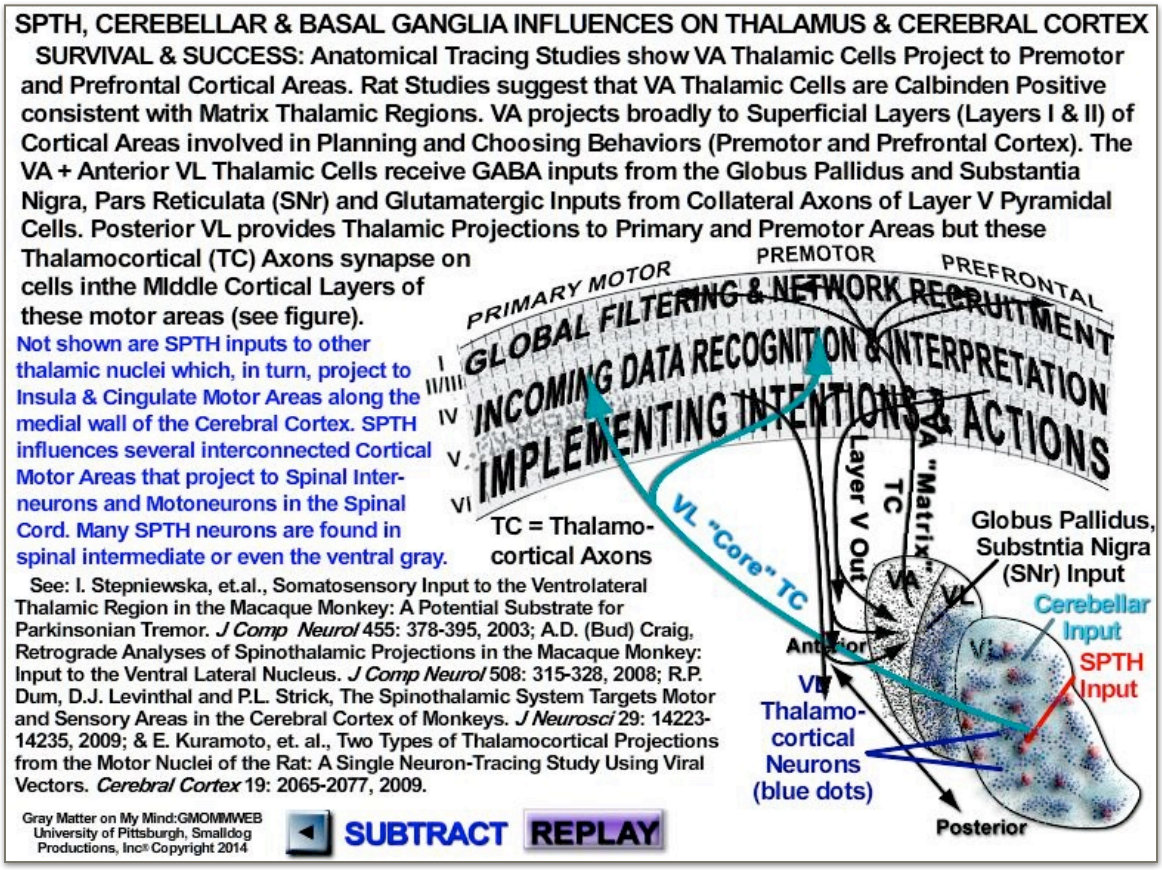

Fig 17-14. Spinothalamic Tract, Cerebellar & Basal Ganglia Projections to Thalamic Nuclei and Cortical Projections Interactive Media file (gec). GO TO: gmomm.pitt.edu
Fig17-14_Interactive Media

These ascending and descending tracts are functionally coupled when we behave as a generic mammal or as a higher primate in particular. Sensory, motor or integrated signals may no longer belong to any one tract or network. These behaviors, while subject to environmental constraints and affordances, have a foundation in our genetic predisposition to wire networks that reproduce a “history” of positive outcomes. Many other gray and white matter structures are involved in these behaviors. The following Interactive Flash file shows ascending inputs to the Ventrolateral (VL) and Ventral Anterior (VA) "motor" thalamic nuclei. These nuclei project to frontal motor and association areas. Differential thalamocortical projections from “Core” Cells in Posterior

VL to Motor, Premotor Cortex and from “Matrix” Cells in VA to Premotor and Prefrontal Cortex is illustrated. Note the competition between excitatory drive due to Layer V Corticofugal pyramidal cell axon collaterals that synapse on VA cells (Layer V Out) and GABAergic inhibitory synaptic influences from the Globus Pallidus and Substantia Nigra (SNr) to the VA nucleus (Globus Pallidus, SNr Input). Other thalamic nuclei and cortical areas associated with the Basal Ganglia, Cerebellar and Spinothalamic Tract are not illustrated in the animation.

BASAL GANGLIA & CEREBELLUM WORK TOGETHER: INTENTION, ACTION & PERCEPTION

Cerebellum (CBM) and Basal Ganglia (BG) provide loop circuitry with both “associative” cortical areas and with traditional “motor” cortical areas.

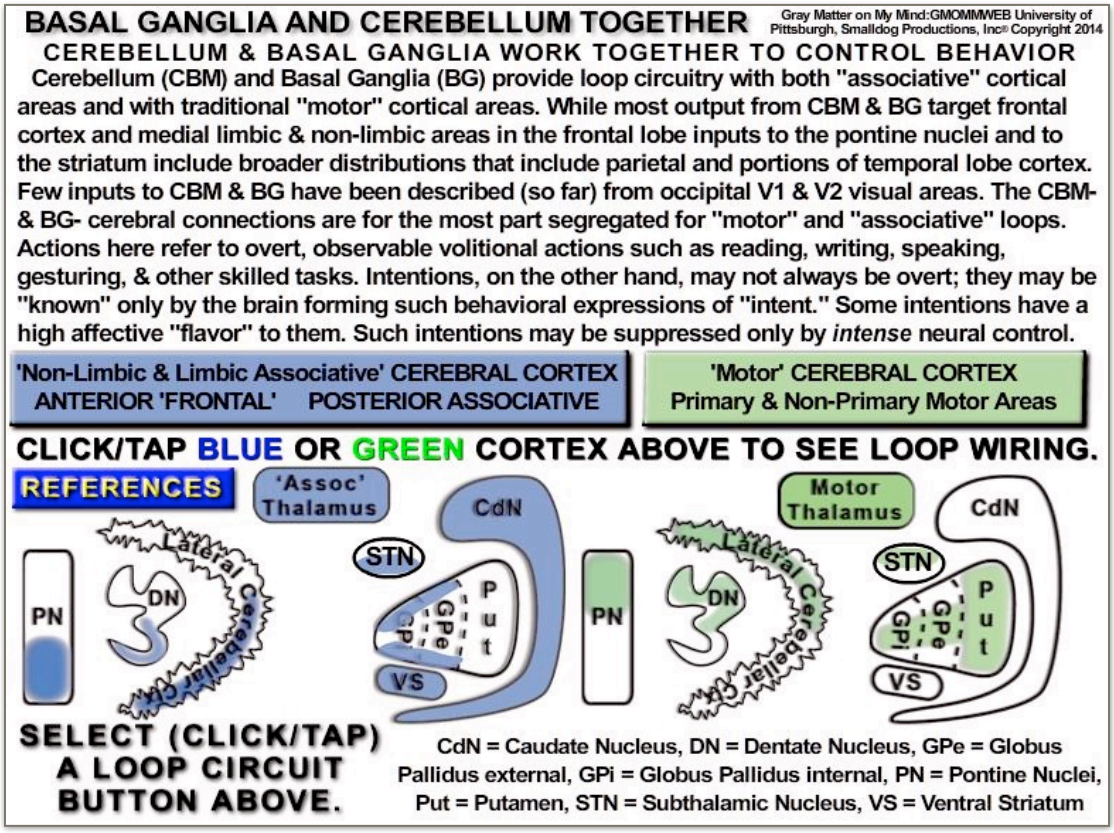

Fig 17-15. Cerebellum and Basal Ganglia work together with Cerebral Cortex to Generate and Control Our Intentions and Actions: Interactive Media File (gec). GO TO: gmomm.pitt.edu *Fig17_15_Interactive Media*

While most output from CBM & BG targets frontal cortex and medial limbic & non-limbic areas in the frontal lobe inputs to the pontine nuclei and to the striatum include broader distributions that include parietal and portions of temporal lobe cortex. Few inputs to CBM & BG have been described (so far) from occipital V1 & V2 visual areas.

Recent anatomical tracing studies have revealed connections between BG & CBM: Subthalamic Nucleus inputs to pontine nuclei and Cerebellar Dentate Nucleus projections to the striatum and pallidum.

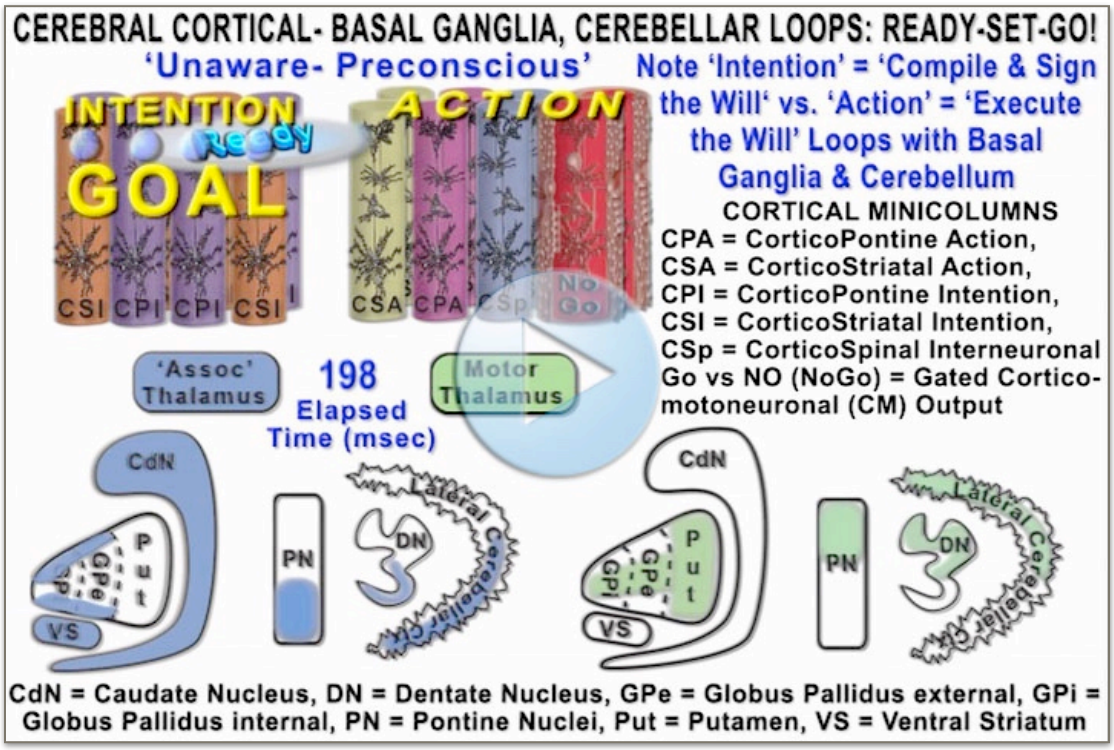

Fig 17-16. Cerebellum and Basal Ganglia work together with Cerebral Cortex to Generate and Control Our Intentions and Actions: Goal-Directed Behavior Movie (gec). GO TO: gmomm.pitt.edu *Fig17-16_Video*

The CBM-cerebral & BG-cerebral connections are for the most part segregated into "motor" and "associative" loops. Actions here refer to overt, observable volitional actions such as reading, writing, speaking, gesturing, & other skilled tasks. Intentions, on the other hand, may not always be overt; they may be known implicitly only by the brain forming such behavioral expressions of "intent." Some intentions have a high affective "limbic flavor" and powerful motivational drive associated with them. Such limbic fueled intentions may be suppressed only by *intense* neural control.

Although the CBM and BG are considered to be side-loops in sensorimotor neural processing their inclusive networks provide optimal perception and action outcomes even though such side-loop contributions are often "hidden" within the depths of a broad integrative functional network. CBM and BG contributions may become self-evident to the subject and the clinician only when there is sufficient pathology to disrupt overt motor and/or cognitive function.

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Chapter 18

MOTOR CORTICAL AREAS AND VOLITION: WILL TO ACTION

> "The circle is a coordination, some of whose members have come into conflict with one another. It is the temporary disintegration and need of reconstitution which occasions, which affords the genesis of, the conscious distinction into sensory stimulus on one side and motor response on the other.…. It is the coordination which unifies that which the reflex arc concept gives us only in disjointed fragments." p. 370
>
> John Dewey, The Reflex Arc Concept in Psychology. *Psychol Rev* 3: 357-370, 1896.

N. Bernstein's circular servo loop hypothesis for adaptive sensorimotor integration was published in the early twentieth century (in Russian) and seems to reflect at least in part Dewey's dissatisfaction with a stimulus-response reflex arc hypothesis. See Bernstein Servo Loop Movie (gec). GO TO: gmomm.pitt.edu Bernstein_Video

WHAT DO WE REALLY KNOW OF OUR OWN THOUGHTS?

To what extent are we consciously aware of our brain's hard work of deep thought? Do we have full conscious control over the amazing cognitive powers of our forebrains? This is a basic question regarding self and self-control. We think of free will as our ability to do, say or think what we want (usually within bounds of societal/moral/legal constraints). What if most of the hard work of thinking, like that for skilled actions, goes on behind the scenes, out of the "reach" of consciousness? Perhaps it becomes available to our conscious brain only when we add sense to the thought. Sense here may be related to activation of receptors for those energies that we recognize in the world around us ("bottom-up") and/or an internal representation of the world ("mind's eye") built upon experience from the "top-down." Maybe it makes no "sense" for the cognitive brain to bother (engage) my consciousness unless I must make some decision that will potentially involve me in the outside world. What if we are unaware of much of what our brain is cogitating for most of our waking hours? After all, I can't read your mind, so what makes me think that I have full-access privileges to all of my own information? Of course there are those individuals who seem to inform you of everything that has happened to them for the past 24 (or more) hours: stream of consciousness? Perhaps there are some brains which "*do not brake*" for inner thoughts that, however fleeting, cross their conscious awareness: self neural events are laid bare for all to hear.

Does this lack of full conscious access to sophisticated neural events that form the essence of oneself strike you as a bit "unnerving"? Does this sound like the raving of a brain whose clutch is not fully engaged? Not really. A number of well-respected neuroscientists are dealing with these very issues of self-consciousness: see references. Invasive single cell recordings in human subjects are not routine measures

for fine-grained study of cognition but global assessments have been done using functional brain imaging (fMRI, PET), electroencephalography (EEG) and other minimally invasive techniques.

VOLITION: WHAT IS IT AND HOW MIGHT WE CONTROL IT?

Do we sense to move, move to sense or does our brain act in a more "loopy" fashion?

Volitional motor control, to be successful, depends upon three elements that together underlie the neural basis for volition. Volition depends upon the human nervous system being: ***1. Complex enough, 2. Sophisticated enough, 3. Confident enough***, to act in a feedforward manner under tolerable environmental conditions. We are actors! Besides feedforward signals, volition uses central & peripheral sources of feedback when available and appropriate. Volition requires reciprocal connectivity within a distributed system (across neural levels and subsystems). It must be engaged fully with the musculoskeletal system. An increasing number of neuroscientists are promoting sophisticated distributed control models for doing one's will. These models suggest that high level control is built upon a consensus by reciprocally connected networks within a heterarchy rather than being dictated by a CEO within a strict serial top-down hierarchy.

Volition-Four Assumptions for normal (or superior) performance:

1. Cognition is within normal range,

2. Our will to do is absolute; we attribute actions to ourselves (agency, ownership, self-control),

3. Action is based on our own timetable (self-imposed),

4. Maximal level of performance is built upon phenotypic expression of our species-specific and individual genetics (without getting into the sticky issue of picking one's parents).

Five Limitations that may impair or cease volition:

1. Cognitive or sensorimotor impairments by birth, or as the result of disease/injury.

2. Our will is half hearted, the goal is not considered to be worth the effort, the reward is unsatisfactory even if the goal is accomplished, our will is partially or fully disconnected from the mechanisms to act due to disease or injury.

3. Time pressures may induce artifacts in performance; pressure for immediate results may limit practice, societal constraints may limit possibilities to perform.

4. The environment in which we must operate may be (or is perceived to be) unpredictable and/or hostile to our person; OR our musculoskeletal, respiratory or cardiovascular systems cannot be fully engaged in the effort.

5. Our self-appraisal of ability may be handicapped by internally generated or externally imposed limitations to expressions of “free” will, and/or perception of self-worth. *(debate encouraged) GEC 2002, 2008, 2011, 2013 ©*

MOTOR CORTEX CODING FOR TASKS REQUIRING PRECISE FORCE/POSITION CONTROL

E.V. Evarts (1968) first showed a strong relationship between motor cortex neuron firing and force production by the contralateral hand. From these initial electrophysiological studies of the motor cortex where neuronal discharge was related to EMG of target muscles there has been a question regarding the actual coding done by single cells in the motor cortex as related to target muscle activity. Motor cortex neurons may have phasic, tonic or phasic-tonic discharge profiles when different types of movements are made. Some of these neurons are layer V Pyramidal Tract Neurons (PTNs). PTNs are identified by antidromically activating the recorded neuron due to electrical pulse stimulation of axons in the medullary pyramid. Some of these PTNs have been further sub-classified as Corticomotoneuronal (CM) PTNs. Cortical CM cells have direct monosynaptic excitatory connections onto ventral horn Alpha and Gamma Motoneurons (MNs). Higher primates, including humans, have abundant CM PTNs while sub-primate species appear to have sparse or no CM cells in their motor cortices.

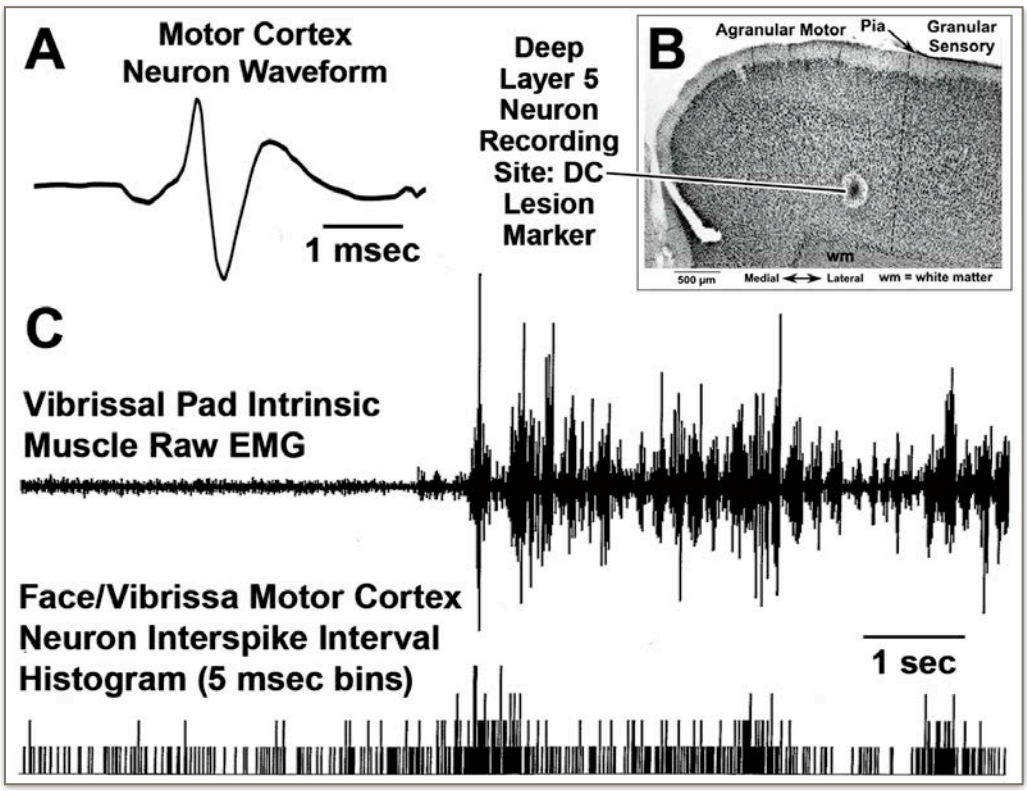


Fig 18-1. Rat Face/Vibrissa Motor Cortex. Layer V Single Cell Firing Rate Related to Overall Level of Intrinsic Vibrissal Pad EMG Muscle Activity: Active Whisking: Rat Whisking In Air (unpublished data, see also Carvell, Miller and Simons, 1996).

The motor cortex and layer V task-related PTNs in particular appear to be capable of contributing

to a precise recruitment of MNs according to the requirement of the task at hand. These upper extremity tasks in primates may require both precise force control for fractionated finger motions as well as discrete control of other muscles and joints to allow for the fingers to be positioned to implement the task. This suggests that not only force but other kinematic properties must be controlled by an ensemble of interconnected neurons within the motor system. Different CM cell assemblies (cell colonies) may be recruited according to the functional requirements of a task including, but not limited to, control of force kinematics across multijoint segments of a limb, e.g., see Griffin, Hoffman and Strick, 2015. Indeed the vast majority of PTNs in multiple cortical areas are not CM cells. These non-CM PTNs have connections with spinal gray neurons in the dorsal horn, intermediate gray and neurons outside of the motor nuclei in the ventral horn (Interneurons), e.g., see Dum and Strick, 1996.

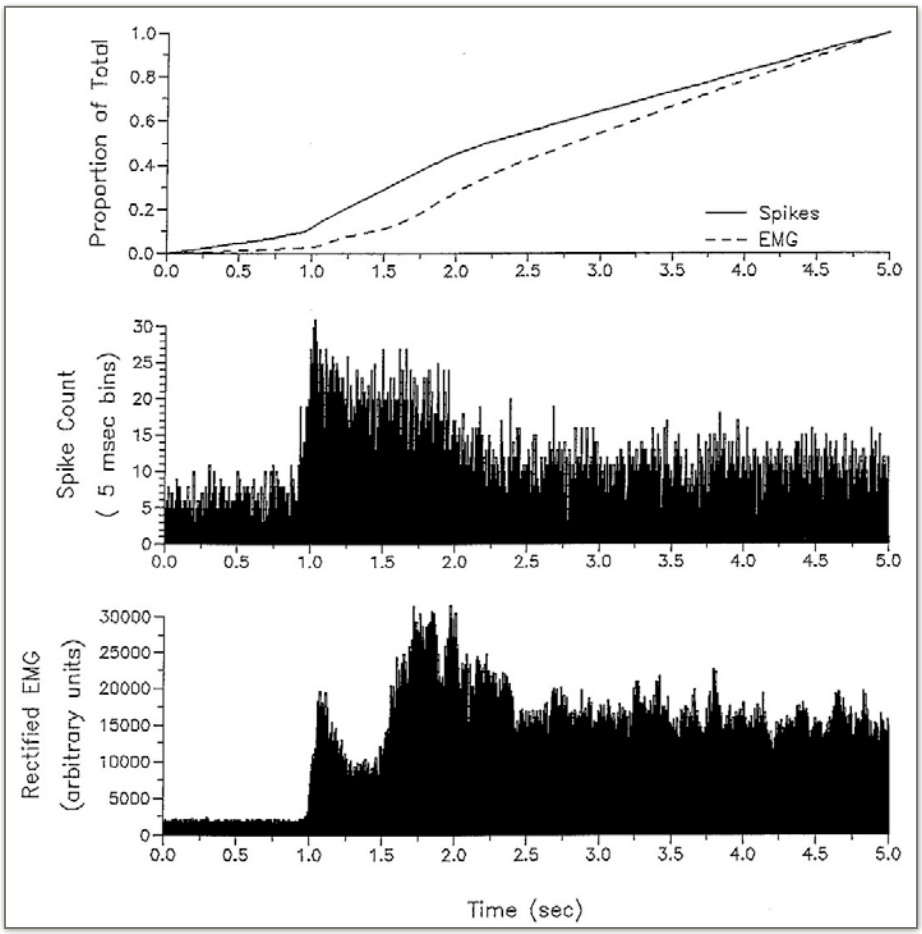


Fig 18-2. Cumulative Histogram of Motor Cortex Single Cell Spiking Related to Cumulative Histogram of Rectified EMG Motor Output: Note Increase in Motor Cortex Spiking Prior to EMG Onset Aligned to 1 sec time mark: Rat Whisking In Air (unpublished data, see also Carvell, Miller and Simons, 1996).

One example of a motor cortex which has sparse and weak CM projections to MNs is the face/vibrissa area of the rat motor cortex. Despite a paucity of direct monosynaptic access to facial nucleus MNs by projection neurons in layer V of the face/vibrissa motor cortex they have an impact on the rat's ability to control active whisking behavior. These motor cortical neurons do not appear to generate the rhythm of whisking since whisking continues even when the face/vibrissa motor cortex is removed.

The face/vibrissa motor cortex neurons do appear to have a role in initiating a whisking bout and motor cortical neuron firing is related to the overall level of intrinsic mystacial pad muscle activity over many whisks as measured by fine-wire electrode EMG. These neurons have a phasic-tonic or tonic discharge profile. Like primate PTNs, neurons in the rat face/vibrissa motor area increase their discharge prior to the onset of muscle activity. The timing of the increase in neuron discharge firing is not related to the conduction delay between cortex and MNs since conduction delay should be less than 10 msec for this pathway while the neuron discharge rate increases many 10s to 100s of msec prior to EMG onset. This suggests that like in primates, the rat motor cortex participates in the preparation for, as well as facilitation of, the motor task: see figures and Carvell, Miller and Simons, 1996.

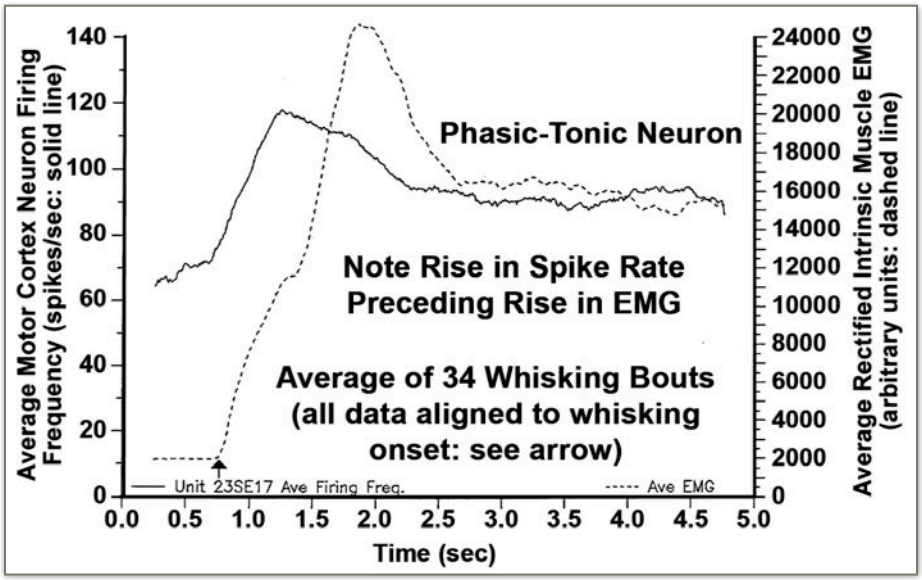


Fig 18-3. Averaged Face/Vibrissa Motor Cortex Cell Spiking (solid line) Related to Averaged Rectified Intrinsic Mystacial Pad Muscle Rectified EMG for 34 Whisking Bouts Spiking and Whisking Bout Onset for all trials are aligned (see arrow). Note Increase in Motor Cortex Firing Rate Prior to EMG Onset: Rat Whisking In Air (unpublished data, see also Carvell, Miller and Simons, 1996).

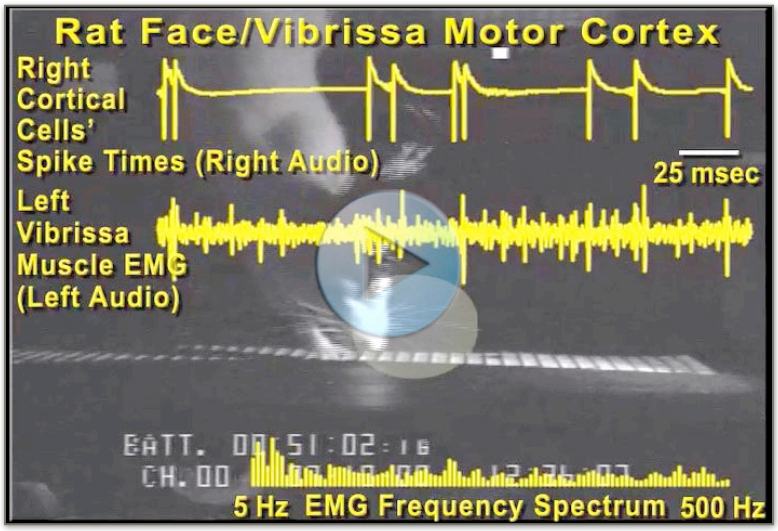


Fig 18-4. Rat Face/Vibrissa Motor Cortex Neuron Spiking Related to Raw Intrinsic Muscle EMG Movie (gec: (unpublished data, see also Carvell, Miller and Simons, 1996). GO TO: gmomm.pitt.edu

Fig18-4_Video

DO SIGNALS FOR VOLITION ORIGINATE IN THE MOTOR CORTEX?

Some neuroscience texts treat

the motor cortex as the origin of voluntary commands that are directly sent to spinal motoneurons that, in turn, directly engage the musculature via alpha motor axons innervating skeletal extrafusal muscle fibers organized as motor units; this is the upper motor neuron (UMN) to lower motor neuron (LMN) to motor unit (MU) simple view of motor control (see below). This model would suggest that the motor cortex acts as a motor controller (a muscle app in your head). While this view is an easy motor control model to teach and remember it does not account for the complexity of motor cortical neuronal properties nor does it give credit to the other neural structures that are integrated into a distributed system for motor control, for recent review see Omrani, et.al., 2017.

One need only read a classic series of experiments published by W. T. Thach in 1978 (see Thach, 1978) to question any straightforward MI Cortical UMN to Spinal LMN to peripheral MU sequence of events.

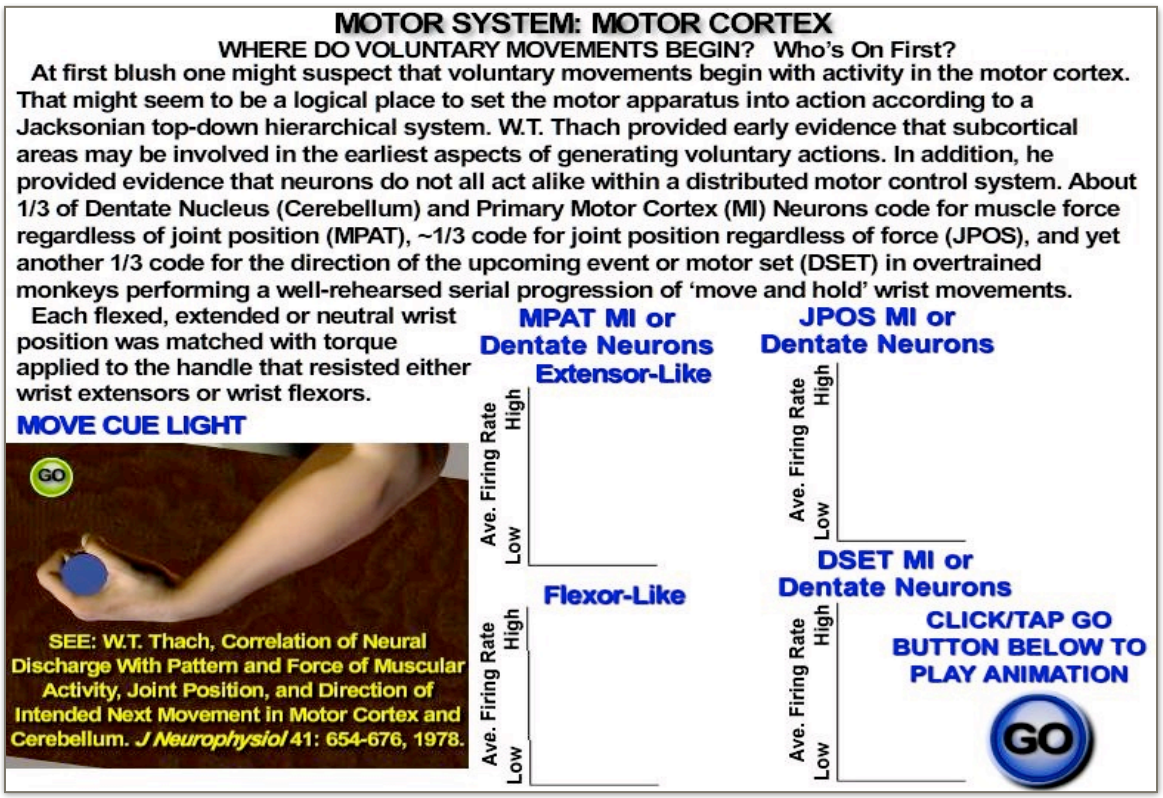


Fig 18-5. MPAT, JPOS, DSET MI & Dentate Nucleus (Lateral Cerebellar Deep Nucleus) Neurons: Distributed Intention, Action Control Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig18-5_Interactive Media]

W.T. Thach provided early evidence that subcortical areas are involved in the earliest aspects of generating voluntary actions. Many cerebellar dentate nucleus neurons (cerebrocerebellum) discharged as early as or possibly earlier than motor

cortex neurons before movement began. By contrast, most interposed nuclei neurons (spinocerebellum) discharged later as the movement unfolded (as measured by the timing of EMG activity of flexors and extensors). In addition, Thach provided evidence that neurons do not all act alike within a distributed motor control system. Within motor cortex and dentate nucleus about 1/3 of the neurons code for muscle force regardless of joint position (MPAT), ~1/3 code for joint position regardless of what muscles are generating force (JPOS), and yet another 1/3 code for the direction of the upcoming event or directional motor set (DSET) in *overtrained* monkeys performing a very well rehearsed serial progression of "move and hold" movements. Each flexed, extended or neutral wrist position was matched with torque applied to the handle that resisted either wrist extensors or wrist flexors. Such discharge properties do not support the idea that motor cortex acts as the sole point for initiation of volitional actions nor as simply the location of the upper motor neuron "muscle in the head."

DISTRIBUTED MOTOR CONTROL: REACHING HETERARCHY - MOTOR & NON-MOTOR CORTICAL AREAS

Many cortical areas participate in the control of reaching movements. The Timing of Cerebral Cortical Areas-Heterarchical Control Interactive Flash file animation shown here does not include visual areas involved in a visually guided reaching task.

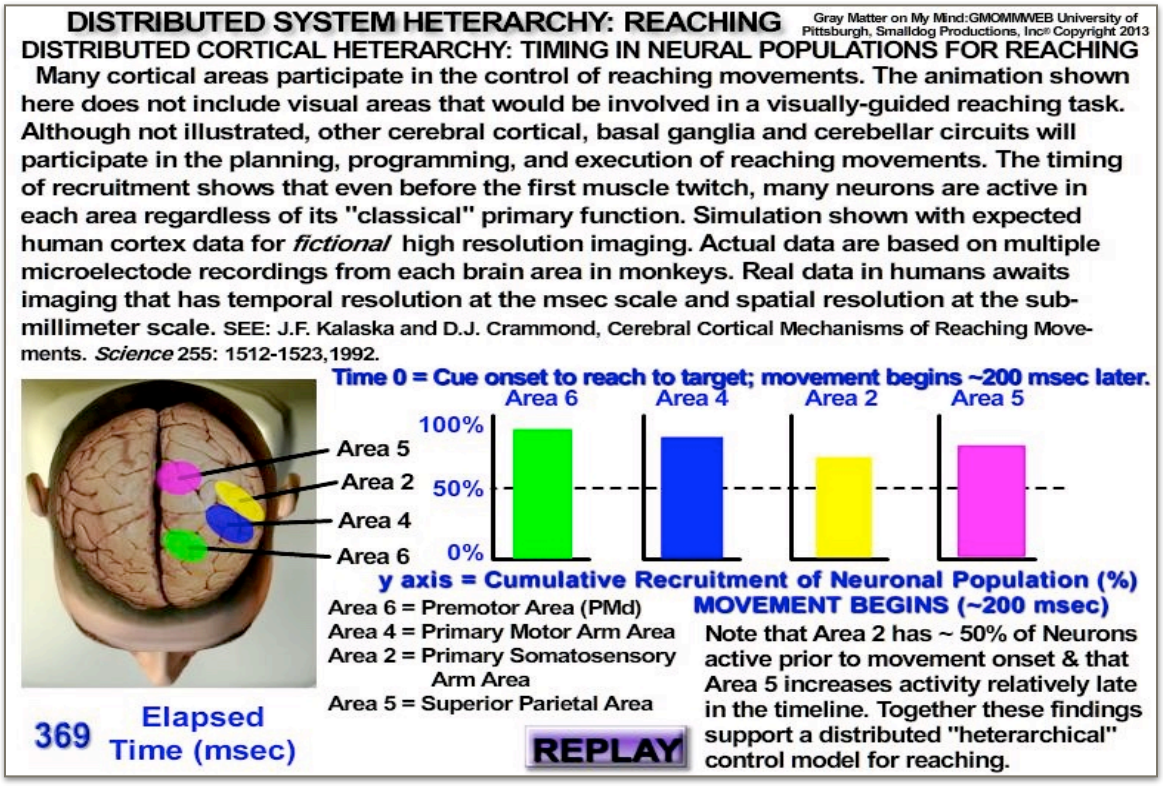


Fig 18-6. Timing of Cerebral Cortical Areas-Heterarchical Control Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig18-6 Interactive Media]

Although not illustrated, other cerebral cortical, basal ganglia and cerebellar circuits will participate in the planning, programming, and execution of reaching movements. The timing of recruitment shows that even before the first muscle twitch, many neurons are active in each area regardless of its "classical" primary function. Simulation shown with expected human cortex data for fictional high resolution imaging. Actual data are based on multiple microelectrode recordings from each brain area in monkeys. Real data in humans awaits imaging that has temporal resolution at the msec scale and spatial resolution at the sub-millimeter scale. Note that Area 2 has ~50% of Neurons active *before* movement onset and Area 5 increases activity relatively late in the timeline. Together these findings support a distributed "heterarchical" control model for reaching and other volitional actions, e.g., see: Kalaska & Crammond, 1992; Cisek & Kalaska, 2010.

REACH AND GRASP GO HAND-IN-HAND; HAND APERTURE CONTROLLED AS YOU REACH FOR AN OBJECT

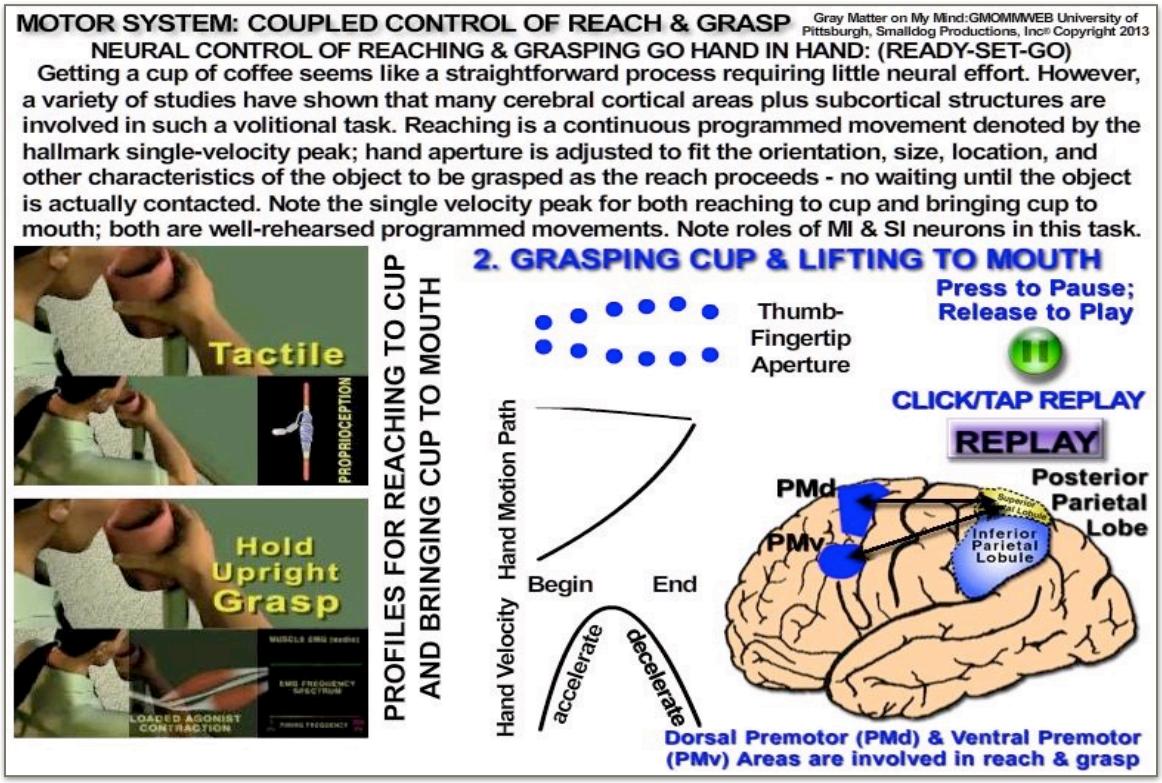


Fig 18-7. Neural Control of Reaching and Grasp-ing Go Hand-In Hand: Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig17-7_Interactive Media]

Getting a cup of coffee seems like a straightforward process requiring little neural effort. However, a variety of studies have shown that many cerebral cortical areas plus subcortical structures are involved in such a volitional task. Reaching is a continuous

programmed movement denoted by the hallmark single-velocity peak; hand aperture is adjusted to fit the orientation, size, location, and other characteristics of the object to be grasped as the reach proceeds-no waiting until fingers contact the object. Note the single velocity peak for both reaching to cup and bringing cup to mouth; both are well-rehearsed programmed movements. Note roles of Portions of the Posterior Parietal, Premotor Cortical Areas, Primary Motor Cortex (MI) & Primary Somatosensory Cortex (SI) neurons in this task simulated in the Interactive Reach Grasp Animate Flash File.

READINESS POTENTIAL: READY TO GO BEFORE YOU KNOW

Cognition infers thought. Thought requires gray matter on your mind. While most individuals consider reasoning as the highest level of function for the human brain, we may not have full conscious access to neural processes responsible for decisions that we make. Our brain may be engaged to do our will before we know what is happening. Some high level decisions are made in a split second and out of reach of conscious "control." Other decisions require a well-choreographed dance of limbic and non-limbic gray that shape our behaviors over a lifetime. When these partners move together, the beauty and grace of human beings is apparent. *When they are out of step, things can get ugly*.

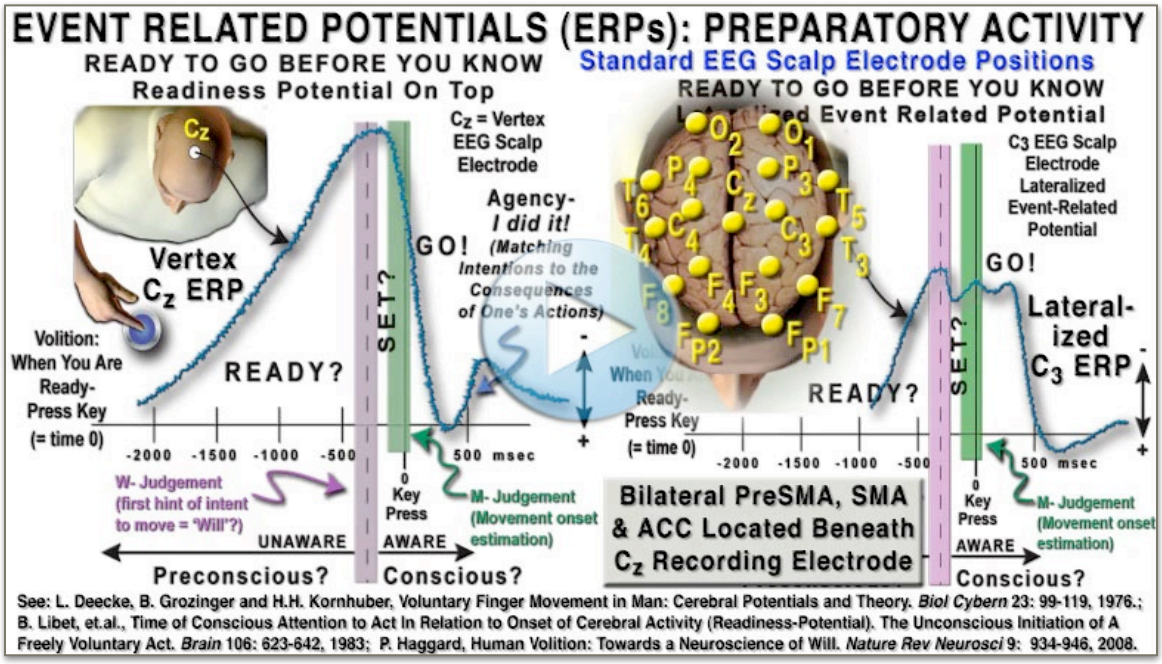


Fig 18-8. Readiness Potential: Your Brain- Ready to Go Before You Know (gec). GO TO: gmomm.pitt.edu [Fig18-8_Video]

The Readiness Potential (RP) is an event-related field potential recorded with EEG electrodes. RP begins long before the onset of a self-initiated volitional movement (NOT

S-R REACTION TIME). RP is thought to represent brain activity from a population of many cells within the cerebral cortex deep to the C_z electrode at the vertex of the skull (see figure). RP is said to be a neural representation of the “mental” recruitment of one's “will” to move. RP in normal subjects reveals significant brain activity before we are consciously aware of our intent to move (see W-Judgement Onset). Cortical lesions may profoundly alter the brain's preparation for action. For example, posterior parietal cortex lesions may significantly shorten the duration of the preconscious ready signal so a person's RP begins temporally close to the “set” period of awareness. Thus, the brain may have only a limited opportunity to abort a “willed” action if the situation changes and the action must be called off. Other studies have shown that the medial hemisphere including the Supplementary Motor Area (SMA proper), preSMA, and Anterior Cingulate Cortex is associated with an “urge to move.” This urge in some individuals where these areas were stimulated may have a sense of agency. This correlates with the RP recording site, the EEG C_z electrode location at the vertex of the skull. A recent study where single neurons were recorded during the RP protocol in human subjects shows increased activity in a portion of task-related cells in the SMA while other cells have a decreased firing during the RP period of many hundreds of milliseconds prior to the “W” judgement. Fewer such neurons are found in the ACC (see Fried, et.al., 2011). Correlating central intentions to one's own actions (agency) appears to require re-afferent data. One individual’s will may be projected onto others by exemplary behavior, coercion or law. History is a time-traveler’s record of such extended will by such individuals and the short-term or long-term consequences of such brain influences.

MESIAL CEREBRAL CORTEX: “HIDDEN” SELF-REFERENTIAL NETWORKS FOR ME TO DO OR DON’T?

Volition assumes a will to do. Intention drives internal goal achievement. Considering one’s wants or needs, the “means to the ends” must be selected while alternative behaviors must be suppressed. Reward expectation for one’s actions drives one’s intention. Rare reward opportunities may drive complex, sophisticated, novel (non-routine) behaviors leading to outstanding achievement: success. This process may begin outside of our conscious awareness: (see “ready” period above) until a few hundred milliseconds prior to action initiation: (see “set” awareness period above).

Ownership of one’s actions (agency) may depend upon an awareness of what is or has happened due to internal “intention” signals and external sensory signals due to our own action. Reward selection beyond one’s basic needs appears to be crucial for a civilized society to prosper.

If indeed we are endowed with the awesome capacity for free will decisions then free will must be tempered by a social and moral compass in a civilized society.

At one extreme rewards may be altruistic (benefit to others) while at the other rewards may be self-centered (me-me-me). Most selected behaviors appear to lead to

outcomes that split the difference although each person may lean one way or the other based upon intention, risk, opportunity and perceived reward value.

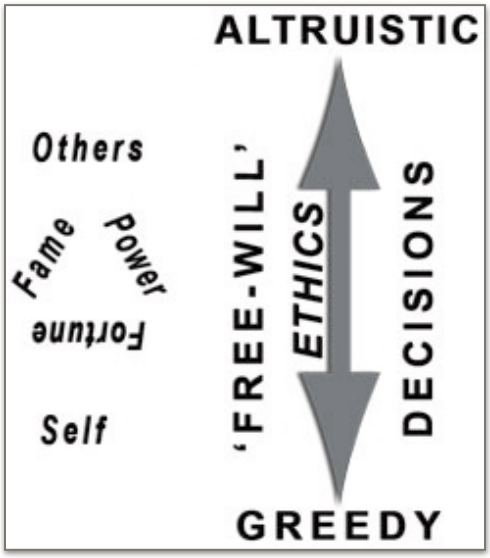


Fig 18-9. Free Will and Human Brain Decisions: What is Your Intent? (gec)

The mesial cortex surrounding the corpus callosum may contain neural networks that in primates together provide the ultimate intelligent control of internally generated, reward-based, novel (non-routine) goal directed behavior. This area of the cerebral cortex includes a major portion of the limbic Anterior Cingulate Cortex (ACC) and the Supplementary Motor Cortex composed of the SMA proper (SMA) and the pre-SMA, see figure). Neuroanatomical, neurophysiological, imaging and lesion studies all suggest a convergence of necessary brain resources as inputs to this mesial cortex and the necessary output from this area to action oriented cortical areas, brainstem and spinal cord to make your decisions look good and be successful. **Mesial frontal areas can be thought of as your "cache cow" to bundle neural codes for complex goal directed actionable sequences associated with high value novel or non-routine behaviors (data mining at its best).** Often output which "looks good" requires learning to gain appropriate insight into those decisions about what to do or not to do, what works and when it should be done. Based on imaging studies, it has been suggested the Precuneus and Posterior Cingulate Cortex are actively involved in generating thoughts which lead to creative, embodied novel behaviors leading to extraordinary rewards when those thoughts are coupled to anterior medial frontal and anterior cingulate areas.

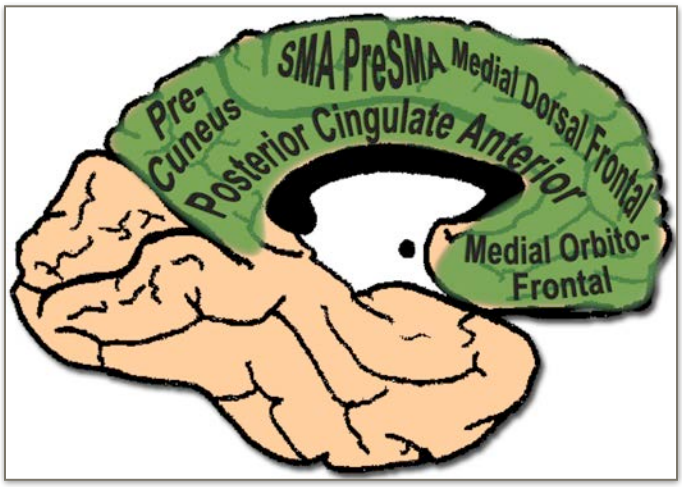


Fig 18-10. Mesial Cerebral Cortex-Self-Referential Creative "Me" to Do or Don't? (gec).

Perhaps you are a shy introverted person who is reluctant to share your self-perceived capabilities with others so you don't. On the other hand you may be a gregarious extrovert who loves to share such self attributes with family and friends (or anyone willing to listen). In either case, have I got a cerebral cortical region for you! The mesial frontal, parietal (precuneus) and cingulate areas are suggested to

be devoted to a self-referenced “me to do or don’t”. This region of the cerebral cortex has been implicated in motor planning; “urges” to do; conflict monitoring; reward-based processing; coupling of attention, motivation & intention to internally-generated action; filtration and selection of optimal performance parameters and error detection/ correction. Such processing is most intense for conflicting behaviors and revision of “subpar” behaviors to optimize transitions from exploration to exploitation. Several subcortical centers appear to be particularly important as part of a distributed network loop; dopamine neurons in the midbrain and basal ganglia loop connections appear to be critical. On one hand, emotions and intentional drive (motivation) may sustain our will to do and succeed. On the other hand, intense limbic overtones add distracting “noise” that may elevate metabolic demands and induce entropy that could reduce the likelihood of achieving the goal. Some level of alertness is required for the brain to function at this high level. The appropriate level of activation appears to follow the “Goldilocks” principle for optimized physiology.

VOLITION: BEYOND THE CEREBRAL CORTEX-BASAL GANGLIA AND DOPAMINE

Recent studies suggest that the Motor Circuit of the Basal Ganglia (BG) is an important source of subcortical drive for the SMA proper and the PreSMA. Experimentally induced Parkinson's Disease (PD) in primates shows that the motor deficits particularly akinesia, hypokinesia, bradykinesia become clinically apparent only after Dopamine (DA) levels are sufficiently reduced to decrease SMA activity levels. DA cells are located in the Substantia Nigra pars compacta (SNc)and the Ventral Tegmental Area (VTA), both of which are located in the midbrain.

It has been suggested that the transition between Preclinical stage of PD and Clinical Signs of Motor Dysfunction is marked by a reduction in SMA activity in Human subjects. Clinical onset of PD does not occur until ~50-60% of DA cells are lost in the SNc. This suggests that both intrinsic circuitry within the BG and external circuitry, including the Cerebellum, provide compensatory mechanisms to maintain function until there is a critical level of DA loss within the striatum

Reduced DA levels in the dorsal striatum results in increased inhibition of Ventral Lateral (VL) nucleus thalamic neurons by pallidal & substantia nigra pars reticulata GABA cells. The VL is an important source of excitatory thalamocortical drive to cortical motor areas including the SMA. Taken together, evidence suggests a high correlation between SMA activity and volitional movement capacity. PD subjects have reduced amplitudes of movement (microphonia, micrographia), slow movement (bradykinesia) and reduced amounts of movement (hypokinesia, akinesia). Such SMA activity levels are fueled in part by adequate DA levels and functional DA receptors in the striatum. Volition is not a unique or restricted property of cerebral cortical networks.

CORTICOBULBAR AND CORTICOSPINAL AREAS TRANSLATE THE EXPRESSION OF OUR WILL INTO ACTION

Virtually all cortical lobes provide corticofugal projections from Layer 5 Pyramidal Cells to Subcortical Brain Structures. These corticofugal projections provide output signals regarding Intentions and Actions. Based on work in monkeys, it is estimated that about 75-80% of all corticofugal axons project to subcortical brain (Non-PTN) and only ~20-25% (PTN) project to spinal structures. Non-PTNs project to subcortical brainstem including centers that give rise to tracts within the Ventromedial Descending Pathway.

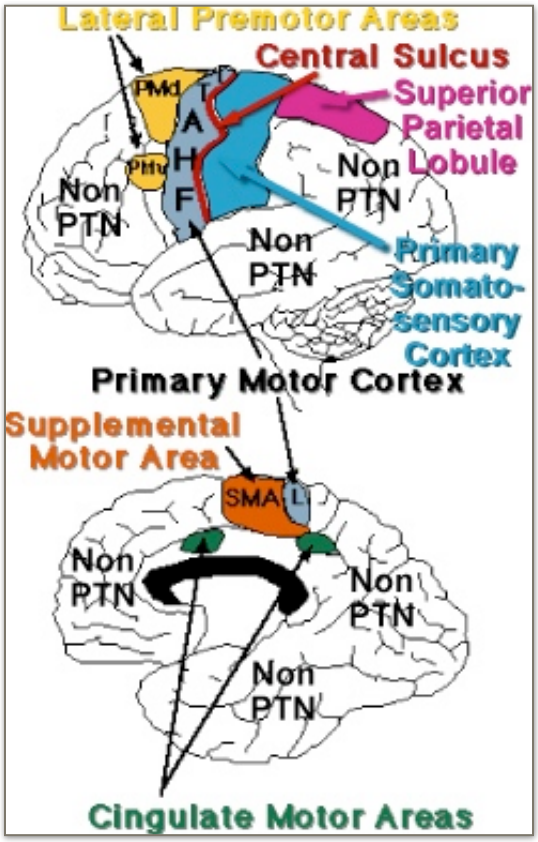


Fig 18-11. Corticofugal Outputs: Non-PTN and Pyramidal Tract (PTN) Cerebral Areas (gec). Dorsolateral & Ventromedial Descending Pathway Interactive Media File

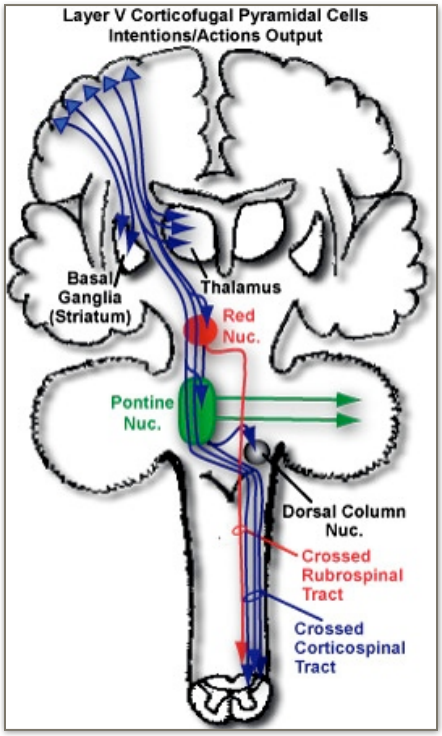
Fig18-11_Interactive Media

PTN refers to Pyramidal Tract Neurons that like their Non-Pyramidal Tract cousins live in layer V of the cerebral cortex. All are pyramidal cells. PTNs are found *ONLY* in the color-filled cortical areas identified in the Corticofugal Outputs figure. The cortical motor areas provide the highest level of control for our volitional motor actions, postures and gestures. These areas do not work alone but network with other cerebral cortical areas, the basal ganglia, the cerebellum, brainstem, and spinal cord. Actual numbers may differ for the human brain.

Lesions of the Cortical Motor Areas can have profound consequences for self-paced and externally-triggered "volitional" movements. It is unlikely that this loss of motor control is due solely to the absence of Pyramidal Tract influences on the spinal cord. Lesions restricted to the Pyramidal Tract produce a lasting deficit in hand dexterity (loss of fractionation of finger movements) but other actions are either not effected or recover at least partially over time. This should not be surprising since 75-80% of corticofugal projections from layer V pyramidal neurons are not destined for the medullary pyramids but for other subcortical brainstem structures.

Loss of Motor Cortex Direct Corticomotoneuronal (CM) connections to distal upper extremity Motoneurons by way of the Pyramidal Tract have the greatest influence on skilled volitional motor control. Therefore, lesions of these cortical motor areas may disconnect important network loops involved in the generation and regulation of movements and postures. All labeled areas except blue are sources of pyramidal tract

axons. Non-PTNs live in the identified areas AND in other cortical areas in all lobes of the cerebrum. *Fig 18-12. Dorsolateral Descending Pathway: Crossed Lateral Corticospinal Tract and Crossed Rubrospinal Tract-Descending Control for Success (gec).*



PTNs contribute axons to the Pyramidal (Corticospinal) Tracts and thus have direct access to spinal neurons that govern sensory input & motor output. Non-PTNs send their axons to synapse on brainstem structures located above and below the tentorium cerebelli. Some of these brainstem nuclei, e.g. Red Nucleus (Rubrospinal Tract) will project descending axons to the spinal cord. Other brain structures, e.g. Thalamus, Striatum, Pontine Nuclei, Dorsal Column Nuclei do not have known projections to the spinal cord.

CORTICAL MOTOR AND NON-MOTOR AREAS THAT CONTAIN PYRAMIDAL TRACT NEURONS

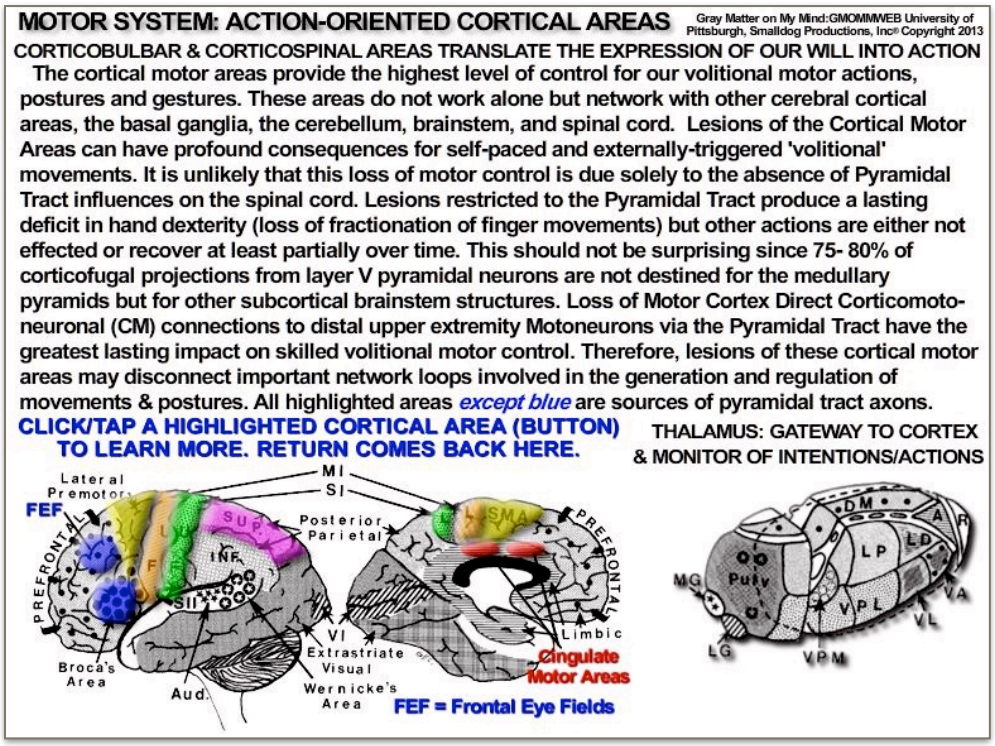


Fig 18-13. The Interactive Media File allows you to explore the multiple cortical areas involved in the generation and regulation of voluntary behaviors (see below). GO TO: gmomm.pitt.edu

Fig 18-13 Interactive Media

PRIMARY MOTOR CORTEX (MI): PRECENTRAL GYRUS BRODMANN AREAS 4, 6

The Primary Motor Cortex (MI) is located in the Precentral Gyrus. MI contains a topographic representation of the contralateral head and body, such that, the head and neck are represented most laterally (towards the lateral sulcus). Just medial to the face is the hand and arm representation, then the trunk, and at the superior aspect, the lower extremity that wraps onto the medial surface in the Paracentral Lobule. The most rostral aspect of the precentral motor cortex is Area 6 caudal. A portion of the exposed surface of MI and all of the precentral gyrus hidden deep within the banks of the Central Sulcus corresponds to Brodmann's Area 4. Pyramidal Tract Neurons (PTNs) in layer V of MI contribute a major projection to the spinal cord (Lateral and Anterior Corticospinal Tracts). These axons descend through the brainstem as the Pyramidal Tract with ~80-90% of the axons crossing in the Pyramidal Decussation in the Medulla to form the Crossed Lateral Corticospinal Tract. The Pyramidal Tract is critically involved in skilled volitional movements especially those requiring fine-hand control (hand dexterity). Compared to all other Cortical Areas that send axons into the LCST, MI has the highest proportion of direct monosynaptic inputs to Motoneurons in the Lateral Motor Nucleus in the Ventral Horn of the Cervical Spinal Cord. The distal limb representation in MI has few if any callosal connections which contributes to a specialized “handedness” in fine motor control of the digits. Not all pyramidal cells project their axon into the pyramidal tract. Most pyramidal cells in layer III have corticocortical or callosal connections, and the majority of layer V pyramidal cells are non-pyramidal tract neurons (non-PTNs). Layer V non-PTNs have corticofugal projections to subcortical brainstem structures.

PARACENTRAL LOBULE: LEG AREA OF MI, SI AND SUPPLEMENTARY MOTOR AREAS PRESMA & SMA PROPER-BRODMANN AREAS 4, 6, 3, 1, 2

The caudal aspect of the Paracentral Lobule contains the Primary Somatosensory (SI, Areas 3,1,2) & Primary Motor (MI, Area 4) representation of the contralateral leg and foot. The Supplemental Motor Area (SMA) is located in the rostral aspect of the Paracentral Lobule (Area 6). The SMA has substantial callosal connections and is typically active bilaterally even with unilateral volitional limb movements. Pyramidal Neurons in layer V of SI, MI, and the SMA send corticofugal axons to the spinal cord (Lateral and/or Anterior Corticospinal Tracts). These axons descend through the brainstem as the Pyramidal Tract with 80-90% of the axons crossing in the Pyramidal Decussation in the Medulla to form the Crossed Lateral Corticospinal Tract. Not all pyramidal cells project their axon into the pyramidal tract. Most pyramidal cells in layer III have corticocortical or callosal connections, and the majority of layer V pyramidal cells are non-pyramidal tract neurons (non-PTNs). Non-PTNs have corticofugal projections to subcortical brainstem structures.

Some scientists who study motor control have suggested that the program represents a motor schema or set of rules to follow. After all, if one is asked to lift their arm up (relative to gravity) the direction will be the same (relative to gravity-up is up) whether you are lying on your side or sitting in a chair, but the muscles engaged will be quite different for the two different postures. You can sign your name large (arm muscles) or small (hand muscles). The SMA is a major cortical target for portions of the Basal Ganglia Circuitry and Cerebellum. The SMA is thought to be a critical area for preparation for upcoming movements; the SMA is often active prior to Primary Motor Cortex in "self-paced" learned activities. Most neurons in the SMA continue to fire as the action continues, i.e., during the execution of the task.

LATERAL PREMOTOR AREAS: DORSAL (PMD) & VENTRAL (PMV)-BRODMANN AREA 6 ROSTRAL

There are two Lateral Premotor Areas: the dorsal Premotor Area (PMd) and the ventral Premotor Area (PMv) that are classified as Area 6 rostral. Like MI these areas have direct projections to the spinal cord by way of the Corticospinal Tracts (Pyramidal Tract). The Supplemental Motor Area (SMA) is found medially in the Paracentral Lobule anterior to the MI leg representation. This corresponds to Area 6 on the medial aspect of the Frontal Lobe. Premotor Cortex and SMA are critically involved in "programming" skilled volitional movements especially those requiring sequential actions from groups of muscles coordinated in synergistic fashion (e.g., reaching, grasping and drinking). A motor program is thought to be a neural representation of the pattern of action not necessarily the specific muscles activated. Some believe the program represents a motor schema or set of rules to follow.

Lateral Premotor & SMA are major cortical targets for portions of the Basal Ganglia, Cerebellum, SI, Posterior Parietal and other "Association" Cortices. These are critical areas in preparation for upcoming movements and are active before Primary Motor Cortex for learned activities. Most neurons continue to fire as the action progresses, i.e., during the execution of the task. SMA and adjacent Cingulate Motor Areas may provide the "urge" to move. Mirror neurons have been identified in lateral premotor cortex (see below).

ANTERIOR CINGULATE CORTEX: CINGULATE MOTOR AREAS-BRODMANN AREAS 24, 31, 32

The Cingulate Gyrus is located in the Medial Frontal and Parietal Lobes. The Cingulate Gyrus is part of the Limbic System and arches from the subcallosal region anterior to the Isthmus posteriorly. The Isthmus of the Cingulate Gyrus is continuous with the Parahippocampal Gyrus on the inferior aspect of the Medial Temporal Lobe. The Cingulate Gyrus is thought to be a major structure involved with those limbic functions which include control of emotions, affect, memory, drives, neuroendocrine and autonomic functions. Through its connections with the Parahippocampal Gyrus, the Hippocampus, and the Amygdala the Cingulate Gyrus provides an important link in

memory processing and transferring of information among limbic and non-limbic cortical areas. Both the Parahippocampal Gyrus and the Cingulate Gyrus receive inputs from "Association" Cortical Areas in the Prefrontal, Posterior Parietal, Occipital, and Temporal Lobes. The Cingulate Gyrus can at once "***bring out the animal in us and help us to be human***." Recently, several Cingulate Motor Areas (CMAs) have been described that have direct projections to the spinal cord Intermediate and Ventral Gray Matter; a direct pathway for limbic influences on segmental motor control mechanisms. "*Attitude adjustment*" and "*get the lead out*" take on a whole new meaning! Cingulate Motor Areas and the Supplemental Motor Areas may be critical areas for the "urge" to move in a goal directed fashion & to link rewards to actions. Some limbic systems have a great (or warped) sense of humor.

PRIMARY SOMATOSENSORY CORTEX (SI): POSTCENTRAL GYRUS-BRODMANN AREAS 3,1,2

The Primary Somatosensory Cortex (SI) is somatotopically organized. The head and face are represented most laterally, then upper extremity, trunk & at the superior aspect, the lower extremity. The leg and foot representations continue onto the medial surface in the Paracentral Lobule. SI (3,1,2) has multiple representations of the same body region across these areas. The Somatosensory Homunculus is distorted, with a Cortical Magnification of those areas that have the densest peripheral afferent innervation (see figure). Area 3 has been subdivided into Area 3a which has a major deep receptor representation (joint, muscle receptors) that is "hidden" within the Central Sulcus. Area 3b (rostral portion of Postcentral Gyrus) receives primarily tactile input from cutaneous and subcutaneous receptors. Thalamocortical (TC) inputs from the ventral posterior thalamic nuclei associated with deep receptors synapse on neurons in Brodmann Areas 2 & 3a of SI and a portion of Area 4 located within the Central Sulcus. Cutaneous TC afferents form the ventral posterior lateral nucleus travel to Areas 3b and 1 of SI. Compared to Brodmann Area 3, Areas 1 and 2 have more complex interactions of thalamocortical and corticocortical inputs. SI provides pyramidal tract connections to the spinal cord to influence dorsal horn, intermediate gray and ventral horn neurons. Recent anatomical tracing evidence in primates suggests that Pyramidal Tract Neurons in Area 3a provide monosynaptic input to gamma motoneurons in the ventral horn.

POSTERIOR PARIETAL CORTEX: SUPERIOR & INFERIOR PARIETAL LOBULES-BRODMANN AREAS 5, 7, 39, 40

The Posterior Parietal Lobe consists of a Superior Parietal Lobule (Areas 5, 7) and an Inferior Parietal Lobule: Supramarginal Gyrus-Area 40 and Angular Gyrus-Area 39. The two lobules are separated by the Intraparietal Sulcus. There are a number of defined subregions around the intraparietal sulcus associated with reach and grasp function. The Posterior Parietal Lobe is thought to be a critical cortical area for representation of our "body image" or "body schema" that is best represented in the Right Hemisphere in most individuals. The Dorsal Visual Stream projects to this lobe.

The Posterior Parietal Lobe provides a four-dimensional spatial reference system (3 spatial dimensions dynamically represented over time) to allow us to relate one body part to another and relate ourselves to the external world. These higher level perceptual processes provide a means to navigate in a changing environment and engage objects in the environment with a high degree of precision. To accomplish this task the Posterior Parietal Lobe must be multimodal; it receives somatosensory, visual, auditory, and vestibular inputs. It has significant connections with the Frontal Lobe, Basal Ganglia, Cerebellum and Limbic Areas.

Pyramidal Tract Neurons in the Superior Parietal Lobule project to the spinal gray. Portions of the Posterior Parietal Cortex and the Lateral Premotor Cortex contain Mirror Neurons that are activated when one watches or performs an eye-hand coordination task. Such task-related neurons allow imitation and imagination (mental imagery) to guide goal-oriented action-perception cycles.

FRONTAL EYE FIELDS AND BROCA'S AREA: CORTICOBULBAR EYE AND SPEECH CONTROL-BRODMANN AREAS 8, 44, 45

An example of a high level "motor" area in humans is Broca's "Motor Speech" Area located in the pars opercularis and pars triangularis of the Inferior Frontal Gyrus of the Language-Dominant Prefrontal Lobe (left hemisphere in most individuals). Broca's Area is thought to be the major area where language is translated into grammatical structure of a phrase and an important site for 'organizing' the articulation of words/phrases.

The Frontal Eye Fields (Area 8, FEF) located rostral to Area 6 in the inferior portion of the Superior Frontal Gyrus and in the Middle Frontal Gyrus is an important area for cortical control of conjugate eye movements (Visual Scanning and tracking of Visual Objects: see movie). The FEF are active from the beginning of a visually guided reaching task. FEF receive inputs from the Posterior Parietal Lobe (the dorsal visual stream target area). Conjugate gaze allows us to move our eyes together to track an object of interest in our visual world. The FEF project to the Paramedian Pontine Reticular Formation (PPRF) in the posterior fossa brainstem. The PPRF is an important brainstem conjugate eye movement control center.

MOTOR CORTEX MAP: WHAT IS REPRESENTED IN THE PRECENTRAL GYRUS

Advanced primates (gyrencephalic monkeys and humans) have well developed finger dexterity and a correlated magnification of cerebral cortical control of hand musculature. Recent studies using neuroanatomical pathway tracing or Intracortical Microstimulation (ICMS) of the Pre- and Post-Central Gyri in monkeys suggest a motor "map" that differs from the standard textbook motor "homunculus." The classic motor homunculus in the precentral gyrus mirrors that of the somatosensory homunculus in the postcentral gyrus (see Motor Homunculus in Precentral Gyrus figure).

Modern studies show an overlapping mosaic map where hand/digit muscles are represented at more than one location and their representation partially overlaps that of more proximal musculature (see flattened map). Recent MI mapping of the arm suggests a “horseshoe” shape where arm musculature (shoulder, elbow wrist) surrounds a distal hand representation, eg., see Hudson, et.al., 2017. Thus, while somatosensory maps may maintain a greater degree of topographic identity e.g., which finger is moving or which finger is touching, motor maps are optimized for control of synergistic muscle groups that may be physically separated, e.g., shoulder muscles and intrinsic hand muscles are structurally separated but functionally linked in reaching for and grasping an object. Such a motor map appears to be devoted to a dynamic function, e.g. reaching & grasping, not to a static body location. Brodmann Areas 3a, 2 and 4r (4 rostral) respond to muscle proprioceptive input. Areas 3b, 1, 2 and 4c respond to cutaneous inputs. Corticomotoneuronal (CM) Pyramidal Cells from Area 4c (4 caudal) target distal muscle Alpha Motoneurons while CM Cells in Area 3a may target companion distal muscle Gamma Motoneurons.

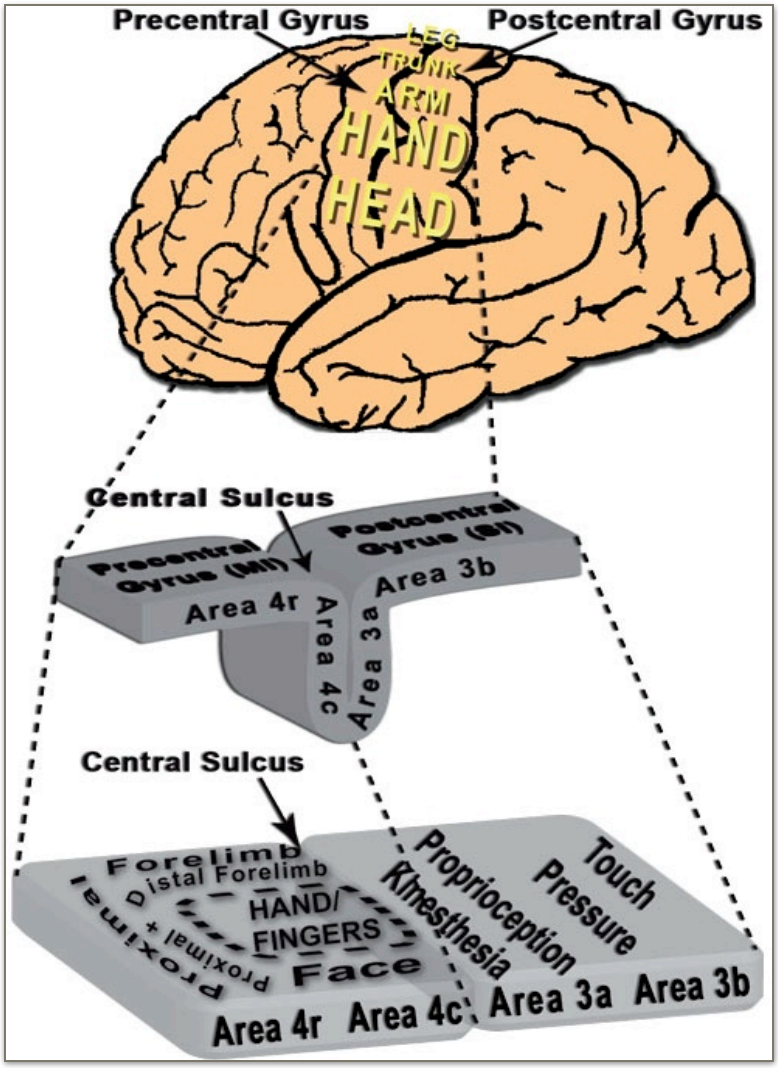


Fig 18-14. Motor Homunculus in Precentral Gyrus-Map by Head/Body Location (gec).

MOTOR MAP: MUSCLES, MOVEMENTS OR MORE?

The motor homunculus of the precentral gyrus generally mirrors the somatosensory homunculus of the postcentral gyrus (see Motor Homunculus figure). Cortical magnification of the Head/Face and hand are obvious distortions in the map as compared to the arm , trunk and leg representations. This extensive digit representation is seen in other subhuman primates but is not obvious in quadrupeds such as the cat. A magnified hand representation is reflected in the ability to fractionate (individuate) digit (finger) motion in adult primates but not in cats.

At one point in the evolution of scientific inquiry regarding motor maps, the job description appeared to be reasonably straightforward. One theory suggests that the motor cortex controls levels of force produced by muscles. A second theory suggests that the motor cortex is not interested in micromanaging muscles but in generating movements. More recent data suggest that neither a “muscle” map nor a “movement” map representation may fully account for the “multitasking” nature of motor areas.

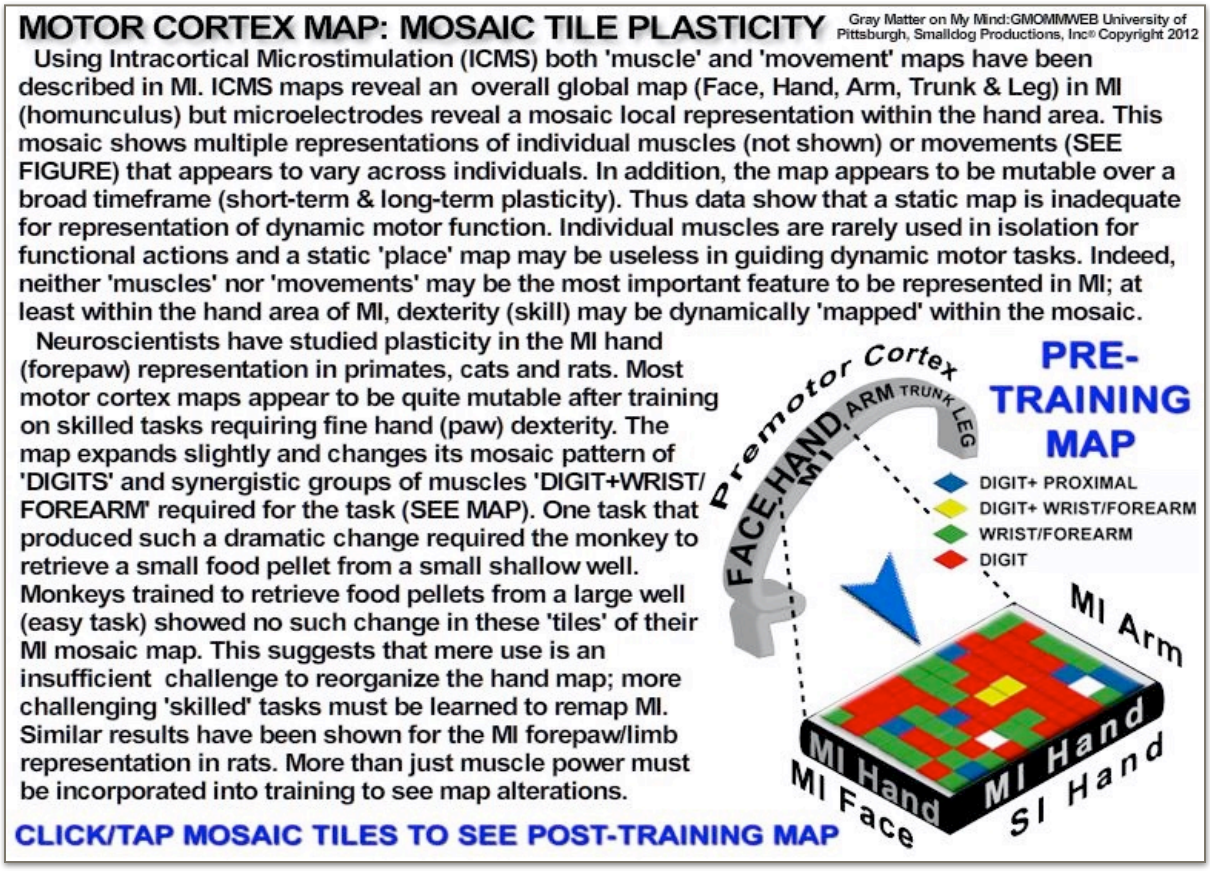


Fig 18-15. Pre-training MI hand map versus post-training MI hand map. Interactive Media file. Note change in MI hand area such that the DIGIT+WRIST/FOREARM (yellow tiles) and DIGIT (hand intrinsic muscles-red tiles) expand their representation after skill training where monkey was required to learn a new pattern of fine finger control to retrieve a food pellet from a small well. Skilled fine finger motor control is not simply an intrinsic hand muscle task (gec). GO TO: gmomm.pitt.edu
Fig18-15_Interactive Media

There are multiple defined cortical motor areas. There are two Lateral Premotor Areas: the dorsal Premotor Area (PMd) and the ventral Premotor Area (PMv) that are classified as Area 6 rostral. The Supplemental Motor Area (SMA) is found medially in the Paracentral Lobule anterior to the MI leg representation. This corresponds to Area 6 on the medial aspect of the Frontal Lobe. The SMA has recently been subdivided into a

Pre-SMA and a SMA-Proper by some investigators. Like MI, SMA Pyramidal Tract Neurons have direct projections to the spinal cord by way of the Corticospinal Tracts (Pyramidal Tract). There are several Cingulate Motor Areas inferior to the SMA that contain Pyramidal Tract Neurons that project their axons to the spinal cord. Using Intracortical Microstimulation (ICMS) both “muscle” and “movement” maps have been described in MI. ICMS maps reveal an overall global map (Face, Hand, Arm, Trunk & Leg) in MI (homunculus) but microelectrodes reveal a mosaic local representation within the hand area.

This mosaic shows multiple representations of individual muscles (not shown) or movements (see flash file above) that appears to vary across individuals. In addition, the map appears to be mutable over a broad timeframe (short-term & long-term plasticity). Thus data show that a static map is inadequate for representation of dynamic motor function. Individual muscles are rarely used in isolation for functional actions and a static “place” map may be useless in guiding dynamic motor tasks. Indeed, neither “muscles” nor “movements” may be the most important feature to be represented in MI; at least within the hand area of MI, dexterity (skill) may be dynamically “mapped” within the mosaic. Neuroscientists have studied plasticity in the MI hand (forepaw) representation in primates, cats and rats. Most motor cortex maps appear to be quite mutable after training on skilled tasks requiring fine hand (paw) dexterity. The map expands slightly and changes its mosaic pattern of “DIGITS” and synergistic groups of muscles “DIGIT+WRIST/FOREARM” required for the task (SEE MAP). Randy Nudo and colleagues have studied motor cortex plasticity in monkeys. One task that producing such a dramatic change required a monkey to retrieve a small food pellet from a small shallow well. Monkeys trained to retrieve food pellets from a large well (easy task) showed no such dramatic change in these “tiles” of their MI mosaic map. This suggests that mere use is an insufficient challenge to reorganize the hand map; novel, demanding skilled tasks must be learned to remap MI, see: Nudo, et.al.,1996, 1997. Similar results have been shown for the MI forepaw/limb representation in rats.

More than just muscular power must be incorporated into habilitation or rehabilitation training to see motor map alterations.

PRIMATE PRIMARY MOTOR CORTEX: NODE FOR VOLITIONAL, SKILLED BEHAVIORS

The Primary Motor Cortex of Gyrencephalic primates is a critical node for distribution of your “will” in a precise fashion. MI does not act alone in the intact nervous system. Contributions from other cortical areas, the basal ganglia and the cerebellum provide a distributed network to refine output through 'nodes' where information is funneled to be sent via descending pathways to segmental motor centers in the brainstem and spinal cord.

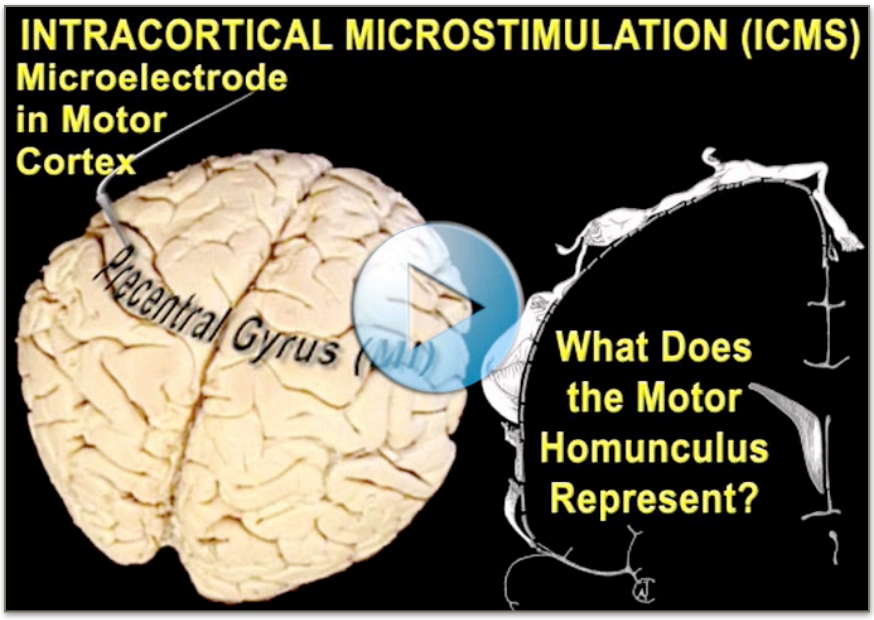


Fig 18-16. Intracortical Microstimulation: How you stimulate the primary motor cortex makes a difference in action outcome (gec). GO TO: gmomm.pitt.edu *Fig18-16_Video*

These nodes include the cerebral cortical areas that contribute to the corticospinal & corticobulbar tracts, the red nucleus (rubrospinal tract), reticular formation nuclei (reticulospinal tracts) and the vestibular nuclei (vestibulospinal tracts).

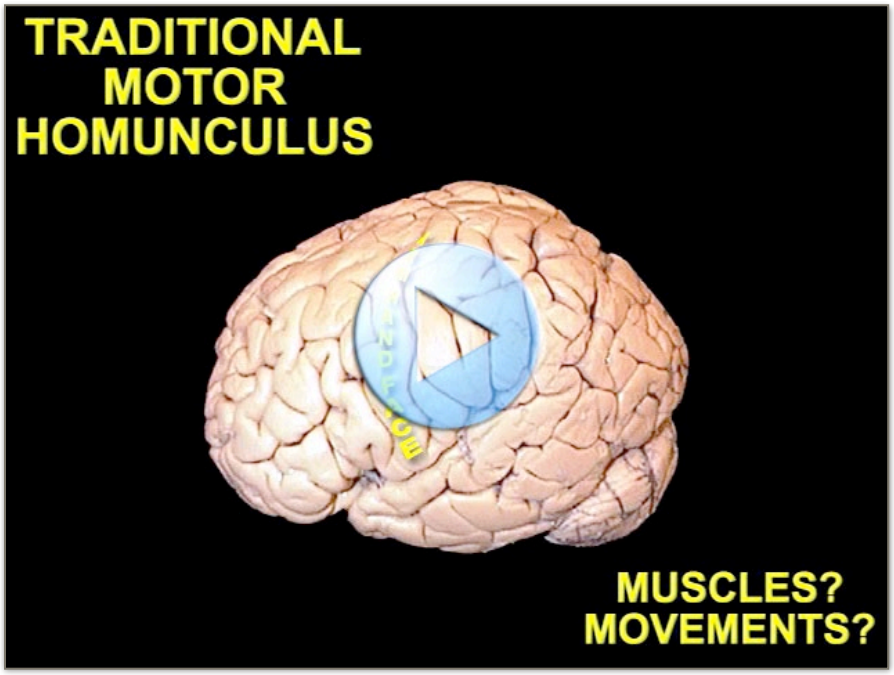


Fig 18-17. Motor Homunculus: Motor Cortex Maps Skilled Actions in Humans (gec). GO TO: gmomm.pitt.edu *Fig18-17_Video*

The two movies presented here suggest that while the motor cortex may have both "*muscle*" and "*movement*" representations, ultimately the motor cortex as part of a broader system provides an output for behaviors that are representative of our actionable volitional demands for reaching a goal in a time- and muscle-efficient, coordinated and graceful manner. The motor map is not a simple topography representing either muscles or body parts in a highly systematic fashion like the proposed SI somatotopy. Goal directed skilled synergies appear to be an important feature of any motor map.

MOTOR MAP: MUSCLES ARE NOT THE END OF THE MOTOR PATH BUT THE MEANS TO THE END

So we have established that some neuroscientists refer to an MI "*muscle*" map, others a MI "*movement*" map and others to an MI map that is "*none of the above*." Try this "experiment."

> Put your left thumb on a location overlying the vastus medialis muscle in your right thigh. Now contract only the muscle fibers beneath your thumb. Next, place your left thumb over the first dorsal interosseous muscle in your right hand but contract only the muscle fibers of the right first dorsal interosseous beneath your left thumb. For both cases you cannot select only muscle fibers within the defined region of a muscle although, in the latter case, your thumb will cover most of the first dorsal interosseous muscle. If you have a trusted colleague place his or her thumb over your muscles, you can rapidly and precisely locate the area of skin contacted with your eyes closed (SI map related to place = somatotopy). The MI map is not really a "place" map like the SI map. Individual muscles and movements are not the end of the motor system; they are the means to an end which is related to your ability to selectively accomplish a particular behavior/task. For example, while it is important that you precisely move the muscles for your thumbs to tap a message while holding your smartphone, the timing of bilateral "thumbing" is necessary to send a coherent message. Motor unit selection is but one aspect of (a spatial aspect) of this process, albeit a critical one for refined actions. In addition, recruitment timing is a critical "non-place" aspect of skilled motor behavior. Are we there yet?

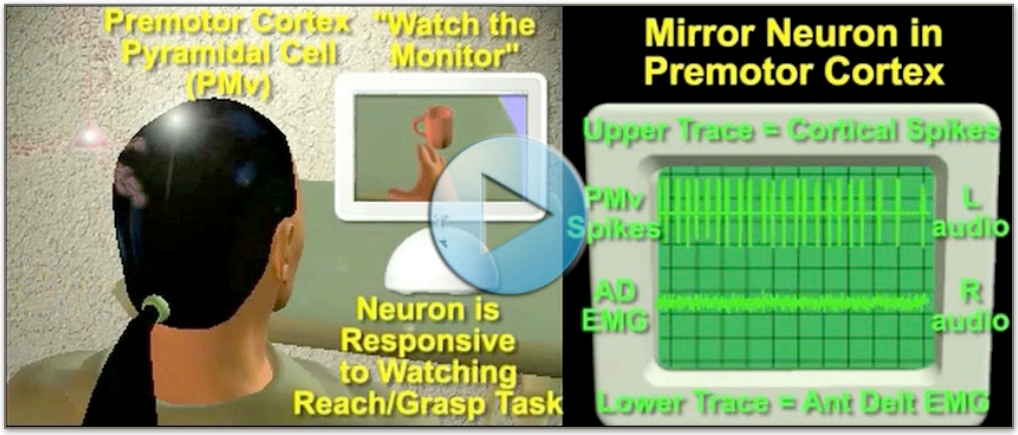


Fig 18-18. Mirror Neuron Movie (gec). GO TO: gmomm.pitt.edu Fig18-18 _Video

The motor system is a neural controller for imagined and actual behaviors or tasks. Action alters the virtual or real body image when you move. The more refined the task (higher skill) the greater the role for the cerebral cortex, at least while you are forming and initially refining the skill. Imitation has an important role in developing sensorimotor behaviors across many species.

Mirror neurons have been identified in portions of the posterior parietal cortex, lateral premotor cortex and even in the primary motor cortex in monkeys. Mirror neurons are activated when a monkey observes another monkey or a human perform an action.

Fig 18-19. Actor (left) and "Spectator" (right) Interactive Toy Play. Both Cats are likely to have portions of Sensorimotor Brain Areas active whether doing or watching the action [assuming the cat on the right is paying attention and mentally engaged in play] (gec).

Most mirror neurons also discharge vigorously when the monkey actually performs the previously observed task. A recent study of MI Pyramidal Tract Neurons (PTNs) in monkeys shows that some of these MI task-related mirror neurons are suppressed while observing a precision grasp by a human subject but facilitated when the monkey performs the grip task. Other MI mirror neuron PTNs are facilitated while observing the precision grip and the firing rate of these cells increases substantially when the monkey does the task. EMG recording from 11 key arm and hand muscles showed robust activation of the muscles when executing the precision grip but no activity when observing the human do the precision grip (see Vigneswaran, et.al., 2013). Thus some neurons in MI may participate in formulating an intent and may provide signals to either suppress an action based on one's volitional will or facilitate the muscles required to perform the action if circumstances warrant its execution. MI may not function as a simple muscle or movement actuator despite its corticofugal output that does provide potent direct access to brainstem and spinal cord motor unit circuitry, e.g., see Schieber, 2011. Recently, single neuron recordings in human cerebral cortex in medial frontal cortex, especially, SMA, and in medial temporal lobe suggest these areas contribute to the mirror neuron system, e.g., see Mukamel, et.al., 2011.

MOTOR CORTEX PROJECTIONS TO SPINAL CORD: PYRAMIDAL TRACT CONNECTIVITY MATURES IN PARALLEL WITH FRACTIONATION OF FINGER MOVEMENTS

The classic motor homunculus of the human precentral gyrus mirrors the somatosensory homunculus of the postcentral gyrus. Cortical magnification of the head and hand (including digits) are obvious distortions in the map. Excluding the head, the hand + digit area accounts for a larger cortical territory than the rest of the body. This

extensive digit representation is seen in other subhuman primates but is not as obvious in quadrupeds such as the cat. This digit magnification reflects the ability to fractionate (individuate) digit (finger) motion by adult but not infant primates nor cats of any age.

A large hand/digit motor representation plus maturation of the pyramidal tract and sensorimotor system networks are critical for development of fractionation of movement. Adult primates have Pyramidal Tract axons that are mature and project to dorsal horn, intermediate gray and the lateral motor nucleus where motoneurons live. Infants have less dense axonal terminations that do not invade the lateral motor nucleus.

The Pyramidal Tract Maturation figure illustrates Pyramidal Tract (Lateral Corticospinal Tract) axon terminations in Infant and Adult Cervical Cord. Dashed lines indicate major axon "trunks" in white matter and major branches in gray matter. Dots indicate locations of axonal "swellings"-presumed sites of synaptic connections. Note change in caliber of axons, number of axon branches & increased density of axon terminations including large "swellings" in adult. **In addition, axon terminations are found in lateral but not medial motor nucleus in ventral horn of Adolescents and Adults *ONLY* (see panel A versus panel B).**

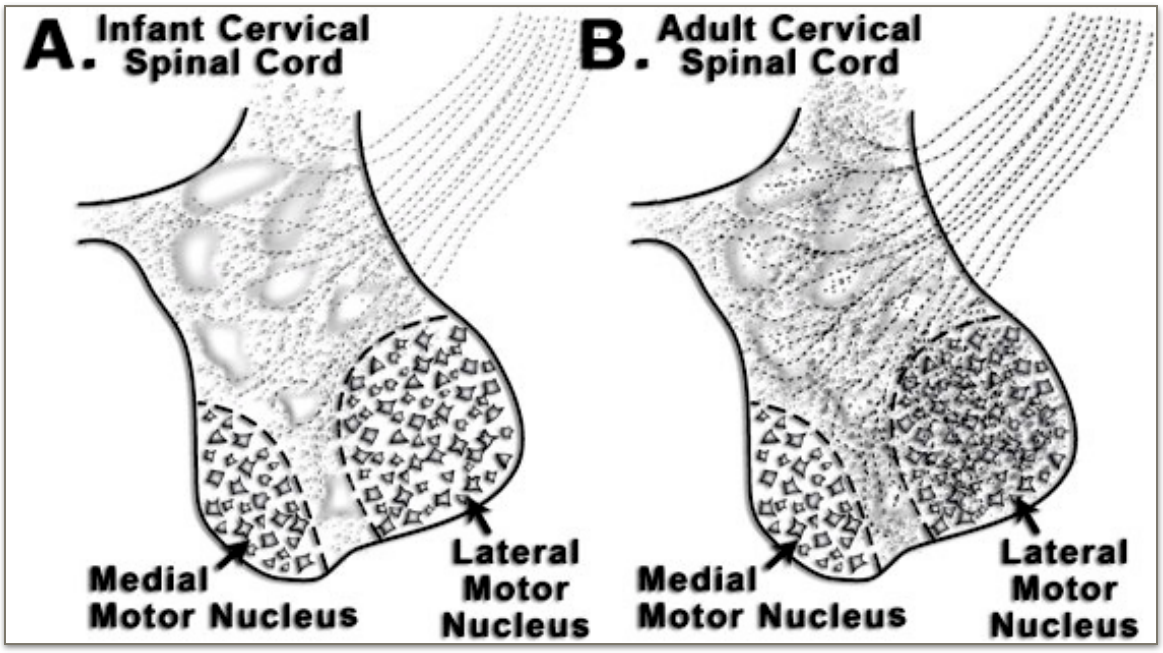


Fig 18-20. Pyramidal Tract Maturation. A. Pyramidal Tract projections to cervical spinal cord in infant primate; B. Pyramidal Tract projections to adult cervical spinal cord (gec).

INTRACORTICAL MICROSTIMULATION (ICMS) OF MOTOR CORTEX: ELECTROPHYSIOLOGICAL MAPPING & AXONAL TRACING OF CORTICOSPINAL PROJECTIONS

Any static homunculus is deceiving in motor cortex since, unlike the somatosensory "map," actual body positions are fluid in a moving body or limb. Thus, any "Euclidean"

coordinates are useless to describe a location unless you can dynamically track the body part of interest. Indeed, proprioceptive, vestibular or visual feedback may be relatively ineffective for fast movements.

Various hypotheses describe "*muscle*" maps or "*movement*" maps based on use of Intracortical Microstimulation (ICMS) in Motor Cortex (MI) where brief, low-intensity microstimulation of a small group of cells in deep cortical layers produces a visible contraction in awake, or lightly anesthetized subjects. Such action may be limited to one or a few muscles, or to a "synergistic" movement about a joint. Maps formed from ICMS are somewhat variable from one experimenter to another suggesting that clear boundaries in any "map" may be elusive and not representative of actual function.

Recent neuroanatomical and neurophysiological experiments show a heavy Corticomotoneuronal (CM) monosynaptic projection from MI (Area 4c) and Primary Somatosensory Cortex or SI (Area 3a) to Alpha and Gamma Motoneurons (MNs) respectively in the Spinal Cord. Injection of a transneuronal tracer (tagged rabies virus) in a distal limb muscle infects both alpha & gamma MNs that innervate Extrafusal & Intrafusal muscle fibers. The tracer crosses the synapse and is retrogradely transported back to CM cells in layer V of the Cerebral Cortex.

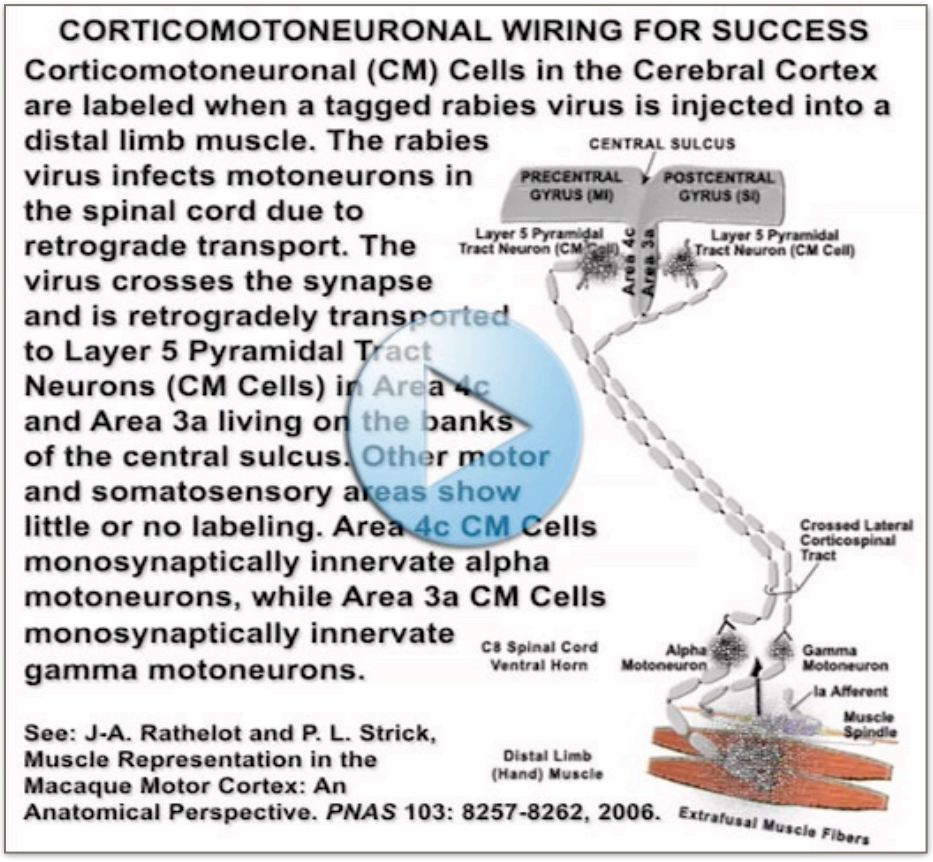


Fig 18-21. MI Corticomotoneuronal Connections: Rabies Virus Tracer & ICMS Stimulation of MI Area 4c, SI Area 3a- Relationship to Alpha and Gamma Motoneurons (gec). GO TO: gmomm.pitt.edu Fig18-21_Video

Intracortical Microstimulation (ICMS) of Area 4 Layer V CM Cells monosynaptically excites a select pool of alpha motoneurons. This results in a muscle twitch. By contrast ICMS stimulation of Area 3a CM Cells does not

produce a muscle twitch but may activate intrafusal muscle fibers in the spindles of the homologous muscle due to monosynaptic excitation of gamma MNs. Thus two adjacent areas within the central sulcus provide discrete alpha-gamma coactivation, an important neural mechanism for fine control of skilled actions: those complex, novel behaviors that characterize success in higher primates.

CORTICOMOTONEURONAL (CM) ELECTROPHYSIOLOGY-SPIKE-TRIGGERED AVERAGING (STA) OF EMG REVEALS MONOSYNAPTIC CM CONNECTIONS

Corticomotoneuronal (CM) Cells in Motor Cortex provide direct monosynaptic excitation of Motoneurons (MNs) in the Ventral Horn. Connections are capable of guiding actions that require synergistic control at selected single or multiple joints. Pyramidal Tract Neurons (PTNs) as Corticomotoneuronal Cells (CM Cells) are not slaves to the muscles they serve and training may induce plastic changes.

A CM CELL monosynaptically connected to extensor motoneurons may be highly active during extension but inhibited during flexion in an alternating isotonic task. The same CM CELL is inhibited during a power grip task that produces extensive cocontraction of flexors and extensors.

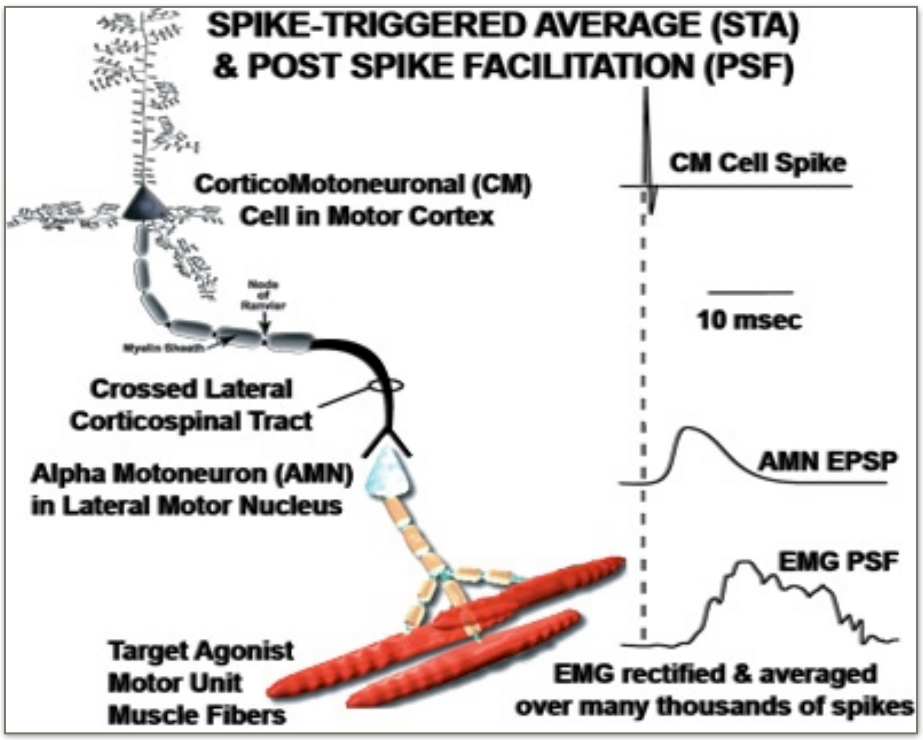


Fig 18-22. Spike Triggered Averaging Technique to Identify Corticomotoneuronal synaptic inputs to alpha motoneurons (gec).

Taken together, recent studies support a nobler cause for motor cortex networks: SKILL! E. Fetz and P. Cheney utilized a method to reveal monosynaptic connectivity between Motor Cortical Neurons (CM cell) and Alpha Motoneurons that innervate specific muscles. Spikes are recorded from a defined CM cell (Pyramidal Tract Neuron or PTN). Each spike triggers a narrow window of data collection of EMG. Spike triggered EMG is rectified and averaged over many repetitions of the task (ramp and hold movement). This Spike Triggered Averaging (STA) provides

robust data regarding which MNs are facilitated by the CM Cell & which are inhibited. STA shows a bias in the pattern of direct CM connections from Motor Cortex to the cervical cord in primates.

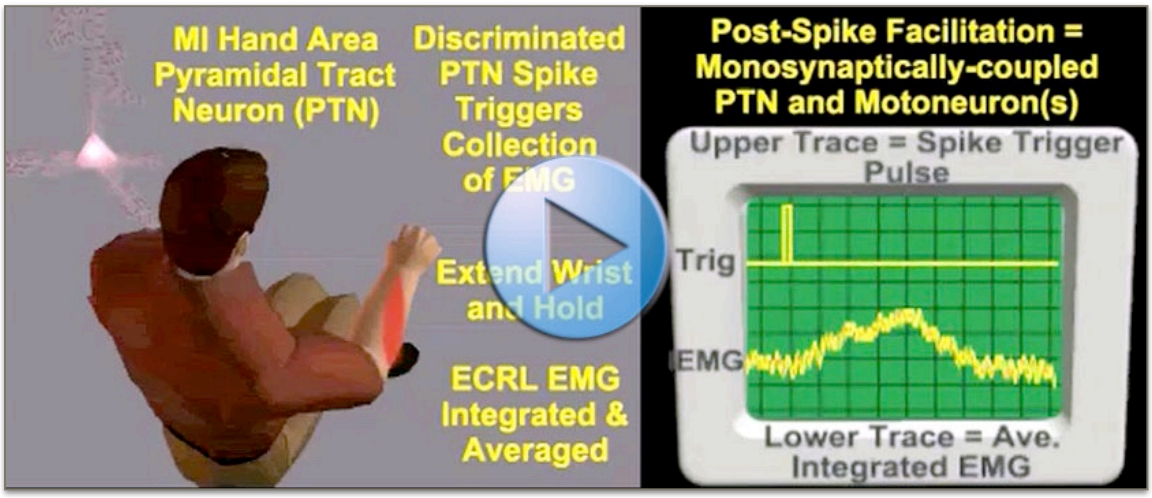


Fig 18-23. MI STA Technique Movie: Post-Spike Facilitation reveals monosynaptic Corticomotoneuronal connection (gec). GO TO: gmomm.pitt.edu *Fig18-23_Video*

Post-Spike Facilitation (PSF) during a reach & grasp task reveals a distinctive mix of CM targets (primate): 1. About 46% of CM Cells target BOTH Contralateral Proximal and Distal Musculature. 2. ~45% of CM Cells target Distal Motoneurons ONLY. 3. The remaining ~9% of CM Cells target Proximal Muscles ONLY (primarily motoneurons controlling the elbow: 'mid arm control'). Along with the CM Cells many more Pyramidal Tract axons synapse on intermediate gray and ventral horn interneurons and propriospinal neurons. The MI STA Technique Movie simulates the STA technique as if performed with a human subject.

PRIMATE MI CORTICOMOTONEURONAL POPULATION: BIASED PROJECTIONS

Corticomotoneuronal (CM) Cells in Motor Cortex provide direct monosynaptic excitation of Motoneurons in the Ventral Horn. Data suggest that the organization of such direct influence is NOT limited to an individual Motoneuron Pool subserving either a single muscle or a single movement. Connections are capable of guiding actions that require synergistic control at selected single or multiple joints. Taken together, recent studies support a nobler cause for motor cortex networks: SKILL!

Pie-chart shows distribution of CM Cells in Primate MI that monosynaptically excite Alpha Motoneurons (AMNs) innervating the Upper Extremity (Spinal levels C5-T1). Note the large contribution to control of our hand and synergistic proximal limb control that projects the hand into our workspace. These patterns are subject to use-dependent plasticity when we develop new motor skills. P&D CM Cells = Pyramidal Cells that

project to both Proximal & Distal Limb Motoneurons. D CM Cells = Pyramidal Cells that project to Distal Limb Motoneurons Only. E CM Cells = Pyramidal Cells that project to MidLimb 'Elbow'.

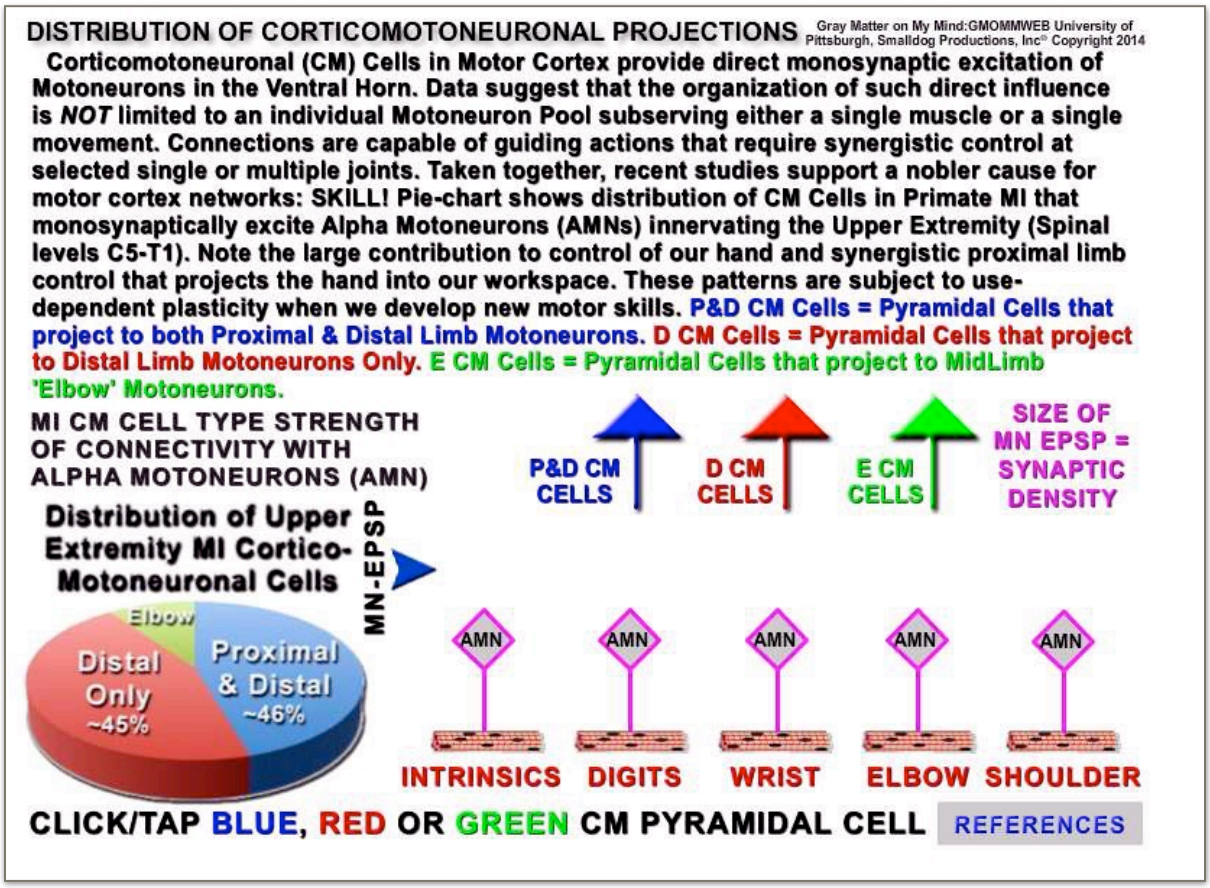


Fig 18-24. Skewed Distribution of Corticomotoneuronal Connections to Upper Extremity Motoneurons and Strength of Monosynaptic Alpha Motoneuron EPSPs due to CM Activation: E CM Cells, P&D CM Cells and D CM Cells. Note differences in the distribution and size of Motoneuron (MN) EPSPs for the three categories of CM cells (gec). GO TO: gmomm.pitt.edu *Fig18-24_Interactive Media*

MOTOR CORTEX NEURONS: DIRECT CORTICO-MOTONEURONAL CONTROL - PRECISION BUILT FROM FLEXIBLE CORTICAL NEURON POPULATIONS

Since the earliest single cell microelectrode recordings in Motor Cortex of behaving monkeys by E. Evarts and others in the 1960s, a clear relationship has been established between force and single cell discharge rate. Thus single MI cells increase their discharge related to static force/torque more than dynamic dF/dt. Many cells in the MI hand area are well-suited to code even the lowest force levels of distal muscles. Precise force (but perhaps not raw power) control is robustly coded by individual MI

neurons (see below). CM cell recruitment within Area 4c “New MI” in the primate precentral gyrus may be related to functional grouping of muscles related to skilled motor tasks, e.g., see Rathelot and Strick, 2009; Griffin, Hoffman and Strick, 2015.

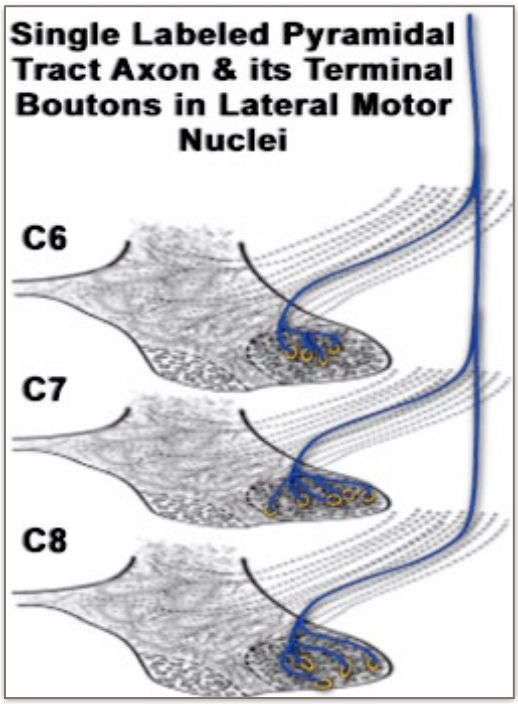


Fig 18-25. Individual Corticospinal Tract axons synapse on multiple interneurons and motoneurons at multiple adjacent spinal levels (gec).

A nonlinear relationship has been shown between the firing rate and duration of firing of Corticomotoneuronal (CM) Pyramidal Tract Neurons (PTNs) and the alpha motoneurons (AMNs) and motor units they target. Thus, relatively few CM PTN spikes initiated in rapid succession leads to AMN facilitation (potentiation) and a relatively rapid rise in muscle tension. The same number of spikes activated at longer interspike intervals (ISI) in the CM cells produces a gradual rise in summed EPSPs onto AMN that prolongs depolarization and will prolong a “tonic” muscle contraction. However, no such robust relationship exists for Motor Cortex single cell activity related to the direction of reaching movements.

Single cell directional specificity coding has not been seen despite an obvious engagement of motor cortex circuitry for fine motor control of multiple muscles involved in complex reaching and grasping tasks (see below). Studies in the last half of the twentieth century provided evidence that the firing pattern of direct Corticomotoneuronal (CM) Pyramidal Tract Neurons (PTNs) in primates has significant influences on Alpha Motoneuron (AMN) Excitability. For example, low intensity Intracortical Microstimulation (ICMS) in layer 5 of the Primary Motor Cortex (MI) can facilitate AMN EPSPs when pulses are closely spaced in time, e.g, see Muir & Porter, 1973. Likewise, Spike Triggered Average (STA) Post Spike Facilitation (PSF) of muscle EMG is potentiated by CM spikes that have short InterSpike Intervals (ISIs), e.g. see Fetz & Cheney, 1980.

Taken together, these studies suggest that a short burst of Action Potentials by a relatively small network of synchronously active CM cells can rapidly produce significant & well-controlled muscle tension. AMN EPSPs are potentiated by such short synchronous bursts of CM descending influences. Training (practice) tends to increase synchrony in PTN (CM) activation and optimizes AMN recruitment for skilled tasks. Such synchrony of motor unit contraction within the same or synergistic distal muscles of the human hand has been documented for the dominant but not for the non-dominant hand: see Fuglevand, 2011. Play flash file to see simulation of the effect of convergent

CM input that facilitates Alpha Motoneuron firing (shorter ISI intervals) and stronger motor unit contraction (tension summation).

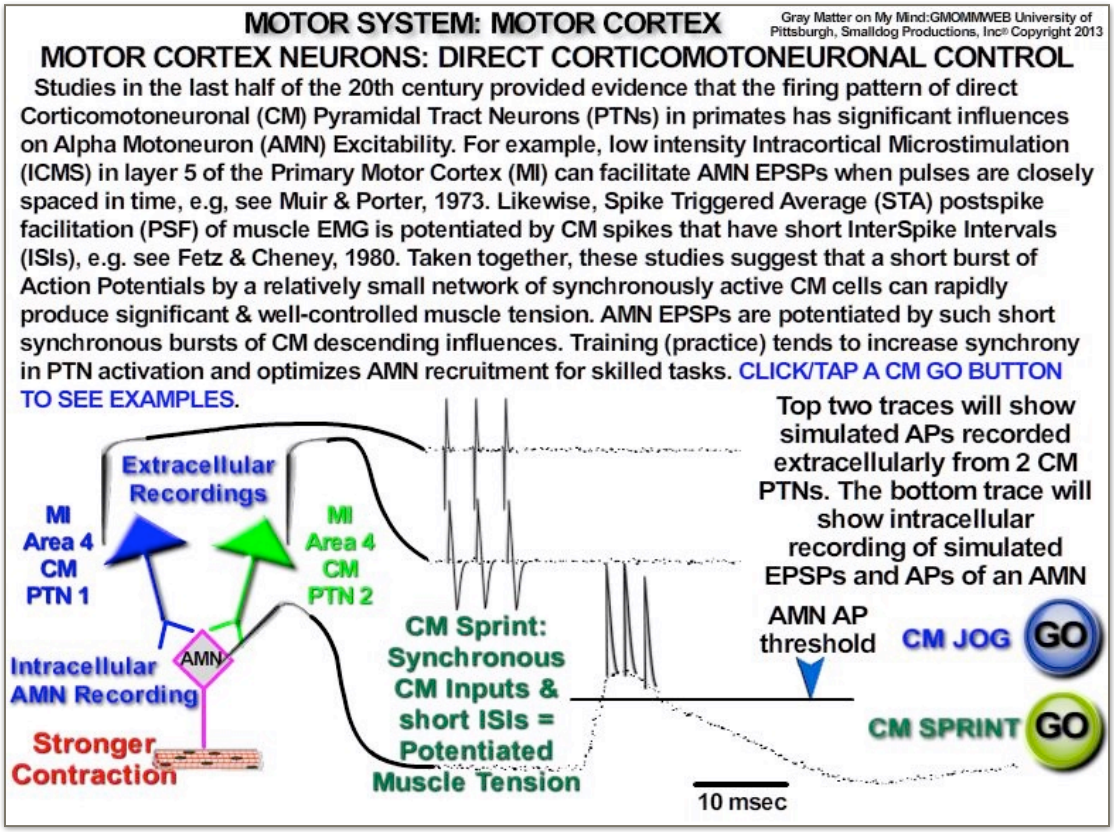


Fig 18-26. Corticomotoneuronal Jog vs. Sprint Activation of Alpha Motoneuron Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig18-26_Interactive Media]

PRIMATE PRIMARY MOTOR CORTEX: CONTROL OF CONTRACTILE PRECISION NOT RAW POWER

Pyramidal Tract Neurons (PTNs) = Corticomotoneuronal Cells (CM Cells) are not slaves to the muscles they serve. A CM CELL monosynaptically connected to extensor motoneurons may be highly active during extension but inhibited during flexion in an alternating isotonic task. Muscles may be grouped as synergists for roles not only to direct movement in the appropriate direction but stabilize joints as needed for the task.

The same CM CELL is inhibited during a power grip task that produces extensive cocontraction of flexors and extensors. The motor cortex projections facilitate either extensors or flexors but not both. Some PTNs facilitate agonist motoneurons and reciprocal inhibitory interneurons (Ia INs) that inhibit the antagonist motoneurons. MI Projections to the Upper Extremity in primates have an Extensor > Flexor and Distal > Proximal Limb bias. Intrinsic Hand Muscles in particular are quite dependent on Corticomotoneuronal connections from MI directly to the alpha motoneurons innervating

these specialized hand muscles that provide exquisite manual dexterity. This relationship is simulated in the Human MI Codes Precision Not Raw Power Movie.

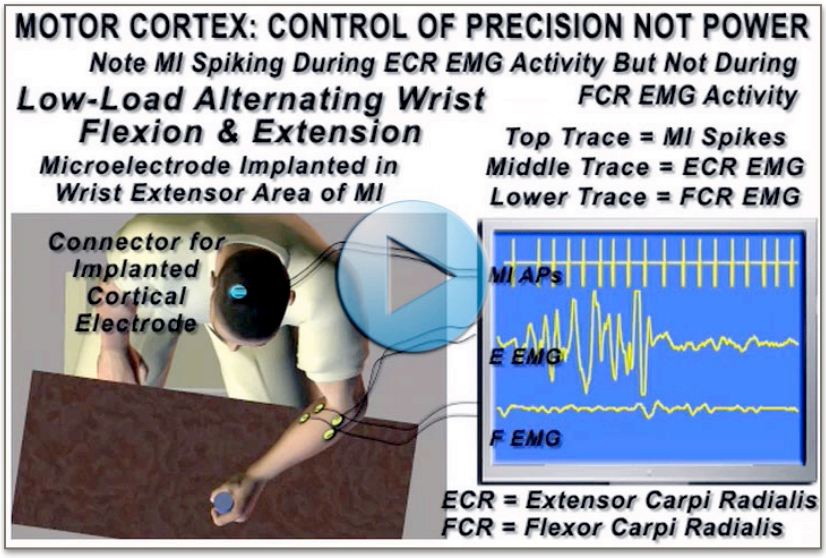


Fig 18-27. Human MI Codes Precision Not Raw Power Movie (gec). GO TO: gmomm.pitt.edu Fig18-27_Video

SHORT & LONG LOOP ADJUSTMENTS TO PERTURB-ATIONS: "PRE-VOLITIONAL" SPINAL, SUPRASPINAL AND MOTOR CORTEX RESPONSES

Perturbations of contracting muscles produces 'compensatory' adjustments at the spinal and supraspinal levels. Depending on the muscles involved, the type of perturbation and the duration of the stimulus a multipeaked response may be recorded.

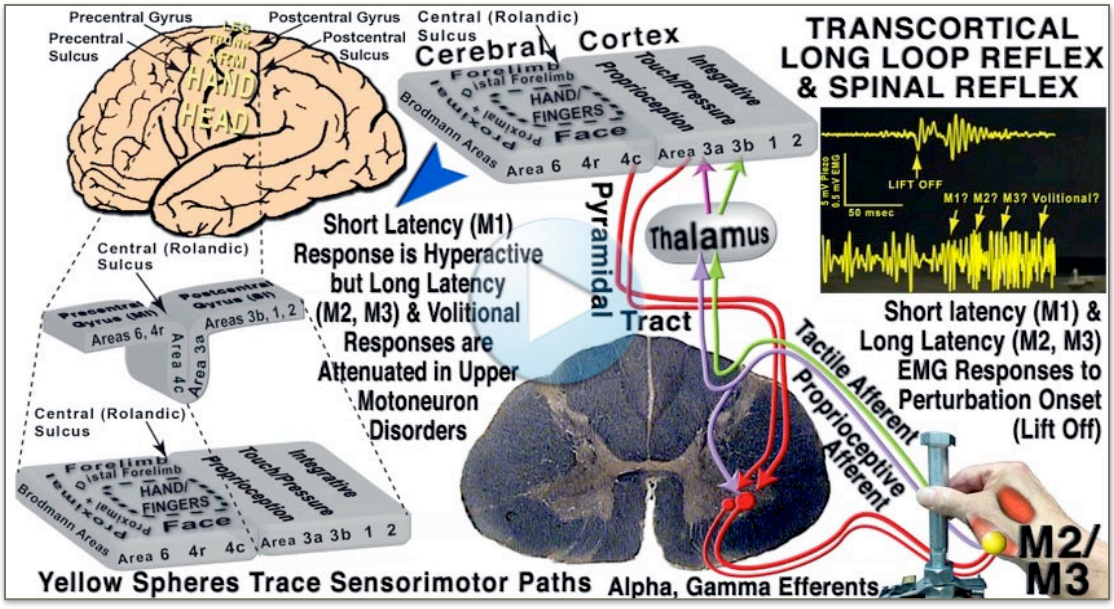


Fig 18-28. M1, M2 and M3 Pre-volitional Automatic Reactions to Limb Perturbation (gec). GO TO: gmomm.pitt.edu Fig18-28_Video

Three peaks of muscle activity have been defined: M1 short loop response @ ~20-30 msec latency, and two later long loop responses named M2 and M3 within an

~50-150 msec latency window for the upper extremity. M1 is thought to use a spinal reflex mechanism, M3 responses are thought to be transcortical automatic adjustments due to long tract connections with the sensorimotor cortex. M2 may combine spinal & supraspinal circuitry. While the exact mechanisms are unknown studies show that an Upper Motor Neuron (UMN) lesion due to an infarct of the sensorimotor cortex or the internal capsule results in altered responses to perturbations.

The hemiparetic limb muscles show an exaggerated M1 response (hyperactive stretch reflex) but NO or much attenuated M2 & M3 responses.

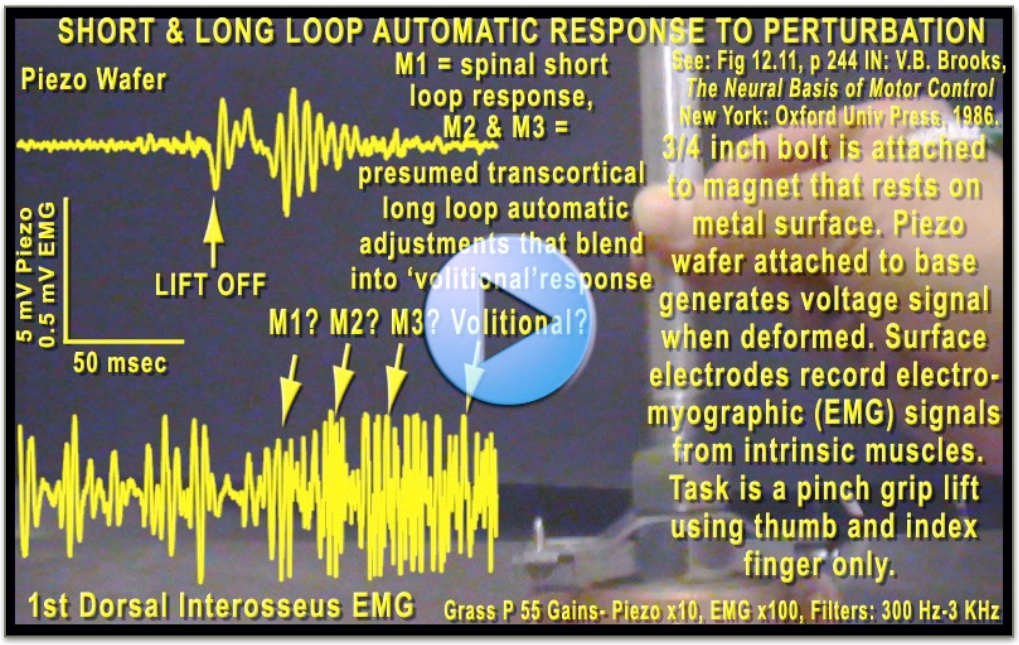


Fig 18-29. Perturbation of Pinch Force: M1, M2, M3 Automatic Adjustments Movie (gec). GO TO: gmomm.pitt.edu *Fig18-29_Video*

Subjects with intact nervous systems show "volitional" EMG activity blending with the M3 response. Volitional responses to stimuli as tested by Reaction Time (RT) experiments show latencies of ~150-250 msec for simple RT while any uncertainty due to complex RT protocols delay response onsets up to 300 msec or longer latencies.

Long loop M2, M3 are modulated by intent. If a subject is instructed to yield to a perturbation the M2, M3 responses are weak or absent, while instructions to resist (intent to resist) produces strong M2, M3 responses.

Individuals with UMN lesions have much attenuated, delayed or missing volitional EMG activity in spastic paretic limbs along with reduced or missing long-loop (M2 & M3) automatic responses. Loss of cutaneous sensation due to local anesthesia of the distal fingers/thumb attenuates long loop grip adjustments. Thus, depending on location, long loop automatic adjustments may be initiated by tactile, proprioceptive or multisensory cues.

CORTICOMOTONEURONAL CONNECTIVITY: CONVERGENCE/DIVERGENCE REVEALED BY TRANSNEURONAL ANATOMICAL TRACING

Rabies virus injected into a distal limb muscle infects alpha & gamma motor axon terminals. Retrograde axonal transport of the virus infects (labels) alpha & gamma motoneurons in the lateral motor nucleus of the ventral horn of the spinal cord. The virus infects those axon terminals that synapse on the motoneurons. From the spinal cord, the rabies virus is transported back (retrograde axonal transport) by way of the lateral corticospinal tract to Corticomotoneuronal (CM) cells in the cerebral cortex: for review see Rathelot and Strick, 2009. Note that the rabies labeled CM cells are found in both pre-central and post-central gyri. Most labeling occurs in area 4c (area 4 caudal) along the banks of central sulcus. Adjacent Area 3a and 4r (area 4 rostral) CM cells are labeled as well. Labeling does not extend into area 6 of MI or to other areas of the postcentral gyrus (SI). Labeling is not restricted to a single anatomical cluster but includes multiple dense clusters within the hand/finger representation as well as lower density labeling of more proximal limb representations in MI.

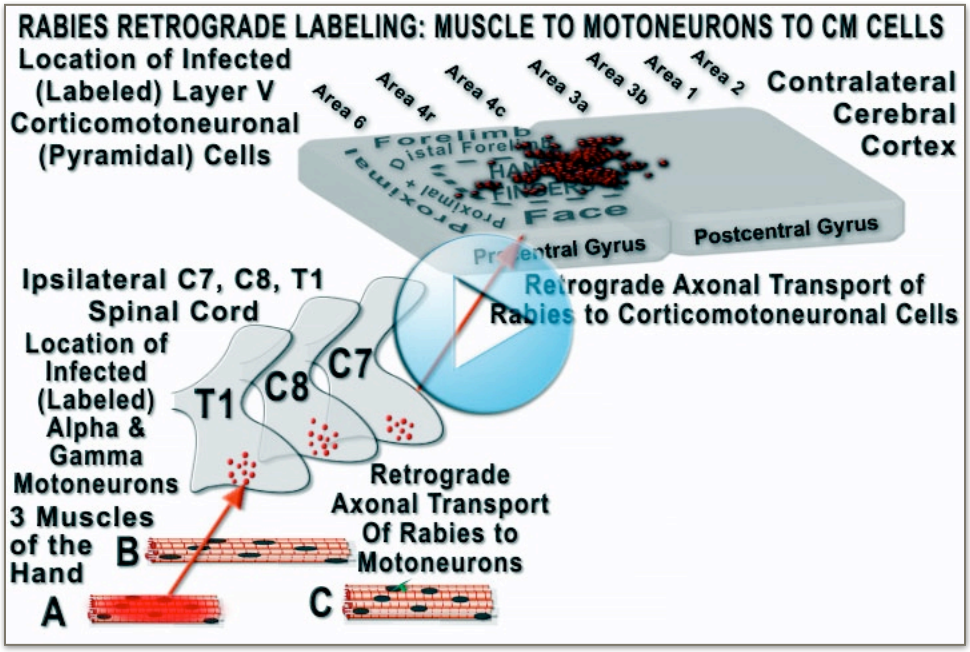


Fig 18-30. Simulation of Retrograde Transport of Rabies Virus Tracing Technique to Reveal Cortico-motoneuronal Connections (gec). GO TO: gmomm.pitt.edu Fig18-30_Video

Tagged Rabies injections into more proximal muscles shows clusters of CM cells more medial to CM cells representing distal hand muscles in MI. CM cells from different muscles have territories that partially overlap one another within MI and area 3a of SI (compare CM label for 3 hand muscle injections in movie below). Thus, fractionation cannot be explained by a simple 1:1 Cortical cell to motoneuron relationship.

CORTICAL MINICOLUMNS FOR INTENTION AND ACTION

Hypothesized model for interaction of Associative (Intention) and Motor (Action) cortical minicolumns to provide the “Ready-Set-Go” sequence of events for implementation of our imagined or actual goal directed volitional motor plans.

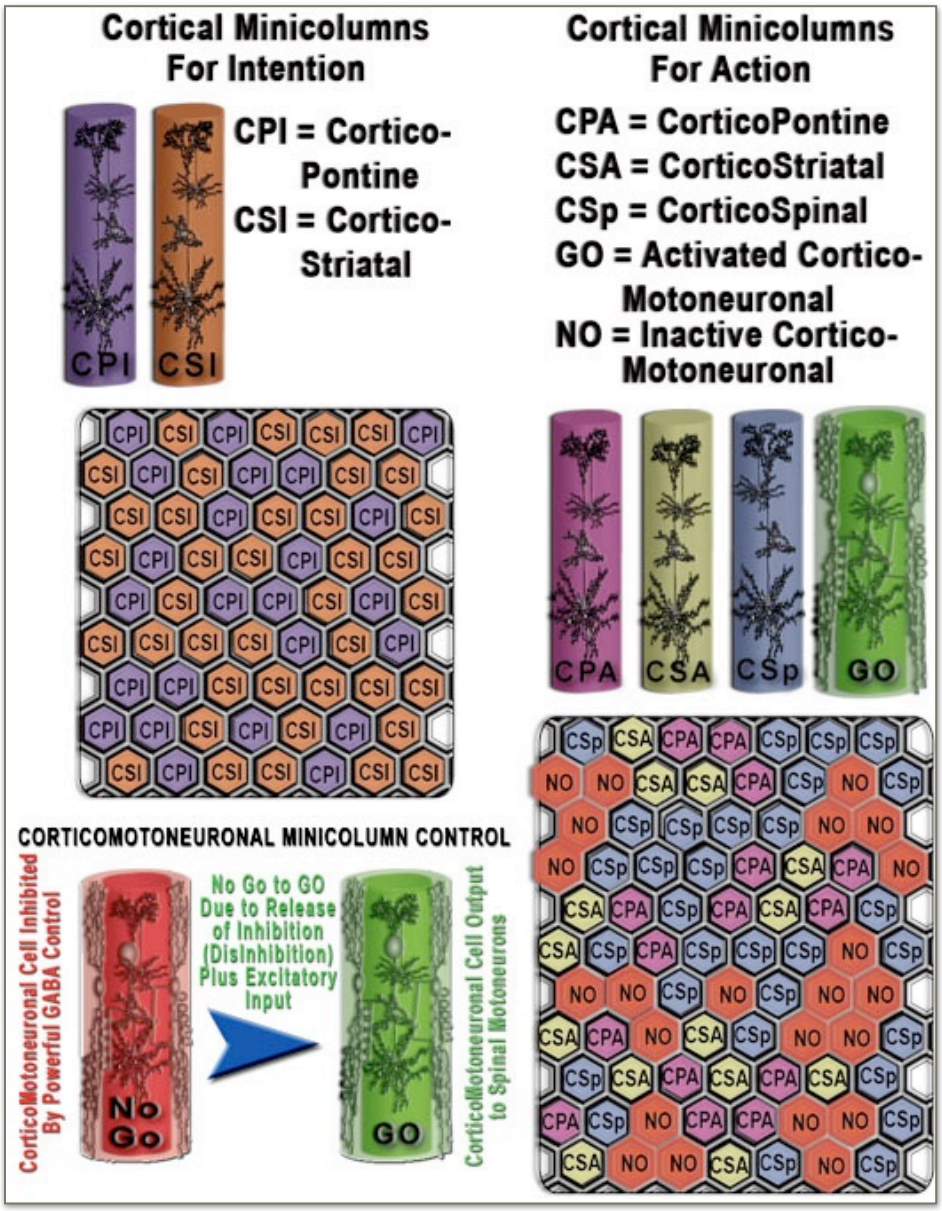


Fig 18-31. Primate Cerebral Cortical Minicolumns for Intentions and Actions: Named for the Corticofugal target of each minicolumn and No-Go to GO Conversion of Corticomotoneuronal Minicolumn Output. Honeycomb pattern illustrates the minicolumns for intention and action as if viewed from the surface of the cortex (gec).

Note that the Actual GO Signal is under tight inhibitory control: see Double Bouquet, Basket & Chandelier GABA cells in No-Go/GO minicolumn. Release to GO requires disinhibition. Minicolumn modules in cerebral cortex are shown in figures as viewed from a transverse section of the cortex (side view of minicolumn) and as viewed from cortical surface (honeycomb array of minicolumns). The minicolumns are labeled according to the major subcortical corticofugal target of the columnar output: basal ganglia (striatum), cerebellum or spinal cord neurons (corticospinal) including direct connections with alpha motoneurons (corticomotoneuronal). Intention minicolumns include Corticostriatal Intention (CSI) Minicolumns and Corticopontine (CPI) Minicolumns.

Action minicolumns include Corticostriatal Action (CSA) Minicolumns, Corticopontine (CPA) Minicolumns, Corticospinal (CSp) Minicolumns, Corticomotoneuronal Action (No-Go to GO) Minicolumns.

WIRED FOR SUCCESS: MINI-COLUMN INTENTION-ACTION - A REGAL THRONE FOR INHIBITORY CELLS IN CORTICOMOTONEURONAL (CM) MINICOLUMNS?

A Proposed Circuit: Chandelier & Basket cells provide powerful inhibition of CM Pyramidal Cells due to GABAergic axo-axonic synapses at the axon hillock and axo-somatic synapses on the CM cell. It has been suggested that Chandelier cells, unlike most other inhibitory neurons, rarely spike until there is elevated excitatory input to the column (demonstrated in SI Barrel Cortex of rats: see Zhu, et. al., 2004). A recent study suggests the role of Chandelier Cells to selectively inhibit some Corticofugal pyramidal cells while having no effect on other nearby pyramidal cells having a different subcortical target: see Lu, et.al., 2017.

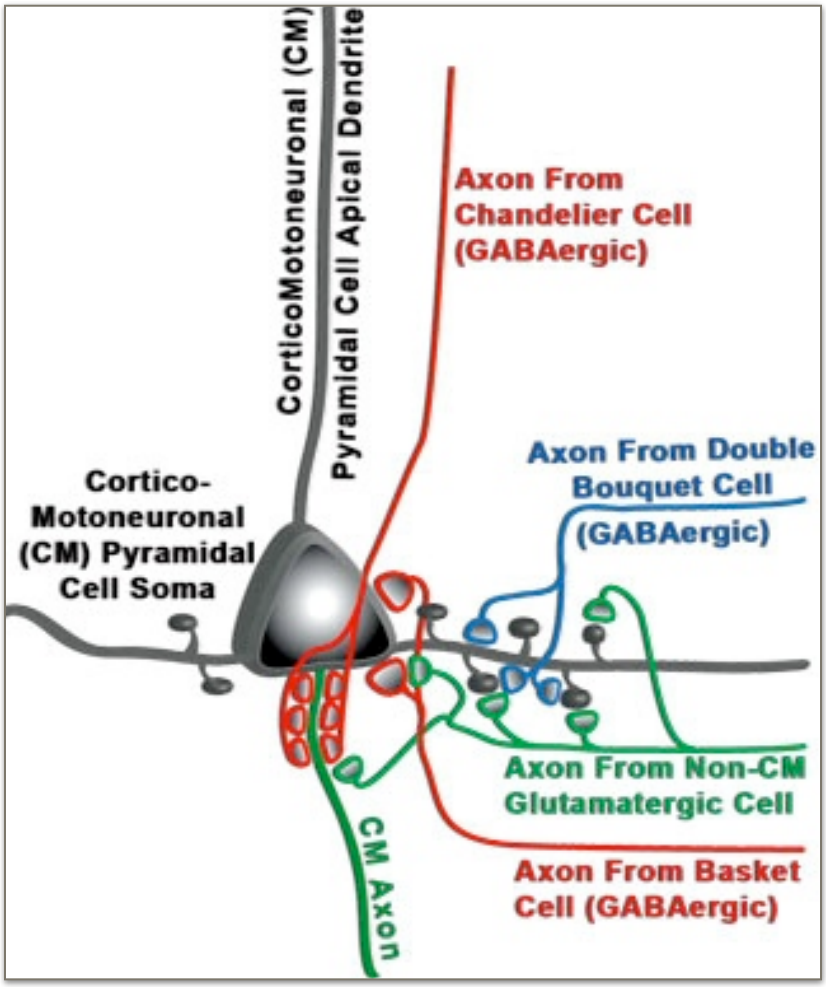


Fig 18-32. Excitatory and Inhibitory Synaptic Influences on Pyramidal Cell (gec).

How could Chandelier cells provide tonic GABA inhibition of the CM Pyramidal Cells if there are low levels of cortical activity?

Inhibitory interneurons may not have to spike to provide release of GABA for inhibition. It has been shown that glutamatergic axon terminals may synapse on GABA axon terminals, see Ren, et.al., 2007; axo-axonic release of glutamate induces the release of GABA from the inhibitory cell's axon terminal even if the GABA cell does not fire an Action Potential, e.g. , see Somogyi, et.al., 1998. Thus axo-axonic synaptic control of GABA release from Basket/

Chandelier cell axon terminals could be effective even when overall excitability is low in the motor cortex. Chandelier cells may paradoxically assist in activating quiet pyramidal cells while also silencing active PCs: see Woodruff, et.al., 2011. Hyperpolarization is enhanced especially for Chandelier cells due to the typical spiking mechanism when excitability increases, Woodruff, et.al., 2011 as might be expected during pre-movement preparatory set (motor set). Large CM cells are likely to require significant excitatory input to fire. Chandelier-CM cell interactions appear to be complex and presumably offers selective recruitment of PCs: some CM cells are encouraged to fire while others are powerfully quieted with direct effects on spinal motoneurons.

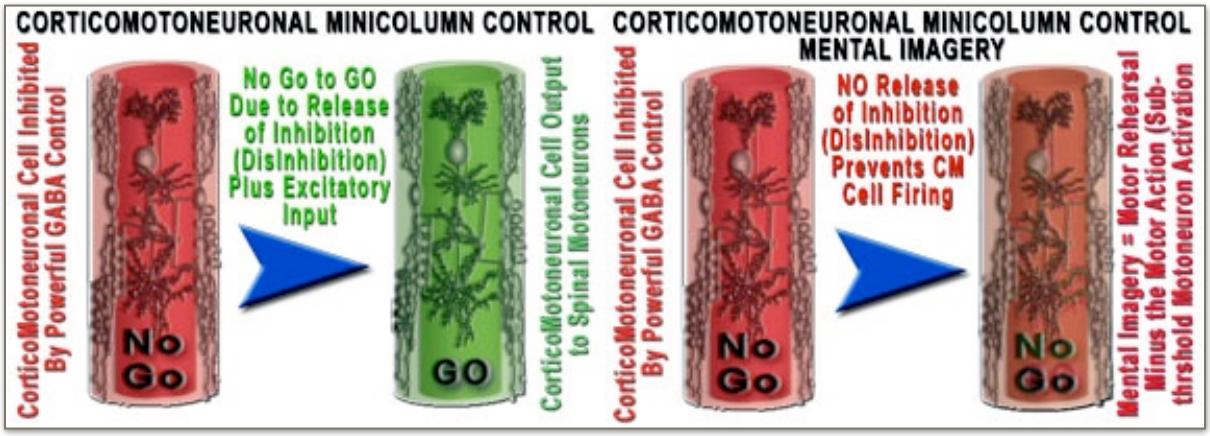


Fig 18-33. No-Go to GO Conversion of Corticomotoneuronal Minicolumn Output and NO-GO Mental Motor Task. Corticomotoneuronal Cells are kept quiet (gec). GO TO: gmomm.pitt.edu *Fig18-33_Interactive Media*

Double Bouquet, Martinotti Cells and other select interneurons may provide GABA inhibition of CM Cell Dendrites & local Inhibitory Interneurons. When direct thalamocortical & corticocortical drive activates the CM minicolumn's Glutamatergic neurons & disinhibitory local GABA interneurons the stage is set to convert a No-Go to a GO state. Figure above shows Corticomotoneuronal minicolumn with CM cell held in inhibited state (No Go) and then release of local inhibition (disinhibition of local inhibition due to DBCs?) plus excitation of CM cell to activate the minicolumn's CM output (GO).

MENTAL IMAGERY: DO INTENTIONS RECRUIT "ACTION" CIRCUITRY EXCEPT FOR MOTOR CM CELLS?

Imagination is a powerful expression of one's intent to act. Microelectrode studies in monkeys and Transcranial Magnetic Stimulation (TMS) or brain imaging studies in humans all suggest that many of the same cortical areas that are active when we actually perform a task are also active although the main players (muscles) are not engaged when we mentally rehearse or observe an actor doing the action sequence.

The majority of these studies suggest that the frontal and parietal cortical areas during imagined task performance provide neural ensemble activity that would engage the musculoskeletal system if the descending motor pathways were allowed to drive the appropriate spinal cord neural machinery. However, EMG measurements show that the muscles are quiescent. Taken together, evidence suggests that the combined sources of descending drive do not depolarize motoneurons (MNs) to threshold in the imagined task but are brought into play when we actually move. Whether the lack of movement is merely the result of low levels of excitation in the motor cortex/MNs during imagined tasks or there is a specific suppression of corticofugal output to spinal motoneurons during our “daydreams” is not yet known. Disinhibition of CM minicolumns in humans is likely to be a critical factor to flip the “Don't DO to DO” switch for precise motor control when we actually do the task.

MOTOR SYSTEM KEEPS ON TRUCKIN' EVEN ON AN IMAGINARY TRIP

Motoneuron excitability in humans can be indirectly measured using H-Reflex testing while a subject performs a task. Recently, investigators have demonstrated a direct correlation of the H-Reflex with the force (and level of EMG) required for a task. This modulation of the H-Reflex does not require the actual output of force but merely the intent to act. The H-Reflex increases if a person pushes a foot pedal harder OR if the person just imagines the required level of force required for the task without actually performing the action. This suggests that the SMC motoneurons receive descending control signals related to both intentions and actual actions. The former signals appear to provide specific sub-threshold inputs to SMC neurons that also participate in the actual movement when stronger descending signals bring SMC alpha motoneurons to threshold. The actual location(s) of control that switches from sub-threshold to supra-threshold activation of Motoneurons has not yet been determined but is likely to involve both cortical and spinal components.

Recent functional imaging studies (fMRI, PET) have investigated brain activity when a subject actually performs a task versus imagining the task. Imagery has been defined in different ways and in one recent study the authors asked normal neurologically intact subjects to perform a task of thumb opposition to one of the four fingers according to a number that appeared on a computer monitor (index= 1, middle= 2, ring= 3, little= 4). Subjects practiced this task until becoming proficient. The subjects were then asked to actually execute the task (E), imagine doing the task as if looking at themselves doing it (out of body experience?) which was called visual imagery (VI), or imagine performing the motor task internally which was called kinetic imagery (KI). EMG from intrinsic muscles showed robust activity when executing the task, a low level of “tonic” muscle activity under the KI condition without actual finger movements and virtually no EMG for the VI condition. fMRI of these subjects done for all three conditions measured activity levels but the researchers also devised an algorithm to assess physiological (not

anatomical) connectivity among the activated areas which included lateral premotor, SMA, primary motor (MI), superior parietal, primary somatosensory, cerebellar, thalamic and occipital areas. One of the intriguing findings was the switch in the physiological connectivity pattern for the E versus KI conditions. While SMA and Parietal cortex had relatively weak “facilitatory” connectivity with MI for the E condition there was a stronger and suppressive effect from these areas on MI during the KI condition. This would suggest that the latter connectional pattern (for KI) may, in part, correlate with the lack of active movement while imagining the execution compared with robust motor activation when the subjects “did their will.” MI was virtually silent during the VI condition. This study cannot address the mechanisms behind such motoneuron suppression with mental imagery but one cannot rule-out corticocortical influences that would maintain tight inhibitory control over corticomotoneuronal cells in MI and the potential descending influences from these cortical areas that may activate spinal mechanisms to inhibit motoneurons by way of corticospinal tract connections to spinal inhibitory interneurons. One would expect the loops between the cerebral cortex and cerebellum plus the loop between cerebral cortex and basal ganglia to be influential in the control process to facilitate “mental” but concurrently suppress physical actionable sequences.

Keep On Truckin’ Movie shows a simulation of how this finding might relate to a daily task for many adults: driving. The first part shows actual action. The second part shows observation of scenario without actual movement. EMG & H-Reflex of the Right Soleus Muscle and Brake Pedal Force are measured. Note that the H-Reflex as a measure of overall excitability of motoneurons can be modulated appropriately for even a nonphysically performed task (subthreshold or weakly suprathreshold facilitation of motoneuron pool reflected in greater response to Ia afferent input) - See: A. Solodkin, P. Hlustik, E.E. Chen and S.L. Small, 2004.

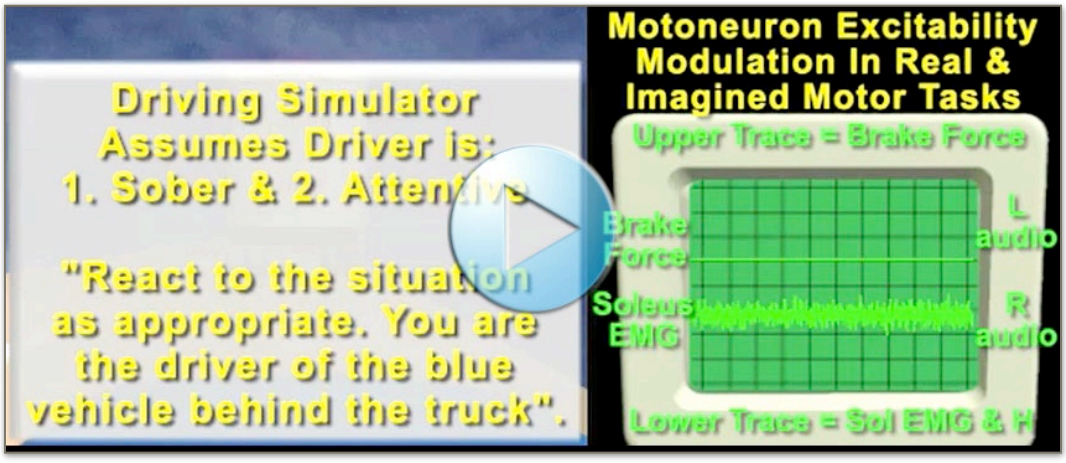


Fig 18-34. Keep On Truckin’ Movie: Supra-threshold & Sub-threshold Motoneuron Facilitation -Actual vs. Imagined Trip (gec).

GO TO: gmomm.pitt.edu [Fig18-34_Video]

MINICOLUMNAR CONTROL: ADVANTAGES OF DOUBLE BOUQUET CELLS TO CREATE HIGH DEFINITION RESOLUTION IN MOTOR CONTROL

Primate cerebral cortex has a variety of GABA interneurons that are rarely or never found in sub-primate species. The human cerebral cortex in particular has a high density of these controlling neurons that may provide a finer-grained architecture for columnar function.

Thus, sub-primate macrocolumns spanning hundreds of microns in diameter containing many hundreds of corticofugal pyramidal cells define the “Standard Definition (SD)” resolution of motor control.

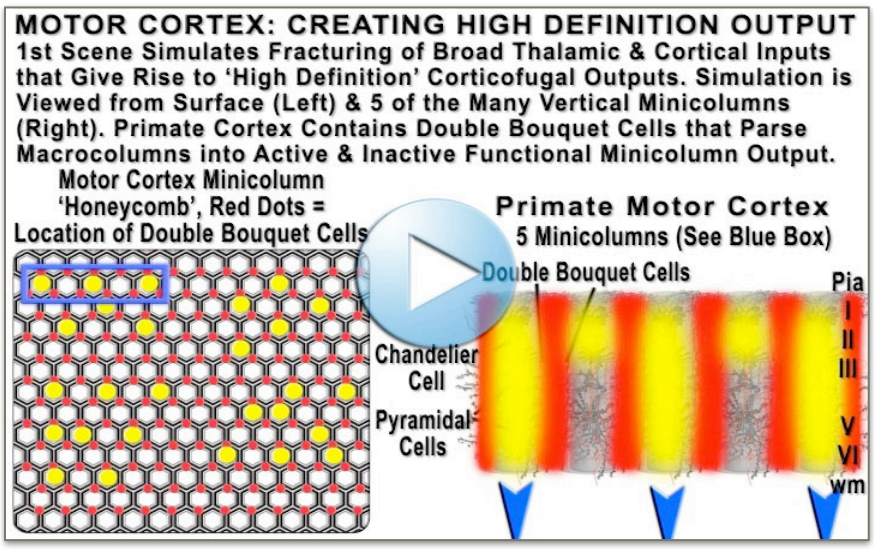


Fig 18-35. Double Bouquet Cells in Primate Cerebral Cortex “Fractures” Macrocolumn into Discrete Minicolumns: Creation of High Definition Cortical Output Movie (gec). GO TO: gmomm.pitt.edu

Fig18-35 _Video

By contrast, the addition of numerous GABAergic Basket cells, Chandelier cells and Double Bouquet cells to human motor cortex provides the means to achieve greater resolution “High Definition (HD)” motor control via minicolumns that each contain only a few corticomotoneuronal (CM) cells that target select spinal motoneurons with strong corticofugal drive. Chandelier cells may simultaneously help to activate quiet pyramidal cells (PCs) and while profoundly suppressing highly active PCs: See Woodruff, 2011. Double Bouquet Cells (DBCs) appear to be particularly well positioned to limit horizontal influence of overlapping pyramidal cell neurites. DBC shunting inhibition may dynamically prune columnar processing to restricted minicolumns. The combination of minicolumns and direct access to spinal motoneurons via CM cells may provide humans precision not attainable in sub-primate species that have few or no DBCs in motor cortex. Movie simulates DBC creation of minicolumn fracturing of macrocolumn inputs.

NOTE: Minicolumn spacing and width in primate cortex is not likely to be as uniform as simulated here nor are double bouquet cells (DBCs) as regularly spaced as illustrated in this animation. Our actual cerebral cortex minicolumn structure is not a simple honeycomb pattern adorned with red dots (DBCs).

COULD DISINHIBITION BE A KEY CONTROL FOR CORTICO-MOTONEURONAL (CM) CELL ACTIVATION?

Although to my knowledge (*GEC*) this disinhibition hypothesis has yet to be tested for Primary Motor Cortex CM cells, there are data that would support inhibition as a potent controlling influence and the release of this suppression as a necessary or sufficient condition for large celled CM output that depolarizes spinal alpha and gamma motoneurons at a suprathreshold level (play movie).

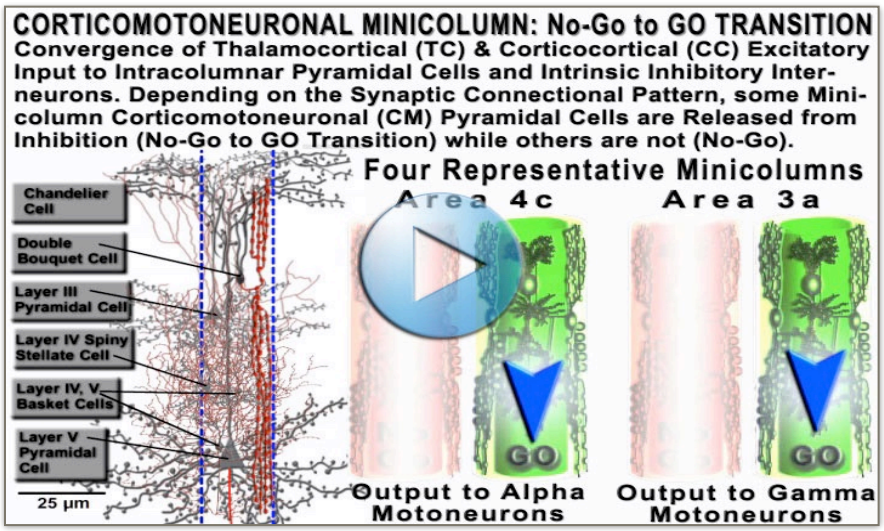


Fig 18-36. Corticomotoneuronal Minicolumn Fracturing: Disinhibition Transition of No-Go to GO Movie (gec). GO TO: gmomm.pitt.edu Fig18-36_Video

1. Published data by Fetz, Cheney and others (see refs) show that CM cells appear to be silent or nearly so until called into action; see also Matsumara, et.al., 1992; Quallo, et.al., 2012. Layer 5 pyramidal cells and presumed inhibitory interneurons are active in forelimb area of rabbit motor cortex during gait. Increased firing alternates between cell types according to different phases of gait cycle: see Beloozerova, et.al., 2003. However, a simple inhibition/disinhibition switching of Layer 5 Corticospinal Pyramidal Cells (PCs) as proposed to "gate" these corticofugal output neurons during the transition from motor preparation to motor execution was not supported by a study of monkey premotor cortex. Notably, these data represent proximal limb recordings in multiple laminae, and Pyramidal Tract Neurons were not identified: see Kaufman, et.al., 2010.

2. Chandelier/Basket cells would appear to be well positioned to keep CM cells quiet until these GABA neurons (& their axon terminals) are inactivated (see Somogyi et.al.,1998; Zhu et.al., 2007; Ren et.al., 2004). Chandelier cells may paradoxically assist in activating quiet PCs at the same time silencing active PCs: see Woodruff, et.al., 2011. Chandelier cells specifically target inhibitory control of layer 5 pyramidal cells that project to Basolateral Amygdala (but not adjacent PCs) which has been implicated in suppressing associative fear responses in mice: see Lu, et.al., 2017.

3. Motor Imagery studies support the notion that cortical neural networks involved in intentions and actions may be active even if spinal motoneurons are not brought to threshold in such "daydreams." For example, a recent study by Hanakawa, et.al.,

2008 shows an increase in BOLD signal in the periRolandic cortex (Area 4 and Area 3) when a person actually performs a task but not when that task is imagined. Other frontal and parietal areas appear to be equally active for real and imagined tasks. Few, restricted frontal & parietal areas are more active for imagined versus real tasks (see also Solodkin, et.al., 2004).

4. A recent study by Sherwood, et.al., 2007 has shown a correlation between motor cortex asymmetry and handedness in Chimpanzees. The motor cortex hand area contralateral to the preferred hand has a higher neuron density in layers 2/3. The asymmetry in density of supragranular Parvalbumin immunoreactive (PV-ir) interneurons was stated to be the best predictor of hand preference. PV-ir (PV+) interneurons are GABAergic Basket and Chandelier Cells.

5. Medial "motor" areas including those in the Anterior Cingulate Cortex may "hold" a notion to move until the cue to perform the action is provided by an internally-generated trigger (will) or perhaps by an external cue to actually bring the intention to action. Such a cue may be due to a network distributed across multiple brain levels.

6. Anyone who has tried to activate motor cortex layer 5 neurons in anesthetized subjects knows that the depth of anesthesia has profound effects on Intracortical Microstimulation. Unless the anesthetic level is very light, no amount of current can produce a localized muscle response. Most of these drugs directly or indirectly enhance GABAergic inhibition. Awake subjects require <50-100 microamps to get a brisk response. Background activity in fast but not slow PTNs in primate motor cortex is suppressed during the transition from sleep to waking: see Steriade, et.al.,1974.

7. A recent study (see Jiang, et.al, 2013 reference) in the rat somatosensory cortex has demonstrated a critical role for two types of inhibitory interneurons located within layer I. Together they increase the probability for activation of a limited number of layer V pyramidal cells while inhibiting many other layer V pyramidal neurons across one or more macrocolumns. One of these layer I GABA neuron types is called a Single Bouquet Cell (SBC) where the soma is located in layer I with a single horsetail axon projecting down into lower layers. The second layer I GABA neuron type is a Neurogliaform Cell (NGC) that has a broad horizontal expansion of its neuropil across many hundreds of microns. Jiang and colleagues suggest that the SBC inhibits local GABA interneurons that target the dendrites, soma and axon hillock of layer V pyramidal cells but does not inhibit the pyramidal cell. The NGC cells provide widespread inhibitory influences on the apical dendrites of many pyramidal cells. The authors suggest the NGC population provides a broad inhibitory influence while the SBC provides a disinhibitory influence on a few targeted layer V pyramidal cells. If such neurons occur in the primate layer I cortex and they have influences similar to those in rat somatosensory cortex, layer I that receives abundant widespread excitatory drive from associative corticocortical and corticothalamocortical drive from thalamic matrix cells may provide a top-down influence that would provide a fractured

pattern of excited (disinhibited) layer V pyramidal cells within a few selected minicolumns (by SBC) while suppressing most other pyramidal cells within adjacent minicolumns (by NGCs or by Martinotti Cells, see: Silberberg and Markram, 2007; Berger, et.al., 2010; Palmer, Murayama and Larkum, 2012). Perhaps in primate cortex that has more abundant double bouquet cells (DBCs) some superficial DBCs may supplement or substitute for the SBCs as found in rat somatosensory cortex. However it is not clear that DBCs target other local GABAergic interneurons in the same fashion as SBCs target GABA interneurons in rats. GABAergic Calbindin-positive interneurons identified in superficial layers of prefrontal cortex in monkeys have morphologies similar to those SBCs and NGCs in rat somatosensory cortex (e.g., see Zaitsev, et.al., 2005). Such a disinhibitory circuit for pyramidal cell activation has been demonstrated in Somatosensory cortex (SI) of mice related to Motor Cortex projections to superficial layers of SI (see Lee, et.al., 2013). A slightly different disinhibitory circuit has been described where VIN GABA interneurons in superficial layers of visual cortex are activated by cholinergic input from basal forebrain cholinergic neurons in awake, walking mice (see Fu, et.al., 2014).

MOTOR CORTEX NEURONS: SINGLE CELL & POPULATION ACTION CODING OF MOVEMENT DIRECTION

Many cells in the MI hand area are well-suited to code even the lowest force levels of distal muscles as single cells.

Precise force control is robustly coded by individual MI neurons. However, no such robust relationship exists for Motor Cortex single cell activity and the direction of reaching movements.

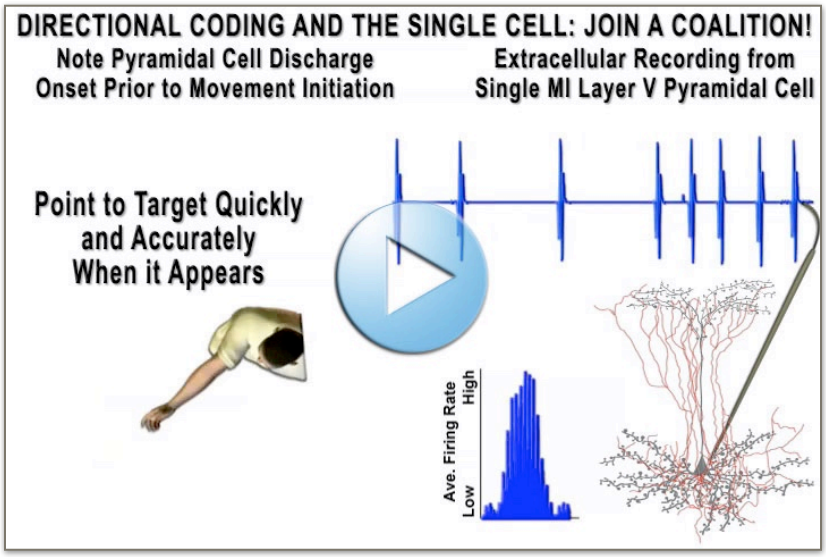


Fig 18-37. Simulation of MI Neurons and Directional Coding of Movement Direction Movie (gec). GO TO: gmomm.pitt.edu Fig18-37_Video

Single cell directional specificity coding has not been seen despite an obvious engagement of motor cortex circuitry for fine motor control of multiple muscles involved in complex reaching and grasping synergistic tasks. Since the 1980s, research by A. P. Georgopoulos, A. Schwartz and others have approached this problem using more sophisticated

computational methodology to describe a directional coding mechanism for reaching into either 2D or 3D space. Directional coding appears to be an emergent property of a neuronal ensemble (population code) not an elemental feature of individual, segregated cells. In addition, multiple cerebral and subcortical sensorimotor areas are involved in this distributed function.

The Simulation of MI Neurons and Directional Coding of Movement Direction Movie allows you to see & hear the simulated response from a Motor Cortex Pyramidal Cell as a subject reaches for that target. Note the movement directions associated with either high, medium or low firing rates of the selected neuron; note the relatively broad directional tuning of individual MI cells. This appearance of the yellow target is the GO signal for the subject to reach for the target. You should hear the modulated neuronal discharge begin slightly ahead of the movement after the target appears which simulates the known property of MI Neurons related to Motor Set. The Pre-movement modulation of activity (Motor Set) typically begins several hundred milliseconds prior to movement onset in MI (mental preparation to move).

The MI Population Encoding of Movement Direction Interactive Flash File allows you to perform a virtual reaching to target experiment by "moving" to different targets and observing the related MI single cell discharge.

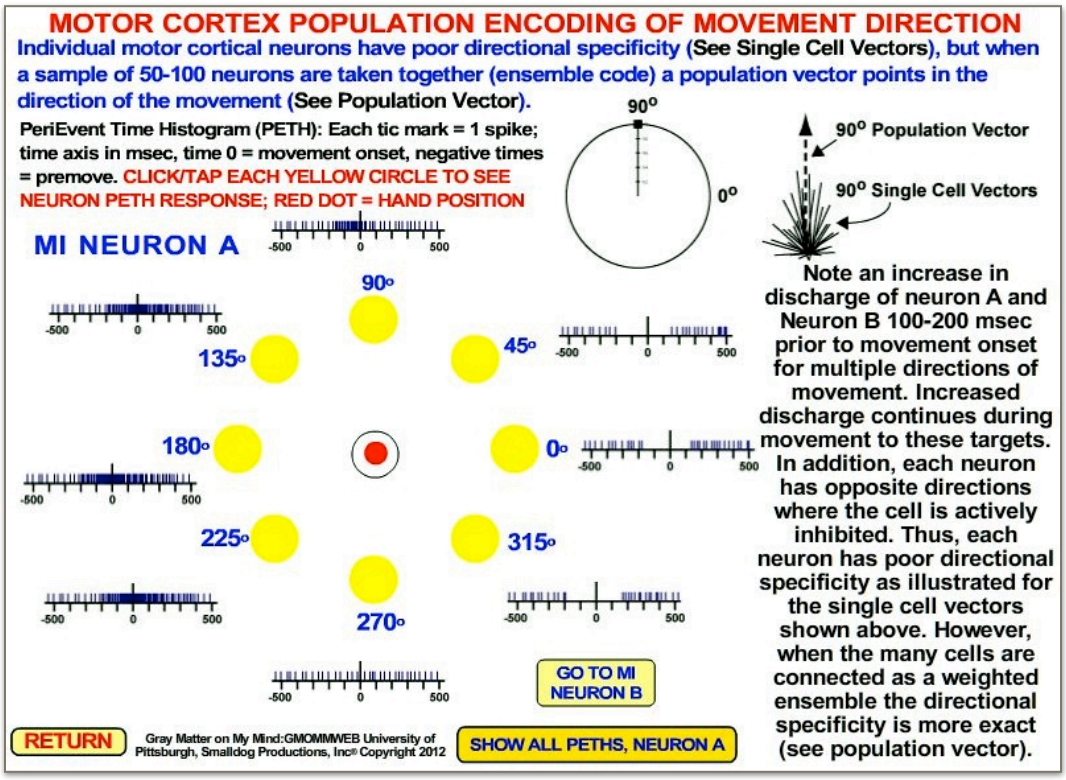


Fig 18-38. MI Population Coding of Movement Direction Interactive Media File (gec). GO TO: gmomm.pitt.edu Fig18-38 Inter-active Media

Note: for some movement directions an individual cell increases its discharge before movement onset and remains very active during the movement but is ***actively*** inhibited before motion directions that

oppose those excitatory angles. This suggests some form of “reciprocal” inhibition within motor cortex networks.

MOTOR SET: “THINK” (SELECT) BEFORE YOU ACT - COMPILE, SIGN & EXECUTE THE WILL

The Lateral Premotor Areas and the Supplemental Motor Area (SMA) are involved in “motor set.” Motor set is the pre-movement activity that characterizes planning and programming of goal directed volitional behaviors. Neurons in premotor areas show a task-dependent modulation of firing that is a critical component of the 'signing of the will' (see Lateral Premotor Motor Set Movie). Many of these neurons are also active when we execute the will. Such neurons must be capable of “holding that action thought” for many hundreds to thousands of milliseconds: what some have called working memory. Recently researchers recorded spiking activity from single cells within populations of neurons in monkey Dorsal Lateral Premotor (PMd) cortex. They demonstrated the ability of PMd neurons to be “multitaskers”. For a two-choice instruction-delay task two separate populations of neurons first “coded” two alternative action choices in working memory. Next, one group of cells became more active according to the target to be chosen during a delay period while a second group of cells were actively inhibited. When the GO signal was given the “correct” choice population of cells dramatically increased their firing while the population of cells representing the alternative choice (incorrect target) were greatly suppressed (see Cisek and Kalaska references and the PMd Action Choice Movie). It has been estimated that 50-70% of neurons in these premotor areas modulate firing related to either motor set or to motor set and movement. By contrast the Primary Motor Area has ~1/3 of its neurons that show such preparatory firing modulation. Premotor areas have extensive corticocortical connections with prefrontal and parietal association areas. They are also well connected with the basal ganglia, limbic areas and portions of the cerebellum. Thus working memory and motor set are distributed processes that depend upon loop networks that integrate and refine neural processes over time.

Fig 18-39. Lateral Premotor Area & Motor Set: Instruction Delay Task Movie (gec). GO TO: gmomm.pitt.edu[Fig18-39 Video](#)

Since feed-forward motor control of skill shows improvement in accuracy, speed and efficient use of appropriate musculature as

we practice, these loops are plastic and modulate neural activity patterns as part of the process of motor learning.

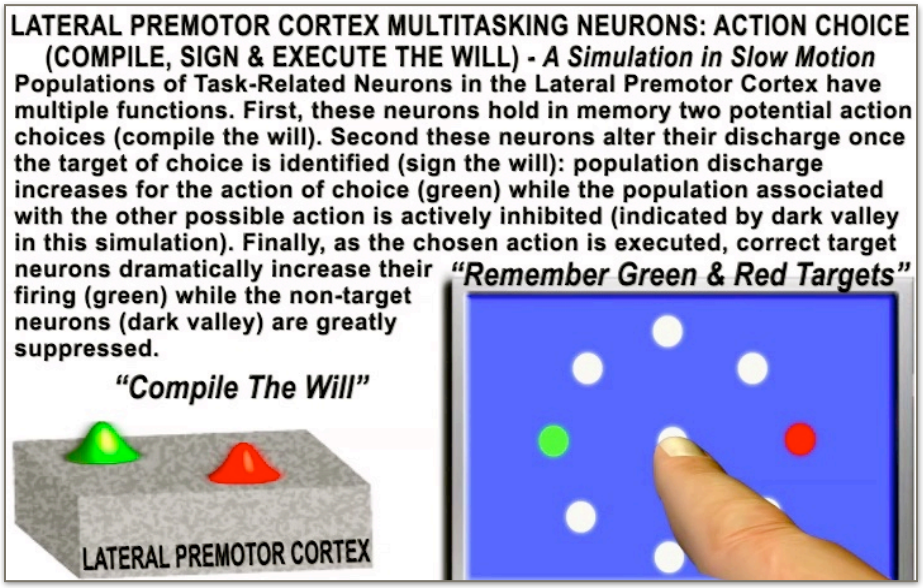


Fig 18-40. PMd Action Choice Movie (gec). GO TO: gmomm.pitt.edu
Fig18-40_Video

Recent studies have shown that motor set is not confined to Supraspinal Neurons. Indeed, many premotor spinal neurons show modulation of their discharge during the pre-movement period corresponding to the Instruction-Delay portion of a goal-directed (target directed) volitional movement. A study by Prut and Fetz (1999) provides evidence that primate premotor interneurons may actually be inhibited during the preparation for volitional movement (instruction-delay) prior to the actual movement. About 30% of the premotor interneurons alter their firing for both premotor and motor components of segmental motor center activity. This percentage is higher than for motor cortex, lateral premotor cortex, supplementary motor area and the putamen: see Cognitive Spinal Interneurons movie.

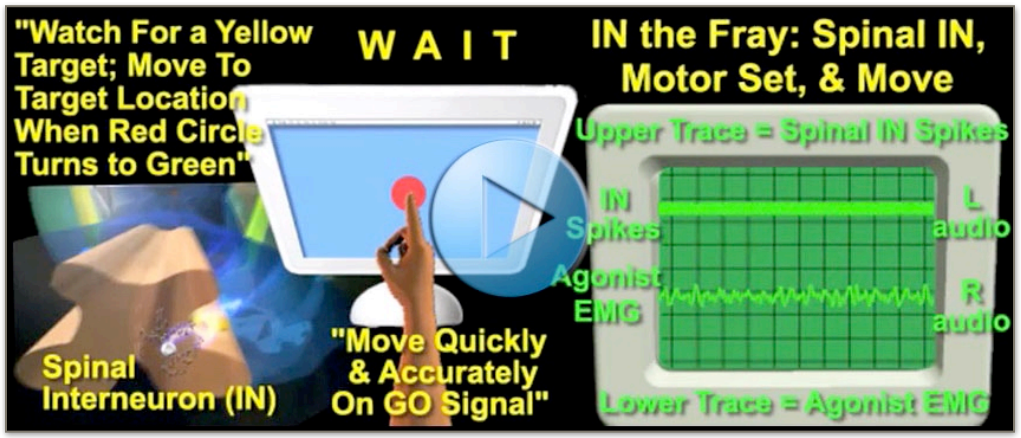


Fig 18-41. Cognitive Spinal Interneurons Movie (gec). GO TO: gmomm.pitt.edu
Fig18-41_Video

MESIAL CORTICAL MOTOR AREAS: SUPPLEMENTARY MOTOR AREAS, ANTERIOR CINGULATE CORTEX AND CINGULATE MOTOR AREAS

Motor Areas on the mesial (medial) surface of the brain have been implicated in higher level processes associated with planning and programming of internally-generated motor tasks that require selection of action sequences to obtain a goal. These areas include the Supplemental Motor Area (SMA) in the Paracentral Lobule, its "long-lost" anterior cousin the preSMA and the Cingulate Motor Areas (CMAs) in the Anterior Cingulate Cortex (ACC). The Supplemental Motor Areas have extensive callosal connections and are typically active bilaterally even with a unilateral motor action. SMAs are heavily connected with other cortical motor areas, association cortex and the "motor" circuit of the Basal Ganglia. In addition, Pyramidal Tract Neurons in the SMA project to the spinal cord to engage segmental motor centers in the ventral horn and Integrative Spinal Neurons in the Intermediate Gray.

Brain Imaging suggests that the SMAs are more relevant for mental rehearsal of and actual performance of motor actions derived from the individual's own will to perform a complex sequence of events (motor plan). This is in contrast to the suggested roles of the Lateral Premotor Areas that are more relevant in motor programs and plans that are triggered/guided by external cues. The Dorsal Frontal Median Cortex (dFMC) anterior to the Pre-SMA plus a portion of the Anterior Insula may have an important role in a final "veto" of impending action. The other areas within this mesial "cognitive" motor region of cortex may contribute to facilitating and/or suppressing endogenously generated actions.

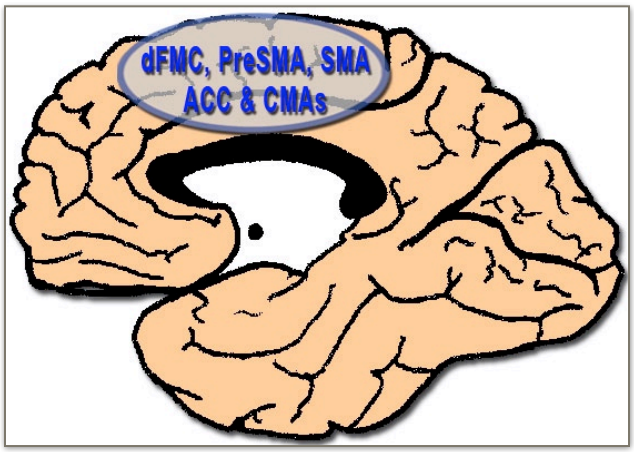


Fig 18-42. Mesial (Medial) "Cognitive" Motor Areas: To Do or Not to Do? (gec).

The Anterior Cingulate Cortex (ACC) has a suggested role in integrating multiple components of implementing one's will in behavioral "coordinates." The ACC has extensive connections with association cortex particularly the prefrontal cortex thought to be responsible, in part, for cognitive processes and executive functions that temporally organize actions in a behaviorally relevant fashion, decisions as to GO versus NO-GO in expression of one's will and judgements based on past history and current circumstances. The ACC has robust connections with other limbic cortical areas, the anterior insula and subcortical structures including the limbic circuit of the Basal Ganglia. These limbic connections provide some "flavor" to one's actions and take into

account reward aspects of the “to do or not to do” weighting performed by successful brains. Finally, Cingulate Motor Areas (CMAs) provide direct output to spinal centers that must be engaged to execute one's will after that will has been signed; these areas have inputs from the Spinothalamic Tract which also has a heavy projection to the Insula. Some investigators have suggested that one's “urge to move” and the individual’s endogenous abstention from some actions is highly correlated with activity levels in these Mesial Motor Areas when connected to lateral prefrontal cortex.

Brain Imaging including regional Cerebral Blood Flow (rCBF) studies are now employed to describe structure-function relationships in the human brain. Early rCBF studies used relatively invasive technology that has since been replaced by other forms of invasive imaging procedures or by noninvasive methods. All of these techniques while providing relatively large-scale glimpses into regional brain activity do not provide the fine-scale spatial and millisecond or sub-millisecond temporal resolution of single-cell recordings. Nonetheless, brain imaging has advanced our understanding regarding the contributions of regional populations of brain cells (neurons and supportive cells) for human brain function. The rCBF movie demonstrates the role of cortical motor areas for simple & sequential motor tasks as defined by early rCBF studies in human subjects.

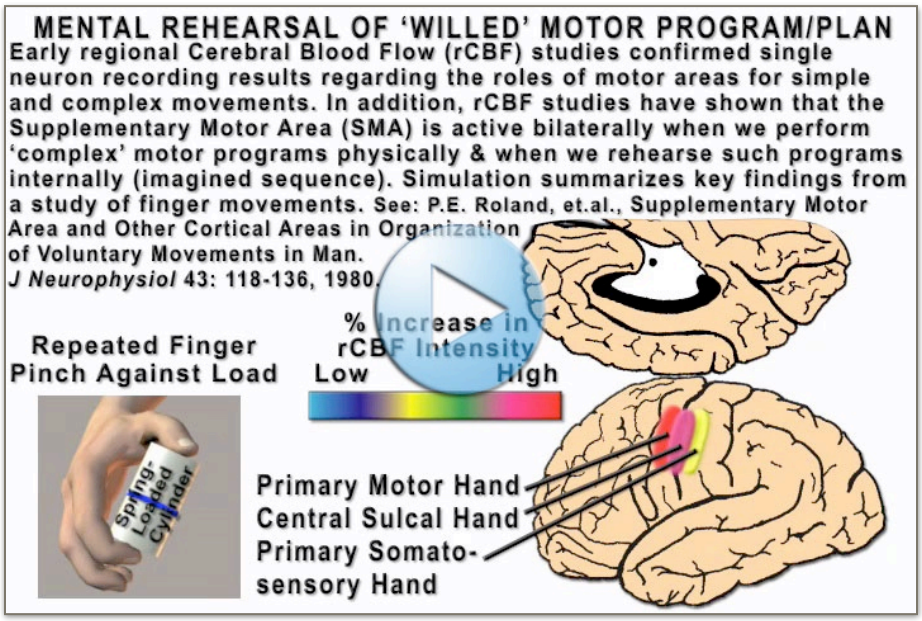


Fig 18-43. Regional Cerebral Blood Flow (rCBF) Study of Cortical Motor Control for Real & Imagined Tasks Movie (gec). GO TO: gmomm.pitt.edu

Fig18-43_Video

MUTABLE MOTOR CORTEX: MOTOR CORTEX PLASTICITY

Multiple studies in multiple species using a variety of techniques together suggest that the motor cortex can change rapidly in response to training. While the mechanisms responsible for this plasticity are not fully understood, most evidence suggests that MI as elsewhere requires use-dependent synaptic changes including Long Term Potentiation (LTP), synaptogenesis, and continued protein production. Motor learning occurs after many repetitions over a long period of training and few studies have looked closely at motor cortex adaptations from early acquisition to over-learning. When an

activity is over-learned the motor system presumably has consolidated network interactions to synchronously activate a “selective” subset of neurons within cortical and subcortical (e.g, basal ganglia and cerebellar) centers. Functional imaging in humans shows increased activity within a number of cortical areas and subcortical areas (portions of cerebellum and basal ganglia) when learning a new motor task compared to performance of a previously learned task. Elevated activity within the motor cortex during initial learning may reflect the role that cortical networks play in “unsupervised” learning when multiple sources of information must be weighed to establish the requirements for the task and optimize neural resources to achieve rapid, accurate performance. Thalamic input to motor cortex particularly during early stages of learning may provide a critical link to MI from the cerebellum, basal ganglia, brainstem and spinal networks. It has been suggested that thalamic input will enhance synaptic function in motor cortex but only if coupled with corticocortical input to MI. This effect appears to be limited to layers II/III pyramidal cells (a source of corticocortical connectivity); no such effect is seen in layer V pyramidal cells (the source of corticofugal outputs to subcortical brain & spinal cord). This suggests that a local motor cortex network is modified prior to output of the revised motor “program.” Plasticity has been studied in SI & MI at the cellular/synaptic level, but not in premotor areas (Lateral & Medial Premotor Areas). Since concepts of motor control are shifting from a hierarchical to a heterarchical model, these areas with direct access to spinal centers may show critical synaptic changes inherent in motor learning.

MUTABLE MOTOR CORTEX: TMS & HUMAN MOTOR CORTEX PLASTICITY

Transcranial Magnetic Stimulation (TMS) has been used in human subjects to “map” MI. Magnetic pulses are capable of producing isolated muscle activation. For example, TMS appropriately positioned may selectively activate the Abductor Pollicis Brevis (APB) muscle.

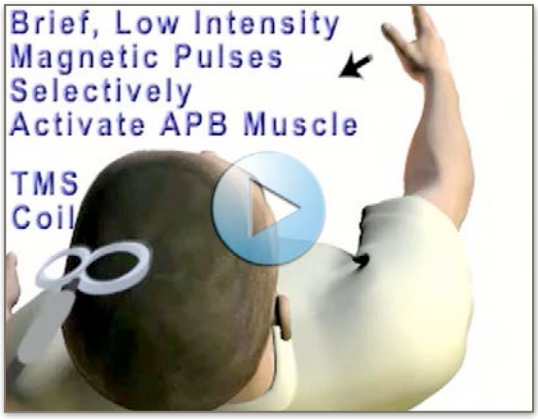


Fig 18-44. The TMS Plasticity Movie above shows the effect of voluntary practice on the motor cortex map; a transient “reorganization” matching the practiced movement (gec). GO TO: gmomm.pitt.edu *Fig18-44_Video*

The amplitude of the evoked response may be potentiated by a paired pulse facilitation: stimulating the median nerve 25-45 msec prior to TMS stimulation of MI potentiates the APB response. Facilitation is greatest when both cutaneous & muscle afferents are stimulated in the Median nerve and effects are time-dependent (intervals 100 msec or longer = no potentiation). The potentiation may

persist for an hour or longer. A recent study using TMS suggests that short periods of practice may transiently alter the MI map. TMS activation of the APB was followed by voluntary practice of thumb flexion/adduction for 30 minutes with no TMS stimulation. Following practice, TMS to the same MI location (APB) now shows a map consistent with the antagonist muscles (thumb motion ~ 180 degrees from the original evoked response). Within an hour post-practice, the TMS map reverts to abduction/extension of the thumb.

Practice effects appear to be use-dependent; indirect evidence (use of NMDA blockers, GABA agonist drugs or repeated MI stimulation to attenuate TMS effects) suggests that TMS-activated plasticity is use-dependent in human subjects. Taken together, these data suggest that implicit "practice perfection" relies upon similar use-dependent synaptic modifications in the motor system as those found in the medial temporal lobe that mediate/enhance one's explicit knowledge-base.

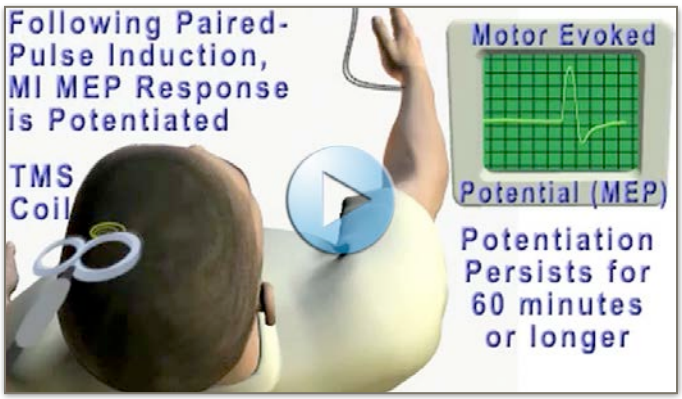


Fig 18-45. The TMS Paired-Pulse Movie shows the effect of correlated peripheral and central activation of MI to produce paired-pulse facilitation. Correlation of hand use & Motor Map Plasticity requires temporal synchrony (gec). GO TO: gmomm.pitt.edu

Fig18-45_Video

MUTABLE MOTOR CORTEX: HEBBIAN ASSOCIATIVE PLASTICITY

D. O. Hebb (1949) hypothesized that repeated use of a synapse will grow the relationship between activity-coupled cells. The concept of a Hebbian synapse has become a springboard for revolutionary research on the synaptic & molecular bases of learning and memory. *In-vitro* methods to study neurons in culture or in brain slices and *in-vivo* recordings of whole cell (soma) and dendritic potentials show rapid changes that may potentiate or depress synapses.

Neurotrophins provide "permissive" or "instructive" roles in maintaining or growing neuronal relationships that may be activity-dependent. Activity may be specific to synapses and/or to the overall activity of the organism (e.g., exercise may influence certain neurotrophins levels). Growing evidence suggests "neurons that play (fire) together stay (wire) together.

The Associative Hebbian Learning in Primary Motor Cortex (MI) movie simulates one example of a Hebbian Synaptic Enhancement called Associative Long Term Potentiation or LTP in Motor Cortex. Simultaneous Somatosensory Corticocortical and

Thalamocortical Input from Ventral Lateral (VL) Nucleus induces LTP (see figure). Hebbian mechanisms have been studied in MI, SI & other CNS areas.

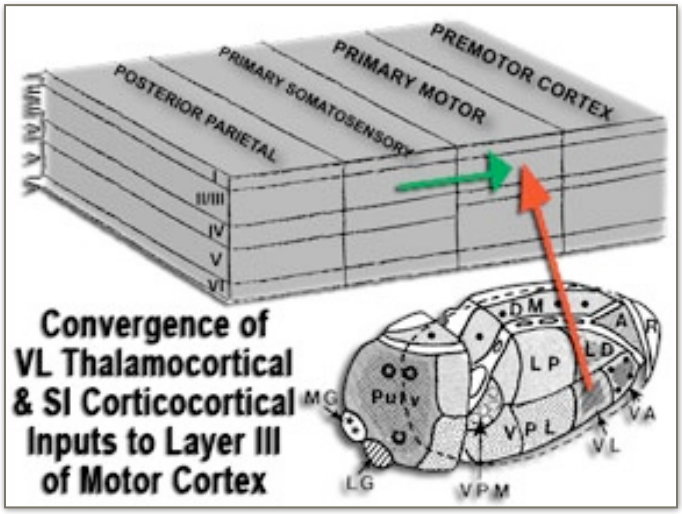


Fig 18-46. Convergent Primary Somatosensory Cortical and Ventrolateral Thalamic Inputs to Primary Motor Cortex (gec).

Motor Cortex Plasticity Simulation Movie simulates associative (cooperative) LTP in MI. Such Hebbian plasticity was seen in layer III of MI but not in layer V. Layer III receives abundant synaptic thalamocortical and corticocortical synapses while layer V does not.

Fig 18-47. Motor Cortex Plasticity Simulation: Hebbian Associative Learning Movie (gec). GO TO: gmomm.pitt.edu Fig18-47_Video

Since layer V represents the "motor" output layer for MI (and many other cortical areas) the Hebbian Learning restricted to supragranular cortex would support the adage of "think before you act" at a spatial and temporal micro scale in cortical columnar processing. One could imagine profound plasticity in other motor areas since they have such a critical role in motor learning and motor control.

Spike timing dependent plasticity (STDP) in corticomotoneuronal (CM) cell connections with alpha motoneurons has recently been demonstrated in monkeys. A cervical spinal cord electrical pulse (indwelling electrodes) is triggered by a motor cortex CM discharge. If a pyramidal cell spike triggers the electrical pulse stimulation within a ~10-25 msec post-spike window, there is potentiation of the muscle response. No potentiation occurs if the spinal cord shock is delayed more than 50 msec after the CM cell fires.

If the timing is zero, i.e., the spinal shock is timed precisely to CM cell firing, the muscle may actually be inhibited. Other muscles show a spike timing dependent suppression associated with appropriately timed stimulation. Such STDP effects may persist for a few days but disappear after that time. Other muscles, presumably not innervated by the CM cell, show no STDP as would be expected if the spinal cord electrical shock is specific for influencing a CM to alpha motoneuron connection. Animals were not trained to perform any specific task. (see Nishimura, et.al., 2013).

UPPER MOTOR NEURON SYNDROME: ALTERED MOTONEURON RECRUITMENT & REFLEXES

An upper motor neuron (UMN) pathology has a constellation of signs and symptoms resulting from loss of both pyramidal and nonpyramidal descending control of motor centers in the brainstem and spinal cord. For example, a lesion of the posterior limb of the internal capsule due to a stroke involving deep branches of the middle cerebral artery typically produces a "classic'" UMN disorder. Damage to descending white matter tracts in the spinal cord may result in an UMN Syndrome that may include all or some of the following signs and symptoms; the actual pattern depends on which tracts are involved. The UMN disorder includes both "positive" and "negative" sequelae.

UMN Positive Signs and Symptoms: Spasticity, Hyperreflexia (hyperactive deep tendon reflexes, clonus, abnormal mass reflex response), Up-going (positive) Babinski and positive Hoffmann Sign.

UPPER MOTOR NEURON (UMN) SYNDROME: PATHOLOGICAL REFLEXES

Pathological reflexes are clinical tests of positive signs of an Upper Motor Neuron Disorder. There are a number of tests described in many neurology texts. Many of these tests are superficial reflexes requiring delivery of a specific stimulus to a specific body location. The most extensively used pathologic reflex test is the Babinski.

Fig 18-48. Normal & LMN Down-going Babinski and Negative Hoffman Reflex Movie (gec, jec). GO TO: gmomm.pitt.edu Fig18-48_Video

The sole of the foot is firmly stroked along a path from heel to lateral border to the ball of the foot. This stimulus produces a flexion of the toes or no response in normal adults and children. However, in our first year of life we normally have an extensor plantar response (up-going big toe & possible flaring of other toes). After age 2 an extensor plantar response indicates a "long tract" lesion: a pathological response. A positive Hoffmann sign (flexion of the fingers and

flexion/adduction of the thumb when the nail of the middle finger is “flicked”) is thought to be a sign of UMN pathology in adults.

A negative Hoffmann is no response. Sustained ankle stretch often produces clonus in UMN disorders. Individuals with a lesion of cerebral motor areas and/or descending pathways typically show pathological reflexes. Babinski will be up-going (toe extension) and the Hoffmann sign will be positive. Therefore an upper motor neuron disorder will show positive responses to these and other tests for “long tract” signs of upper motor neuron involvement. A rapid and sustained stretch of the plantarflexors may elicit clonus in an individual instructed to relax and not resist the motion. Clonus is seen and felt as a damped oscillatory clonic response to sustained high velocity muscle stretch. Clonus may be tested at the ankle, patella, and wrist.

UPPER MOTOR NEURON (UMN) SYNDROME: “SPASTIC” PARESIS

UMN Negative Signs and Symptoms: paresis/paralysis, loss of dexterity, poor muscle fractionation, abnormal motor unit recruitment, altered muscle synergy, shock (initially), no clinical or electrophysiological evidence of muscle denervation.

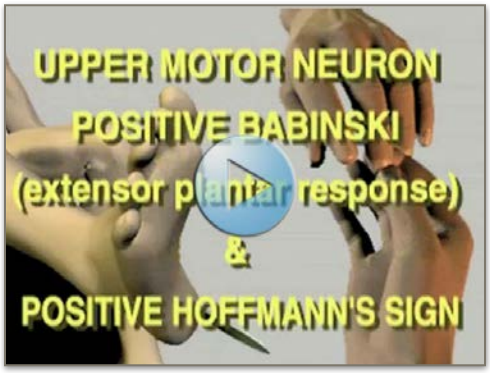


Fig 18-49. UMN Up-going Babinski and Positive Hoffman Reflex & Clonus Movie (gec, jec). GO TO: gmomm.pitt.edu *Fig18-49_Video*

Neural control of voluntary movement requires cooperation of many motor control centers located at all levels of the nervous system. Here we are concentrating on the descending pathways that synapse upon the segmental motor centers (SMCs) in the spinal cord, and the alpha motoneurons that provide the neural link to skeletal muscles in the periphery.

Fig 18-50. Normal Motor Recruitment Movie: Good Fractionation and Strength (gec, jec). GO TO: gmomm.pitt.edu *Fig18-50_Video*

Damage to the former results in an UMN Syndrome, damage to the latter, LMN Syndrome. Damage to the long tracts does not result in degeneration of motoneurons in the SMCs. However, a total transection of the spinal cord does isolate the spinal circuitry below the level of the

lesion causing altered motor output with loss of volitional control. Incomplete or unilateral lesions result in varying forms of functional weakness and loss of dexterity.

The first movie (Normal Motor Unit Recruitment) shows an example of normal voluntary movement. The test of ankle dorsiflexors illustrates three principles: 1). The movement is restricted to the appropriate muscles (normal fractionation). 2). The motion is full (normal range as the foot is dorsiflexed against gravity to touch the examiner's hand). 3). The movement shows normal strength (the examiner cannot “break” the isometric contraction). This screening does not guarantee that the muscles can be used in functional activities, e.g., gait where contractions must be precise & fast. This test requires holding a slowly building isometric tension. A second movie (Upper Motor Neuron Motor Recruitment Movie) shows paresis due to an UMN Disorder. Volitional movement is not restricted to the appropriate muscles (poor fractionation). As the foot is lifted, the knee and hip are activated as well. As resistance is applied recruitment spreads to ankle inverters, toe extensors, knee flexors, hip flexors, abductors and external rotators. This screening suggests that during gait there will be poor foot clearance during swing and an inversion of the foot accompanying attempts to dorsiflex. This may lead to toe-drag and an unstable ankle if weight is borne on the lateral border of the inverted foot. An abnormal recruitment pattern is typical for UMN disorders.

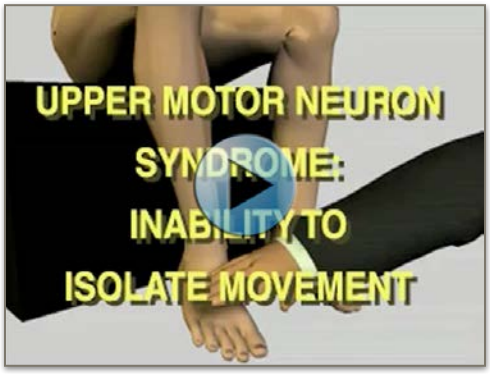


Fig 18-51. Upper Motor Neuron Motor Recruitment Movie: Poor Fractionation (gec, jec). GO TO: gmomm.pitt.edu *Fig18-51_Video*

VOLITIONAL CONTROL IS NOT ABOLISHED FOLLOWING AN ISOLATED PYRAMIDAL TRACT LESION

Most individuals would expect to find a severe spastic hemiplegia (UMN Syndrome) contralateral to a lesion of the Corticospinal fibers. A. L. was a 70 year-old man who suffered from severe left hemiballism (incessant involuntary movements). His neurosurgeon cut the middle third of the right Crus Cerebri. The reported results were: 1. hemiballism was immediately & permanently abolished and 2. volitional movement was not abolished in the contralateral limbs. He gained almost full control of his musculature, had a persistent Up-going Babinski, some loss of dexterity, but good return of muscle power. Spasticity was not present up to his death 2.5 years later. An autopsy revealed almost complete degeneration of the right medullary pyramid. The surgical cut spared the Non-Pyramidal Tract (Non-PTN) axons laterally (Parieto-Temporo-Occipito-Pontine Axons) and medially (Fronto-Pontine Axons); see Bucy, et.al., 1964 reference.

Partial mid-cerebral peduncle or total medullary pyramid lesions in monkeys show similar results. Post-Op animals can right themselves, have good head, neck & trunk

control, good ambulation. The major deficit appears to be a reduced distal limb dexterity. Some cases show a “permanent” loss of fractionated finger movements. Spasticity as defined clinically does not develop although a Positive Babinski may be present (see Kuypers, 1981). Spared Rubrospinal Tract and other Descending Tracts originating in the Brainstem (and influenced by Non-PTNs) are not lesioned and may provide significant motor control. Sparing of CorticoPontine Axons after lesioning the corticospinal axons may preserve a critical CerebroCerebelloCerebral Loop that is important in regulation of precise motor control. Cortical and cerebellar connections with the Red Nucleus are preserved after a pyramidal tract lesion. The Rubrospinal Tract influences short propriospinal neurons plus lateral motor nucleus motoneurons and interneurons. All are involved in motor control of limb musculature.

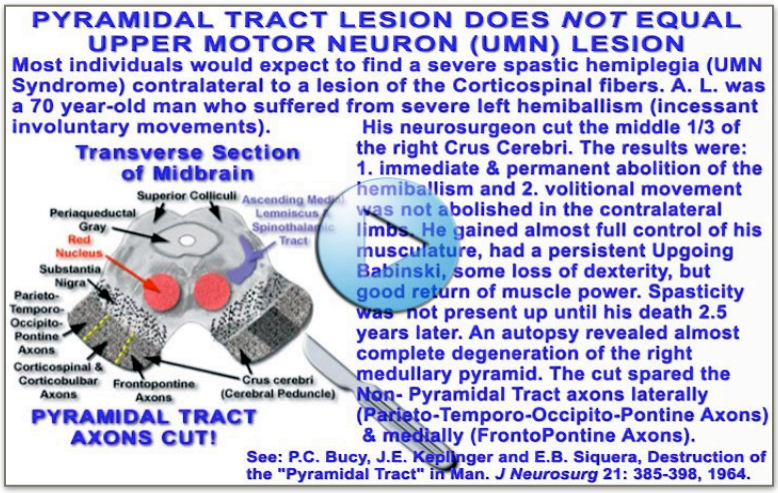


Fig 18-52. Partial Cerebral Peduncle Lesion Movie: All Volitional Movement is Not Lost (gec). GO TO: gmomm.pitt.edu
Fig18-52_Video

TRADITIONAL VOLITIONAL CONTROL MOVIES (CLASSICAL UMN TO LMN CIRCUIT)

A manual muscle test checks an individual's ability to activate a particular muscle/muscle group in isolation. Early studies of voluntary movement stressed the importance of the Pyramidal Tract (PT) & direct, monosynaptic connections between motor cortex & a small pool of Agonist Alpha Motoneurons. Thus, Pyramidal Tract Neurons (PTNs) represent Upper Motor Neurons and Alpha Motoneurons are the Lower Motor Neurons.

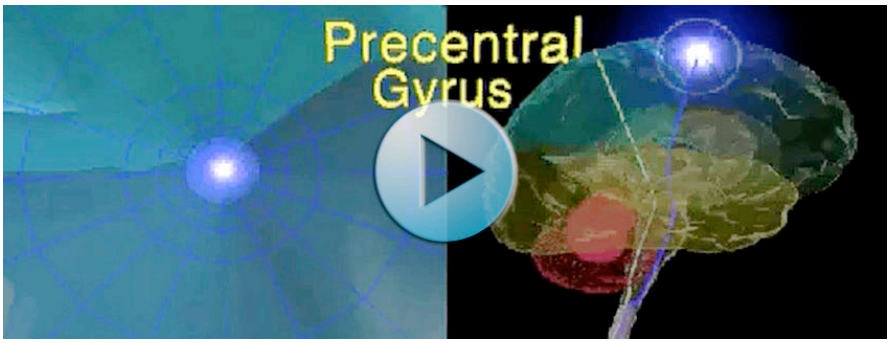


Fig 18-53. LCST Pathway from Cerebral Cortical Layer V Pyramidal Tract Neurons to Spinal Gray (gec, dh). GO TO: gmomm.pitt.edu
Fig18-53_Video

Recent studies cast doubt that such a simplified system controls skilled actions. Many cortical and subcortical areas participate in the signature and the execution of one's will. While PT

lesions may result in reduced dexterity of movement, muscle power and “gross” muscle function returns and there is no spasticity (as classically defined) if the PT is selectively involved. Lesions restricted to the Pyramidal Tract are rare. Most UMN lesions involve cerebral gray and/or white matter or spinal lesions of descending tracts including PT and Non Pyramidal Tract axons. Such lesions produce classic UMN signs and symptoms including spasticity. The Lateral Corticospinal Tract (LCST) Movie illustrates UMN pathway to Segmental Motor Centers (SMCs) in Lateral Motor Nucleus.

The LCST to SMC Activation Movie illustrates LCST input to Agonist and Antagonist SMC Alpha and Gamma Motoneurons and Interneurons.

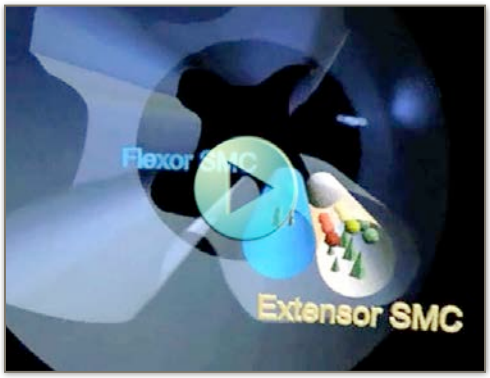


Fig 18-54. LCST to SMC Activation Movie. Large & Small Pyramids in spinal gray = Alpha & Gamma Motoneurons, respectively. Red Spheres = Ia Inhibitory Interneurons. Blue beams = LCST Input to Agonist (Extensor) SMC. Red Beams = Reciprocal Inhibition of Antagonist (Flexor) SMC Neurons. Shower of Small Particles = Nonspecific Modulatory Influences on SMC (gec). GO TO: gmomm.pitt.edu *Fig18-54_Video*

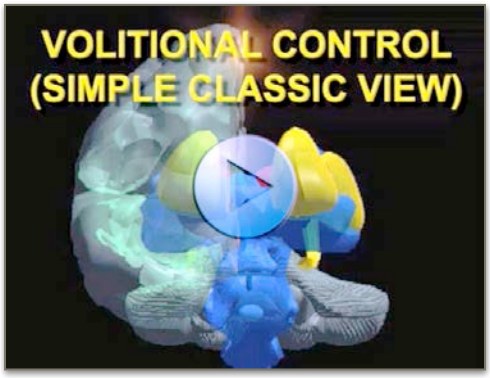


Fig 18-55. Simple Classic View of Upper Motor Neuron to Lower Motor Neuron Control of Volitional Action Movie (gec). GO TO: gmomm.pitt.edu *Fig18-55_Video*

VOLITIONAL CONTROL MOVIE (DISTRIBUTED CONTROL CIRCUIT)

A maximal voluntary contraction requires intact motor units at the peripheral level, intact descending pathways to activate the appropriate segmental interneurons & motoneurons, and intact central sensorimotor control centers. These centers are reciprocally connected in a distributed network spanning all levels of the CNS.

Fig 18-56. “New” Distributed View of Sensorimotor Control of Volitional Action Movie (gec). GO TO: gmomm.pitt.edu *Fig18-56_Video*

In addition, one's ability to maintain precise levels of force or limb position for any length of time appears to be dependent upon somatosensory input to update these motor centers after movement has been initiated. A distributed system may call

upon neurons in multiple brain areas to contribute to each of the stages in a volitional task: “compiling the will”, “signing the will” and then appropriately “executing the will”. A simple UMN to LMN circuit is inadequate to fulfill the demands of goal directed voluntary movement. This process includes “signing the will” before “executing the will”: a “legalization” of neural control to be certain that the wiring will stand up in the court of successful actions that define extraordinary human behaviors. Both of these components are typically built upon a previous ”compiling of the will” where intentional goals are coded. Single cells are unlikely able to accomplish this in isolation but an emergent population code should be quite capable of such a feat.

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Chapter 19

HIGHER FUNCTIONS: WIRED FOR SUCCESS

WHY DO WE HAVE SO MUCH GRAY MATTER ON OUR MINDS?

Through extensive intrinsic and extrinsic white matter connections, the human cerebral cortical gray matter extends our perceptual and behavior repertoire to include:

1. FRACTIONATION - the ability to move body parts independently and to localize motor actions to a limited set of appropriate muscles activated with precise timing.

2. ENHANCED SPEED, AGILITY, ACCURACY, AND ADAPTABILITY IN GOAL-DIRECTED MOTOR BEHAVIOR.

3. REFINED MOTOR LEARNING AND ENHANCED MOTOR PERFORMANCE IN SKILLED TASKS.

4. THE ABILITY TO DEFINE AND TO REFINE THE PERCEPTIONS OF as well as THE MANIPULATIONS OF OUR ENVIRONMENT

- by superb manual dexterity & eye-hand coordination in use of tools and devices

- by improved control of communication skills and expressions of one's being: e.g., reading, writing, drawing, painting, sculpting, dancing, sports, music, computations and other expressions of abstract reasoning.

5. CREATION AND TRANSFORMATION OF OUR IDEAS, THOUGHTS, AND WILL INTO IMMEDIATE OR DELAYED ACTIONS/GESTURES AS APPROPRIATE FOR THE SITUATION; this requires “executive” planning, programming, judgement and a “working memory” for the generation & regulation of goal directed purposive behavior.

6. THOUGHTFUL SELECTION OF REWARD-BASED “POSITIVE” BEHAVIORAL CHOICES WHILE SUPPRESSING BEHAVIORS HAVING POTENTIALLY “NEGATIVE” OUTCOMES.

WIRED FOR SUCCESS: WILL TO WAY - NO WAY; IS “FREE WILL” A PERCEPTUAL ILLUSION OR VIRTUAL REALITY?

Volitional behavior is often associated with “free will.” Philosophers and scientists have debated the existence of 'free will' for centuries. Whatever the answer may be, volitional movements are typically associated with internally generated action sequences based upon one's thoughts or upon one’s decision to respond to an external cue to move in a controlled fashion. It has been said that volition must be tied to the actor to reflect a will. Our will is linked to our inner being, thoughts and to events, objects and people in the world around us. The intensity of one’s will may be the driving force to facilitate one particular behavior while suppressing all others.

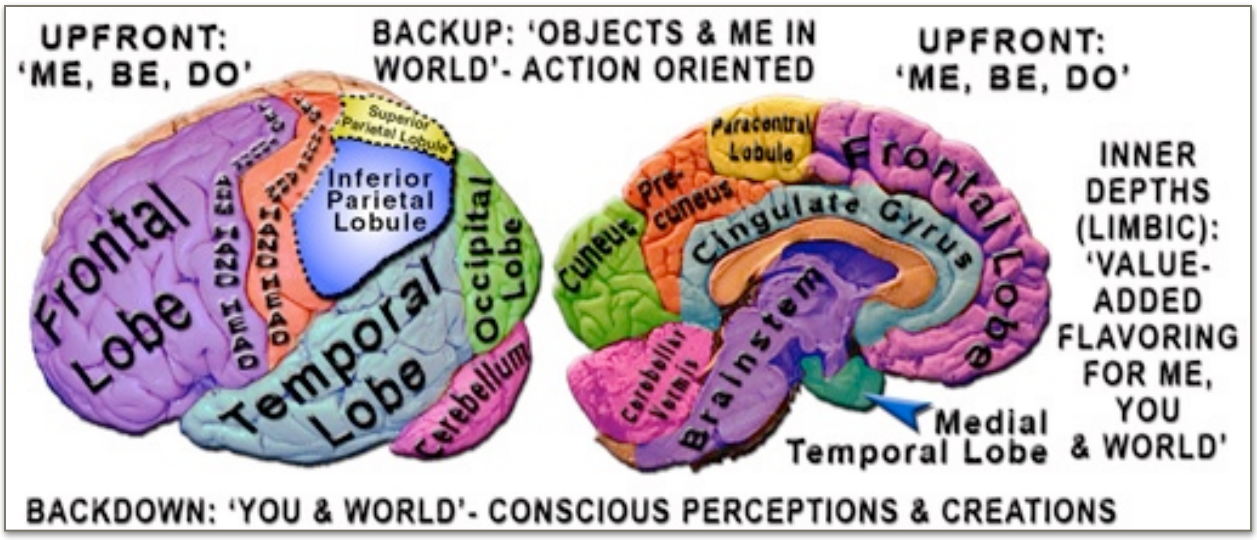


Fig 19-1. Cerebral Contributions to Human "Personhood": Upfront, Backup, Backdown and Inner Depths. Cooperation among neural networks provides a beautiful sight to behold; when disparate events among neural networks fray the fabric of binding, things can get ugly! (gec)

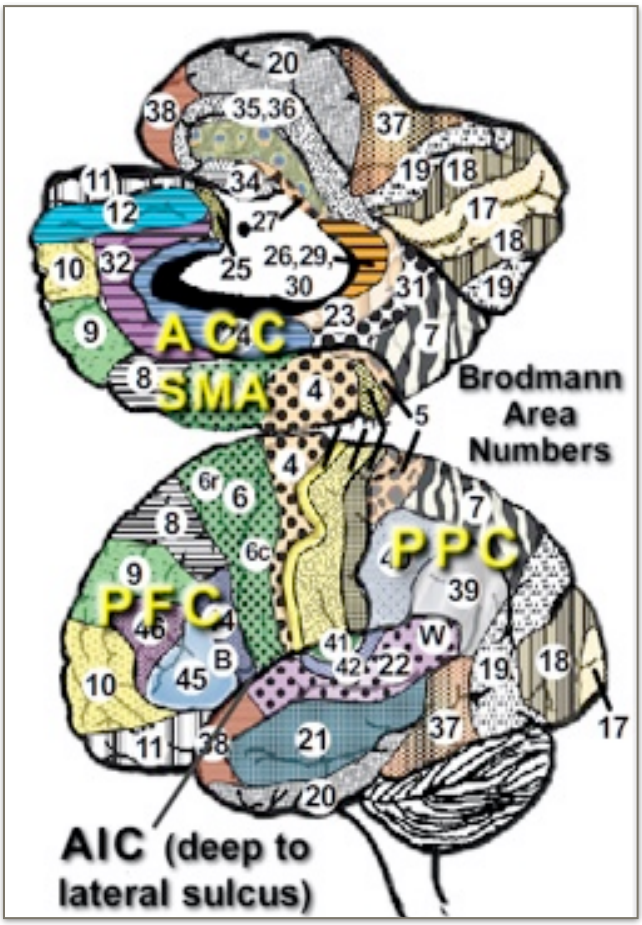


Fig 19-2. Cortical areas related to "compiling and signing the will'": the recognition that it has been signed and then getting all parties in the same room before "execution of the will." (gec)

Ownership of one's actions requires knowledge of the event in a predictive/" postdictive" manner. This requires a sense of agency that may relate to internal signals of intention (efference) and to external signals generated by one's action (re-afference). Scientists suggest that the neural basis of volition involves mesial frontal cortex: Anterior Cingulate Cortex (ACC), medial prefrontal cortex and the Supplementary Motor Area (SMA) particularly the pre-SMA portion of the Supplementary Cortex. Awareness of one's actions may include the Anterior Insular Cortex (AIC) plus the ACC. These areas have direct access to brainstem & spinal centers to generate action and "pickup'" sensations.

Association areas in the posterior parietal cortex (PPC) & prefrontal cortex (PFC) are suggested to be “upstream” regions critical to thoughts and perceptions associated with one's will. Such “feedforward-upstream” processing may not be fully within our cognizance.

Finally, brainstem sources of dopaminergic, noradrenergic, cholinergic, serotonergic and other modulatory inputs to these cortical areas may facilitate or suppress cortical areas to enhance neural circuits to either SELECT and DO or SUPPRESS and DON'T.

MESIAL FRONTAL SUPRACALLOSAL CEREBRAL CORTEX: YOUR “DO” POINT FOR SUCCESS

Volition assumes a will to do. Intention drives internal goal achievement. Based upon one’s wants or needs, the “means to the ends” must be selected while alternative behaviors must be suppressed. Reward expectation for one’s actions drives our intention. Rare reward opportunities may drive complex, sophisticated, novel (non-routine) behaviors leading to outstanding achievement: success. This process may begin outside of our conscious awareness until a few hundred milliseconds prior to action initiation. Ownership of one’s actions (agency) may depend upon an awareness of what is or has happened due to internal intention signals and external sensory signals related to one’s own action. Reward selection beyond one’s basic needs appears to be crucial for a civilized society to prosper. At one extreme rewards may be altruistic (benefit to others) while at the other rewards may be self-centered (me-me-me). Most selected behaviors appear to lead to outcomes that split the difference although each person may lean one way or the other based upon intention, risk, opportunity and perceived reward value.

The mesial frontal lobe superior to the corpus callosum may contain neural networks that in primates provides the ultimate intelligent control of internally generated, reward-based, novel (non-routine) goal directed behavior. This area of the cerebral cortex includes medial prefrontal cortex, a major portion of the Anterior Cingulate Cortex (ACC) and the Supplementary Motor Area (SMA) composed of the SMA proper and the pre-SMA. Neuroanatomical, neurophysiological, imaging and lesion studies all suggest a convergence of necessary brain resources as inputs to this mesial frontal cortex and the necessary output from this area to action oriented cortical areas, brainstem and spinal cord to make your decisions look good. Often that requires learning to gain appropriate insight into those decisions about what to do or not to do & what works. This region of the cerebral cortex has been implicated in motor planning; “urges” to do; conflict monitoring; reward-based processing; coupling of attention, motivation, affect & intention to action; filtration and selection of optimal performance parameters and error detection/correction, e.g., see Paus, 2001; Shackman, et.al., 2011 for review. Such processing is most intense for conflicting behaviors and revision of “subpar” behaviors to optimize transitions from exploration to exploitation. **These mesial frontal areas can be thought of as your brain’s “cache cow” for bundling complex goal directed**

actionable sequences associated with novel or non-routine behaviors. In addition to lateral frontal cortex, several subcortical centers appear to be particularly important as inputs and as part of a distributed network loop; dopamine neurons in the midbrain and basal ganglia loop connections are critical. On one hand, emotions may sustain our will to do and succeed. On the other hand, excessive limbic overtones could provide distracting 'noise' that may elevate metabolic demands and challenge goal achievement.

COGNITION: IS AWARENESS OF OURSELVES & OTHERS AN INSULAR VIEW OF REALITY?

Recent imaging studies of the human brain suggest that the cortex deep to the lateral sulcus (insula) may have greater importance than just a visceral or autonomic sensorimotor representation. The insula, in particular the Anterior Insular Cortex (AIC) also named FrontoInsular Cortex may be a critical area to help form the neural basis for human awareness.

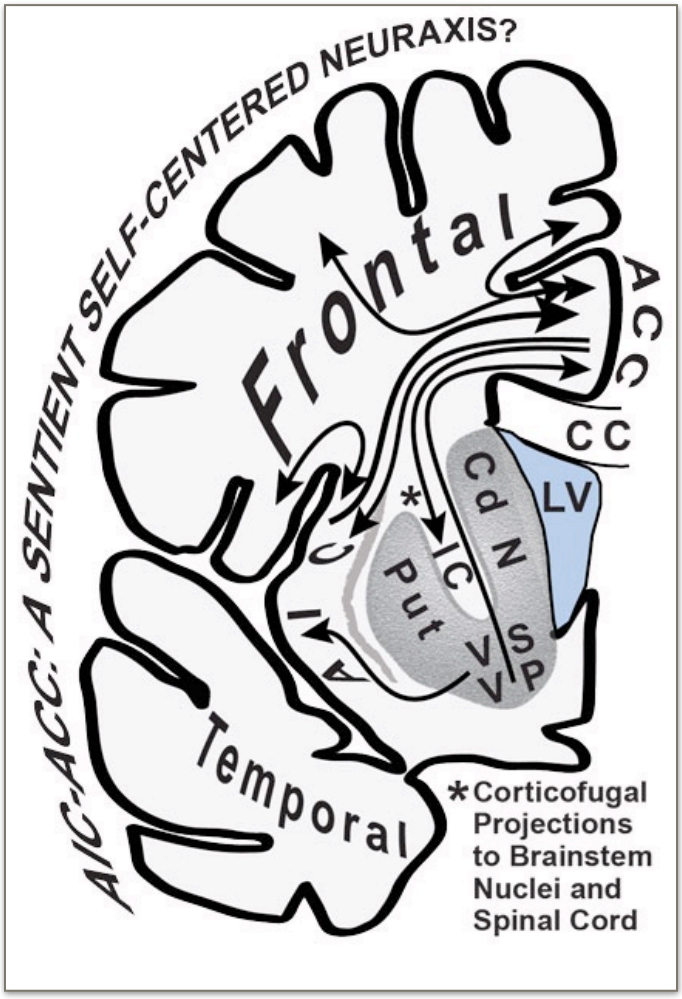


Fig 19-3 Insula buried in the lateral sulcus may be out of our view but not invisible to the mind's eye which "observes and respects" the wisdom of this phylogenetically old cortex. The insula may have an important role in our ability to be aware of ourselves and possibly link our self-awareness to the "feelings" of others. The insula does not work alone (see text and figure). ACC = Anterior Cingulate Cortex, AIC = Anterior Insular Cortex, CC = Corpus Callosum, CdN = Caudate Nucleus, IC = Internal Capsule, LV = Lateral Ventricle, Put = Putamen, VS & VP = Ventral Striatum & Ventral Pallidum. DoubleArrows represent reciprocal connectivity (gec).

Such a representation of the self is dependent upon recognition of salient sensory data from within (interoception) coupled to extrinsic data. The representation may have a significant limbic flavoring such that it places one's awareness of "feelings" in context with that of others (social communicative cues). It is suggested that the anterior insula participates in a nonlinear

time-buffered representation of salient events within one's personal history anchored to the present. The representation of those times when highly charged instances occur may be expanded such that any “playback” appears to be in “slow-motion”; such “flavored” (emotionally tagged) events may be the least forgettable, e.g., see Craig, 2009. Awareness “mapped” within the AIC has direct connections with mesial frontal cortical areas that have been implicated in the will or urge to move: Anterior Cingulate Cortex (ACC) and nearby structures including the PreSMA, SMA proper and adjacent prefrontal cortex. The ACC (especially Cingulate Motor Areas) and the Insula receive projections from the Spinothalamic Tract. Placing a social and/or an emotional “tag” onto our thoughts and feelings such that we define our inner being may include both AIC & ACC. This AIC-ACC combination may provide the ability to “read” emotional state of others and place their gestures and social cues regarding their feelings into a nonverbal communicative context and allow us to govern behavior according to those cues. Interestingly a particular type of projection neuron called a Von Economo Neuron (VEN) is found in these two areas but not other cortical areas in higher primates, e.g., apes and humans. Despite a paucity of direct evidence, it has been suggested these VENs provide rapid processing of inputs to the AIC and ACC. The axonal targets of VENs in uncertain. VENS are virtually absent at birth but increase in number within the first year of life. The AIC-ACC axis may provide at least a partial neural network for “insight,” pleasurable versus non-pleasurable tags (emotional salience) to events, actions, desires or wants based on an internal drive, and other human traits related to social and moral norms. This is a personal, perhaps autobiographical virtual representation of reality since each brain personalizes its (my/your) view of the world. We select and amplify some emotionally tagged data but disregard & attenuate the rest.

WIRED FOR SUCCESS: WE’RE LOOKING GOOD VS. YOU HAVE A PROBLEM-ACC THE “FIXER?”

We have all been there. You (your brain) has chosen an action sequence that satisfies your needs, provides the desired reward and runs economically without a hitch (error-free). Backslapping and “high-fives” all around for the responsible brain network. Suddenly there's a problem (think man-made disaster). Now the blame game begins and its *your* problem if you are the Anterior Cingulate Cortex (ACC) in charge of monitoring “success.” Perhaps the context or environment has changed, or errors mysteriously creep in or the expected reward is not forthcoming: time for “plan B.” Scientists suggest that the ACC may be in a perfect position to get the memo and perhaps to be the “*fixer*.” The ACC has access to emotional, motivational, cognitive and even motor circuitry to lead the effort. When things screw up, an EEG potential called the error related negativity (ERN) is recorded at the C_z location at the top of the skull ~50-150 ms after an erroneous action followed by a longer lasting (~300-500 msec) positive potential. This negative/positive EEG potential is recorded above the mesial frontal area that includes the ACC. fMRI studies have shown a hotspot in the ACC when subjects must choose a correct response during difficult cognitive tasks e.g, Stroop test.

The ACC may not only detect errors but be on alert when errors are likely to arise and a rapid shift in action must occur for the brain to succeed. Recent studies show ACC neuronal discharge linked to reinforcement learning. When trial & error learning begins, the search phase (exploration) shows ACC neuronal spiking associated with reward feedback. When the first correct action sequence occurs some ACC neurons discharge with reward feedback & action. Thereafter, these ACC cells may spike only when action is initiated (exploitative phase). **This dramatic switch may be the "lightbulb over the head" moment of insight: use this behavior. It works. Together, these findings suggest that neural networks in the ACC rapidly respond to changing conditions that relate to suboptimal versus optimal performance. Rapid behavioral adaptation in a changing world depends at least partially upon ACC monitoring of potential "hiccups" in the neural coding "software" for success.** The ACC receives strong dopaminergic neuromodulatory inputs from the ventral tegmental area and provides a strong driving output to the locus coeruleus (LC) that, in turn, provides a major source of adrenergic energizing of the cerebrum, brainstem and spinal cord. For review see Posner, 2004.

WILL TO WAY: ANTERIOR CINGULATE CORTEX (ACC)- LINKING REWARD-BASED COGNITION & EMOTION TO ACTION

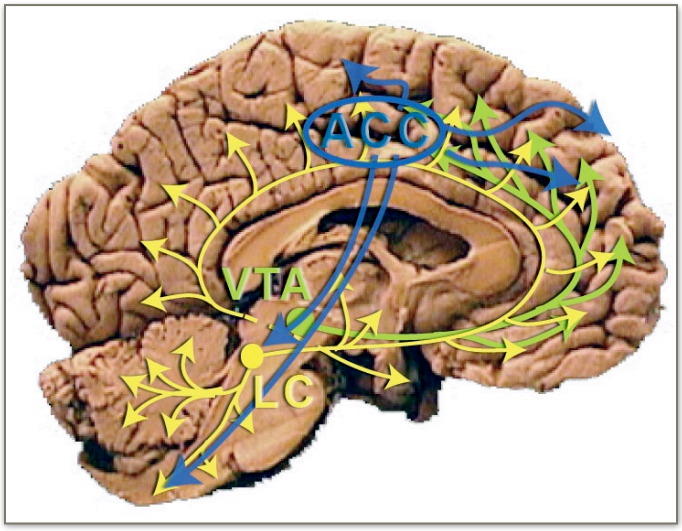


Fig 19-4. Anterior Cingulate Gyrus as a source of excitatory drive (blue arrows) to the locus coeruleus (LC in yellow) and to the spinal cord. LC provides adrenergic drive to many CNS areas. Frontal Cortex including the ACC receives Dopaminergic Neuromodulatory Input from the Ventral Tegmental Area (VTA in green) (gec).

Some ACC neurons provide a signal that correlates task choice with reward valuation. Such cells rapidly switch discharge from signals about choosing appropriate behavioral choices to those actions that get the reward. This "insight" marks the transition in learning from an exploratory phase to an exploitative phase. ACC is well connected with cortical & subcortical cognitive, limbic and motor areas. ACC contains pyramidal tract neurons that project to the spinal cord; it is well placed to assist in the translation of intentions into "value-added" goal directed actions. A recent study shows a robust direct connection from several portions of the ACC, somatosensory, posterior parietal plus several lateral & medial motor areas to thoracic

preganglionic sympathetic motoneurons innervating the adrenal medulla, in addition to multisynaptic influences from prefrontal “cognitive” areas to those autonomic motoneurons causing vascular adrenaline release: see Dum, Levinthal and Strick, 2016.

The ACC has a strong excitatory drive to the Locus Coeruleus (LC). LC Noradrenergic (NOR) neurons have a broad distribution of axonal projections to brainstem, cerebellum, spinal cord & cerebral cortex. NOR and increased adrenaline in the blood may increase alertness & alter network excitability to enhance selective attention & binding among networks. The ACC has a strong Dopaminergic modulatory influence from the Ventral Tegmental Area (VTA). Cingulate cortex is very influential.

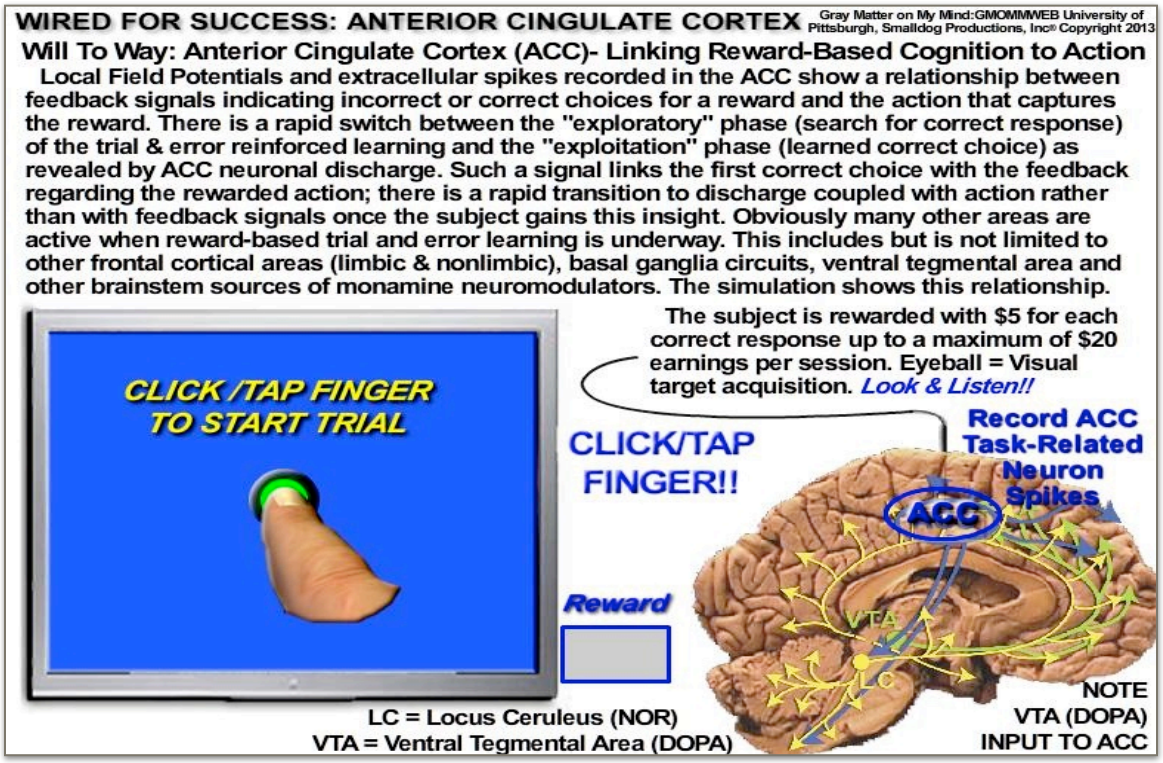


Fig 19-5. Reward-based Firing Alteration in Anterior Cingulate Cortex Interactive Media File: Switch from Exploration to Exploitation (gec). GO TO: gmomm.pitt.edu
Fig19-5_Interactive Media

Local Field Potentials and extracellular spikes recorded in the ACC show a relationship between feedback signals indicating incorrect or correct choices for a reward and the action that captures the reward. There is a rapid switch between the “exploratory” phase (search for correct response) of the trial & error reinforced learning and the “exploitation” phase (learned correct choice) as revealed by ACC neuronal discharge. Such a signal links the first correct choice with the feedback regarding the rewarded action; there is a rapid transition to discharge coupled with action rather than with feedback signals once the subject gains this insight. Obviously many other areas

are active when reward-based trial and error learning is underway. This includes but is not limited to other frontal cortical areas (limbic & non-limbic), basal ganglia circuits, ventral tegmental area and other brainstem sources of monamine neuromodulators. The ACC Reward interactive flash simulation shows this relationship.

WIRED FOR SUCCESS: WILL TO WAY-NO WAY COGNITIVE & MOTOR CIRCUIT CONVERGENCE

The Cerebellum (CBM) and Basal Ganglia (BG) provide loop circuitry with both "associative, "cognitive" cortical areas and with traditional "motor" cortical areas.

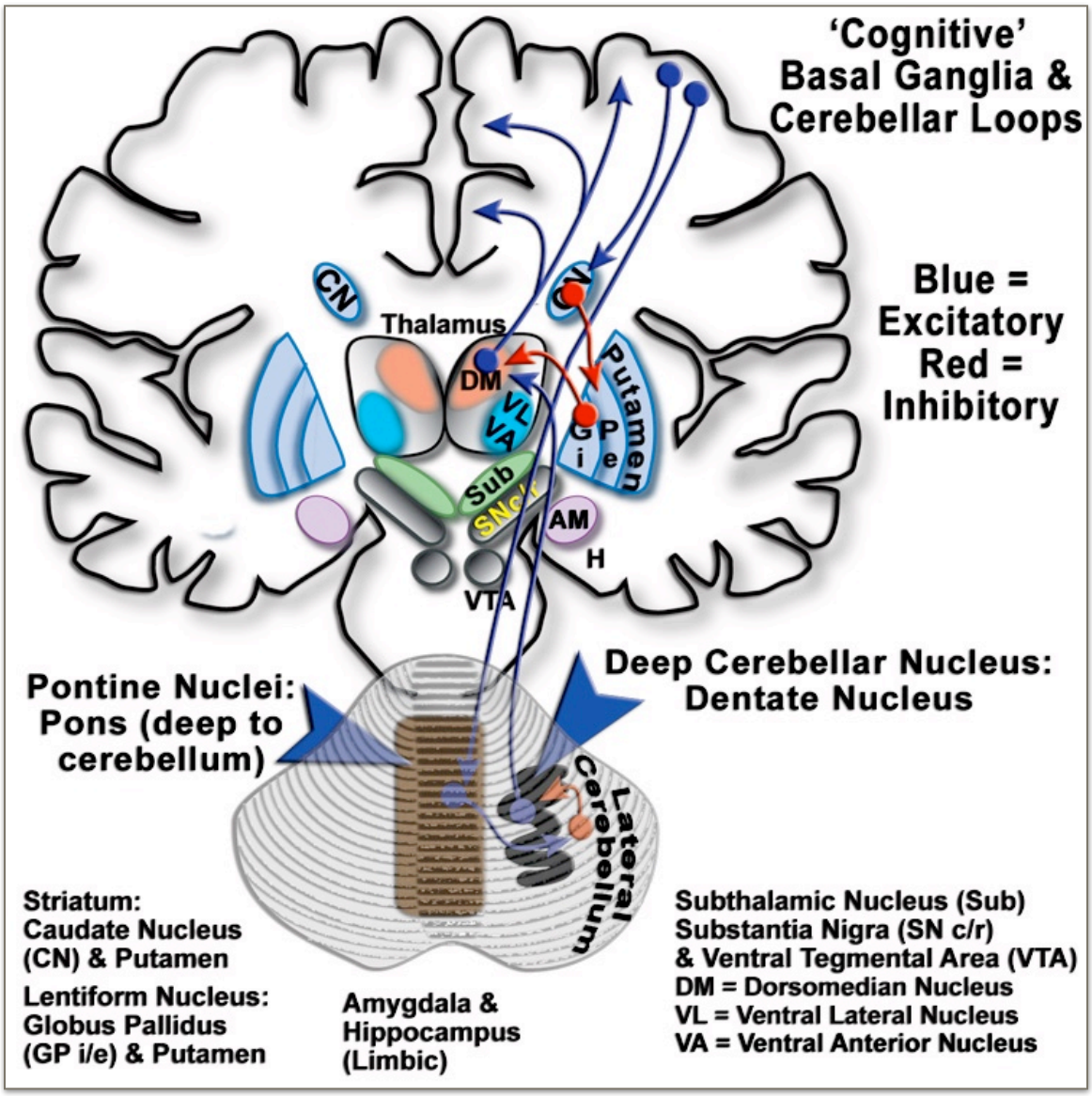


Fig 19-6. "Cognitive" Circuit Loop Connections with the Basal Ganglia and the Cerebellum. Note the differential excitatory versus inhibitory inputs to the thalamus (gec).

While most output from CBM & BG target frontal cortex and medial limbic & non-limbic areas in the frontal lobe, cerebral cortical projections to the pontine nuclei and to the striatum include broader distributions that include parietal and portions of temporal lobe cortex plus the frontal and limbic projections. Actions here refer to overt, observable volitional acts such as reading, writing, speaking, gesturing, & other skilled tasks. Intentions, on the other hand, may not always be overt; they may be "known" only by the brain forming such behavioral expressions of the "will."

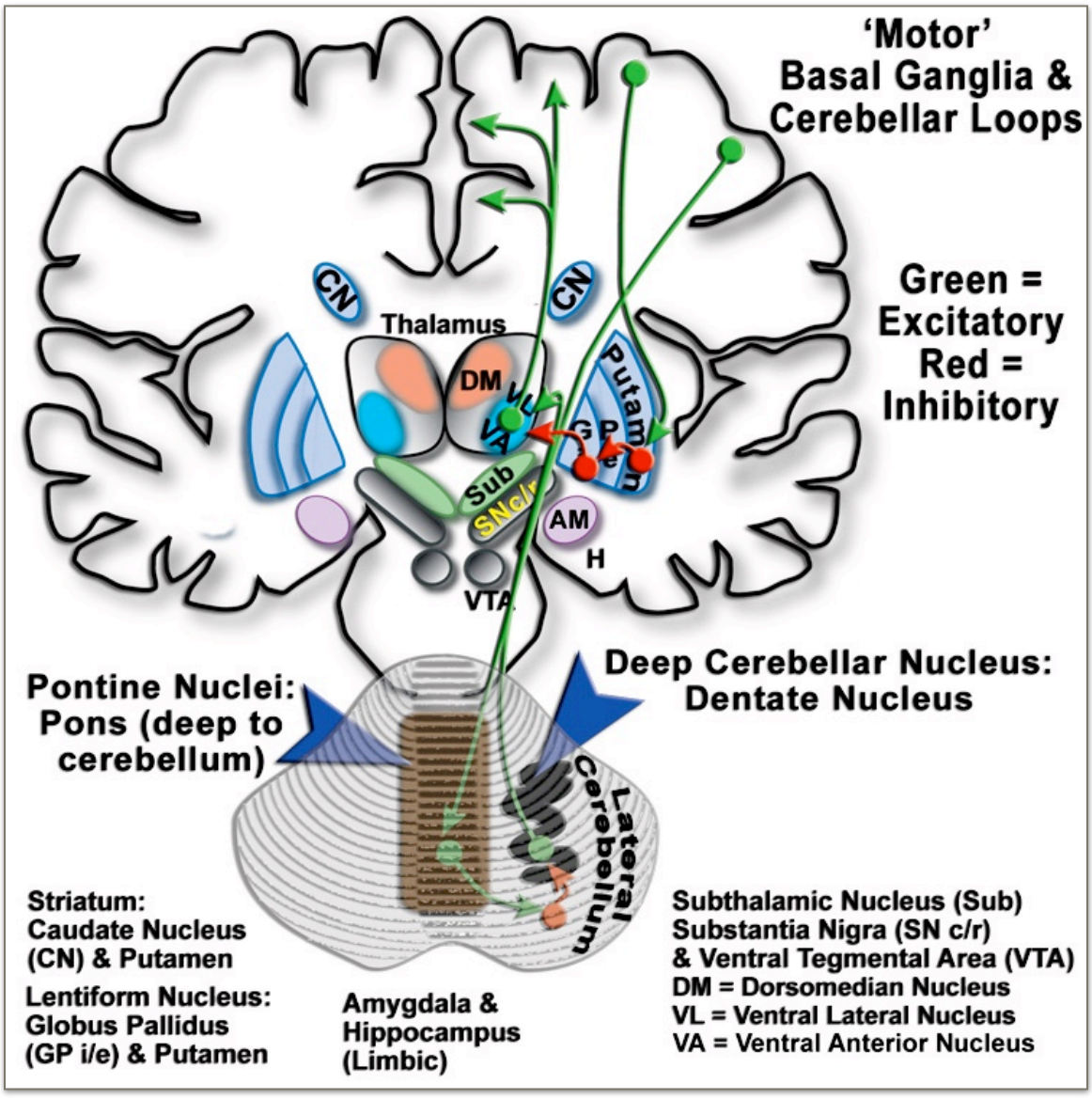


Fig 19-7. Motor Circuit Loop Connections with the Basal Ganglia and the Cerebellum. Note the differential excitatory versus inhibitory inputs to the thalamus (gec).

Some intentions have a high affective "flavor" to them. Such intentions may be suppressed only by ***intense*** neural control. Some neurons in Mesial Motor Areas may

increase firing when we choose an action, while others may increase firing when we halt our will before it is acted upon!

WILL TO WAY-NO WAY COGNITION: HOW MUCH DO WE REALLY KNOW ABOUT OUR OWN THOUGHTS?

To what extent are we consciously aware of our brain's hard work of deep thought? Do we have full conscious control over the amazing cognitive powers of our forebrains? This is a basic question regarding self and self-control. We think of free will as our ability to do, say or think what we want (usually within bounds of societal/moral constraints). What if most of the hard work of thinking, like that for skilled actions, really goes on behind the scenes, out of the "reach" of consciousness? Perhaps it becomes available to our conscious brain only when we add sense to the thought. Sense here may be related to activation of receptors for those energies that we recognize in the world around us ("bottom-up") and/or an internal representation of the world ("mind's eye") built upon experience from the "top-down". Maybe it makes no "sense" for the cognitive brain to bother (engage) our consciousness unless we must make some decision that will potentially involve the outside world. What if we are unaware of what our brain is cogitating for most of our waking hours? After all, I can't read your mind, so what makes you think that you have full-access privileges to all of your own information?

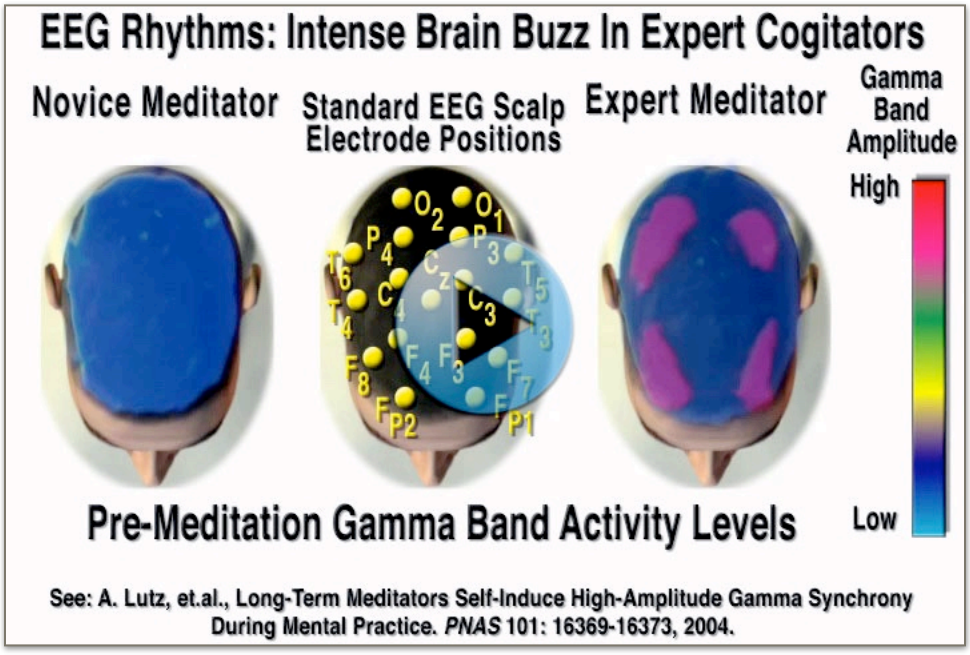


Fig 19-8. Meditation, Large Scale Brain Binding and Experience Simulation Movie (gec). GO TO: gmomm.pitt.edu Fig19-8_Video

A. Lutz and colleagues (Lutz, et.al., 2004) measured EEG activity in 8 veteran practitioners of objective-less meditation (mean age 49) versus 10 young novices (mean age 21). The young subjects had one week of instruction prior to the EEG measurements during meditation. Compare this to the experts who had 10,000 to 50,000 hours of practice over 15-40 years. Experts showed profound increases in gamma band (25-42 Hz in this study) EEG activity compared to novices. A direct correlation was described between the

extent of mediation practice with the amplitude of the Gamma band activity levels. Activity within “hotspots” of prefrontal and posterior parietal cortex showed high levels of synchronized gamma oscillations (binding) in expert but not novice meditators.

According to the authors, *Objectless Meditation* is a form of mental training where practitioners contemplate no specific object or person but self-induce a cognitive/ emotional state of well-being. This “altered state of consciousness” is accompanied by a significant change in EEG oscillations within frontal and parietal association areas. The “hotspots” of synchronized gamma band oscillations seen in these areas suggest a binding of cerebral areas involved in perception, intention and executive decisions. In addition, the “horseshoe” shaped inter-hemispheric corticocortical gamma activity across parieto-occipital and prefrontal EEG recording sites suggest shared function between right brain and left brain. Binding is thought to be one method of getting networks within different brain areas “on the same page” during cognition and other higher level cerebral functions. The lack of such a significant increase in gamma band activity in younger rookie meditators implies either a training effect, age effect or lack of specific talent for this mental processing. The strong correlation between the level of gamma activity and the hours of experience with meditation but not age shown in this study is consistent with a training effect. It would be instructive but technically tedious to follow changes in EEG patterns in novice subjects as they gain experience with meditation. Perhaps filtering out external stimuli and “concentrating” on an internal state of calm accesses our deepest thoughts of contentment that would otherwise be hidden from our cognitive self. SEE: A. Lutz, et.al., 2004.

WIRED FOR SUCCESS: WILL TO WAY-NO WAY; WHO DONE IT? AUTHORSHIP, AGENCY & SELF CONSCIOUSNESS

Might you think it absurd to suggest that you may not be able to instantly recognize an arm or hand as your own versus a body part belonging to someone else? After all you have been building your body image (body schema) since you were a youngster naming body parts (e.g., where are your eyes?). This internal representation is built upon inputs from multiple sensory modalities and from central perceptions that together provide a historical context for your being (soma/psyche). Your body schema appears to be best integrated in your parietal lobes (especially right posterior parietal cortex in most individuals). Likewise you should know that it is your body part that is acting when you initiate a volitional task. This “gnosis” appears to be built upon your intentions, perceptions and actions integrated across multiple areas of the cerebral cortex, thalamus and other subcortical structures, e.g., lateral cerebellum, basal ganglia. Some “gnosis” appears to be based upon implicit learning principles that may place the information in a “subconscious” rather than a true conscious realm of knowledge. Conscious interpretation of data would be characteristic of explicit, declarative learning. Clinical & experimental lesion studies show that significant sensory loss, profound deafferentation, parietal lobe lesions, certain thalamic lesions and schizophrenia may

distort or destroy our body awareness/agency. Some of these lesions may also deprive the individual of full control of their will. Such an example is the “alien hand” syndrome described by neurologists where the individual no longer has full control of behaviors that utilize the “foreign” extremity. Interestingly, under certain circumstances, “mistakes of attribution” may occur in a neurologically intact subject. This raises a fundamental question regarding the role of preconscious or unconscious processes versus conscious awareness in making decisions about perceptions and actions that guide volition. How sure might one be that the memory of a brief event recalled by a witness was what actually happened? Our brains do not record the history of our being to a DVD or DVR.

B. Libet (B. Libet, et.al., 1983) and many others (see references) have provided evidence for preparatory event-related large scale field potentials which begin hundreds to thousands of milliseconds prior to the onset of a movement. The following simulation describes these scalp EEG recorded potentials related to the onset of a voluntary action: see Readiness Potential: Ready To Go Before You Know Movie. It is proposed that the Readiness Potential (RP) is the summed excitatory activity of a large population of cortical neurons beneath the scalp electrode. However, the RP is a result of not just local circuit connections but also longer range corticocortical connections and cortical loops with the thalamus, basal ganglia and the cerebellum (see references).

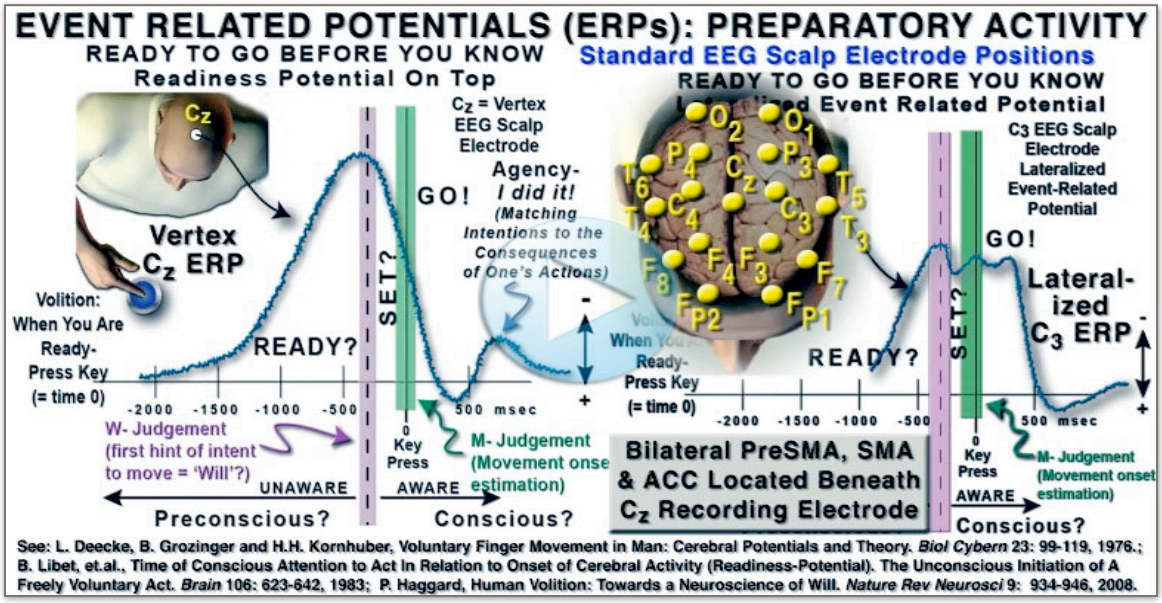


Fig 19-9. Readiness Potential: Ready To Go Before You Know Movie (gec). GO TO: gmomm.pitt.edu [Fig19-9_Video]

E. Daprati and colleagues (1997) looked at the question of “agency” & “ownership” using a novel approach. Thirty young adults with no history of neurological or psychiatric disorders (mean age 28.8 years) and 30 subjects diagnosed with schizophrenia (DSM-IV, mean age 34.5 years) were asked to identify the gloved hand reflected in a mirror &

viewed on a video monitor. One video camera imaged the gloved hand of the subject (using mirrors), another imaged the gloved hand of an experimenter. Subjects' hands were hidden from direct view. One of three hands was randomly shown on the screen as the subject moved his or her hand from one posture to another: the subject's own hand (S), the experimenter's hand doing the same motion (E-Same) or the experimenter's hand using a motion different from that of the subject (E-Diff). Subjects were asked to identify the hand as their own or not.

Control subjects would not make mistakes when seeing their own hand (S). Only a rare mistake was made by subjects with schizophrenia when shown their own hand. Likewise, both groups did not make mistakes when the hand shown was that of the experimenter in a position different from their own hand (E-Diff) condition. However, schizophrenic subjects made many mistakes when the hand shown was that of the experimenter in a position that mimicked their own hand position (E-Same) condition. Mistakes were greater for subjects having hallucinations (77% error rate) or those showing delusional thoughts (80% error rate). Error rates were ~50% for those schizophrenic subjects who did not experience hallucinations or delusions. A fascinating finding of this study was the error rate in young healthy subjects for the E-Same condition: control subjects made errors ~30% of the time!! This suggests that normal brains can make errors regarding "who done it" under these experimental conditions. Pondering these findings should prompt you to wonder about the absolute accuracy of eye witness accounts of even recent events, yet alone distant events only recently brought back to the witness's attention. Memories appear to be a reconstruction of an integrated event including affective, multisensory & perhaps motor aspects reconstituted by networks that may include those brain areas originally activated during the event.

Our brain may have occasional incorrect attributions of visual cues while ignoring correct proprioceptive cues from our own body. Since proprioceptive information is often utilized outside of conscious attention this may not be surprising. However, these findings also suggest "illusions" can "trick" our visual perceptions (think magician) and our multi-sensory body image. Schizophrenia seriously disrupts one's body schema, e.g., see: E. Daprati, et.al., 1997. If, as suggested in the first chapter of this book, my conscious self lives on borrowed time (non-conscious networks provide the loan), then occasionally a payment may be missed and an illusion may be the consequence. If too many payments are missed your credit rating within your social network may suffer.

Direct electrical stimulation of the posterior parietal cortex (Brodmann Areas 39, 40) in human subjects produces a sense of movement, desire or an intention to move even though no movement is generated (as monitored by EMG). By contrast direct electrical stimulation of Area 6 premotor or Area 6 of MI results in muscle activation but no conscious awareness that the movement occurs and even denial that any movement happened. This is an indication that proprioceptive feedback to premotor and motor cortices does not appear to be a source of conscious sensory awareness of action,

while posterior parietal cortex provides a sense of movement even if overt actions are not generated, see Desmurget, et.al., 2009. Agency tied to one's action seems to require normal communication between frontal and parietal cortex.

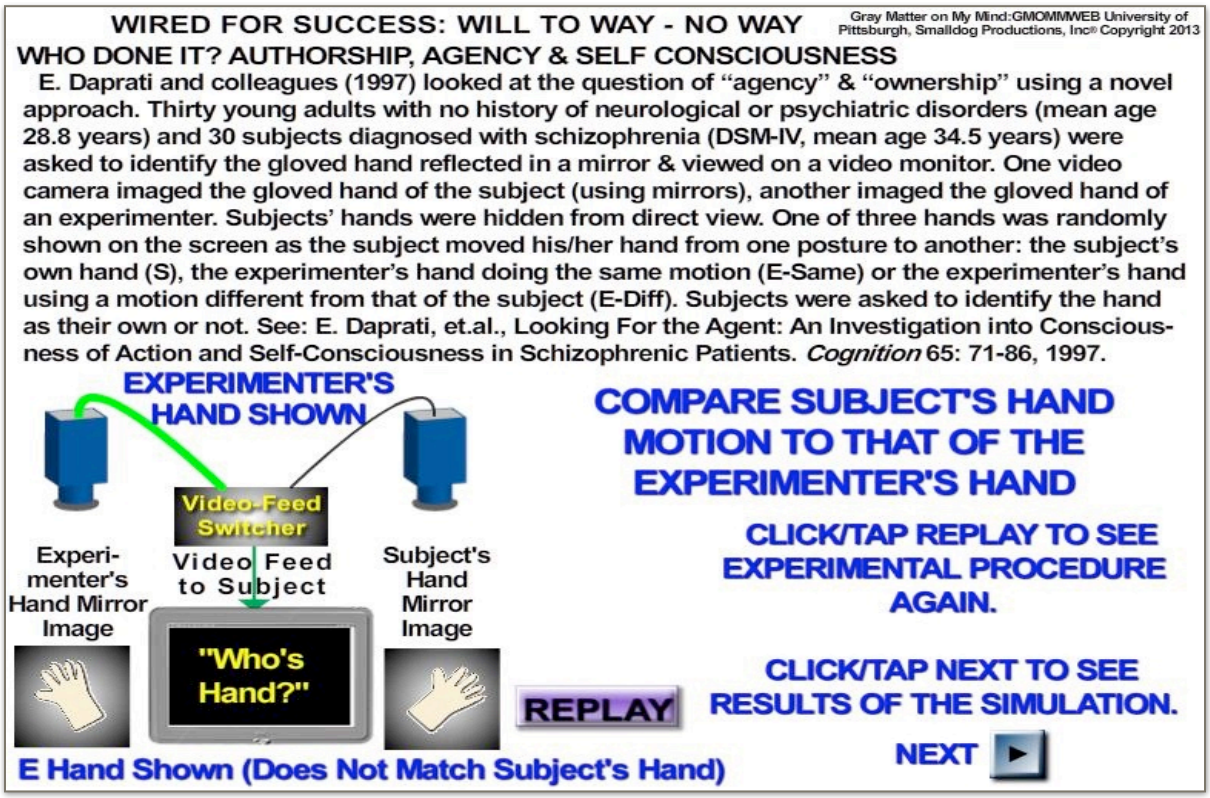


Fig 19-10. Who's Hand Is This: Misattributions of Agency/Ownership Interactive Media File(gec). GO TO: gmomm.pitt.edu [Fig19-10_Interactive Media]

WIRED FOR SUCCESS: SKILL MOTOR CONTROL & LEARNING

> Definition of Motor Control: "Motor control consists of the mechanisms by which an organism regulates and coordinates its actions to perform a task and achieve a goal; in addition, these mechanisms incorporate both neural and non-neural elements that are shaped by (or to) the constraints and affordances of our internal and external environment." © George E. Carvell, 1990.

When we are first learning a new task we attend to details of the motion, and we use many forms of feedback. We tend to move slowly in a discontinuous fashion. As we practice, we gain insight into the requirements of the task, make fewer errors, move faster and more efficiently. The transition to a continuous movement pattern marks an initial stage of motor learning and skill acquisition. We may alter our posture as well as movement path to optimize performance. Mental as well as physical practice are critical

ingredients, and perfecting practice schedules is always a challenge. The novice often tends to “guide” the object or body part to the target center. As learning ensues the person begins to “launch” the “missile” with a faster motion and learns the biomechanical “rules” of the task. If any talent for the task resides in the motivated learner, performance improves. Feedforward neural control becomes more important than feedback as skill improves and the task becomes over-learned. The environment influences what we do and how we do it. Posture & Movement do not occur in a vacuum.

Skill means different things to different people. Use of the word skill is often preceded or followed by value-added modifiers e.g., highly skilled, unskilled, skilled craftsman, skilled golfer, etc. Skill implies nature/nurture talent for a particular goal directed behavior. Often an over-learned task is done with such agility and confidence that the task is made to look easy. Whether the action be implemented at the tip of the tongue, point of a pen, on the strings of a musical instrument or head of a golf club, what is common to all is the precision of coupling intention to action by the performer. In most cases the nuances of the “perfected intention” cannot be reported in detail to an observer but are implicit for the actor and emergent in the action. While coaches, teachers and therapists may convey the rules and “tricks of the trade” to the performer, the actual coupling of intention to action emerges as a behavior that, for the most part, is out of reach of the individual's consciousness. For the skilled teacher and the novice learner this leads to a paradoxical situation early in motor skill acquisition. The teacher may convey explicit rules, “tricks,” and details of performance but the learner may have difficulty translating those guides into an implicit sequence of actions. Once insight into the requirements for the task has been established (by the learner), performance may become more automatic and “go underground” in the brain. Although the teacher can provide 'knowledge of results' regarding performance, it is the performer's insight that leads to accurate self-evaluation of performance. The slope of the learning curve climbs rapidly as performance improves (fewer errors & more consistent outcome). Self-evaluation of performance appears to be a critical, necessary & complex interaction among both limbic and non-limbic brain areas capable of retaining data and precisely judging how well intentions match actions. Insight for skill may not be the “lightbulb” over the head but the implicit “*aha*” moment when the cognitive/motor circuitry switches strategy from *Exploration to Exploitation (see above).*

Most definitions of skill speak of learned motor patterns, programs, plans and feed-forward control. Some definitions include a task related environmental component and others include metrics of the task itself such as speed, accuracy, form and adaptability. N. Bernstein and others hypothesize that, at least for skilled motor behaviors, our brain operates on an error signal which reflects the difference between the desired intent and real action. We improve performance as our practice cycles neural events through a comparator “filter” to reduce error. A heterarchical or modified hierarchical distributed control mechanism shares responsibility across all levels of the nervous system from

the beginning of the intent to the execution of the action. When choosing skill levels for therapeutic interventions remember safety = trump card.

SKILL: BUILDING A BETTER PRODUCT BY OPTIMIZING RESOURCES-DOING MORE WITH LESS?

When profit margins shrink, companies must increase productivity by enhancing efficiency: producing more with less. Likewise, you improve your productivity and build skill through repeated practice of a task. You reduce total energy consumption by recruiting a limited (but sufficient) number of motor units within a select group of muscles to move faster and reduce errors. Such improved efficiency may be the direct result of the motor system's ability to generate motor programs which contain relevant parameters for feedforward control of the neural machinery to recruit optimal motor unit expression of the desired output. Of course, neurobiological "software" like digital software must be periodically updated to fix "minor bugs" and to maintain operational outcomes for adaptation to new circumstances, e.g., environmental changes, as the need arises. Feedback for such program modification is provided by both afferent and efferent signals.

Fig 19-11. Skill Hill Movie. Carving precise action molehills out of 'generic' sensorimotor mountains! (gec) GO TO: gmomm.pitt.edu Fig19-11_Video

While enhancement of performance may include peripheral muscular training effects, your neuromuscular system plays a leading role in optimizing spatiotemporal recruitment of motor units as you learn the nuances of the task. As illustrated in the SKILL-HILL Movie, the transition may be "bumpy" at first as the nervous system optimizes the solution to the motor problem. Eventually the motor output hill becomes slim, trim and smooth. Note the greater trimming of temporal versus spatial aspects of recruitment as skill transitions from novice to expert. You trim the temporal profile (move faster, optimize temporal aspects of motor unit activation) but at some point you can trim the spatial profile of motor unit recruitment only so far. The muscles required for the task can only be limited to a minimal extent before you no longer can reproduce a motion path (you need sufficient actuators to do the task).

Solving a motor problem may require some “mathematical” calculations within the networks responsible for learning and refining a new motor skill (MOTOR GEOMETRY Movie). Consider learning a golf swing where the object is to hit the ball far and straight. The golfer must learn basic rules about how to hold the club, how to stand to “address” the ball on the T and how to contort the body to swing the club while keeping the head down and eyes on the ball. Perhaps the most difficult challenge is consistency, fluidity & accuracy. Some professionals suggest that a golfer should learn to swing the club in a single plane. This infers that the brain must reduce the many degrees of freedom (think of the math involved in calculating the area of a sphere [$A = 4 \pi r^2$]). If the motion path is simplified to a single plane, the area of a circle formula is reduced to [$A = \pi r^2$].

The key of course is orienting the plane (and the head of the club) to intersect precisely with the ball on the T, and then repeating the key features of the motor program in a consistent fashion from one swing to the next. Practice, motivation (and some level of talent) would seem to be critical. There are many “programs” marketed to assist the golfer. However, they all appear to use explicit learning where the golfer is an external observer for a task that requires implicit learning (internal neural network representation).

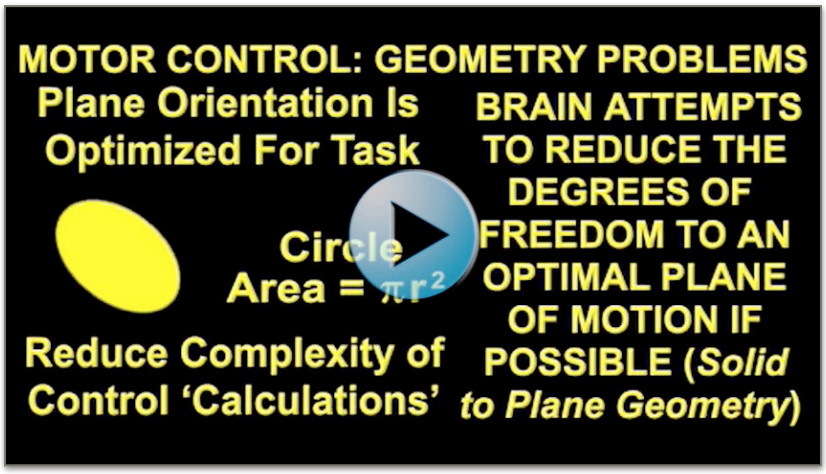


Fig 19-12. Motor Skill Geometry Movie. Skill = Reducing Degrees of Freedom for Precise Control of Optimized Motion (gec). GO TO: gmomm.pitt.edu *Fig19-12 Video*

The golfer must realize that although pi is a constant, it is an “irrational” number with an infinite succession of non-repeating decimals. Practice leading to over-learning may result in successive addition of decimals (& precision) but absolute perfection may be many decimal places removed.

SKILL: CONSTRAINTS AND AFFORDANCES IN OPEN AND CLOSED TASKS

Thomas Edison is reported to have said that genius is 1% Inspiration and 99% Perspiration. Exercise may not require genius but choosing the correct exercise does require consideration of the goals to be accomplished. If strength or endurance is the major goal, the perspiration: inspiration ratio is different from that needed for the development of a fine motor skill. While sweating may not be discouraged, exercises designed to develop skill should be both engaging and challenging for the learner to take full advantage of motor system plasticity. If you pay close attention to joggers,

intact humans have very similar patterns of movement but each tends to have nuances in gait that are distinguishing at best and awkward at worst. If you watch them over days, weeks or months the pattern is remarkably constant: a mind-numbing rhythm generation that evokes little inspiration for the runner or the observer. On the other hand, if one watches the swing of a professional golfer, the action may or may not be inspiring to the observer, but if the swing is true to form, it appears to be quite inspirational to the golfer. A. Gentile, 1987 has proposed a taxonomy of tasks according to the requirements of the actor related to the environment in which the task is done. Closed tasks are those in which the variability is minimal from one time to the next. Action is typically driven by consistent pacing and unchanging environmental constraints: think tennis serve. Open tasks require the actor to anticipate and/or react to environmental affordances. Feedforward Predictive motor control becomes particularly important as the open task gets more difficult (moving within a changing environment while manipulating objects/tools): think tennis volleys. The level of task difficulty relates to transport of the body and manipulation of objects as one moves in a relatively uncertain environment. Closed tasks suggest learning of consistent, stereotypical movement patterns, while open tasks provide the challenge of learning generalizable rules that correctly predict (anticipate) changing conditions related to one's body and the object being manipulated. Pacing (external versus self) may impose significant limitations for timing. Control of timing & its cousin, speed, is a rate-limiting neural processing step in many motor learning situations. Our musculoskeletal system by its very nature is a low-pass filter for timed behavioral events (we must optimize control for skeletal inertia, for inherent delays in muscle dynamics & minimize fatigue); although doublets may occur in motoneuron firing, motor units typically do not sustain firing rates above ~40-50 Hz. Nevertheless we can move in a fast or ballistic fashion utilizing agonist-antagonist bursts of short duration that results in a rapid smooth motion of an extremity. Taken together, 1. our ability to acquire, retain and improve skill requires plasticity of neural networks and 2. coaches/therapists cannot use a “one size fits all” approach to assist the learner.

ALL MOVEMENTS ARE NOT CREATED EQUAL.

Goal directed movements obey certain rules related to speed, accuracy, amplitude, load, behavioral context, and environmental constraints/affordances.

R. S. Woodworth described the relationship between accuracy and speed. He demonstrated that the best accuracy occurs when eyes are open and movements are slow. Note that vision provides the greatest contribution to accuracy at the slowest speeds. Closing the eyes increases error that is *relatively* constant at all speeds (proprioception equivalent at any speed?). However, errors tended to overshoot for fast and undershoot for slow movements with eyes closed. This suggests there are limits to proprioception for achieving maximal accuracy. If the subjects did not attend to the task (automatic), performance is actually poorest at the slowest speed which then levels off

for all but the fastest movements (accuracy asymptote at fastest speed). Woodworth, states:

> "We may put these results in another form as follows: at high speeds the accuracy contributed by voluntary attention, using either the muscle (joint) sense or the eyes, amounts to zero. By decreasing the speed we greatly increase the accuracy due to visual control, but do not increase that due to the muscle sense." R.S. Woodworth, Accuracy of Voluntary Movement. Psychol Rev Mono Suppl 3: i-114, p.31, 1899.

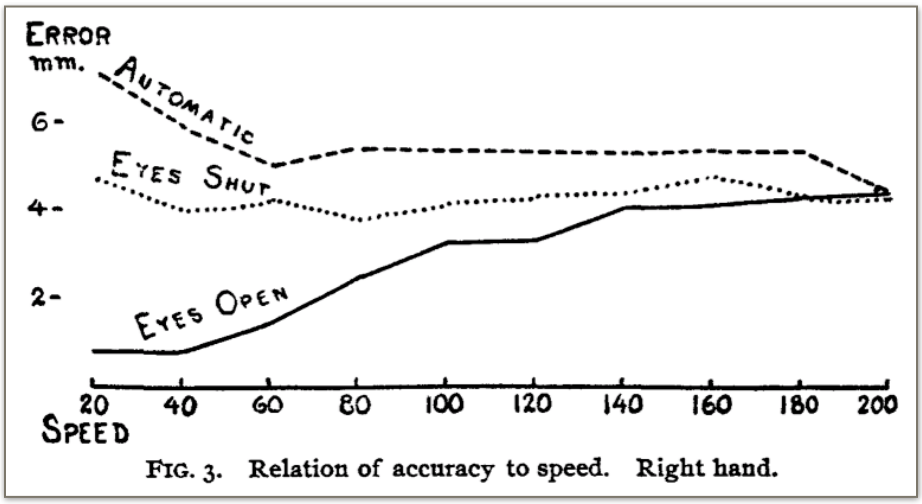


FIG. 3. Relation of accuracy to speed. Right hand.

Fig 19-13. Woodworth's Speed-Accuracy Tradeoff Experiment. Accuracy Related to movement speed to target: speed in beats per minute of metronome , i.e. 60 = 1 Hz, 120 = 2 Hz, 180 = 3 Hz (public domain) Woodworth, Fig. 3, p. 30, 1899.

Interestingly, Woodworth's experiment for the left hand shows errors increasing more dramatically with eyes open (as compared to right hand) and for all three conditions errors are greatest for the fastest speeds, suggesting that use and handedness have an important role in speed-accuracy relations (at least for repetitive cyclic movements to targets). Practice would be expected to reduce error for both hands.

Fitts, 1954 suggests that movement size matters. Smaller amplitude movements can be performed with greater accuracy than larger movements. Fitts and others have confirmed the speed-accuracy tradeoff and have described differences for small versus large movements: to increase accuracy move slower or reduce range. Talent, motor learning, and practice improve performance at any speed appropriate for the task. Fast, accurate reaching is accomplished with an almost linear trajectory characterized by a single velocity peak. However, the task at hand alters the velocity profile.

Pointing to an object versus grasping an object have similar average velocity peaks. Acceleration phases are similar but the deceleration phase is much shorter when contact with object is not required; this results in a shorter movement time (MT). Likewise, reaching to grasp a tennis ball versus a lightbulb alters deceleration and MT but acceleration is similar for both objects. Placing one's fingers around the thin glass requires greater care (longer deceleration phase).

The MOVE IT Interactive Flash File shows characteristics of “non-programmed” discontinuous movements and “programmed” continuous or ballistic movements. Note: the Swiffy Flash File does not show all animated videos but the traditional Flash file faithfully renders all content.

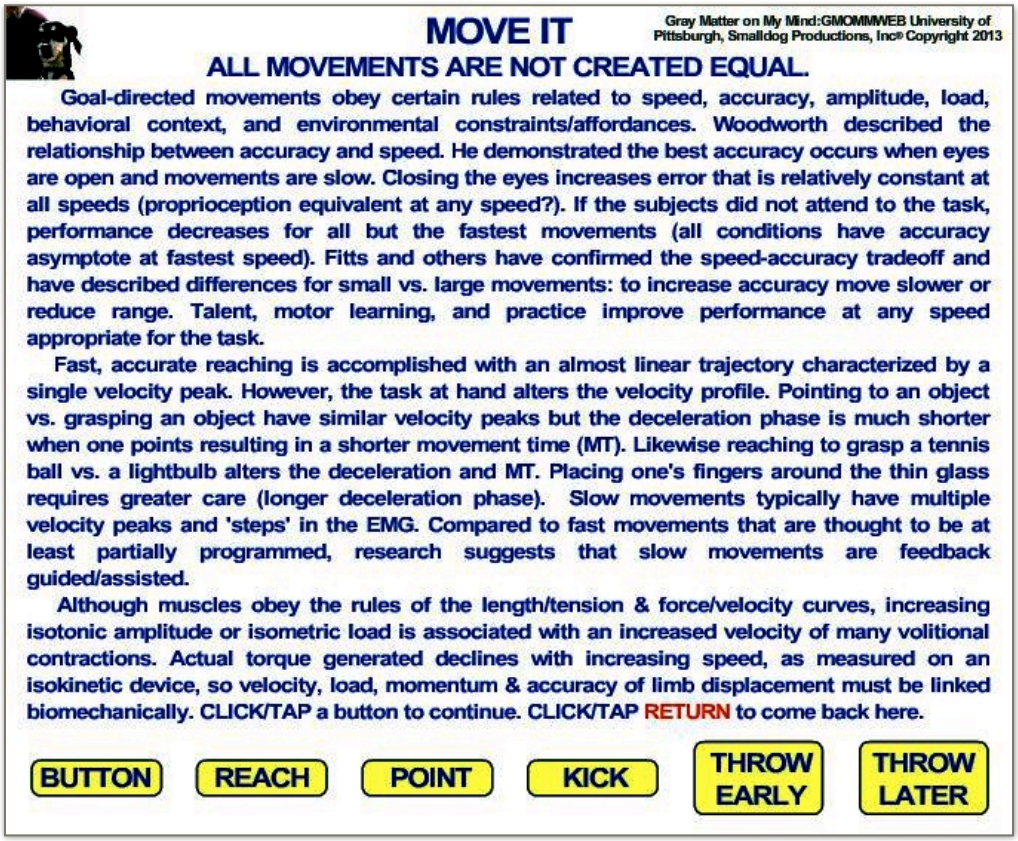


Fig 19-14. MOVE IT Dis-continuous, Continuous and Ballistic Movement Character-istics: Inter-active MediaFile (gec). GO TO: gmomm.pitt.edu

Fig19-14 Interactive Media

WIRED FOR SUCCESS: SKILL - MOTOR CONTROL & LEARNING - MUSCULOSKELETAL SYSTEM CONTROL

PREMISE: The musculoskeletal system requires an electrical system to function. The nervous system requires a musculoskeletal system to realize actions plus sensory organs to interact with people and things within a dynamic environment. Actions and Perceptions are coupled within a cyclic and plastic neural ensemble distributed across all levels of the nervous system. All movements are not created equal. Motor Control of a power grip is not the same as that for a precision grip although the two may be used together for the task at hand. For example, an electrician must use a precision grip to open the “jaws” of wire-cutting pliers and precisely position the aperture around a wire before switching to a power grip to cut the wire (PLAY MOVIE below). A skilled craftsman does this with agility and efficiency. With practice, the tool becomes a telescoped extension of the extremity. A novice or an individual with sensory loss recruits excessive motor units (agonist & antagonist). As learning ensues, cocontraction of finger muscles is reduced for precise motions. Power grip uses cocontraction to

stabilize the hand & wrist and to generate torque. Precision grip of an object or tool requires preconscious somatomotor integration. Neurological insults may compromise the task. Tactile & proprioceptive inputs, Dorsal Column Medial Lemniscal Pathway plus Somatosensory Cortex are required for discrete spatiotemporal cues when performing the task. Motor Cortex and the Corticospinal Tract are required for fractionated finger movements and fine control of force. Posterior Parietal Cortex is required for: spatial perception, a body image that keeps the virtual person intact, adding the tool as an extension of the virtual image, an internal imagery of doing the task plus generating control signals for reach and grasp based on multiple sensory cues and intent. Premotor Areas provide motor programming to keep the synergy intact and organize preparatory mental actions to generate feedforward control.

Programs are shared with & modulated by other cortical, brainstem and spinal centers. The cerebellum and basal ganglia, in concert with primary cortices and anterior (prefrontal) & posterior (parieto-occipito-temporal) association cortex optimize control parameters for “signing” and “executing” the will. Such loops, may be particularly important for acquisition and refinement of the learned task. The brain-stem contains gray matter critical to signing and executing the will: e.g., thalamus, red nucleus, pontine nuclei, inferior olive, reticular formation, dorsal column nuclei. Not to be outdone, both cortical & subcortical limbic areas probably initiate the process and keep driving us to the conclusion that this wire needs to be cut and “self” should be the cutter.

Fig 19-15. Precision and Power for Cutting a Wire Movie (gec). GO TO: gmomm.pitt.edu Fig19-15_Video

WIRED FOR SUCCESS: SKILL MOTOR CONTROL & LEARNING- CIRCUIT TIMING

... --- ... (SOS) is Morse code for rescue. A code is an abstract representation that can be shared among those who are able to decipher its meaning (SOS distress call from sinking Titanic in 1912). Rapid communication between neurons in the nervous system is coded primarily by dots (Action Potentials or APs). One AP looks much the same as another. So how can we distinguish an action versus a perception versus an intention code? The specific location of neurons in gray matter and the commute of APs along a prescribed axonal traffic highway within the

white matter help to simplify the process: e.g., thalamocortical APs arriving in layer IV of the Primary Somatosensory Cortex (SI) from the ventral posterior lateral nucleus are likely to be a code of somatosensation coming from a particular area of the body. How about impulses shared by corticocortical connections with SI: are they sensory, motor or a more abstract code? Dots can be accumulated by synaptic input to a cell and the average may be summed to generate one or more dots as output by the post-synaptic cell. This integrate and fire mode is a basic "*default*" mode of coding. However, we know that inputs are neither equal (spatial/temporal summation) nor even of the same polarity (excitatory & inhibitory). LTP may convert presynaptic dots to dashes in the postsynaptic cell. Spacing of dots & dashes may be altered by GABAergic inputs and by adaptation properties of the postsynaptic cell. The temporal pattern of firing may be critical to neural coding, especially for "higher order" processes such as selective attention, perception and volitional action. Synchronous firing of cells in a network may provide an efficient coincidence detection code that generates rapid depolarizations & hyperpolarizations to activate & inactivate a cell assembly in a harmonious fashion. Aging may alter GABAergic control of precise network interactions in skilled behaviors , e.g., see Heise, et.al., 2013. Synchrony of firing in a cell assembly may result in an efficient sparse spike code. That code, in turn, may generate rhythms at various frequencies. It has been suggested that gamma (40-70 Hz) oscillations relate to consciousness, selective attention, intention and 'signing the will' for volitional actions. Gamma oscillations among widely distributed cells may be one solution for the binding problem. The binding problem exists within a distributed network because cells at some distance from one another need help to get "on the same page." It has been suggested that an emergent, working coalition of transiently "bound" cells generates an ensemble code to connect the dots. A cause-effect relationship is far from settled for a solution to the binding problem and even less consensus exists among "circuit busters" regarding the possibility of "hardwiring" the cell assembly to form a more permanent "printed circuit" within the brain. Skill development may alter Oligodendrocytes and/or oligodendrocyte progenitor cells and therefore optimize white matter providing rapid, coherent passage of signals among networks, e.g., see Fields, 2005 and Bengtsson, et.al., 2005.

WIRED FOR SUCCESS: SKILL MOTOR CONTROL & LEARNING - ENGAGING AND CHALLENGING THE SYSTEM TO IMPROVE PERFORMANCE

Improvement in skill infers learning: a measurable change in behavior/performance. Accuracy, agility and efficiency should improve. Other metrics such as speed and adaptability may also change if they represent critical aspects of the task. Despite an improved performance, our brain may not be working harder just more efficiently. Synchrony among neurons in motor cortex may enhance coincidence detection among cell assemblies forming both local and distant coalitions.

Cell assemblies may provide better synchronization of motor unit recruitment through descending tract influences on segmental motor center interneurons and motoneurons. Motor unit recruitment should be more specific, eliminating unwanted and excessive muscular activity. As the degrees of freedom problem is solved (see Bernstein Movie) by the relevant neural & musculoskeletal elements, movements should become more fluid with less co-contraction.

Overall levels of electrical activity within the cortical and subcortical motor centers may actually decline as networks increase productivity (more or better with less); sparse spike coding may replace a less-efficient integrate and fire mode during the execution of the will. Some select neurons may prolong their discharge as they mentally prepare the network for the task to come (motor memory, motor planning & executive functions). Synchrony and rhythm may not be limited to cortical centers as the skilled actor signs and executes the will. Basal ganglia and cerebellar circuits may play an increasingly important role as an over-learned task becomes more automatic. Dopamine levels, at least within the striatum, appear to be particularly important. Although there is some evidence that stimulation of motor cortex may alter the map, it is still unclear when such artificial recruitment may act as a functional network in humans. When intelligent digital networks become therapeutic & practical let us hope that the silicon-carbon amalgam will be able to enhance performance and be able to learn from the neural networks that the digital orthosis/prosthesis serves. For those now involved in rehabilitation of individuals recovering from a sensorimotor system lesion, interventions must rely upon indirect methods to “retrain” the system. An emphasis upon activities that are engaging, challenging and skilled may provide better functional results than those that emphasize only strength, range or endurance. However, deconditioning may require exercises to get the peripheral musculoskeletal and neuromuscular systems strong enough, limber enough and resilient enough to benefit from skill activities where the perspiration: inspiration ratio often is inverted. As one transitions from novice to expert, one should anticipate a change from a dominant feedback to a feedforward control and optimal neural processing.

DISTRIBUTED SENSORIMOTOR CONTROL: NOVICE VERSUS EXPERT

While simple additions and subtractions of excitatory and inhibitory synaptic potentials due to singular, specific neurotransmitters may have been necessary and sufficient to explain neuronal interactions in the past that is no longer the case.

Summation of EPSPs & IPSPs may be necessary but not sufficient to explain distributed motor control according to current concepts. Firing patterns as well as firing rates of neurons determine how well they communicate with one another. In addition, neuromodulatory influences on voltage-gated ion channels may modify ion channel expression in dendritic trees; attenuating or accentuating certain forms of integrative potentials, e.g., back-propagated dendritic Ca^{++} spikes producing axonal burst firing.

Fig 19-16. Dart Thrower-Novice versus Expert and Neural network Binding Movie (gec). GO TO: gmomm.pitt.edu [Fig19-16_Video]

Moreover, synchronous oscillations (binding) within a distributed motor system may contribute significantly to the coupling of neural networks responsible for movement preparation and regulation of the movement plan once it has begun.

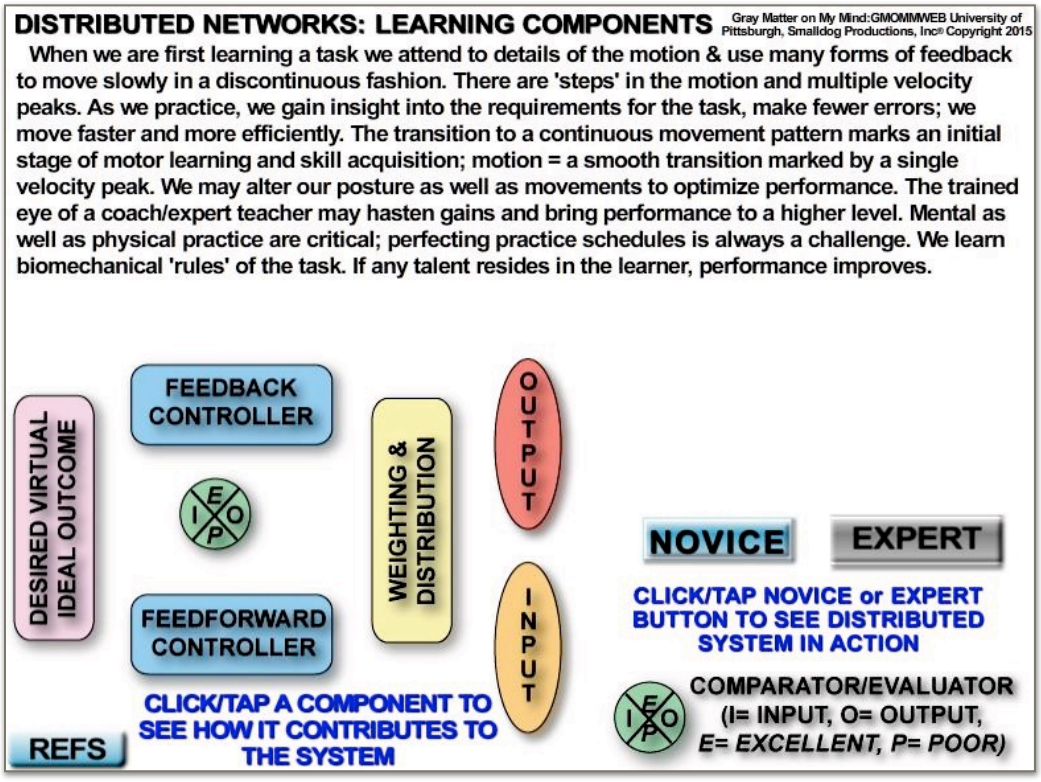


Fig 19-17. Distributed Modified Hierarchical Sensorimotor Control: Novice Feedback Dominant versus Expert Feedforward Dominant Motor Control Interactive Media File (gec). GO TO: gmomm.pitt.edu [Fig19-17_Interactive Media]

When we are first learning a new task we attend to details of motion, and use many forms of feedback to move slowly in a discontinuous fashion. The novice dart thrower often tries to “guide” the dart to the target center. Of course the thrower must eventually let go, since he cannot carry the dart to the bullseye. There is poor synchrony among brain areas since the performer has not yet gained insight into all the task requirements. Motor drive may be excessive & neural discharge timing is often inefficient. As learning ensues, the thrower begins to “launch” the missile with a faster motion & learns the biomechanical “rules” of the task. If any level of talent resides in the motivated learner, performance improves.

The skilled actor moves in a rapid, smooth, accurate and continuous fashion. There is a single velocity peak. Control gravitates to feedforward mechanisms (see ‘Expert’ Network; motor & sensory components are synchronized (see overlap) and are complementary (I-O handshake is optimized). Feedback is intermittent, efferent > afferent feedback with few errors. Performance evaluations are Very Good to Excellent.

WIRED FOR SUCCESS: SKILL MOTOR CONTROL & LEARNING

Evidence from animal and human studies of motor system plasticity suggests that neuronal connections may be modified rapidly. Lasting modifications of “maps,” synapses, and motor representations have been described at cerebral cortical and sub-cortical levels when appropriate challenges induce skill development. Given an adequate intensity and duration of a challenging task, one sees synaptic modifications in at least some portions of the motor system that may persist beyond the period of training. Rapid changes have been associated with short-term potentiation or depression and persistent synaptic modifications have been associated with synaptogenesis and long-term potentiation (LTP) or long-term depression (LTD) in animal studies where such measurements can be obtained. We now know from in-vitro studies (brain slice or cell culture) that synapses may change shape within a matter of minutes and from *in-vitro* & *in-vivo* studies of rodents that the shape & size of a dendritic spine may change over a longer duration of time (hours or longer). Mechanisms responsible for such changes implicate Ca^{++} ions, NMDA receptors, LTP, glutamate levels, metabotropic glutamate receptors and dynamic actin in synaptic spines. A recent rat study suggests that continuous protein production is essential for reorganization of the motor map due to skill training and that skill-training prior to injection of protein synthesis inhibitors into Motor Cortex (MI) has a partial neuroprotective effect. Skill but not “non-skill” training produces an expansion of the dendritic arbor for some MI neurons and synaptogenesis. Both parallel fiber and climbing fiber synaptic connections onto cerebellar Purkinje cells are modified by skill training in rats and synaptic modifications appear to be retained for weeks after the cessation of such bouts of skill training. Climbing fiber input to the cerebellum appears to be particularly important in motor learning where we must recalibrate the system to adapt to task requirements.

Skill training in rats (acrobatic) consisted of rope & chain climbing, traversing rope ladders, narrow elevated runways, seesaws, etc. The non-skill group had ~equivalent physical exercise in the form of treadmill locomotion or wheel-running (aerobic). The aerobic group showed enhanced metabolic profiles in active brain areas (angiogenesis and improved perfusion) but no significant change in synaptic profiles or dendritic arbors as was found in the acrobatic group. Acrobatic (skill) tasks are thought to be both engaging and challenging for the rats in training (although subjects did not fill out a self-report assessment). Voluntary Aerobic Exercise (e.g., rats running in wheel) may transiently increase levels of neurotrophic factors e.g., BDNF & GDNF that may provide neuroprotective benefits for some but not all brains or brain areas.

Fig 19-18. Rat Race Movie. Benefits of Voluntary Aerobic Exercise (gec). GO TO: gmomm.pitt.edu
Fig19-18_Video

WHEN RATS ARE PROVIDED A RUNNING WHEEL IN THEIR HOME CAGE, MANY TAKE FULL ADVANTAGE OF THE OPPORTUNITY TO MOVE EVEN IF THEY ARE GOING NOWHERE: THE RAT RACE. THIS PHYSICAL ACTIVITY IS THOUGHT TO PROMOTE ANGIOGENESIS WITHIN BRAIN AREAS THAT REQUIRE INCREASED PERFUSION. FURTHERMORE, PHYSICAL ACTIVITY MAY BE ONE WAY TO KEEP NEURONS HAPPY. PHYSICAL ACTIVITY'S IMPACT ON NEUROTROPHIC FACTORS AND GENE EXPRESSION MAY BE NEUROPROTECTIVE (at least in rats). COMPARE THIS CARROT APPROACH TO THE STICK APPROACH OF TREADMILL RUNNING.

RATS THAT PARTICIPATE IN INTENSE AEROBIC PHYSICAL ACTIVITIES SUCH AS TREADMILL TRAINING OR WHEEL-RUNNING APPEAR TO HAVE A METABOLIC RESPONSE TO INCREASED ENERGY DEMANDS WITHIN THE BRAIN AS WELL AS IN SKELETAL MUSCLE. THESE ANIMALS HAVE ANGIOGENESIS (IMPROVED PERFUSION) BUT NO SYNAPTOGENESIS IN MOTOR AREAS. THE LATTER IS SEEN WHEN ANIMALS MUST RUN AN OBSTACLE COURSE TO PERFORM DEMANDING ACROBATIC TASKS (SEE ACROBATIC RAT). TREADMILL RUNNING DOES NOT APPEAR TO BE A RAT'S PREFERRED MODE OF TRAINING (FORCED EXERCISE). FORCED EXERCISE MAY INDUCE STRESS REACTIONS THAT ARE COUNTERPRODUCTIVE TO THE BENEFITS OF AEROBIC EXERCISE.

Fig 19-19. Treadmill Running Rat Movie. Aerobic Exercise and Possible Stress Response (gec). GO TO: gmomm.pitt.edu
Fig19-19_Video

RATS TRAINED TO PERFORM ENGAGING & CHALLENGING ACROBATIC SKILL TASKS SHOW SYNAPTOGENESIS AND SYNAPTIC GROWTH WITHIN PORTIONS OF THE MOTOR SYSTEM (EVIDENCE FOR LONG LASTING CHANGES IN MOTOR CORTEX AND CEREBELLAR CORTEX IN RATS). MODIFIED SYNAPTIC PROFILES MAY PERSIST FOR WEEKS OR LONGER FOLLOWING TRAINING.

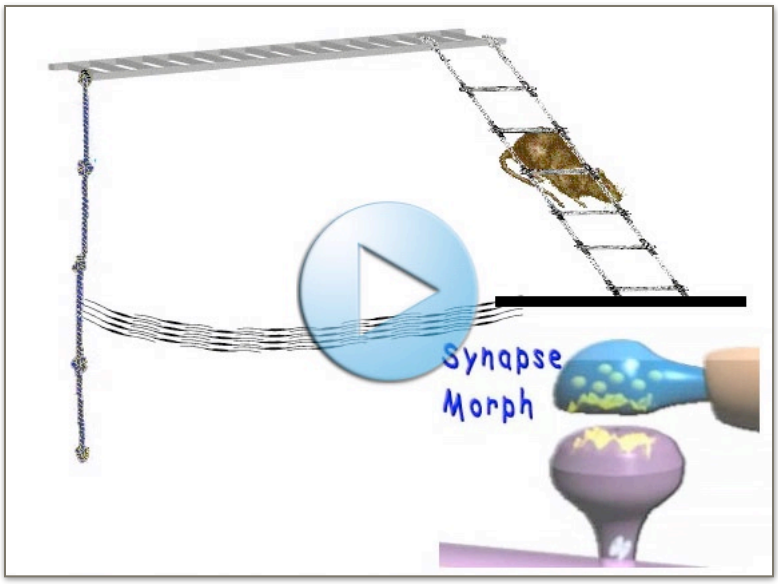


Fig 19-20. Acrobatic Rat Movie. Novel Skill Exercise and Synaptic Plasticity (gec). GO TO: gmomm.pitt.edu
Fig19-20_Video

WHEN WE STEP ONTO THE STAGE CALLED LIFE: DO WE SENSE TO MOVE, MOVE TO SENSE OR JUST ACT? (SOME GENETIC AND EPIGENETIC BRAIN ASSEMBLY REQUIRED!)

Although the title above sounds “Shakespearean,” the question gets to the essence of sensorimotor control particularly for higher primates such as ourselves. C. S. Sherrington was convinced that we sense to move since his work suggested to him and others that sensory input is required to evoke motor output for many if not most actions that we take. James J. Gibson and other ecological theorists on the other hand, suggested the opposite. Unlike most prevailing views in the early twentieth century, Gibson, 1966 insisted that humans use motion to acquire meaningful sensory information from affordances in the environment, e.g, active touch. Such an action-oriented brain will certainly utilize its circuitry differently than one governed strictly by stimulus-driven neural networks. We actively seek information about our world rather than wait for stimuli to “passively” evoke a behavioral response.

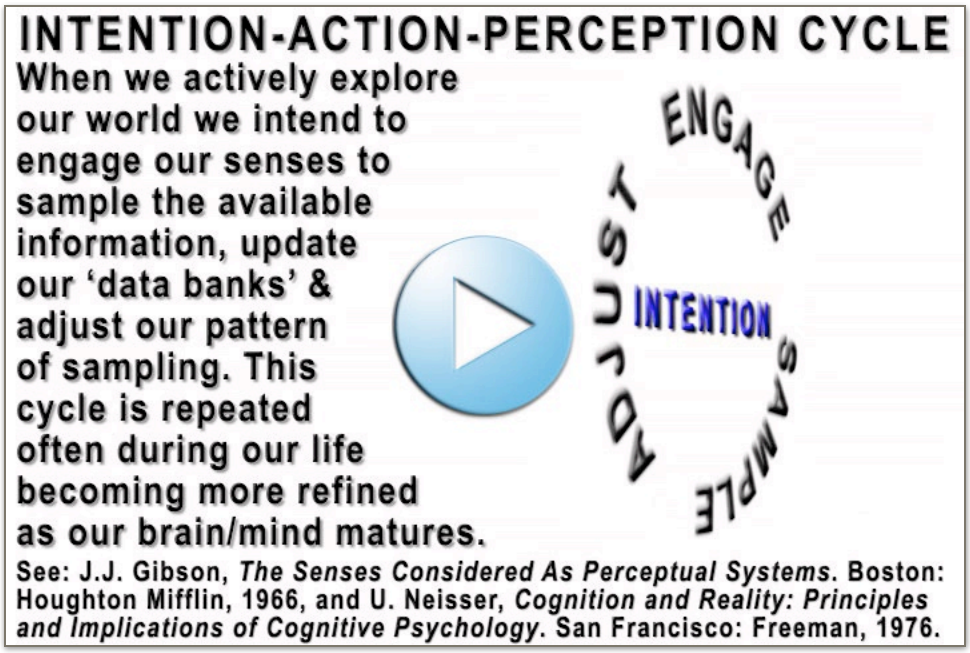


Fig 19-21. Intention-Action-Perception Cycle Movie (gec). GO TO: gmomm.pitt.edu Fig19-21_Video

U. Neisser, 1976 has hypothesized that we gain knowledge about ourselves related to the world by perceptual cycles. An "Action-Perception Cycle" view of brain function hypothesizes that what we experience is related to our ability to explore and gain information about our world. This is not seen as a one time process but an evolution of sampling, modification, and directing ourselves to gather further information. One supposes that the action-perception cycle is an intentional process resulting in learning that allows for increased sophistication in our perceptions & actions as our "schema" of the present environment and the cognitive "map" of the world grow and become fine-tuned over our life cycle to enable us to more precisely predict the future and then intelligently form memories related to past experience. Another voice has suggested that we as humans are wired such that we solve motor problems by reiterative looping of information. Nicholai A. Bernstein, 1967 proposed that our nervous system, connected to sensors and actuators, performs circular "servo" operations where we utilize information from present or past performance to compare such data to an internal model of intended outcomes. Our nervous system makes such comparisons and derives an error signal that is incorporated into our memory and recalibrates and regulates the system for the current or next iteration of the task. Practice is therefore essential along with both afferent and efferent information derived from actual performance. This feedback data from the actual events (afferent and efferent) are compared to the desired, anticipated outcome to fine-tune performance (error detection-error correction). Some researchers use Bernstein's model as a blueprint for a self-organizing system that creates order from chaos (often unpredictably); others interpret Bernstein's model of the nervous system as a heterarchical or modified hierarchical information processing distributed network. Supporters and detractors abound in the scientific community for all of these views.

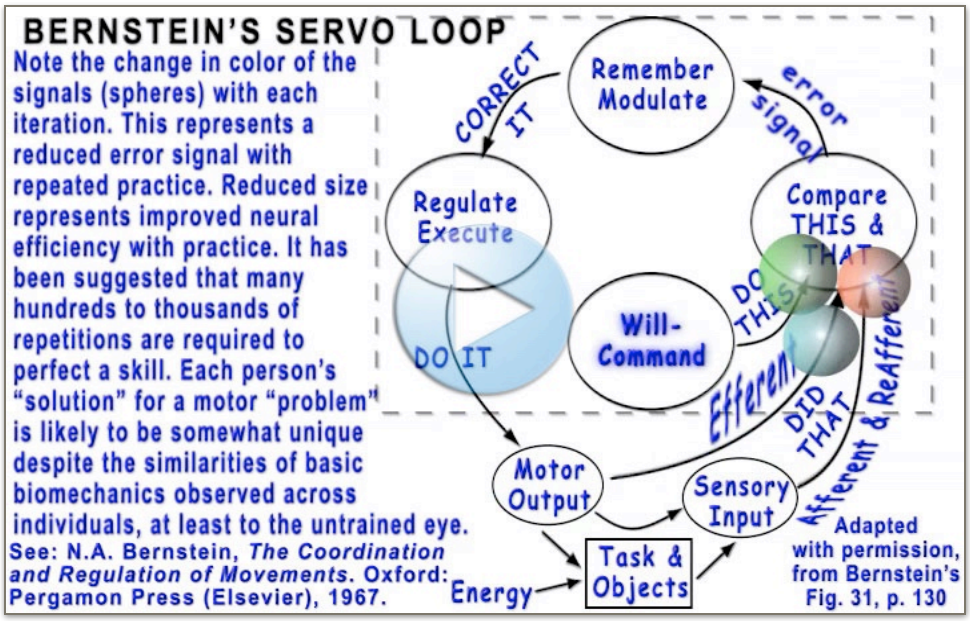


Fig 19-22. Bernstein's Circular Servo Loop Hypothesis for Adaptive Sensorimotor Control Movie (gec). Large File: Be Patient! GO TO: gmomm.pitt.edu Fig19-22 Video

When we wire our brain for success perhaps all three wiring possibilities may unfold as we step onto the stage according to: 1.) the individual's talent, the extent of training and the difficulty of the task involved and 2.) the desired (or required) precision of actions produced by a body governed by one particular brain (e.g., some people are better performers than others). Whatever the neural basis for sensorimotor control of skill turns out to be, the actual performance by a talented, practiced individual seems to be an expression of elegant control.

Imagine the restrained power & smooth swing of a professional golfer, the graceful motions of a ballerina or the delicate manipulation of neural tissue by an experienced neurosurgeon. *By contrast, now imagine a squirrel foraging for nuts after consuming a double-espresso*.

CEREBRAL CORTEX WIRED FOR SUCCESS: MINICOLUMN HYPOTHESIS

WIRED FOR SUCCESS: VERTICAL & HORIZONTAL ORGANIZATION OF CEREBRAL CORTICAL MINICOLUMNS

A minicolumn or microcolumn is a vertically connected narrow column of neurons bridging all layers of the cerebral cortex.

These structural/functional cortical cell groups are hypothesized to be basic cell assemblies in primate neocortex. Minicolumns/microcolumns are less obvious in sub-primate species. Primate neocortex has a large number of double bouquet inhibitory interneurons (see figure) that align their axonal "horsetails" in a narrow vertical pattern: a crucial delimiting factor that may define the longitudinal border of a microcolumn.

One hypothesis suggests that the microcolumn is centered around the soma of a layer V pyramidal cell; the structural/functional unit may be only ~25-50 microns in

diameter centered on the infragranular pyramidal cell's corticofugal output (see blue dashed lines in figure) rather than being centered on the corticopetal afferent input from the thalamus as has been suggested for a “macro” column (several hundred to many hundreds of microns in diameter).

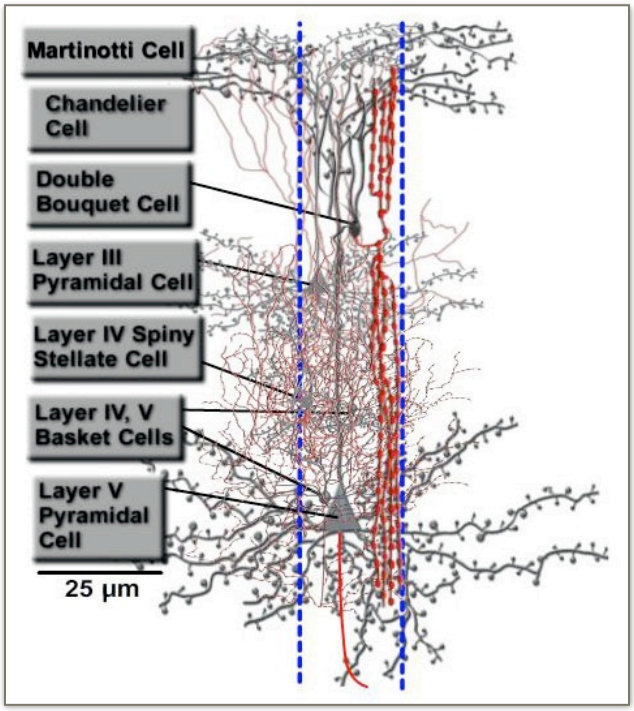


Fig 19-23. Cerebral Cortical Minicolumn: Cortical Interneuron and Projection Neuron Components. Interactive Media File illustrates Columnar Organization and Neuron Components (gec). GO TO: gmomm.pitt.edu

Fig19-23_Interactive Media

Illustrated is a proposed microcolumn that contains a representative sample of the cell types that would comprise the column: layer III pyramidal cell, layer IV spiny stellate cell, layer V basket cell, layer V pyramidal cell, chandelier cell (not shown) and double bouquet cell who's soma is located in upper layer III. The actual microcolumn would contain perhaps 60-100 cells within the vertical column. A “macro” column would contain thousands of neurons.

READY-SET-GO INTENTION & ACTION MINICOLUMNS

Hypothesized model for interaction of associative and motor cortical minicolumns to provide the “Ready-Set-Go” sequence of events for implementation of our imagined or actual goal directed volitional motor plans. Note that the actual GO Signal is under tight inhibitory control: see Double Bouquet & Chandelier GABA cells in No-Go/Go Corticomotoneuronal minicolumn. This hypothesis proposes that release to GO from NO GO requires disinhibition of Corticomotoneuronal Cells.

MINICOLUMNS FOR ACTION (A) AND INTENTION (I) Include:

- **CPA = CorticoPontine Action Minicolumn,**
- **CSA = CorticoStriatal Action Minicolumn,**
- **CPI = CorticoPontine Intention Minicolumn,**
- **CSI = CorticoStriatal Intention Minicolumn,**
- **CSp = CorticoSpinal Interneuronal Projection Minicolumn,**
- **Go Versus NoGo = Gated Corticomotoneuronal (CM) Output Minicolumn.**

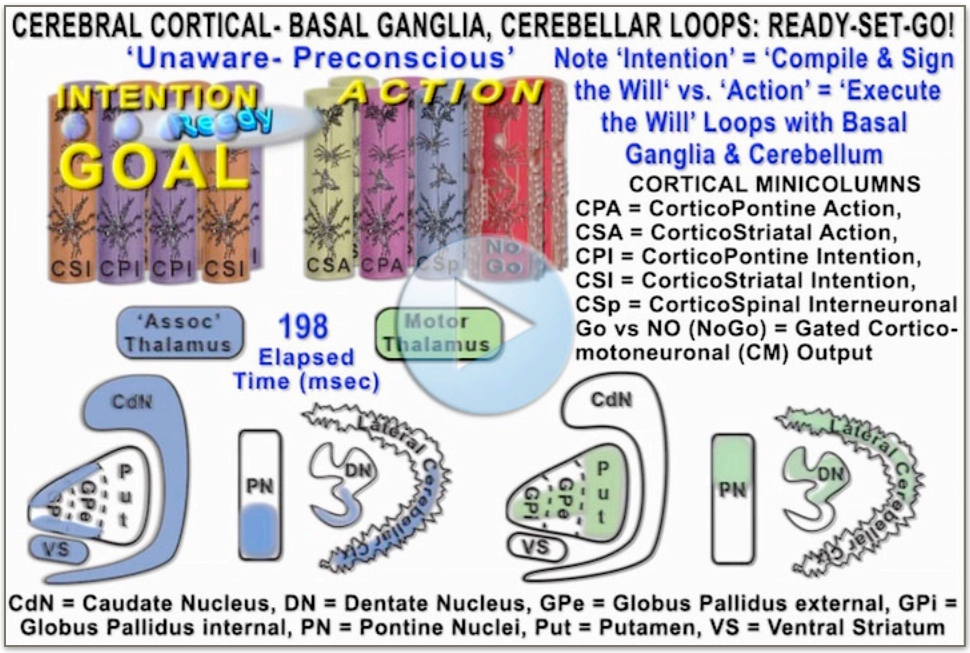


Fig 19-24. Ready-Set-Go Cortical Minicolumns linked to Basal Ganglia and Cerebellum for Intention and Action Movie (gec). GO TO: gmomm.pitt.edu Fig19-24_Video

WIRED FOR SUCCESS:

HYPOTHESIZED INTENTION-ACTION MINICOLUMNS FOR EARLY-LEARNING, LATE-LEARNING AND OVER-LEARNING

The following simulation illustrates hypothesized cerebral cortical minicolumnar activity patterns when we are first learning, followed by altered patterns as we become skilled and further changes later when the task becomes most "automatic" and more precise. Activity of deep structures is not shown. Actual distribution of Intention and Action Minicolumns may not be as segregated as shown here. CSp minicolumns connect to both spinal cord and brainstem premotor neuron networks. NoGo-GO minicolumns provide direct corticomotoneuronal output to spinal motoneurons and corticofugal output to brainstem neurons that, in turn, provide driving input to spinal motoneurons. Note that early learning shows relatively prolonged activity in many minicolumns and broad activation of many "GO" minicolumn output to multiple motoneurons. At this stage of learning the nervous system is attempting to seek an optimal solution to the motor problem. Movements tend to be relatively slow, feedback-assisted, discontinuous movement patterns with multiple velocity peaks.

The neural basis for early learning shows a spatiotemporal dispersion of activity while both preparing for (compiling and signing the will) and doing the task (executing the will). Early learning shows prolonged activation across many cortical minicolumns (map expansion?). This initial stage of learning precedes "insight" into the identification of the best solution for the motor problem for a particular individual. Feedback and feedforward signals maintain activity. Cortical output to subcortical brain and spinal cord interneurons and motoneurons is not yet optimized for spatiotemporal efficiency.

Late learning shows a spatiotemporal consolidation of activity while both preparing for (compiling and signing the will) and doing the task (executing the will). There is

reduced activation within fewer minicolumns (network consolidation?). This stage of learning indicates “insight” into identifying the best solution to the motor problem. Networks use feedforward more than feedback data. Cortical output to subcortical brain and spinal cord interneurons and motoneurons is better optimized for spatiotemporal efficiency. Overall neural activity may actually be reduced even as optimal firing is obtained within key cortical and subcortical areas, e.g., see Poldrack, et.al., 2005; Steele and Penhune, 2010.

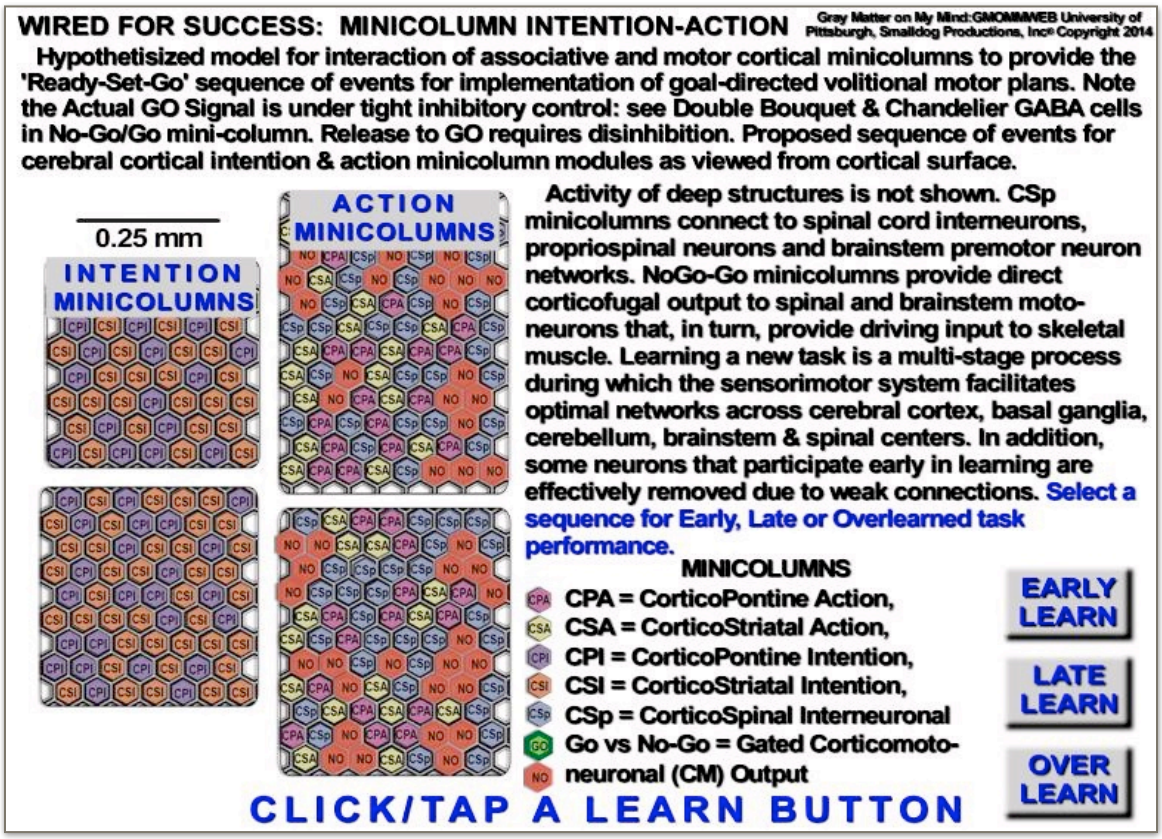


Fig 19-25. Proposed Minicolumnar Contribution to Intention-Action Learning-Early, Late and Over-Learning Interactive Media File (gec). GO TO: gmomm.pitt.edu
Fig19-25_Interactive Media

Over-learning occurs after many thousands of repetitions; over-learning shows a greater spatiotemporal consolidation of activity both preparing for (compiling and signing the will) and doing the task (executing the will): a shrinking not an expanding cortical territory, e.g., see Picard, et.al., 2013. High skill uses implicit learning and memory rules. Will Execution is more efficient; much “heavy lifting” may occur in subcortical networks (particularly basal ganglia and cerebellum). Those fewer cortical minicolumns that are active tend to fire for a shorter duration and they tend to fire more synchronously. Spatiotemporal integration is enhanced resulting in higher skill and greater efficiency. Entropy (activity in non-task related minicolumns) is further reduced during the period of

over-learning. Although the actions of the highly skilled performer may seem to be almost magical to the novice, the skilled brain may simply be regressing to the least common denominator for a series of events that have been repeated over thousands to hundreds of thousands of iterations. Of course, some native talent may be necessary for the highest level of performance. While the neural mechanisms may increase their efficiency due to increased spatial and temporal consistency in motor synergy recruitment in skilled vs. novice performers, the measured kinematics may not change in proportion to the skilled performance, e.g., see Sawers, et.al., 2015.

FRACTURED MINICOLUMN PATTERNS: GABA CELL REGULATION OF PYRAMIDAL CELL OUTPUTS

Minicolumns (microcolumns) in normally developed human cerebral cortex are ~ 25-50 microns in width. Pyramidal cells and both excitatory and inhibitory interneurons are interconnected in a vertical (radial) fashion to form each minicolumn. While it is still uncertain how such modules interact to create a functional unit, GABA interneurons have a critical role in regulating excitability. Double Bouquet Cells (DBCs) may parse the vertical columnar organization while Basket Cells and Martinotti Cells may limit pyramidal cell recruitment and "pace" their spiking. Chandelier cells because of their potent inhibition of the axon hillock of pyramidal cells distributed across minicolumns have profound influence on minicolumnar corticofugal output as well as local and distant corticocortical outputs.

HUMAN CEREBRAL CORTEX MINICOLUMNAR CONTROL OF SPINAL MOTONEURONS = PRECISION

Primate cerebral cortex has a variety of GABA interneurons that are rarely or never found in sub-primate species. Human cerebral cortex in particular has a high density of these controlling neurons to provide a fine-grained architecture for columnar function.

Thus, sub-primate macrocolumns spanning hundreds of microns in diameter containing many hundreds of corticofugal pyramidal cells define the "Standard Definition (SD)" resolution of motor control. While such patterns of activation lead to well-controlled, stereotypical behaviors common to the species, the ability to break free of such stereotyped behaviors may be facilitated by a finer control made possible by fractionated minicolumnar selection.

By contrast to a macrocolumn pattern, the addition of numerous GABAergic Basket cells, Chandelier cells and Double Bouquet cells to human motor cortex provides the means to achieve greater resolution "High Definition (HD)" motor control by way of minicolumns.

Each minicolumn contains perhaps one or two cortico-motoneuronal (CM) cells that target select spinal motoneurons with strong corticofugal drive. Double Bouquet Cells (DBCs) appear to be particularly well positioned to limit horizontal influence of overlapping pyramidal cell neurites. DBC shunting inhibition may dynamically prune

columnar processing to restricted minicolumns. The combination of minicolumns and direct access to spinal motoneurons by way of CM cells may provide humans precision not attainable in sub-primate species.

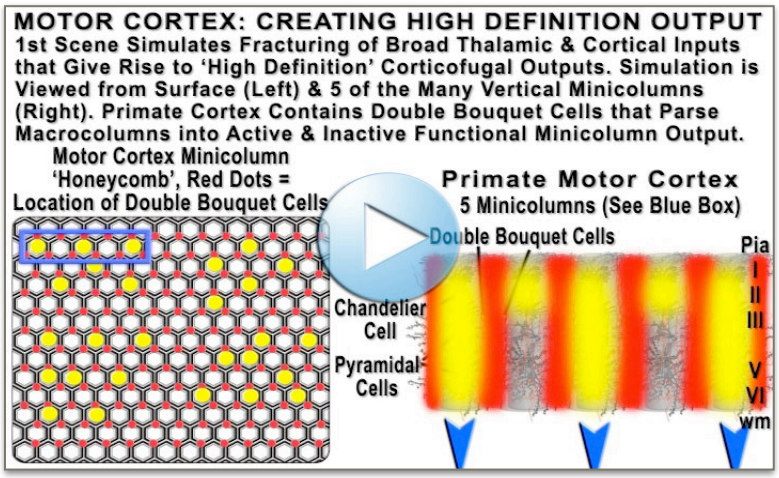


Fig 19-26. Corticomotoneuronal High Definition Output-Double Bouquet Cells and Fracturing of Minicolumn Activation Movie (gec). GO TO: gmomm.pitt.edu
Fig10-26_Video

WIRED FOR SUCCESS: MINICOLUMNS-TYPICAL & AUTISTIC

The animation below simulates a fracturing of minicolumnar activation due to GABAergic regulation (green = excited, red = inhibited minicolumn in the animation). The sphere above each minicolumn represents the excitatory drive to activate each column. Depending on the pattern of GABA cell connectivity, the minicolumns are not uniformly activated such that an area containing hundreds of such columns (macrocolumn) has a fracturing that is altered by subtle changes in inputs & columnar integration; one row of nine minicolumns is illustrated in this animation.

The differential fracturing would send neural "images" that would presumably inform downstream cortical or subcortical structures about subtle differences in sensory, motor or integrated information. Relative synchrony within & across such "fractured" networks could result in binding and the ability to build a global "gestalt" perception, action or thought.

Fig 19-27. Normal Minicolumn Fracturing Movie (gec). GO TO: gmomm.pitt.edu
Fig19-27_Video

AUTISM MINICOLUMNOPATHY: LOSS OF NORMAL FRACTURE PATTERN & LONG CORTICAL CONNECTIONS

M. Casanova and colleagues have proposed that a minicolumnopathy is present in the cerebral cortex of individuals diagnosed with Autism Spectrum Disorder (ASD). The changes include smaller somata of pyramidal cells, reduced dendritic arbors, narrower

widths of minicolumns (denser packing) and altered GABA neuron populations. In addition, there is evidence to suggest that while local columnar connectivity is intact, long-range inter-areal axonal projections are inadequate. Such changes might provide high sensitivity for the feedforward input to the minicolumns (high definition first image) but inadequate processing of intercolumnar interactions, i.e., a lack of minicolumn fracturing that generates a unique macrocolumnar "signature" projected to other cortical areas and to subcortical targets. Note the narrower width, increased number of minicolumns as well as the lack of inhibition of any minicolumn in the animation (no neural image fracture) compared to normal.

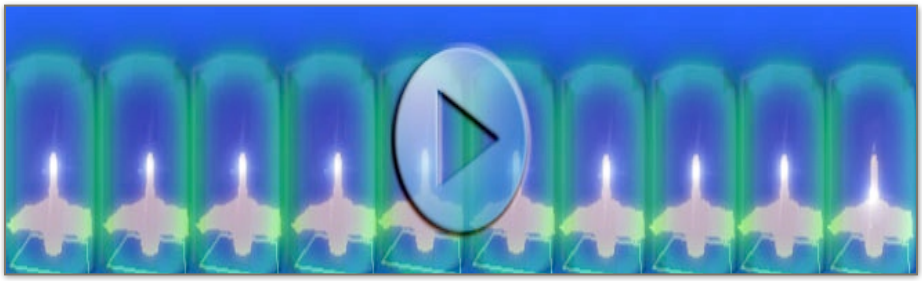


Fig 19-28. Autism Minicolumn Non-Fracturing Movie (gec). GO TO: gmomm.pitt.edu Fig19-28_Video

Such changes in the gray and white matter may at least partially explain some of the neural peculiarities often experienced by individuals who have ASD. For example, these individuals may experience hyperacuity of sensations such that details are "rendered" in very high definition but the ability to place those details into a broader, global context is quite limited. Thus, the "gestalt" of a facial expression may be uninterpreted although the individual features of the face in isolation are well recognized. Lack of a fractured minicolumnar pattern plus inadequate long-range corticocortical connections may limit binding for complex neural processing needed for the perceptual and cognitive "insight" that lead to social contextual interpretations of subtle behavioral cues.

PREFRONTAL CORTEX: ESSENCE OF THOUGHTFUL HUMANS- DECIDER OR DELIBERATOR?

Executive functions are often attributed to the Prefrontal Cortex (PFC). However, no-PFC Cortex, Thalamus, Basal Ganglia and Cerebellum all have loop connections with PFC. Decisions are likely to be the result of Distributed Control. Nevertheless, scientists have ascribed the most human of brain functions to circuits that reside in the PFC; think "The Thinker" sculpture. This is the one area of the mammalian brain that has developed the most phylogenetically and ontogenetically (especially for post-puberty brains). Fuster, 2013 states the PFC has a role as a master enabler of novel actionable neural processes due to the capacity of PFC networks to encode working memory and temporal organization of complex goal-directed behavior. A snarky analogy regarding the PFC's role in deliberation might go like this: "*I (the PFC) may not have sole ownership of this masterpiece (the whole brain) but I merit a first or last authorship NOT a 'tween author position (it was my idea/I have the last word).*"

HUMAN PREFRONTAL CORTEX (PFC) FUNCTIONS (with ample assistance from connected non-PFC cortical and subcortical brain). it is not clear whether PFC ALWAYS "shares" credit! *gec, updated 2014*

- MOTOR/COGNITIVE "EXECUTIVE" PLANNING (SHORT-TERM AND LONG-TERM: LIFETIME?)
- MOTOR/COGNITIVE JUDGEMENT (decisions required to solve the problem at hand)
- SELECTION OF APPROPRIATE AND SUPPRESSION OF INAPPROPRIATE BEHAVIOR ACCORDING TO CURRENT CIRCUMSTANCES (environment, context, social & moral values, motivation, affect, drives, perceived necessity, etc.)
- FORMATION/STORAGE? OF INTERNAL BEHAVIORAL REPERTOIRES BASED ON REPRESENTATIONAL MEMORY (forming inner virtual models of reality to govern the timing of behavior: *your brain should pause briefly after reading this!*)
- TEMPORAL ORGANIZATION OF THE SEQUENCE OF NOVEL (NON-ROUTINE) MOTOR OR COGNITIVE EVENTS INCLUDING SHORT-TERM WORKING MEMORY.
- ESTABLISHING AN APPROPRIATE BALANCE BETWEEN "IMPULSIVE" (GUT-REACTIONS) AND "CONSTRAINED" (INTROSPECTIVE) BEHAVIORS WITHIN SOCIAL/MORAL BOUNDS.
- SEEKING (EXPLORATIVE BEHAVIOR) AND REALIZING (EXPLOITATIVE BEHAVIOR) UNUSUAL OPPORTUNITIES FOR EXTRAORDINARY REWARDS (OFTEN HIGH RISK: HIGH BENEFIT STATISTICAL NEURAL CALCULATIONS) FOR SOCIETAL AND/OR PERSONAL GAIN (wise, clever, cunning, speculative, insightful, ingenious, calculating, lucky).
- BALANCING ALTRUISTIC WITH "GREEDY/SELFISH/HEDONISTIC" BEHAVIORAL CHOICES ACCORDING TO INTERPERSONAL RELATIONSHIPS WITH OTHERS VS. PERSONAL NEEDS, WANTS OF THE SELF: INCLUDES EXPLICIT "CONSCIOUS" AND IMPLICIT "NON-CONSCIOUS" LEVELS OF NEURAL PROCESSING (again your brain should pause and reflect).

Pyramidal neurons in the prefrontal cortex have greater synaptic contacts per unit area than primary sensory (V1), parietal (Area 7a) and temporal visual (TE) association cortices. Extensive opportunity for synaptic plasticity exists in frontal cortex (Areas 10, 11, 12). The human frontal cortex undergoes massive development of the neuropil within the first several years of life. While cell packing density stays relatively constant over time, the dendritic field begins to fill the frontal brain parenchyma at a time when its owner is a toddler beginning to define his or herself as an individual within the family. This neuropil development may have many other growth spurts, e.g, during puberty and to a lesser extent during those unusual periods of unforeseen challenges to one's being throughout adult life. Pyramidal cells in the intact, normal adult prefrontal cortex receive

massive synaptic inputs, e.g., see Elston, 2000, 2003 and Fuster, 2008. A high spine density approaching that of PFC pyramidal neurons is said to exist for pyramidal cells in the Inferotemporal (IT) cortex, as might be expected for an area involved in high level visual perceptual processing, e.g., see Elston, 2003.

PFC TEMPORAL ORGANIZATION OF COMPLEX NOVEL BEHAVIORS AND WORKING MEMORY

Neuroscientists who study the prefrontal cortex have emphasized its role in the ability to temporally organize complex behaviors that are novel or are being modified to allow for a revised behavior to obtain a reward. One critical component of this process is the ability of neurons to hold information over a sufficient time-period to make decisions based on prior, current and predictive future data relevant to the task at hand. These executive decisions are thought to require neurons capable of persistent firing to hold these data in "working memory".

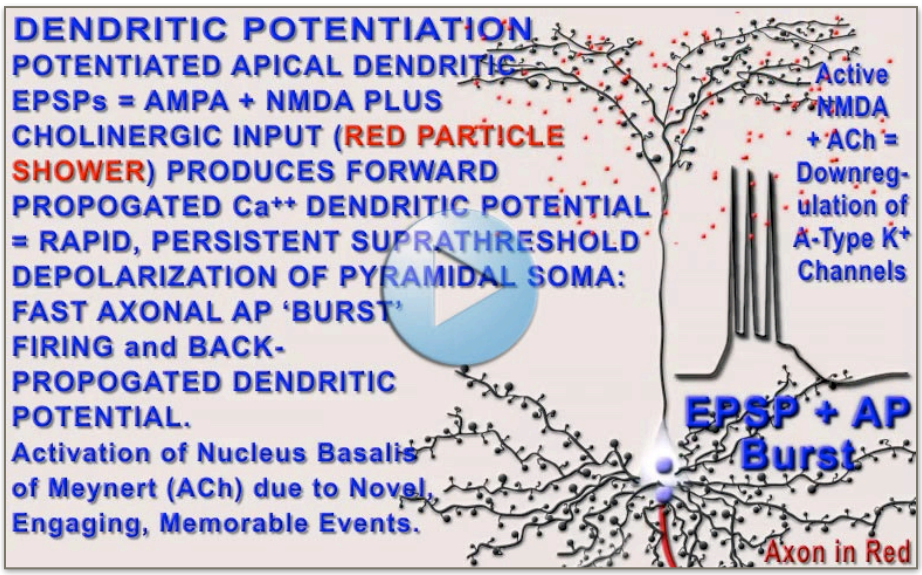


Fig 19-29. Dendritic Potentiation: Acetylcholine (Ach) + AMPA + NMDA generates Dendritic Potential and Burst Firing of Pyramidal Cell (gec). GO TO: gmomm.pitt.edu *Fig19-29_Video*

There are a number of studies which provide evidence for specific mechanisms involved in working memory at the microscopic and molecular levels. For example, certain potassium channels in dendrites and dendritic spines may attenuate depolarizing inputs. If these hyperpolarizing K^+ channels are closed and/or down-regulated by neuromodulatory inputs, EPSPs are more likely to trigger a propagated dendritic potential, a sustained depolarization of the soma and a persistent firing of the neuron. Such sustained activity is thought to be essential for at least some forms of working memory. The Dendritic Potentiation Movie illustrates one example of this persistent firing. Although ACh is this modulating influence in this example there is evidence that monoamines and other neuromodulatory molecules are involved as well.

EVOLUTION OF PREFRONTAL CORTEX: AN "UPFRONT" STORY OF BRAIN EXPANSION

THE FOLLOWING STORY IS SOMETIMES 'SHARED' AS A SUPPLEMENT TO LECTURE MATERIAL REGARDING PREFRONTAL CORTEX STRUCTURE/ FUNCTION RELATIONSHIPS.

A Story About A Dog, A Cat, A Human and The Prefrontal Cortex

Please Suspend All Sense of Reality Before Continuing.

Murphy a black flat-coated, male retriever and ***Jasmine (Jazzy)*** an agile, friendly, female domestic cat were the older & wise four-legged siblings of our family. One day I was putting together a slide for a neuroscience lecture that shows the evolution of Prefrontal Cortex (PFC) illustrating an increasing size of the frontal lobe across species and the proposed functions/dysfunctions associated with the PFC. ***Murphy*** and ***Jazzy*** were "helping" me with this task. As they looked at the slide that included Fuster's PFC figure illustrating the successive growth of the PFC across species, ***Murphy*** points to the Cat Brain (specifically the small shaded PFC of the cat brain) and begins to chuckle: See Fuster, Fig 1 page 1150,1981.

Without missing a beat, ***Jazzy*** remarks that he (Murphy) should take a closer look. "The dog brain has more black in the front and that fact is appropriate in your case since there is nothing going on in that dark abyss of your so called brain."

Murphy retorts by commenting that ***Jazzy*** doesn't even know her own name because she never comes when called.

Jazzy: "I come when I want. I am an independent soul that doesn't act like a fool by wagging my tail and barking like I was obsessed whenever one of the bipeds arrives at home."

Murphy: "Well, you have to go to the 'sandbox' to do your business and then stink up the whole place."

Jazzy: "Well I'm not the one who has to bark and be on a leash whenever you go out to make a deposit or in your case make a withdrawal from the bank of poop."

Murphy: "At least I get to walk with the adoring bipeds everyday, while you act all snooty and barely acknowledge that the humans exist until it's dinner time."

Jazzy: "OK big boy let's go outside, I've got some shredding to do with these claws!"

Murphy: "You're ON. I'm gonna make you wish you never learned to talk!"

George: (the biped making the slide and enjoying the repartee until now), "**OK ENOUGH! Go to your rooms.** You have a 30 minute timeout! No TV, No internet, No Video Games, No SmartPhone, No Updating Social Media (you may add your favorites to this list). Calm down and use this quiet time to think about what good friends you are to one another."

Later that evening (after timeout had expired) all three of us are together again and watching the "news". As the program unfolds, ***Murphy*** and ***Jazzy*** look at one another with puzzled expressions on their faces. Finally at the end of the broadcast they comment about the PFC slide and the huge size of the PFC in humans.

Jazzy: "Remember the PFC slide *(that ruined my social networking like forever)* that we were looking at earlier? It stated that the PFC is where the brain makes wise choices, logically interprets terabytes of information and lets you act in an intelligent fashion. So, after watching the 'news' and all the annoying commercials that interrupt any possible logical train of thought, we are wondering: '*With All Due Respect-What the heck do you bipeds do with all of those neurons in your giant frontal cortex?' "*

Murphy: "Yeah, you don't seem to be very nice to one another and you do seem to be trashing the environment and it appears that you keep repeating your mistakes decade after decade, century after century (***Murphy*** devours history books). **PLUS-**you must be very needy or insecure since you are encouraged to buy all this stuff so you can be smarter or sexier than the next biped and all of that stuff must stress you out since there are so many pharmaceuticals you must buy to treat all the illnesses that seem to be the result of an excessive neediness." Murphy takes a breath.

George: (defending the bipeds) "Well you have to realize that the local, national and international news pick spectacular events to report which often amounts to bad or sad news that will sell commercial time to the general public. This is not representative of humans as a whole. There are many, many humans who are very responsible, go out of their way to help one another and try to make this earth a better place to live for all of us. They are using their frontal cortex in a positive fashion ***and*** after all, we are still a work in progress. Go back and look at a more comprehensive description of human history, we are not all bad ogres-*even if we all seem to like Shrek and Princess Fiona*."

Jazzy (who devours science fiction books and sci-fi videos): "Does that mean that when the computers finally take over the world (next generation of IBM's WATSON?) we will move forward and evolve to a higher level (the singularity)?"

George: "Jazzy, you need to go back to your video collection and again watch Stanley Kubrick's 1968 film '2001: A Space Odyssey'-***remember HAL?***"

You should now take a deep breath and resume reading with your normal mind set.

The more anterior aspects of the frontal cortex are "new" in an evolutionary sense in primates and include 'granular' neocortex (having a well-defined layer IV like that found in granular sensory cortex). Humans have a huge expansion of this 'granular' frontal neocortex which may be small or non-existent in other species. Bolstered by cortical and subcortical forebrain plus posterior fossa brainstem structures the PFC endows its owner with the capacity to choose thoughts and behaviors according to rule-based judgements governing selection of those mindful processes. Although this new

'granular' PFC certainly is not identical to granular sensory cortices, perhaps this frontal 'granular' cortex provides a new "sense": an explicit and implicit sense of self-identity with a unique relationship to the world e.g., A. Damasio's "autobiographical self" (Damasio, 2010).

This unique sense of oneself in nature is a creative "me" to be, and to do, i.e., to solve non-routine complex problems presenting both high risk and the potential for great reward. The ***mature, well-wired*** human PFC provides a number of critical nodes in our circuitry for success (see references).

Human PFCs have collectively and sometimes singularly forever altered the world we inhabit far beyond the influence of other species.

HUMAN PFC and POSTERIOR ASSOCIATION CORTEX CAPABILITIES MAY BECOME AN UNWANTED SOURCE OF IRONY-AMERICA THE GRAY: AGING CEREBRAL CORTEX

Americans are coming of age – literally. "Baby-boomers" will soon swell enrollment in Medicare, and draw social security from coffers that may be unable to meet demand. Health care demands will parallel the rise in median age of our society. The number one risk factor for a number of neurodegenerative diseases, e.g., Parkinson's Disease (PD) and Alzheimer's Disease (AD) is age. There is good news and bad news.

Although now there is no cure for PD or AD a number of very bright neuroscientists are working furiously to define pathological processes, create potential diagnostic tools, and establish potential treatments (lifestyle and medication) for neurodegenerative diseases. There are scientists who believe some forms of AD are not only treatable but also preventable.

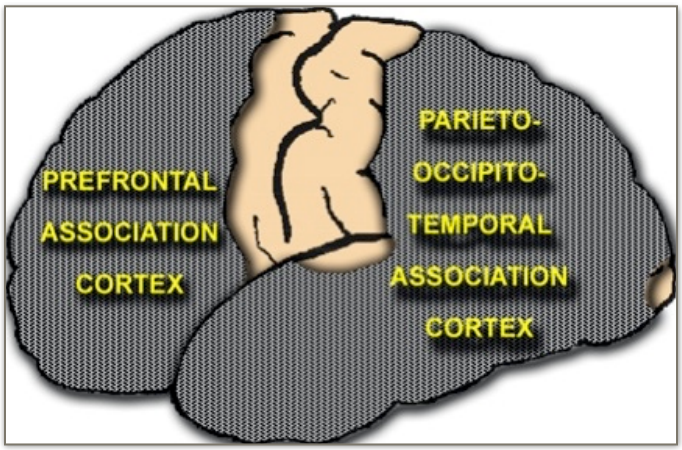


Fig 19-30. Prefrontal (Anterior) and Parieto-Occipito-Temporal (Posterior) Association Cortices: At Risk Higher Level Cerebral Cortex (gec).

Contrary to older ideas, normal aging does not appear to be associated with significant cell loss in most cerebral gray matter. While this older idea regarding neuron loss appears to be unfounded in normal aging, profound cell loss within "higher" level cerebral areas is characteristic of AD and other forms of dementia. This cerebral cortical cell loss in AD robs the brain of the very essence of what makes us human.

1. Of all layers, layer I of the cerebral cortex appears to atrophy in normal aged primates. For young adults, Layer I is cell sparse but has many horizontal long-range

corticocortical axonal projections and apical dendritic tufts from supragranular and infragranular pyramidal cells. A number of neuromodulatory chemicals may have profound effects on these synaptic connections. Many of these dendritic branches and synaptic connections appear to be lost with age. Who cares? Remember that superficial cortical layers receive substantial input from matrix projection neurons in higher order thalamic nuclei. Through thalamocortical loops, this connectivity may be essential when coupled with intrinsic cortical connections in solving the "binding problem" for normal cognitive function. Apical dendrites of layer V pyramidal cells under certain conditions may generate dendritic NMDA and Ca++ potentials that induce persistent "burst" firing in these neurons. Recent findings in rodents suggest such activity may be critical for "global" binding across multiple cortical areas involved in perceptual and cognitive processes. Loss of small inhibitory interneurons in superficial layers would compromise control of layer I excitability. For example, a recent study of human cerebral cortex has characterized a GABAergic interneuron called a Rosehip cell (RC) located in cortical layer I. RCs have not been identified in other species and evidence suggests RCs have a critical role in regulation of excitability in apical dendritic tufts of pyramidal cells. RCs are electronically coupled and may participate in generating rhythms important for higher level (top-down) processing critical for cognition (see Boldog, et.al., 2018). Collapse of human cortical layer I with aging would remove these GABAergic influences for higher level functions.

2. Adding candles to the birthday cake year after year has consequences beyond a potential increased fire risk. By middle age (50+ human years) or perhaps earlier (see Shaw, et.al., 2014) our gray matter may have a nonuniform "thinning" that may be due to cell shrinkage and/or neurite loss but ***not*** substantial neuron loss; the prefrontal cortex and medial temporal cortex are particularly affected; some individuals have more involvement than others. Certain neurotransmitters and neurotrophins may be altered or diminished and ~30% of axospinous and axodendritic synapses may be lost in superficial layers of prefrontal cortex. Based on monkey electron micrographic studies, presynaptic axosomatic GABAergic boutons on pyramidal cells in Area 46 of prefrontal cortex may actually be enhanced in aged monkeys who show cognitive impairment (e.g., see Soghomonian, et.al., 2010), while axospinous synapses in supragranular layers of Prefrontal Area 46 are reduced and this loss is correlated to working memory decline: See Peters, et.al., 2008. Thus, too little depolarizing input may have to compete with relatively strong inhibition in cognitive circuitry; now add impaired mechanisms to generate persistent burst firing in pyramidal cells (due, in part, to collapse of superficial cortical layers) and we have a potentially unfortunate combination for thinking brains. So, I may ask you to write down your phone number.

3. White matter does seem to diminish to some extent in normal aging. Gray and more so white thinning may account for slightly enlarged ventricles and a reduced brain volume (but not weight) in aged brains. Myelin abnormalities appear to be

substantial in association cortex, e.g., as shown in prefrontal cortex in aged monkeys. Demyelination and remyelination is accompanied by an increased number of oligodendroglia and the level of myelin abnormalities in Prefrontal Cortex is correlated with cognitive decline (as measured in aged monkeys). Distribution of voltage-gated K^+ channels in paranodes may alter nerve conduction properties. Since cognition may depend upon correlated firing of cerebral neurons to solve the binding problem, a variable conduction velocity may tax neurons struggling to function within the distributed network. Slowed or disrupted temporal sequencing of thought (altered executive function) and action sequences occur in many elderly. Paradoxically, association cortex is the evolutionary "weak-link" in the human brain since myelination is poor there and thinning of gray greater compared to primary cortical areas even in young adults, e.g., see Braak, et.al., 2000. The cerebral cortex is not the only region influenced by age. Volume as measured by MRI decreases with age in the caudate nucleus, cerebellum and hippocampus, all regions of importance in cognitive function, e.g., see Raz, et.al., 2005. With longevity, the organ that best defines us as human is susceptible to insults that have little impact on other species.

4. Dementia including Alzheimer's Dementia is related to a neuronal cell loss particularly in association cortex, hippocampus, and some subcortical structures. Not all neurons are susceptible and left hemisphere is typically involved more than the right hemisphere in AD (see references). AD shows abnormal function in neurons 'attacked' by Beta Amyloid plaque formation and neurofibrillary tangles. Neuronal loss may be substantial in later stages of AD. Pathological changes are found for glia as well, which may have quite significant consequences.

5. Although the aging brain movies are "tongue-in-cheek" animations, accumulating evidence suggests in addition to genetic factors there is an important role for lifestyle factors in preservation of brain structure and function as an individual ages due to "reserve", compensation and/or maintenance of brain function: for recent review see: Cabeza, et.al., 2018. The second movie suggests also that making lifestyle changes while beneficial in theory, in practice may be difficult to achieve for many individuals. Nevertheless, meeting the physical and mental challenges of aging may provide sufficient rewards to be worth the effort.

Fig 19-31. Tongue-In-Cheek Older View of Normal Aging Brain (gec). GO TO: gmomm.pitt.edu Fig19-31_Video

6. Recent research suggests normal aging produces little neuronal loss although glia plus neurites & synapses are affected within particular areas of the cerebral cortex. Connectivity may be altered but to some extent this decline may be modified by internal genetic & external epigenetic factors, e.g., lifestyle.

Fig 19-32. Tongue-In-Cheek Newer View of Normal Aging Brain (gec). GO TO: gmomm.pitt.edu Fig19-32_Video

ALZHEIMER'S DEMENTIA: THE THIEF IN THE NIGHT

As the population in the United States and elsewhere ages the proportion of individuals diagnosed with Alzheimer's Disease (AD) or other forms of dementia rises dramatically. AD-related Cytoskeletal Alterations have the following statistical likelihood: 10% of 1410 autopsy cases show first changes in age group 21-47 while last 10% do not show changes till ages 81-104, see Braak et al, 2000. Those in late "middle" age or early "golden" years define the 80% majority of those first diagnosed with AD; for you invincible youngsters out there please take note of these statistics. AD brains suffer gray and white matter loss especially in those cerebral association areas including the medial temporal lobe (parahippocampus, hippocampus and entorhinal cortex) which provide us with our extraordinary higher cognitive functions. Braak, et.al., 2000 hypothesize that our species' most recent and weakest evolutionary link for dementia is found in the association cortical gray located in the center of the gray matter "bridge". The primary cortical areas are more evolved and at less risk of dysfunction due to AD pathology and these areas form the pillars holding up the bridge "roadway". For individuals who have AD the bridge is collapsing. Thus, the very essence of what defines our behavior as uniquely human may be our species' weakest link as the brain matures and the individual blossoms as a cogitator: i.e., the very definition of irony.

Cognitive changes in AD parallel gray matter loss in limbic & non-limbic association cortex. Total gray matter loss is relatively minimal in normal aged subjects. AD gray matter loss is different for the two hemispheres. As stated above, primary sensory and motor areas are relatively spared until quite late in the disease. Imaging techniques coupled with high-power computational algorithms allow us to "watch" these changes occur over consecutive human brain scans. There is a rapid & significant progression of gray matter loss (atrophy) correlated to cognitive decline over a period of ~18 months in many AD subjects, see Thompson, et.al., 2003. AD cytoarchitectural changes are layered on top of the gray and white matter alterations characteristic of normal aging (see Normal Aging section above).

This author does not pretend to be an expert in the substantive knowledge related to the biochemical, genetic and ultrastructural changes characterized in AD for either animal-related or human research studies.

There are however several lines of research that have their very roots in the first description of the brain pathology in a case study presented in 1907 by the German psychiatrist Dr. Alois Alzheimer. The individual was a 51-year old female who had characteristic cognitive and other "mental" changes for what is now known as Alzheimer's Disease (AD). After this individual died, Alzheimer described changes in both neurons and glia in his post-mortem microscopic brain analysis. Most of the current research is focused on neurons rather than on glia.

According to English translations of Alzheimer's original case studies these pathological changes appeared predominantly in the upper layers of the cerebral cortex with some neurofibrillary tangles remaining even after the cell disappeared; he described significant neuronal loss in the upper layers, he described also abnormal plaque (miliary foci) formations (see Stelzmann, et.al., 1995, Graeber, et.al., 1997, Graeber and Mehraein, 1999).

Alzheimer described abnormal miliary foci now known to be Beta-Amyloid plaques as well as abnormal intracellular neurofibrillary tangles (tau tangles). The *APOE* allele appears to be associated with Beta Amyloid plaque formation. There are different alleles of *APOE* (2-4). If an individual inherits the *APOE4* allele from both parents that individual has a higher statistical risk of developing AD. Much research has centered on plaque formation and pharmaceutical agents to combat this abnormal protein accumulation in the brain. As of this writing there is no successful treatment that BOTH reduces or eliminates Beta Amyloid plaques AND provides a concurrent improvement in cognitive function. One drug now developed and approved for a select group of AD patients reduces or eliminates the plaque but these studies show no concurrent improvement in cognitive status. In addition, through use of PET scans specific for Beta Amyloid accumulation, researchers have found that some older individuals have brains loaded with Amyloid plaques ***BUT*** suffer no significant cognitive deficits.

Perhaps researchers are barking up the wrong tree (so to speak).

Despite the current obsession with amyloid plaques related to neurons, recent discoveries suggest glia may play a central role in the progression of both structural and functional losses in AD. These studies have centered on the roles of both astrocytes and microglia in early vs. late stages of the disease. A number of recent studies have focused on the role of microglia which appear to form an "immune" system for the CNS. Microglia along with astrocytes appear to share a duty to eliminate amyloid plaques early in AD, often with limited success. However, these microglia and an associated allele called *TREM2* may turn to the "dark side" in later stages of AD. Early in AD microglia and associated *TREM2* assist astrocytes in APOE plaque removal. Later in the disease there is an enhanced accumulation of neurofibrillary tangles (abnormally

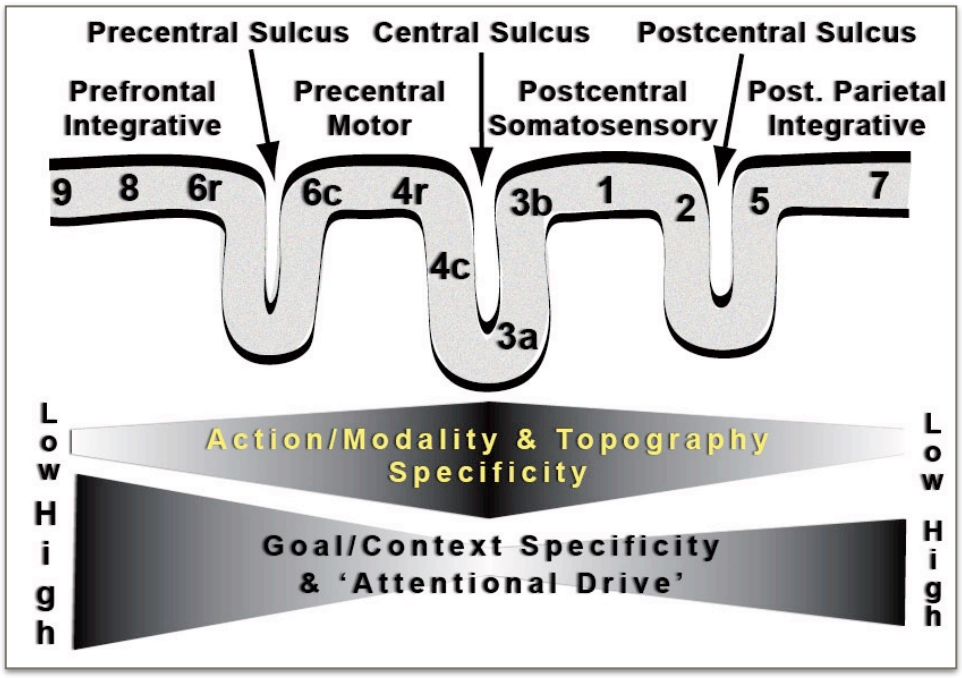
configured Tau proteins) within the neuron soma and neurites, including axons and axon terminations. Tau is a protein that when normally configured anchors microtubules within the axon and other portions of the neuron. If Tau begins to assume an abnormal dense configuration of the protein, microtubules become malformed and microglia appear to attack the "Bad" Tau within intracellular compartments of the neuron to destroy soma, axons and synapses (45% loss of presynaptic boutons in AD compared to cerebrums of healthy aged individuals: e.g., see Perl, 2010). There is currently no PET scan specific to abnormal Tau so much of this work is performed in animal models of AD (genetically modified mice) and fewer studies of post-mortem human brain specimens. Abnormal Tau accumulation has ***NOT*** been studied using PET imaging in awake human subjects. It is too early to say whether microglia attacking intracellular accumulation of "Bad" Tau is truly responsible in a "if-then" fashion for brain atrophy and associated neural deficits but the correlational data are certainly intriguing (in mice). If an intervention is discovered that prevents microglia from turning to the "dark side" and prevents associated cognitive decline in humans that would indeed be welcome news for many who suffer from this horrific disease (see Hong, et.al., 2016, Graeber, et.al., 2016, Perl, 2010; Ulrich and Holtzman, 2021 for recent reviews).

BRODMANN AREA GRADIENTS FOR DATA SPECIFICITY: ACTION/MODALITY/TOPOGRAPHY SPECIFICITY VS. GOAL/ CONTEXT/ATTENTION SPECIFICITY

The cerebral cortex anterior and posterior to the central sulcus includes motor and sensory areas utilized in control of actions and "preconscious/conscious" perceptions. The Rolandic (Central) sulcus separates frontal & parietal lobes. Those Brodmann areas closest to this landmark (Areas 4c, 3a, 3b) have high resolution representation of the somatosensory periphery (small, discrete, unimodal receptive fields: 3a = proprioceptive, 3b = tactile) and specific, task-dependent corticomotoneuronal control of spinal & bulbar motoneurons (localized, discrete motor synergy: 4c to Alpha MNs, 3a to Gamma MNs). As one moves to more anterior (4r, 6c, 6r, 8, 9) or more posterior (1, 2, 5, 7) areas, the topography of motor or sensory representations becomes more coarsely grained (larger & multimodal receptive fields & complex motor synergy involving greater degrees of freedom) and more context-dependent (activation of networks due to internal central drive greater than external peripheral drive).

The gradients extend beyond those closest to the central sulcus, i.e., from single-digit into double-digit Brodmann Areas. The latter include prefrontal (anterior) association, parieto-occipito-temporal (posterior) association cortices and limbic cortices (not illustrated in Brodmann Area Gradients figure). As one moves into these more "distant" association areas any "concrete" topographic map disappears and is replaced by more abstract representations of internal states/conditions related to the person as a singular entity and that individual's personal history. Such a personal representation

often (perhaps always) is flavored by limbic, affective “labeling” indicating some relative importance or salience to the data. This may either make the data easier to reconstitute later with a positive emotional overlay or alternatively to “bury” it so that any full reconstitution of “images” and events is very unlikely to occur.



A similar gradient can be imagined related to the primary visual cortex (Area 17) and to the Primary Auditory Cortex (Area 41) surrounded by unimodal and multimodal association areas (Areas 42, 22).

Fig 19-33. Brodmann Area Gradients: “Central Out”” Vs. “Borders In” Specificity, Darker = higher specificity, Lighter = lower specificity for each gradient (gec).

Fig 19-33 Key:
9 = Prefrontal Executive Function,
8 = Frontal Eye Fields,
6r = rostral/anterior lateral premotor or supplemental motor areas (context-dependent motor programs/plans)
6c = caudal/posterior precentral motor synergy inputs to SMC INs (proximal > distal)
4r = rostral/anterior precentral motor to distal > proximal SMC INs & MNs.
4c = caudal/posterior precentral motor monosynaptic corticomotoneuronal (CM) drive to distal > proximal MNs
3a = proprioceptive receptive & CM drive to distal > proximal gamma MNs
3b = discriminative tactile receptive
1 = tactile complex receptive
2 = tactile & proprioceptive integrative
5,7 = multimodal integrative, context-dependent, action-perception orientation

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A recent study of corticocortical connectivity in the primate brain suggests the prefrontal cortex has a greater number of cortical areas that project to it compared to more posterior and inferior cortical areas, e.g., see Markov, et.al., 2014. Thus, in big brains, a gradient seems to exist in a roughly posterior to anterior manner related to collecting sufficient data to determine appropriate behavior decisions and to enable other cognitive processes. This Posterior to Anterior gradient may provide massive serial/parallel processing for extraordinary data transfer and intricate information processing. Many but not all of these cortical areas have reciprocal connectivity.

Thus as one moves away from the primary cortical areas one loses the specificity of the sensory or motor construct that is replaced by a more abstract representation that may no longer be so topographic but may be more specific for the motivation and internal context in which perceptions, thoughts and actions are represented.

The ability of the brain to “reconstitute” those original topographic/modality/action specificities based upon past experience (memory) may be one way for the brain to recreate “scenes” from the past. These replayed memories are not exact replicates but abstracted constructs that have an emotional overtone to making their “maps” strong and representative of important self-defining moments of one’s personal history. Such a “backward” associative to primary cortical flow of information related to recall would be consistent with the hypothesis of Meyer and Damasio, 2009, see also: Damasio, 2010.

HIGHER FUNCTIONS
AGNOSIAS

Astereognosis is the inability to distinguish common objects by palpation. Parietal Lobe lesions may cause such deficits although lesions of the Dorsal Column Medial Lemniscus pathway or a lesion of the Lateral Corticospinal Tract may make the gathering of information difficult to impossible. The posterior parietal cortex is thought to be critical for perception of felt objects but it is unlikely to be the sole area for such perception. Posterior Parietal Cortex (PPC) particularly the right PPC has been described as a location for integrating multimodal inputs to generate a 4-Dimensional

Spatial Reference System (3 physical dimensions referenced over time). This area utilizes combined tactile, visual, vestibular and possibly auditory data to provide such a "body image" that allows us to be aware of our environment so that we can navigate space and use objects for haptic tasks. Such a body image or body schema may be compromised by profound sensory loss (severe deafferentation or limb amputation), PPC gray matter lesions, subcortical white matter lesions that disconnect the PPC or mental disease that includes hallucinations and delusions (schizophrenia). It has been suggested that our body image is influenced also by insular and limbic areas that provide an affective overtone to our physical being. For example, when your spouse asks if such & such a piece of apparel makes them look fat you must "weigh" perceptions, affect (and your options) before you get yourself in trouble.

Conscious perceptions integrate information from multiple sensory channels. While each sensory modality begins as a separate entity associated with the receptors for that particular physical energy, perceptions mix these data and frequently have layered upon them an affective (emotional) component that enriches the experience and makes it a more memorable event for the first person. The individual sensory channels begin with a high level of order in the anatomy and physiology but integration tends to increase the level of entropy within the system. Even the sensory pathways have some degree of randomness when one investigates the sensory channel at the cellular or sub-cellular level. The neuronal interactions within the perceptual apparatus often introduces some degree of entropy that must be reined in (binding?) to bring order out of potential chaos.

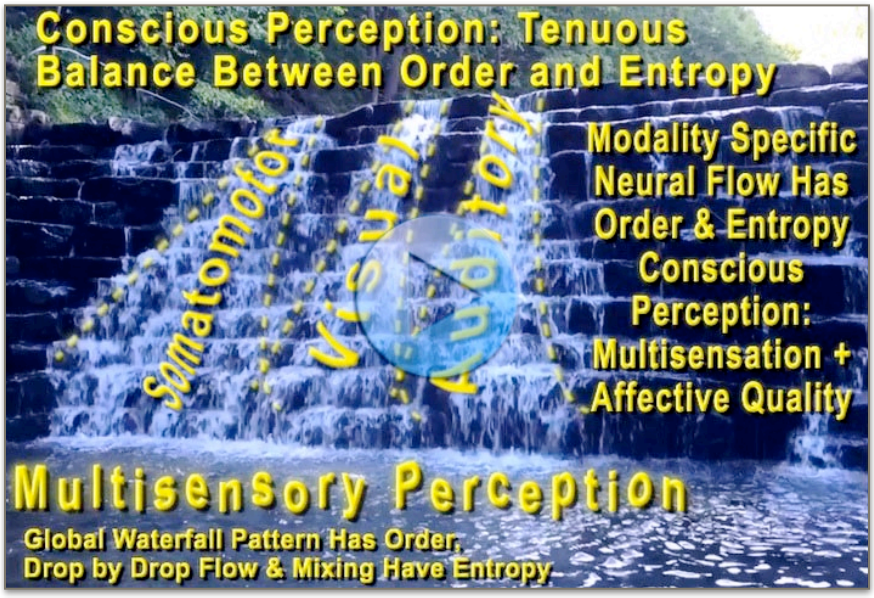

Fig 19-34. Waterfall Sensory Perceptual Integration Movie (gec). GO TO: gmomm.pitt.edu *Fig19-34_Video*

The Waterfall Sensory Perceptual Integration Movie is an example of this dynamic process. The visual and auditory sensory components are obvious to the second hand observer but the somatomotor component may be more elusive. For me as the person capturing this event, the somatomotor component was integral to the process since I was precariously balancing on a rock in the middle of the stream trying to steady my smartphone device to record the movie.

The total experience including the environmental conditions while taking the video had an affective quality layered upon it making this a memorable event for me as the first person recording the scene rather than as a second hand observer. Indeed, the ability for top-down selection of highly correlated neuronal networks in the hippocampus from Anterior Cingulate Cortex projections suggests that any remembered salient event creates an ordered (sparse) synchronous network and prevents other potential networks from coming "on-line" that would introduce noise into the system, e.g., see P. Rajasethupathy, et.al., 2015.

Occipital or inferior temporal lobe lesions are often locations of lesions that may lead to a general visual agnosia or more specific deficits in identification & perception of what we see. Inferior temporal lobe lesions may result in prosopagnosia where an individual can no longer recognize faces of individuals formerly known to the person who has such a lesion. This lack of facial recognition may extend to the loss of self-recognition when seeing one's own face in a mirror or a photograph! This is not to be confused with the tendency one may have when looking in the mirror as one ages and suddenly seeing one's parent in the mirror.

Some perceptual agnosias may be accompanied by anosagnosia where the individual is unaware of the extent of the deficit or may deny such deficits. For you as a clinician this may be a "jaw dropping" experience. You will now have a realization of the seemingly effortless ability of the brain to encode perceptual information and link that data to another person. Such abilities go missing if posterior parietal, temporal or occipital association area lesions occur despite the patient's capacity to see, hear and feel when screened for such basic sensory cues. Higher level processing and top-down influences may no longer link the periphery to one's own internal representation of the world for the individual with agnosia. Such "stealth" processing becomes apparent (at least to the outside observer) only when that link has been broken. Of course pharmacologic alterations or even recovery from anesthesia may partially and transiently expose these brainy "undercover" links. Sudden awakening from sleep could also provide unusual illusory circumstances for some individuals with no known brain dysfunction. Such "strange circumstances" rapidly dissipate as the brainstem brings on-line the neural machinery for the awake, alert brain. Once the brain's "clutch" becomes fully engaged, the neural machinery again links the bottom-up extrinsic sensory events to the top-down influences over the neural representations of these data. Structures beneath the foramen magnum, within the posterior fossa plus the supratentorial brainstem and the cerebral cortex must work together.

A revealing case study of visual agnosia combined with prosopagnosia and anosagnosia is found in Oliver Sack's book "The Man Who Mistook His Wife For a Hat", first published in 1970-New York: Touchstone, 1998. The case of Dr. P (for which the book is titled) demonstrates the tragic consequences of disconnection between early stage and later stage visual processing. "A rose by any other name is still a rose" is true

only if it can be perceived as such; in Dr. P's case this was perceived by smell *NOT* by vision. Intact brains do not typically separate senses at higher levels at least when processes are related to the perception of a common object of interest. Such objects emit multimodal cues to our senses with limbic "affective" qualifiers. Abstract reasoning is built upon an internal representation that combines all relevant data (bottom-up and top-down) that can help the brain formulate an "ephemeral and ideational" virtual neural world that enriches our lives. One wonders whether Dr. P suddenly "*saw*" the rose in the "mind's eye" when the scent disclosed the object (rose) that previously was described as an abstract geometrical shape by visual inspection. This would suggest a "breaking of the rules" regarding the property of unity for conscious perception (see below).

Some individuals have not only a robust intrinsic representation of such a rich virtual world but also the capacity to share that world with others: e.g., accomplished authors, actors, musicians, entrepreneurs, preachers and teachers.

APHASIA

Aphasia represents a dysfunction in the ability of an individual to communicate with language or a failure in the ability to understand language communicated by another. Such deficits are not due to a fundamental loss of hearing nor a loss in the ability to formulate concepts that are to be articulated. The language and communication deficits do not indicate a general dementia where one's thoughts and memory are distorted, disjointed or confabulated.

Common forms of aphasia have been described as related to the area of gray matter lost or of the white matter that normally connects these areas.

Broca's aphasia is typically associated with lesions of the inferior frontal gyrus (pars opercularis and pars triangularis) in the language dominant hemisphere (left for most persons). A lesion of Broca's area leads to dysfunctions in articulated speech often with a distressing inability to formulate words and phrases to express one's meaning. This "motor," "expressive" or "non-fluent" aphasia is said to include altered speech patterns that may be unmelodic, agrammatic or telegraphic with increased effort in one's attempt to symbolically communicate one's own thoughts or respond to what others have said. These individuals typically have good language comprehension but lack the motoric capacity to actively articulate those thoughts that seem to be at the tips of their cerebral tongues: frustrating for the person who suffers from this aphasia and for loved ones attempting to listen to this communicative struggle.

Wernicke's aphasia is typically associated with lesions of the posterior aspect ogf the superior temporal gyrus in the language dominant hemisphere Lesions may include portions of the inferior parietal cortex (angular gyrus or even supramarginal gyrus). Individuals with Wernicke's aphasia may be quite talkative but their words and phrases may be confabulations or "nonsense" phrases that do not communicate the person's intent. Wernicke's aphasia is often called "sensory," "receptive" or "fluent" aphasia

associated with poor comprehension and expression of verbalized concepts. Individuals who have Wernicke's aphasia may use incomplete sentences, circumlocution when the correct word cannot be expressed and other words or phrases may be substituted. Depending upon the exact location and extent of the lesion, these individuals may or may not be self-aware of their limitations. They readily engage their speech articulators but the essence of language (its symbolic meaning) may be largely missing.

AGENCY AND SELF AWARENESS

If I asked you to now define those cerebral cortical areas that define ***you*** as a singular human being with a unique personal history you might name the dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC) or medial temporal lobe. I would suggest that the DLPFC while being very important in controlling what you choose to do (or don't) may not really represent you as a unique being *with feelings*. Likewise, although the PPC appears to be important for constructing an internal representation of you in four-dimensional space (space/time) the PPC is likely to provide a dynamic, flowing "caricature" of yourself (not you as a *feeling being*) in your world. These are only some of the areas of importance for agency (see discussion of agency above). If we consider agency ***PLUS*** self-awareness we must look deep. Data from human brain imaging and the defined deficits reported for localized cortical lesions suggest that such a representation of oneself may require cortex buried in the lateral fissure (insula) and cortex deep within the longitudinal fissure along the medial portion of the cerebrum (medial/inferior prefrontal cortex, cingulate cortex, paracentral lobule, precuneus) plus the medial/inferior temporal cortex (see Medial Cortex: Areas Related to Self-Referential Brain Processes figure); for recent review see Haggard, 2017. The cerebral cortex does not work alone in this process. Brainstem nuclei (forebrain and posterior fossa brainstem) are critical to the basic, "generic" foundation, i.e., the underlying infrastructure for formulating or "energizing" such individuated cortical selves.

Returning now to the idea of the brain-mind conundrum, could there be an occasion where the two are partially separated? Individuals who have reported "body schema" deficits due to neurological disease may provide empirical evidence that the persona in the mind may be partially "decoupled" from the brain that supports the mindful self.

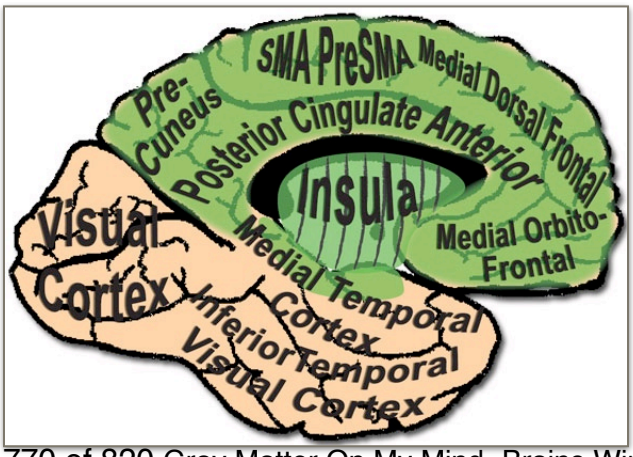

Fig 19-35. Medial Cortex: Areas Related to Self-Referential Brain Processes (gec).

This would suggest an abnormal binding within networked brain circuitry unravels a normally unified sense of a conscious self. Perhaps the vivid hallucinations incorporating highly detailed, "fractured" visual images as described by some

subjects in Sacks' book *Hallucinations* provides a transient window into a cortical minicolumnar fracturing that has become unbound by the normal coalescing mechanisms (see below).

After reading Oliver Sacks' *Hallucinations*, 2012 and a number of other references, one must think twice about the brain being organized as a strict hierarchical command structure. Many hallucinations appear to persist even when the person recognizes that the experiences are not real. If the "brainy top boss" allows this to continue within the organization then the shareholders may revolt and demand a change at the top. This does not seem to be the case, suggesting at least a portion of your working brain uses a heterarchical organization where control is distributed. An organization with such shared responsibility may tolerate or perhaps even encourage such "creative" processing if the entire system is not pushed beyond a tolerable homeostatic deviance. Such intolerable processes might be delusions of grandeur, loss of touch with reality, or emergence of aberrant behaviors. Some creative cognitive processes originating within the brain (mind) may convince the board of directors to override the "CEO's" insistence that such an unconventional thought is a "dumb" idea.

THEORY OF MIND: SEARCH FOR THE NEURAL BASIS OF HUMAN CONSCIOUS EXPERIENCE - A DAUNTING TASK

Those who study consciousness propose three fundamental properties that must be incorporated into any theory for the Neural Correlates of Consciousness (NCC): ***subjectivity, intentionality and unity*** : e.g., see Crick & Koch, 2003; Damasio, 2010; Dehaene, 2001; Dehaene & Changeux, 2011; Edelman & Tononi, 2000; Fuster, 2013; Haggard, 2008, 2017; Koch, et.al., 2016; Ramachandran, 2011; Tononi & Koch, 2008.

NCC coding of ***Subjectivity*** will be a difficult property to describe in detail since currently we do not have instrumentation to reveal my mind's interpretation of a conscious event (there are currently no detailed neuronal measures to read my mind).

We might infer a person's mental processing by actions or gestures suggesting what the individual is thinking but such inferences at best will be incomplete and at worse may be completely inaccurate

Intentionality infers mental effort plus conscious or non-conscious attention to the particular neural events that define one of many possible thoughts or experiences selected by my brain at any instant in time. Such neural events may originate internally, e.g., thoughts, or they may be a representation of external events brought to mind by the senses or an integrated reinterpretation of prior experiences. Such focused attention requires the exclusion of myriad other events which mental effort *could* intentionally be brought to consciousness (think judicious GABA inhibition for such suppression).

Unity suggests that the various neural components of a conscious experience are bound together such that many representations coalesce into a singular (*gestalt?*) event in the mind. Various theories have been proposed to account for such neural binding to

support a unified perception (see references). What do you think is required for a unified thought? Is this thought a unique pause in one's stream of consciousness and a binding agreement among the neural network parties involved?

Most cognitive neuroscientists suggest conscious experiences depend upon long-range reciprocal communication across local networks and likely between the front of the brain and the back of the brain. The parieto-occipito-temporal posterior association areas may be most critical for NCC related to external events while the anterior frontal areas may contribute most significantly to intrinsic processes in the conscious (and non-conscious) realm, see Koch, et.al., 2016. Such reentrant communication may form a unified binding of distributed networks due to an anterior-posterior "handshake" of relevant data: see Brain Anterior-Posterior (A-P) Handshake Movie.

This distributed reciprocity of messaging is simulated as multiple regional handshakes plus a global A-P handshake. It is likely that multiple localized handshakes within specific areas of the telencephalon and diencephalon complement a long-range "global" reciprocity of data sharing. In addition, there is growing evidence that a rich astrocyte population in the human cerebral cortex has communicative properties consistent with local and/or global network synchrony. A distributed and long-lasting activation of cortical networks appears to be essential for the awake brain to be conscious although there is no consensus regarding the actual mechanisms responsible for such activation patterns.

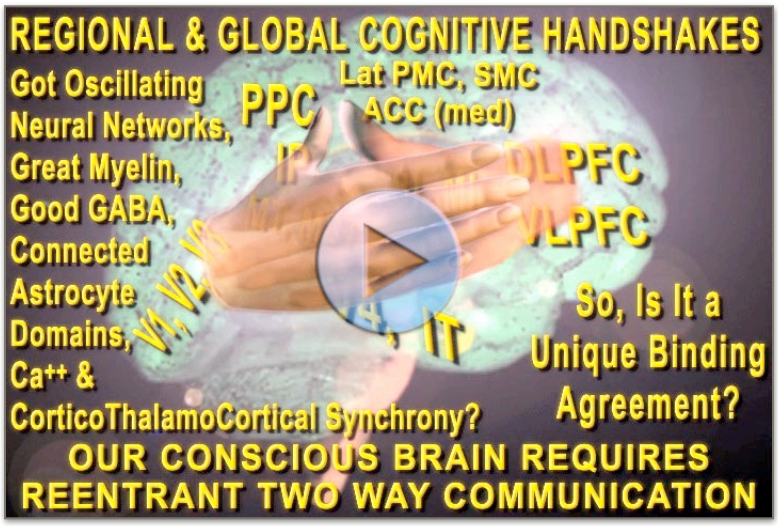

Fig 19-36. Brain Anterior-Posterior (A-P) Handshake Movie: Distributed Networks for Creative Conscious Brains (gec). GO TO: gmomm.pitt.edu *Fig19-3_Video*

The Distributed Cell Assemblies: Reentrant Persistent Firing Movie illustrates a persistent firing distributed process. Note the sustained firing in multiple cell colonies (working memory) during the instruction delay period before a cue to act.

There are a number of theories, hypotheses or frameworks regarding the neural basis for consciousness (see references above). Each speculative proposal must begin with an operational definition of consciousness. Typically these definitions include the tripartite properties stated above *(Subjectivity, Intentionality, Unity)*. Some scientists state that consciousness may be a property that exists but cannot directly be measured

in non-human species or even in humans. Some theorists insist that consciousness exists only in brains that are complex enough and sophisticated enough to support the abstract nature of consciousness. Such brains may be found only in human or non-human primates. Self-organizing principles may create individual internal views of the world known only by the brain containing those interactive neural networks. The following attributes regarding the NCC are still unknown: 1. what is the minimal number of neurons that must participate?; 2. where do these neurons live?; 3. what cells other than neurons must be engaged? and 4. how must these elements communicate with one another for a brain to be consciously aware of a person, place or thing (including the person owning that brain)? There is likely no single answer to each of these questions (see below).

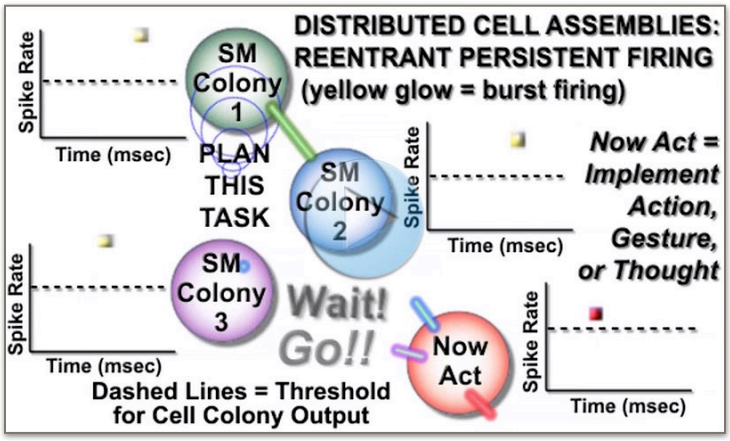

Fig 19-37. Network Reentrant, Persistent Activity (Working Memory) Coding Movie (gec). GO TO: gmomm.pitt.edu Fig19-37_Video

Some theorists suggest that there are different levels of consciousness which process data across multiple levels of the nervous system. Such a parsed neural basis of consciousness seems to be cognitively exhausting if one considers *Unity* to be essential to conscious percepts or thoughts. Likewise, *Intentionality* and *Subjectivity* seem to be properties requiring neural processing in the cortical/subcortical forebrain at least for thoughts, meaningful percepts or behaviors other than reflexive or automatic reactions. Moreover, although I may have self-awareness of being a conscious being, my brain has some neural networks with emergent properties to process much information outside of full conscious access. How does my brain interpret such data? Maybe it's just me, but I want to know what my brain is doing. Perhaps your brain is better at such high level processing, but then I will never know unless you can explicitly explain it to me. That would be awesome!

Again, as disconcerting as it may be, if you think your *conscious* "free will" choices direct all of your behaviors, some part of your brain is "messing with your head."

If survival of our distant ancestors consistently required a time- and energy-consuming conscious awareness to guide all of their behaviors (e.g., spending most of their waking hours sitting on a rock contemplating the meaning of life), present day humans might be quite a different species. Survival often and success sometimes requires rapid responses to many challenges in our environment rather than a casual contemplation on more "lofty" matters. Nevertheless, our brains are complex enough and sophisticated enough to choose those times and places where it may be

appropriate for introspection and contemplation (the rock may be an optional accessory).

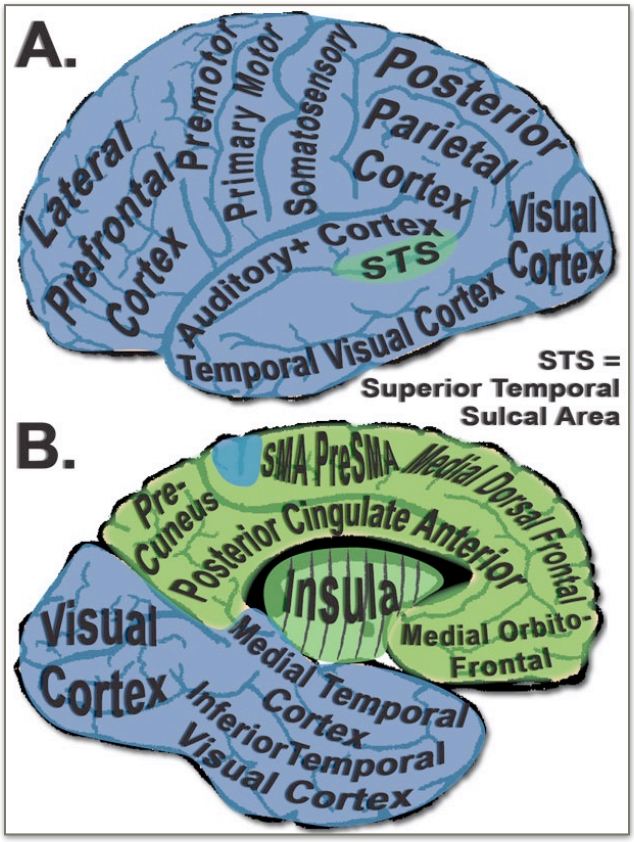

Fig 19-38. A. Lateral Cerebral Cortical Surface and B. Medial Cerebral Cortical Surface. Two Large Scale Regions denoted by color. "Out There Coupled to In Here" Networks (Blue) "In Here-Self" Networks (Green) (gec). GO TO: gmomm.pitt.edu Fig19-38_Video

However, as sentient beings, this self-reflection typically does not prevent us from losing touch with the world if circumstances warrant our attention to something or someone other than ourselves. Free will, as defined by philosophers and cognitive neuroscientists, is a magnificent addition to our basic neurobiology and to human society. It is our personal responsibility to do no ill with this gift provided by our complex neural machinery.

Your neural building (brain) contains rooms (specific brain areas) having a basic macroscopic architecture similar to the brains of other human beings. However, each of us personalizes ***our*** own rooms by the artifacts we choose to place there plus those furnishings that we find pleasing and purposeful ("self" cerebral areas). Your cerebral gray on its surface may literally and figuratively look just like mine: many of my genes are just like your genes. However, beneath any superficial thin gray "veneer" the wood pattern of your brain and my brain may be quite different in the fine details of the microarchitecture and the specific neural events created within: e.g., see references by Casanova, et.al., P.S. Churchland, Cisek & Kalaska, Craig, Crick, Custers, Damasio, Dehaene, Demertzi, et.al., Edelman, Fuster, Haggard, Hallett, James, Koch, Kringelbach, Lamme, Ledberg, Libet, Moore, Nachev, Peters, Posner, Ramachandran, Rolls, Tononi, Wenderoth.

So, now after you have completed many years of education, created a strong will within a mature mind and gained essential practical life experience, your friends and relatives may state (about your brain) - "We love what you have done with the place" or the unspoken assessment may be - "Wow, what a dumpy man-cave." Substitutions for your favorite unspoken negative assessment are permitted.

Finally, scientists and mother nature provide ample evidence to support the notion that your building (body and brain) will have some “settling” and “weathering” over time. Periodic maintenance will be required to keep your cerebral castle looking “spiffy.” You may be able to do some of these repairs yourself, e.g., see Kempermann, 2008; Anacker & Hen, 2017 for recent reviews regarding factors influencing adult hippocampal neurogenesis. More complex problems may require professional help (assuming you have access to and options for a wise healthcare choice).

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Chapter 20

NERVOUS SYSTEM ORGANIZATION: 19th to 21st CENTURY EVOLUTION OF UNDERSTANDING (SCIENTISTS' INTERPRETATION OF DATA)

INTRODUCTION

Neuroscience as a specific defined "branch" of science is a youngster. Depending on your read of history, neuroscience as a specific defined entity is roughly 75-100 years old. This section of Gray Matter On My Mind attempts to compare changes in thinking regarding concepts and principles of nervous system structure & function from the nineteenth to the twenty-first century. This is not a comprehensive treatise regarding the history of neuroscience; a limited number of topics are considered, those concerned primarily with sensorimotor function. Information is provided not to define any "final answer" but to provoke discussion of how the brain may do its job. There are a number of books that do provide a more comprehensive history of neuroscience and attempt to tackle some of the major issues regarding our incomplete understanding of the nervous system. There are books written for the "lay" public by distinguished neuroscientists (many are Nobel Laureates) who attempt to explain basic concepts regarding the scientists' thoughts about the "*big picture*" about how our brain works; some of these books are listed in the chapter 20 references.

Neuroscience is a defined area of science including a broad conglomeration of scientists represented by virtually all traditional branches of the basic sciences & engineering and more limited branches of clinical science research. There are a vast number of journals that are totally or partially devoted to neuroscience research from molecular to behavioral. All have a common theme: in one way or another the research investigates the electrochemical molecular complexity that we call a nervous system.

I use the following table (see below) in one of my graduate courses as a springboard for discussion of some earlier and more recent founding principles and concepts in neuroscience. In addition, I introduce the students to the scientists who have formulated these early "classic" interpretations of nervous system structure and function. More "modern" twentieth and twenty-first century neuroscientists and their concepts and principles are integrated into these discussions to build upon or challenge the classics. I ask my students to read original research and reviews to "distill" big picture ideas and interpret the findings of their own research or the research of others. The list is not meant to be comprehensive either in scope or in detail. The topics chosen are those that I deem to be most applicable to health professionals who evaluate and treat individuals recovering from neurological insults to cognitive, sensory and motor systems which contribute to physical function.

19th > 20th Century Concepts	20th > 21st Century Concepts
1. Top-Down Hierarchy	1. Distributed Heterarchy
2. Stimulus -> Response	2. “Rhythms” & “I-O Handshake Loops”
3. Neuron Dictates Fixed Function	3. Networks & Emergent Properties
4. Synapses: No or Slow Change	4. Synapses are Morphing Machines
5. Compartmentalized Function	5. Distributed Function & Cell Assemblies
6. Enlightened, Ordered “Autocracy”	6. Cooperative, Messy “Democracy”
7. “Point to Point” One-Way Data Flow	7. “Binding” of Interconnected Ensembles
8. Adult = Fixed Circuitry	8. Age-Span Development/Plasticity
9. Nature vs. Nurture	9. Genome & Environmental Manipulation
10. Systems/Reductionist Research	10. Molecular/Creationist Research
11. Study Cell/Trace Paths/Map Structure-Function Relations	11. Study Networks/Image Brain/”Light-Up” Particular Cells/Access DNA & Proteins
12. Science Will Answer All Questions	12. Science Will Question All Answers
13. Lesion = Dissolve to Primitive State	13. Lesion = Redistribute Control, Rewire
14. Rehab = Developmental Facilitation/ Reflex Hierarchy/Palliative Care	14. Rehab = Preventative/Regenerative “Cybernetics” & “SensoriMotor Learning”

Fig 20-1. Conceptual Transitions From the Nineteenth to the 21st Century (gec).

1. HIERARCHY, MODIFIED HIERARCHY, HETERARCHY

HIERARCHY: A hierarchical control model has been proposed by a number of scientists. A one-way, top-down control model was proposed by John Hughlings-Jackson at the end of the nineteenth century. Since then hierarchical control has been revised according to anatomical and physiological findings that suggest a more flexible information flow. Nonetheless, even these modified hierarchical models suggest that information builds through stages that require a serial flow from simple to more complex (e.g., bottom-up for sensory processing) or from highly integrated commands to targeted executioners of such commands (top-down control of volitional movements). Modified hierarchical models tend to include reentrant connectivity such that the flow of information (once begun at one location or another) is a distributed data acquisition, modification and encoding of information. This flow may occur in a somewhat serial fashion but the flow is likely also to utilize parallel processing of particular streams of information each having particular “symbolic codification” of data.

HETERARCHY: By contrast, a more recent proposal by some neuroscientists suggests that the nervous system uses a heterarchical control that distributes the "signing of the will" and the "execution of the will" across multiple neural networks located within "higher" and "lower" regions of the neuraxis. Such control is made possible by reentrant connectivity and "multitasking" neurons that share responsibility for neural representation of intentions, actions and perceptions. Thus, neurons in a network may function differently depending upon the timing of events in an evolving process. Parallel and serial processing may occur but the critical factor is reciprocity of connectivity that, given time and access to information, dynamically regulates network participation in neural processing. This model suggests that function is derived, for the most part, as an emergent property of a coalition (group) not as the fixed property of individual members (neurons). Some coalitions may be highly structured and relatively "hard-wired" e.g., highly evolved sensory & motor pathways, while others may be quite transient and emerge only when a particular "issue" arises-for example in decision-making and perceptual judgments. Of course, access to information for the brain like any other complex organizational structure may have some coalitions in a better position than others to make "decisions" and form "judgements" about the utility of data and its relative prioritization within the system. Thus, there is a caveat. Nervous systems as complex as ours may not be served well by a pure "democracy" but may do quite well by utilizing well-informed and responsible representatives of the "wishes" of network coalitions. Some neuroscientists suggest that there are neural networks within mammalian brains that can "bias" the probability (within the brain's network math) so one outcome is more likely than most others: a winner take all scenario. *Even so, we do not always get what we want!*

W. J. Davis provides a very concise overview of heterarchical organization as related to simple invertebrates that contrasts to a hierarchical organization as classically defined for mammalian nervous systems: see Davis, 1976. Davis suggests that even bigger, more complex brains may be organized as a heterarchy although he adds the caveat that some neurons may have privileged access to certain information unavailable to other cells: "your eyes only."

2. STIMULUS TO RESPONSE REFLEXES, NEURAL RHYTHMS, CENTRAL PATTERN GENERATORS

Sir Charles Sherrington and colleagues at the end of the nineteenth and beginning of the twentieth century did experiments to reveal reflexive neural control circuitry. Such investigations suggested that particular sensory stimuli are both necessary and sufficient to produce simple to complex evoked responses in reduced (lesioned) nervous systems. Such spinal or brainstem reflexes were suggested to be a framework for functional activities such as locomotion and postural control. By chaining reflexes together complex, integrated multilimb actions could be triggered by the appropriate stimuli. However, a contemporary of Sherrington, Graham-Brown performed a series of

experiments suggesting no such requirement for sensory stimuli to generate complex actions. Graham-Brown showed in a decerebrate animal, immediately following an acute thoracic spinal cord transection, hindlimbs stepping on a treadmill even after complete lumbosacral dorsal rhizotomy (all lumbosacral dorsal roots were transected). Graham-Brown suggested that stepping is due to a centrally generated rhythm based upon agonist-antagonist mutual inhibitory cycling: half-centre hypothesis for central pattern generators (CPGs). Since then, many experiments have supported the concept of CPGs for rhythmic motor output and have suggested that while sensory input may certainly modulate CPG output, many motor activities do not require *specific* sensory input to either trigger or guide such actions. While reflexes may play a role in daily activities such actions are not likely to be the sole building blocks for complex behaviors even in many invertebrates. Sensory input does appear to be very important for informing the organism about its immediate or distant environment but such input may just as often be used in a feedforward context (predictive control) rather than a reactive, feedback context: see Catching a Ball Movie. Sensory inputs may be critical for updating behaviors that require precise control of sustained force and/or position and object manipulation. Such I-O (Input-Output) handshakes among different components of the sensorimotor system would ensure that messages are both sent and received at the appropriate time.

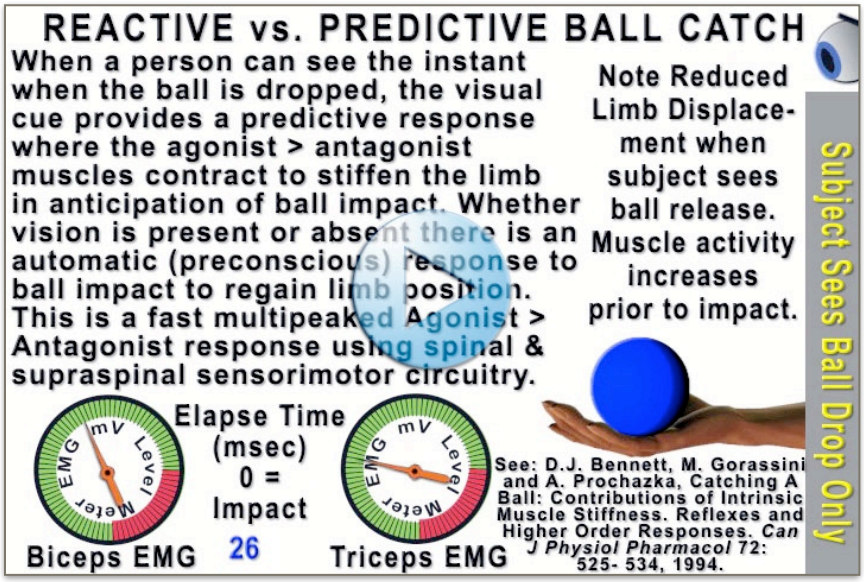

Fig 20-2. Catching A Ball Movie: Advantages of Anticipatory Cues to Reduce Limb Displacement Due to Perturbation (gec). GO TO: gmomm.pitt.edu Fig20-2_Video

Recent studies in sensorimotor control of posture and movements have focused on how the nervous system uses sensory data in both predictive and reactive acquisition modes. Some researchers have emphasized the continuity of data flow rather than transmission of discrete sensory data packets for maintenance of posture or precise guidance of fine movements. The proponents of fluidity in sensory data flow might consider parsing of feedback vs. feedforward information an artifice of time rather than a mechanistic separation. Nonetheless, our nervous system must be capable of determining the beginning and end of discrete events. Fortunately we have peripheral

rapidly adapting sensory receptors and central GABAergic inhibition to define temporal pauses in data flow.

3. NEURON FIXED FUNCTION VERSUS NETWORK EMERGENT PROPERTIES

Early neuroscience research stressed descriptions of single cells and discovery of their individual “talents” as players within a system that was being described at its “primal” level of sophistication. Nevertheless, early investigators including Ramon y Cajal, Lorente de No, Sherrington, Eccles, Adrian, Erlanger, Hodgkin, Huxley, Brodmann, Mountcastle, Hubel & Wiesel, Evarts and many others provided detailed analyses of anatomy and physiology of nerve cells. Such experimentation often focused on identification of individual cells and relevant hypotheses regarding their role in nervous system excitability & communication. Remembering that it was not until the mid twentieth century that synaptic ultrastructure was confirmed at the electron microscopic level, the assumptions of many early investigators appears to be confirmed by new methods that allow us to explore the nervous system with increasingly detailed spatial and temporal fidelity. Taken together, results of recent investigations of simple and more complex networks suggest that neurons may not have fixed functions. As part of one or multiple dynamic networks, neurons must be “conversant in multiple dialects” to provide functional neural assemblies. Such networks often share resources across a web of reciprocally connected local cell groupings. Adaptable telencephalic networks blanket a genetically endowed ultrastructure (brainstem) that has been assembled over a long evolutionary timespan. Such adaptable networks presumably form the foundation of species-specific survival circuitry and nuanced connectional specificity within an individual's particular wiring for success. An emergent property garnered from the probabilistic congruence of activity from a population of cells is thought to expand the integrative and calculative capabilities that on a cell-by-cell basis would be either exhaustive or even impossible for disconnected or sparsely connected single cells. Networks often have nonlinear properties so that simple addition or subtraction of elements may result in multiplicative facilitation, profound suppression or oscillatory network behaviors.

4. NEURON DOCTRINE AND SYNAPTIC PLASTICITY (HARD-WIRED DIGITAL CIRCUITS DO NOT APPLY)

Two major theories attempted to describe the fundamental organization of the central nervous system in the nineteenth century. One theory proposed a global lattice of continuously connected cells into a reticulum. The reticular theory was championed by J. von Gerlach & C. Golgi. A contemporary of Golgi, Santiago Ramon y Cajal developed a modification of Golgi's staining technique to visualize and then render the histological details of neurons and glia (highly detailed drawings). Although light microscope magnification limits resolution of fine detail (to the micrometer level), Cajal argued that each neuron is a separate entity that connects to other neurons indirectly,

i.e., a physical gap exists between cells: the Neuron Doctrine. Moreover, Cajal asserted that neurons have a specific directional flow of information. Dendrites & Dendritic Spines collect information from other neurons that flows to and is integrated at the soma. Output from the soma occurs by way of branches of an axon that has multiple axonal swellings (boutons). We now know that chemicals (neurotransmitters) released by axon boutons provide signal transmission to other excitable cells. Charles Sherrington, at the end of the nineteenth century, named the cell to cell junction (gap), as hypothesized by Cajal, a synapse. The synaptic cleft is ~20-30 nanometers wide (revealed by electron microscope). The synaptic membranes contain a large population of specific proteins seen as a pre-synaptic density and a post-synaptic density in the electron microscope.

Currently the only way to see the exquisite ultrastructural details of a synapse is by electron microscopy of fixed and stained dead tissue. Such an image might lead one to the conclusion that a synapse is a fixed structural entity. However, recent methodology provides a dynamic view of synaptic changes related to use-dependent mechanisms of plasticity. Two-photon microscopy of living neurons combined with laser activation release (uncaging) of caged glutamate to activate excitatory synapses reveals individual synaptic spines whose motion is made visible by fluorescent dye labeled proteins, e.g., Green Fluorescent Protein (GFP) Actin. Such studies provide direct observation of rapid dynamic spine motility. Actin is one of the components of the cytoskeletal filament web that provides stability (static actin) and mobility (dynamic actin) to the synaptic elements. Evidence suggests that many synapses have use-dependent plasticity related to learning and memory.

5. COMPARTMENTALIZED SINGLE CELLS VERSUS DISTRIBUTED FUNCTION & CELL ASSEMBLIES

Early investigators attempted to define neural coding according to an individual cell's fluctuations in membrane potentials. A cell's “job description” could be defined by where it lives and what extrinsic excitatory input drives its firing. Much of early systems neuroscience has been defined by experimental approaches using methodology to explore the principles outlined above. Thus, sensory systems have been defined by electrophysiological and anatomical investigations of ascending pathways & receptive field properties of individual neurons activated by appropriate stimuli. Motor systems have been defined by actions produced by electrical or optical microstimulation of cells in motor centers or by recording single cell activity in motor areas in behaving animals. Some studies of simple invertebrate nervous systems have suggested that a single cell may play different roles when brought on stage by differential behavioral requirements. These cells could be classified as multitasking: function defined by how it is incorporated into overlapping networks utilized in different behaviors.

Modern methods that allow the scientist to monitor activity from many neurons simultaneously and anatomical techniques that demonstrate precise connectional

patterns have expanded our concepts regarding the job or jobs done by neurons interacting with one another in a distributed network. Information flow is not a one-way street and cells may contribute to function differently depending on the influences of both bottom-up and top-down circuitry. For example, it has been suggested that the thalamus is perhaps more important as a monitor of our corticofugal intentions and actions than as a gateway for ascending inputs. For many matrix cells in higher-order and first-order thalamic nuclei the major drive for these thalamic cells comes from axon collaterals of layer V pyramidal cells in the cerebral cortex. The loop back to the cortex from the matrix cells may activate multiple vertically organized cell columns due to horizontal spread of excitation. Corticofugal (motor) output modulates sensory inputs at multiple levels of processing. Cell assemblies appear to be both adaptable and flexible using multiple coding strategies to meet the demands of complex nervous systems. Use of Opsins to depolarize or hyperpolarize specific cell types allows for targeted circuit activation or inactivation *in-vivo* in behaving animals.

6. AUTOCRACY, DEMOCRACY NERVOUS SYSTEM GOVERNANCE

How the mammalian brain governs itself and the body that it inhabits has been debated at least since the time of Hippocrates. One view suggests that higher levels (presumably association areas of the cerebral cortex) exert dominant control over the rest of the nervous system. These areas have privileged access to all the information required to make rules that will optimize “law and order” and provide necessary guidance over the rest of the community of neurons. This fits well within a top-down hierarchical model of nervous system organization. Such concepts of rule by one or by a few fits within the “chain of command” organizational charts for many governments & corporations. Hughlings-Jackson and others would suggest that complex brain interactions require firm but “benevolent” guidance from intelligent leaders who can make informed decisions.

Recent discoveries provide a different view of the organizational principles in complex nervous systems. Many areas from “higher” to “lower” nervous system levels have reciprocal *NOT* one-way connections. Imaging studies and new anatomical tracing techniques suggest a relatively broad sharing of activity among neural networks; such sharing of control would not be predicted from a strict top-down chain of command model. The brain uses the best information available to solve problems within the constraints and affordances of the environment in which it exists. Like some organizations that encourage “grassroots” input for decision-making, this “decentralized” schema suggests that the brain gathers all relevant information to arrive at “pragmatic” solutions for simple to complex tasks. Coalitions may be made and broken as the need arises. Some aspects of decision-making in this schema are not always predictable suggesting some degree of self-organizing principles at work. However, this organizational paradigm is unlikely to be a “pure democracy.” Influence and control

require access to information. Some imaging studies suggest that there may be "special" networks which alone have privileged access to vital data. Occasionally, there are explicit "intelligence leaks" (Freudian slips?), while subliminal subconscious biases may influence more of our behaviors than we will ever know.

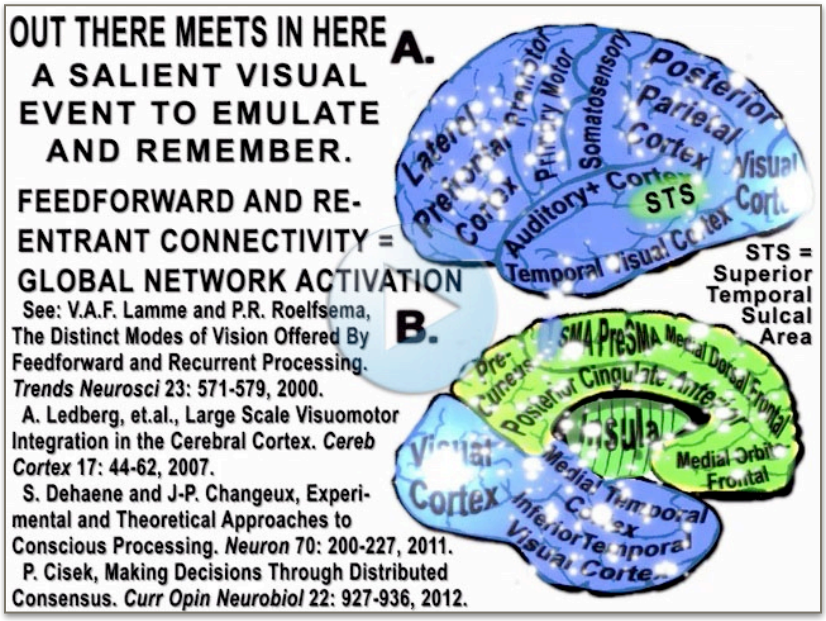

Fig 20-3. Brain Web Movie: Out There (World) = Blue, In Here (Self Related to World) = Green (gec). GO TO: gmomm.pitt.edu
Fig20-3_Video

So, perhaps we should look at the brain as a wonderful heterarchical/ modified hierarchical playground filled with lively youngsters (in a Darwinian sense) but one *with* adult supervision. The critical question remains. Who are the responsible adults that bring "order" out of potential "chaos" in this dynamic environment? I know what you are thinking; go frontal young man. For me, both that particular brain area and that age group may be the wrong place to go. Nevertheless, it is still unclear what *adult* network or networks in your brain is (are) responsible for pulling back, at the last possible spit-second, that adjective sitting on the tip of your cerebral tongue that if released would have gotten you into deep trouble with your boss. The adults in this playground may NOT be excitatory but *inhibitory* neurons stationed in strategically appropriate cortical and subcortical locations. If you still insist that excitatory prefrontal cerebral cortical pyramidal neurons are the only "adults" providing order in your brain's playground, you should read the following clinical case: see E.K. Richfield, et.al., 1987.

7. ONE WAY POINT TO POINT DATA FLOW VERSUS BINDING AMONG NETWORKS

Much of the information from the previous six topics suggests that any one-way point to point data flow is the exception not the rule for nervous system communication. "Uploading" and "downloading" of data may be relatively meaningless in the normally functioning "brain internet" except perhaps when we are learning. Convergent and divergent connections provide a rich sharing of data that is often "filtered" at synaptic cell stations by active processes, e.g., GABA inhibition and/or glutamatergic facilitation. Thus the nervous system can dynamically optimize its signal strength gain and set a

signal to noise ratio that improves communication among connected neural web “users” in a context-dependent fashion.

One of the many unresolved issues regarding nervous system function is how the brain can get diverse signal processing areas “on the same page at the same time.” This binding problem is significant since each separate network may provide only one or a few pieces of the puzzle of unified brain function. There are those neuroscientists who suggest that the brain uses temporally specific patterns of activation to bind disparate areas so that a unified neural process emerges. Such binding may involve at least transient oscillations among certain neurons that then show coincident firing. One suggested frequency band of “binding” oscillations is the gamma band (~30-70 Hz) as seen in EEG or local field potential recordings. Some scientists suggest that this gamma binding is dependent upon corticocortical and corticothalamocortical loops that can engage both local networks and more global cell assemblies. However, it is still unclear whether this oscillatory coherency in cell activity is the basis of unified network function or only an epiphenomenon of some other causative process that has yet to be revealed. Nevertheless, there are many neuroscientists pursuing this binding problem and gamma band neuronal activity as linked to perception, consciousness, volition and other cognitive processes.

8. HARD WIRED CIRCUITS VERSUS AGE-SPAN PLASTICITY

Many early investigators of nervous system anatomy and physiology concentrated on discovery of fundamental properties of neurons, pathways and circuit wiring within specific areas of the brain. Although there were a few of these investigators that hypothesized potential for plasticity in brain wiring, many scientists held the view that adaptive changes in wiring was part of development in the young but not a fundamental property of older “hard-wired” adult brains. The difficulty of teaching an old dog new tricks is a natural example (the older dog needs a wise, understanding and patient teacher).

The ability of the brain to operate in a normal fashion depends upon a balanced level of electrical and chemical signaling among many neurons connected within regulated networks. Young and old brains can be modified. Our brains contain sophisticated chemical laboratories that attempt to maintain a balance of potentially volatile biochemical reactions. Early studies showed that communication between neurons requires synapses with chemically gated receptors. Recent research suggests a more diverse and complicated interaction among neurons using both autocrine and paracrine chemical messengers producing both short-term and long-term effects on individual cells and cell assemblies. Inspired by Lorente De No’s drawings of synaptic “knobs” * D. O. Hebb (1949) hypothesized that repeated interactions will grow the relationship between activity-coupled cells. The concept of a Hebbian synapse has become a springboard for revolutionary research on the synaptic & molecular bases of learning and memory. *In-vitro* methods to study neurons in culture or in brain slices and *in-vivo*

recordings of whole cell (soma) and dendritic potentials show rapid changes that may potentiate or depress synapses. Neurotrophins provide “permissive” or “instructive” roles in maintaining or growing activity-dependent neuronal relationships. Activity may be specific to synapses and/or to the overall activity of the organism (e.g., exercise may influence certain neurotrophin levels). Growing evidence suggests "neurons that play (fire) together, stay (wire) together." * R. Lorente de No, Synaptic Stimulation of Motoneurons as a Local Process. J Neurophysiol 1:195-206, 1938.

9. NATURE VERSUS NURTURE OR GENOME & ENVIRONMENT MANIPULATION

At one time scientists interested in behavior and the neural underpinnings of behavioral control broke into two “camps.” One camp hypothesized that the most important influence on brain development and maturation is the genetic inheritance of the individual (nature). This would suggest that optimal behavior is directly related to one's ability to pick her parents. The other camp hypothesized that the world in which the individual finds herself is critically important to optimal function (nurture). This would suggest that the brain may benefit (or be harmed) from exposure to epigenetic environmental stimuli and events that can shape the nervous system beyond its genetic endowment. This issue is still unsettled although the pendulum seems to be more centered than when competing researchers attempted to push our thinking about this issue towards one extreme position or the other (**nature *OR* nurture**).

Scientists are now engaged in sophisticated experimentation to reveal the DNA sequences responsible for generation of particular proteins that are the ultrastructural and regulatory backbones of normal cell function and how altered genes, in turn, alter proteins in disease states. Since we know that our nucleic acids are subject to epigenetic macro- and micro-environmental influences that directly alter DNA expression, it would be difficult to ignore either nature or nurture.

While Charles Darwin did not have access to the gene banks that are now available through university-based scientists, the National Institutes of Health (NIH) or through commercial sources, he did appreciate the link between heredity and the environment. This hypothesized link is both necessary and sufficient for biological entities to adapt to changing demands. Indeed without that adaptation, Darwin might suggest that biology would not evolve and would no longer remain as a viable carbon-based contributor to the changing environment of our planet.

10. REDUCTIONIST TO “CREATIONIST” RESEARCH

Reductionist neuroscience research attempts to study specific circuits within a complex nervous system by targeting specific groups of cells or by removing influence by “higher” levels of the nervous system (*in-vivo* studies in intact versus lesioned animals). Alternatively a portion of the nervous system may be removed and studied in a dish (*in vitro* studies of brain slices or cultured neurons). Such anatomical,

physiological and pharmacological methods have revealed the nature of reflexes, individual neuron properties and the implied nature of sensorimotor integration as revealed by losses in control when certain regions of the nervous system must function in isolation. Such research has also been fundamental in tracing pathway connections by observing the location of degenerating axons and axon terminals following a localized nervous system lesion. Using axonal tracing techniques neuroscientists can locate the termination or source of cell connections by visualizing anterograde and retrograde transported dyes in brain or spinal cord tissue sections.

Currently, molecular and "creationist" research techniques explore the nervous system at a finer-grained level. It is now possible to "transfect" cells with a virus that includes the genetic machinery to induce nuclear DNA to produce a light-sensitive opsin. Opsins are transmembrane protein channels that when activated by light at the appropriate wavelength open an ion channel; except for photoreceptors these opsins are not normally expressed in the brain. The newly inserted opsins may open channels for cation influx (Na^+ or Ca^{++}) or anions (Cl^-) in the opsin-expressing neurons. Thus shining light on a group of opsin-expressing cells within the *in-vivo* brain may excite or inhibit the cell assembly. Currently this technique known as optogenetics is applied in non-human species. In the future this technique could provide a mechanism to activate or inactivate brain structures in humans. Using gene "knockout" techniques researchers can demonstrate the effect of missing proteins resulting in abnormal development of the nervous system. Scientists can discover specific defects in gene transcription that lead to inherited nervous system disorders. The ability of molecular researchers to describe the static or even dynamic 3D structure of proteins may allow scientists to substitute a similar structural molecule to regain function lost by the absence of such proteins in neurons of subjects with genetic or acquired diseases linked to protein abnormalities. Tissue engineering and "cyborg" neural prosthetics were at one time the province of science fiction. Now these methods are being explored as potential methods for rehabilitation. The rapid advancement of technology and the potential for amalgamation of carbon-based neurobiology and silicon-based circuitry provides not only promise for biomedical interventions but also a challenge to twenty-first century bioethicists & healthcare providers.

11. SCIENCE: QUESTIONS AND ANSWERS

Science has an important role in discovery about the nature of our world (universe/multiverses) and the inanimate and animate objects that dwell within that (those) world(s). By its very nature, science requires rigorous proof of "facts" and testing of hypotheses/theories. Scientists are, and should be, skeptics that do not always agree about how one should interpret results from experimental investigations. At one point early in the life of neuroscience there was great hope that our understanding about how nervous systems work would lead us to a manageable set of concepts and principles that could then be "tweaked" by later generations of neuroscientists. We are still waiting!

As more information swells the neuroscience literature, many disparate “facts” have been gathered but compelling overarching principles that once were thought to be “rock solid” are now being questioned. Such fragmentation of knowledge may be a byproduct of our own making since the field of neuroscience continues to grow substantially and technology allows us to dynamically explore the nervous system in finer-grained detail. We (the royal we) can now explore neural events as they unfold at a level of detail unimaginable even a decade ago. At some point (soon I hope) some bright neuroscientists will attempt to bring some order out of this potentially chaotic molecular knowledge-base. Unfortunately, granting agencies primarily fund proposals having specific aims that test well-formulated hypotheses that can be addressed within a short time span; this leaves little time or incentive for contemplating long-range big ideas for most scientists in this competitive field. There are a few senior scientists, many of them Nobel Laureates, who are paid to contemplate the “Big Picture”. Their hypotheses often inspire new work.

Scientists tend to be highly inquisitive, competitive, fiercely independent and intellectually collegial. Colleagues who are deemed to be accomplished scientists are held in high esteem. Typically, scientists will approach problems first with their own team and ask for “outside” help only after exhaustive “in-house” problem-solving. They will collaborate on projects but typically only if such partnerships advance their particular field of study. ***Science unpublished does not exist.*** Experimentation therefore is goal-directed and rigorous controls must be incorporated into the design. Accomplished, well-published scientists tend to be “conservative” in the interpretation of their findings in peer-reviewed publications and are skeptical of interpretations for which data appear not to be supportive.You do not want to be a poster child for how not to conduct science.

Fig 20-4. Signpost for Responsible Research Design: actually a photo of a warning sign posted along the bank of the rapid flowing Youghiogheny River, Ohiopyle State Park, Pennsylvania (gec).

Science and ethics should not be opponents. Scientists should consider not only the advances that can be gained by a particular track of discovery but also the potential impact of their work on nature and humanity: see sign that may be interpreted differently by the lay public and those scientists who consider discovery as a method to ethically move our understanding of nature forward.

12. LESIONS & REHABILITATION: DISSOLUTION OR REWIRING?

Early work with animals and clinical studies suggested to some investigators that nervous system lesions produce a compromised system that reverts to a more primitive state. This premise is based upon concepts of a hierarchical organization and altered

reflexes in spinalized, decerebrate or decerebellate “reduced” nervous systems. Hughlings-Jackson, Sherrington and later Holmes and Parkinson described positive and negative signs & symptoms of nervous system disorders that are still considered to be hallmarks for clinical diagnosis. However, while these evaluative procedures help to target the location of the structural pathology they do little to guide rehabilitation.

Rehabilitation principles in the early days of therapeutic interventions for nervous system disorders were based primarily upon the work of these early investigators. As such, stimulus-response reflex activation and attempts to reproduce the orderly developmental sequence from more primitive to increasingly more sophisticated nervous system integration were built into these approaches. “Plasticity” or “rewiring” was often seen as a negative consequence of the injury.

Rehabilitation principles today appear to be more optimistic given the extensive literature suggesting that plasticity may provide positive outcomes. Technology has expanded the repertoire of techniques that can be incorporated into therapeutic approaches. We know much more about motor learning principles that may take advantage of the plasticity that remains within the altered nervous system. Work has begun to directly link machine-based technology to neuronal networks. Such brain-machine composites may one day provide advanced opportunities for the therapist to interact much more directly with the patient's nervous system. Neuroprosthetics in the future may become an “upgrade” for biofeedback techniques (e.g., EMG Biofeedback) utilized today. Such cybernetic interfaces will likely incorporate artificial intelligence within manufactured silicon-based circuits to assist our biological carbon-based circuits.

SUMMARY: CONCEPTUAL TRANSITIONS to TWENTY-FIRST CENTURY NEUROSCIENCE

1. Sensorimotor control requires distributed network interactions among neurons at many levels of the nervous system. A simple top-down hierarchy, and S->R circuitry cannot account for the complexity, sophistication and confidence that characterizes most mammalian behavior. Reflexes are subject to central modulation and Central Pattern Generators (CPGs) generate complex rhythms. CNS monitors and modulates sensorimotor behavior. Skill built on talent and experience may deteriorate when errors creep in due to altered states of neural or musculoskeletal function; speed drops and predictions fail.

2. Once an action or gesture begins, it may be quite difficult to separate sensory from motor function in all but the most elementary neural processing; most skilled actions occur because of both feedforward and feedback circuitry across multiple nervous system levels. Most of this processing occurs outside of our conscious awareness.

3. Some scientists suggest certain functional deficits that, on examination, may appear to be motoric are actually the result of subtle or sub-clinical sensory integrative deficits; loss of skilled dexterous behavior that utilizes active touch is one such example.

4. A once conceived “rigid” adult brain is now seen as just the opposite. It may be fortunate that the nervous system is physically so malleable; that matches the physiological & biochemical plasticity so elegantly demonstrated for molecules, single cells, and cell assemblies using twentieth and twenty-first century technology.

5. No neuron is an island unto itself. Neurons by their very nature share information. Neurons may reinforce their connections through synaptic potentiation or reduce efficacy through synaptic depression. One such reinforcing mechanism conceived by D. O. Hebb (1949) suggests that neurons form relationships based on their interactions. Short- and Long-lasting Hebbian mechanisms include ionotropic & metabotropic synapses plus neurotrophins that arrange & strengthen such a marriage (grow together). Plasticity is a lifelong process that includes not only synaptic modifications but changes also to neuronal membrane proteins at non-synaptic locations (e.g., dendrites). Altered Voltage-gated channels in distal versus proximal dendrites may compartmentalize such plasticity.

6. Neurons use both analog (e.g., EPSP & IPSP) and digital (AP) signals to gather, integrate and distribute information. Mechanisms may include simple cumulative math (integrate & fire) or more temporally restrictive (coincidence detection) coding; both codes may contribute to neural network function. Inhibition saves the CNS from potential chaos of too many EPSPs, regulates the size of the network involved in neural processing at any one time and provides a temporal “filter” to harmonize neuronal firing.

7. The synapse one a fundamental site for adaptation of a neuron’s function. While older views suggested stable connections as might be seen by microscopic pictures of fixed tissue, recent evidence points to fluid membranes that dynamically adjust their morphology. Rapid adjustments of intracellular architecture and biochemistry results in altered postsynaptic and often presynaptic elements of the synapse. Technology permitting visualization of living neurons and their connections allows scientists to study synaptic responses to biochemical, bioelectrical or even nucleic acid (DNA/RNA) challenges. Modern technology provides evidence that plasticity may occur at non-synaptic locations of neurons, in glia and perhaps in microvasculature perfusing nervous system parenchyma. Genetic manipulations, regenerative nanotechnology, & brain biochemistry will rule in twenty-first century.

8. Defining the neural basis for “volition” and “will” was once a topic for “soft” sciences only but is now within reach for the brave mechanistic neuroscientist. While cortical networks are a “no-brainer” target for investigation, expect to see headlines for brainstem modulatory systems and subcortical gray matter (e.g., basal ganglia, cerebellum, thalamus, amygdala, etc.).

9. Despite science-fiction accounts, our brains are not computers and computers are not brains (not quite yet). That does not rule-out a potential symbiotic relationship between silicon and carbon in the near future. Questions remain: how casual a relationship will this be and how will evolutionary pressures shape such interactions? Brain-Machine Interfaces (BMI) are now a serious area of research at least at the "proof-of-concept" level of investigation. Barring some unexpected catastrophic negative sequence of events, we should expect important advances in BMI at the translational research level of research in this century and robots will find a home in health care.

10. Biology of living entities is deceptively clever. What appears to the untrained observer to be so straightforward in its operation is an illusion of evolutionary success. While the organism is not required to be a mathematical genius nor a brilliant biochemist, many of its constituent cells handle such tasks on a routine basis without the overhead of expensive contracts, indirect costs or book deals. Like the lithium battery, the living cell keeps on going despite burdensome loads placed upon it. Skill may depend upon "bulking-up" of key intracellular and membrane-bound proteins within a distributed group of neurons.

11. While biologists in general, and EEG specialists in particular have known for some time that the brain has rhythm, neuroscientists are just beginning to understand how well a neuron, synapse or network can "dance" when coupled with an appropriate partner or partners. Evolution is not a game-show; it is a deadly serious set of rules for survival. The constituents of the cell membrane that render it fluid provide necessary machinery for survival and adaptation to changing events; robust cells thrive despite threats. When all goes well the dance is beautiful to behold, if not, things can get ugly.

12. Imaging studies in human and non-human species provide large-scale functional resolution. Relatively few investigators study brain activity at the cellular level in mammalian subjects that are awake and performing a "meaningful" task. Most cellular or sub-cellular (molecular) studies generate reams of data from reduced *in-vivo* or *in-vitro* or even *in-silico* preparations. Only recently has behavior been tied to such high spatiotemporal resolution data. Noninvasive Brain Imaging technology still lacks the critical spatiotemporal detail required for most "circuit buster" neuroscientists. Expect the situation to change this century as technology & clever experimentalists cross that barrier to gain direct insight into the workings of the human brain. Based on current and previous animal studies, perhaps methodology incorporating light-activated neurons (e.g., channel rhodopsin incorporated into specific transfected cells selectively excited by fiber optic light targeting) may cross this barrier. Perhaps introduction of this light-activating protein could occur by filling bio-nanospheres with the protein and introducing the bio-nanospheres by way of a small cannula surrounding the fiber optic filament.

13. Translational research that applies basic research to clinical conditions is still struggling to get its footing. It is a rare scientist who has the skill, tools, experience and desire to directly apply basic/animal research to clinical questions/human subjects. The

critical mass of highly qualified scientists willing to commit to such investigations is not now in place but certainly should be in the very near future. Scientists who received dual PhD and clinical degrees may represent a strategic workforce for these translational approaches. The opportunities and fiscal resources for such critical research is growing. Owing to technological advances and potential funding priorities, the twenty-first century should be a time of great advances in applied research that will directly impact clinical practice. However, if insufficient funding becomes an issue, basic research leading to such translational applications may be seriously compromised. Some critics would say much money has been spent on neuroscience research but insufficient progress has been made in curing brain disorders. Quite a few of these individuals are “masters” of their smart-phones but have no clue regarding the sophistication of the software and hardware permitting them to be so “cool.”

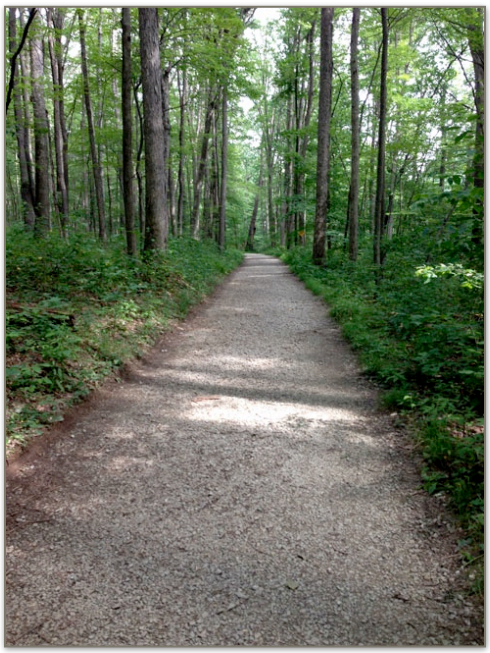

Fig 20-5. A Long Trail for Neuroscience. The human race must move forward to discover where this trail of scientific evidence leads us (gec).

14. When considering the effect of a circumscribed lesion of gray matter at one location of the nervous system, one must consider not only the loss of the local circuits in that damaged area but the effect also of a disconnection with other brain areas normally connected to that area. Distant circuit deprivation invariably will alter the functional properties of those previously connected neuronal circuits that are not directly involved in the lesion. There are few, if any, isolated self-sufficient islands of neural function in complex mammalian central nervous systems. Since the brain seems to be malleable to some extent throughout its lifespan, the effect of disconnection will differ for the acute versus the chronic phase of post-lesion recovery. Expected outcome differs according to the rehabilitation ABCs: A. the extent and location of the lesion(s); B. access to quality health care at time of the event (if acute) and then appropriate healthcare interventions following the insult; C. perhaps the individual’s age when the insult occurs.

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