Biomimetic Intracortical Microstimulation in Human Somatosensory Cortex for a Bidirectional Brain-computer Interface

by

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Submitted to the Graduate Faculty of the

Swanson School of Engineering in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2021

UNIVERSITY OF PITTSBURGH

SWANSON SCHOOL OF ENGINEERING

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July 1, 2021

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Intracortical microstimulation (ICMS) of human somatosensory cortex can restore tactile sensations to people who have lost them. While ICMS can elicit tactile percepts that feel like they originate in the paralyzed hand and can improve brain-computer interface (BCI) control, the percepts can vary in terms of quality and naturalness. The goal of this work was to understand how modulating ICMS parameters can affect stimulation-induced tactile perception in humans. To this end, I asked how ICMS amplitude and frequency shape tactile perception. I found that ICMS amplitude consistently increased intensity. Surprisingly, increasing the ICMS frequency evoked more intense percepts on some electrodes but evoked less intense percepts on other electrodes. These different frequency-intensity relationships were divided into groups which also evoked distinct percept qualities at different stimulus frequencies. Further, changing the spacing between individual pulses without changing the overall charge or number of pulses changed the evoked percepts on half of the tested electrodes.

I then created ICMS pulses trains based on neural data from non-human primates that represented different features of the cortical response to mechanical tactile input. Using these biomimetic ICMS trains, I found that biomimetic trains that mimicked the spiking patterns of individual cortical neurons had electrode specific effects and did not generally improve naturalness. However, biomimetic trains that mimicked the recruitment of populations of neurons by varying stimulus amplitude were able to increase the perceived naturalness across many tested

electrodes. These stimulus trains also increased the intuitiveness of stimulation, resulting in percepts that felt more like real mechanical input. Finally, we found that compared to fixed parameter stimulation, these biomimetic trains produced percepts that were more focal and were more likely to have the quality of “poke.”

Biomimetic modulation then might provide a superior way to encode sensory input by evoking more focal percepts and improving the naturalness and intuitiveness of evoked percepts. Future work will need to evaluate if biomimetic amplitude modulation can produce similar effects in other people with electrodes implanted in somatosensory cortex. This method then can improve upon sensory feedback algorithms for bidirectional BCIs, potentially improving the functionality in future clinical applications.

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Preface

I feel very fortunate to have been able to be at the University of Pittsburgh and work on this awesome project. Both of my parents dropped out of high school. I grew up with my father who most of my youth spent periods of times working at Walmart, cleaning people's cars, or not working at all. So, getting to this point, to work in a lab making contributions to our understanding of such cutting-edge technologies, is something I am very proud of and feel very lucky to have had the opportunity to do. Of course, I would not have had this opportunity if Rob had not selected me as a student, which I am eternally grateful for. I come from a bit of a non-traditional background in terms of my education and had no prior experience with BCI research, so I am glad Rob saw something in me and believed that I would do good work as a graduate student.

Another person that I am eternally grateful to is Nathan Copeland, our first participant implanted with arrays in somatosensory cortex. Almost all the work presented here was done in Nathan. His commitment to the research is incredible and admirable. Even though I know my experiments were often not the most exciting for him, he was always willing to do them, because he knew this work could help people like him one day. Beyond just being a great and dedicated participant, I have also grown to think of Nathan as a friend. One of the worst parts about graduating is that I will not be able to work with him anymore. Nathan's mark on the field of BCI research in general is truly something special, and I cannot wait to see the movies based on his life (or at least the one being produced in India right now).

I would also like to thank our second participant with a somatosensory implant, Mr. Dom. Although I did not get to work with him as much since he has been enrolled for less than a year, he is an awesome dude and I know that he will also make great contributions to the field. I love

how interested he always is in the science, and I hope that our lab can continue to foster that excitement.

I would also like to thank all of the members of my committee. Although I am often a very independent person and maybe didn't utilize my committee to their full capacity, every single one of them at some point or another has provided support for my ideas and helped me shape them into something even better. I do not think I could have asked for a better group of people to evaluate my work.

Last but not least, I would like to thank my fiancé Madeline. Although she was only part of my life for less than half the time I was in the program, in that time she provided me with great moral support and gave my life a new purpose that helped drive me through the finish line for this work.

1.0 Introduction

The ultimate goal of ICMS of somatosensory cortex is to restore fully naturalistic and functional sensations to people with spinal cord injuries. To create these naturalistic percepts, stimulation would likely need to recruit neurons in a manner similar to normal activation. Stimulus trains that are built to emulate neural activity are known as "biomimetic." Using biomimetic approaches stands in contrast to using "adaptive" approaches, in which the user would need to learn arbitrary mappings of sensation evoked by ICMS to tactile input. In a very basic sense, biomimetic can refer to simply aligning the areas of evoked sensation and input to the artificial limb (Abbasi et al., 2020). However, more advanced approaches would involve recruiting individual neurons in a way that completely mimicked normal recruitment (Fagg et al., 2007; Saal & Bensmaia, 2015). This likely will require more sophisticated technology than is currently available.

Utah electrode arrays recruit neurons up to 2 mm away from the electrode, and typically 500 μm away (Overstreet, Klein, & Helms Tillery, 2013). Neurons recruited this way are recruited simultaneously. Therefore, targeted stimulation of individual neurons with biomimetic trains is not possible with current implants. Additionally, many different types of neurons exist in the brain, and the role of these different neurons are only beginning to be understood (Swanson & Maffei, 2019). Likely, these neurons play different roles in the processing of somatosensory information. Targeting neurons of specific types with specific trains biomimetically encoded to the input will require a better understanding of how these neurons work together to process tactile information normally.

Current approaches to sensory feedback with ICMS align evoked projected fields with the input to the robotic limb (S. N. Flesher et al., 2021). However, the ICMS trains provided are modulated linearly by force, which doesn't align with how neural activity is normally evoked in the cortex. In response to tactile input, the somatosensory cortex responds at a higher amplitude during the onset and offset transients, resembling more closely the derivative of force(Callier, Suresh, & Bensmaia, 2018). Regardless, even with non-biomimetic approaches, sensory feedback can improve robot control (S. N. Flesher et al., 2021).

One method to create biomimetic trains that has recently become available is TouchMime (Okorokova, He, & Bensmaia, 2018). TouchMime is a software that can take in force profiles and output simulated neural activity. This simulation is based on data collected in peripheral nerves and cortex of non-human primates. This approach has been used successfully for creating biomimetic feedback for stimulation of peripheral nerves (George et al., 2019; Giacomo Valle et al., 2018). These studies found that biomimetic feedback could improve the perceived naturalness of elicited sensation and improve the function of the hand for tasks that involved manipulating objects. Previously, no work has investigated if biomimetic approaches can improve sensations evoked by intracortical microstimulation.

In this work, I have investigated the efficacy of intracortical microstimulation (ICMS) for restoration of somatosensation and how parameters of ICMS affect tactile perception. The ultimate goal of this work is to better understand how electrical stimulation affects the somatosensory cortex and consequently perception so we can design better tools and algorithms for restoring touch in a bidirectional brain-computer interface (BCI). Each chapter in this dissertation explores a small aspect of this goal based on experiments I have conducted during my graduate studies. All these findings are united under the framework of biomimetic stimulation, which I believe based

on the findings in this dissertation, provide a better strategy for providing sensory feedback than traditional linear methods.

The second chapter is based on a first author book chapter from the *Handbook of Clinical Neurology* and discusses much of the background of this work. This chapter covers the history of cortical stimulation and brain-computer interfaces as well as some of the relevant neuroscience. It also points out many of the current limitations and discusses biomimetic stimulation as a potential solution to some of these problems.

The third chapter discusses general methods that are relevant to all the studies presented afterwards, including participants, implants, and stimulation protocols.

The fourth chapter is based on two manuscripts, one currently in review and one currently in preparation, and discusses the work I have done looking at the stability of recording quality, impedances, evoked sensations, and material on both stimulated and non-stimulated electrodes. I found that generally signal quality decreases over time on both stimulated and non-stimulated electrodes, but stimulation does not affect this trend in a significant way. The ability to detect stimulation also only ever improved over time. Interestingly, we found, in collaboration with Tracy Cui's lab, that explanted electrodes with only a small amount of charge injected showed demetallization on one implanted array but not the other. These results indicate that even small amounts of stimulation, under certain conditions, can lead to electrode damage. While physical damage may occur, we did not find that potential damage affected signal quality or the ability to evoke percepts, but it is possible that damage could lead to sudden failure in the future.

The fifth chapter shows some preliminary results for signal and stimulation stability in a third participant (P3). The vast majority of the data in this thesis was collected from participant P2, who has been implanted for more than 6 years. At this time, participant P2 has been implanted

for less than one year, but it is nevertheless important to summarize the results here. Specifically, I describe in comparison to similar results collected in P2.

The sixth chapter is based on a paper currently in revision at *eLife* and focuses how parameters of stimulation affect perception of intensity and quality. Amplitude and train duration were found to have consistent effects on perception, where increases in either of these parameters resulted in increases in intensity. Frequency, however, had electrode specific effects in which some electrodes had higher intensities at higher frequencies, while most electrodes had the highest intensity at a lower frequency. I found in both tested participants that these electrode specific effects clustered spatially in the cortex, implying that this has to do with the underlying structure. I also found in one participant that these electrode specific effects related strongly to the evoked perceptual qualities. These results then imply that different areas of somatosensory cortex will respond differently to stimulation, which we believe to be related to the structural organization of cortex for processing stimulus features.

The seventh chapter is based on a conference proceeding from *IEEE NER 2021*, which was selected as a top 10 conference paper and for full publication in *Transactions on Neural Systems and Rehabilitation Engineering* and delves a bit more into stimulus frequency in a different manner. I investigated if changing the timing of pulses, or more specifically the spacing between pulses, while maintaining the same overall charge and number of pulses could result in changes in perception. I found that on half of tested electrodes, changing just the spacing between pulses could result in perceptible differences. I found further that increases in the spacing decreased the frequency perception, like what has been shown previously with vibrotactile input to the hand of intact people. This work provides evidence then that the timing of ICMS pulses behaves like

normal tactile input and provides further evidence that the cortex might be organized for feature encoding, where some areas of cortex are more sensitive to the timing of pulses.

The eighth chapter is based on a manuscript in preparation and explores the phenomenon of habituation. Habituation refers to decreases in perceived intensity of sensation following long period of continuous stimulation. This phenomenon has been observed in other stimulation modalities, such as the peripheral nervous system and visual cortex, and was also found here. We found that completely continuous stimulation, even with burst modulation, resulted in extinction of perception over time. Providing intermittent stimulation, in which stimulation was provided for short periods with longer breaks in between, was able to maintain perception over longer periods of time. These results then imply an intermittent stimulation paradigm might be better for maintaining sensation over long periods of time, which would provide better functional feedback for a bidirectional brain-computer interface.

The final chapter is based on another manuscript in preparation and explores how biomimetic encoding of stimulation affects the evoked perception. I found that biomimetic frequency modulation did not generally increase naturalness but instead had electrode specific effects, which aligns well with our previous findings on the effects of frequency. Biomimetic amplitude modulation, however, was able to increase the naturalness and intuitiveness of stimulation and evoke more focal percepts in one participant.

Tying all this work together, in the conclusion I discuss in detail why biomimetic amplitude modulation can provide a superior method to encode sensation. With biomimetic modulation of pulse trains, based on output from TouchMime, we can a) reduce the total charge injected, potentially improving electrode longevity, b) provide intermittent stimulation transients, resulting in maintained perception for long periods of time, c) stimulate electrodes with individualized pulse

trains based on electrode specific relationships (based on SA and RA type output from TouchMime), and d) improve the overall naturalness and intuitiveness of evoked percepts with biomimetic amplitude modulation.

Future work will need to evaluate the efficacy of biomimetic stimulation in more participants and on bidirectional BCI control. These approaches can potentially be improved by newer technologies with more targeted stimulation and can be informed further with experiments in animal models.

2.0 Background

This chapter is taken directly from a first author book chapter published in the Handbook of Clinical Neurology titled: "Bidirectional Brain-Computer Interfaces" and modified slightly for this dissertation (C. L. Hughes, Herrera, Gaunt, & Collinger, 2020). *Permission was obtained by Elsevier publishing to use this chapter in my dissertation (Order number: 5107221262154)*

Brain-computer interfaces (BCIs) are devices that allow neural activity in the brain to be recorded or modulated by a computer system. BCIs can be used as a basic research tool to investigate brain function but are more commonly associated with their potential to improve the quality of life for individuals affected by debilitating disorders of the brain, spine, limbs, and sensory organs. While there are many approaches to creating an interface with the brain and many technologies that can fit the definition of BCI, we focus on devices that are implanted in the cortex itself (intracortical BCI) or on the surface of the brain. For BCIs to achieve the ultimate goal of fully and completely replicating able-bodied function, they will need to integrate both motor and sensory capabilities. Here, I will describe the basic concepts and rationale behind a bidirectional BCI that not only translates neural activity recorded from primary motor cortex (M1) into control signals for a device but also provides somatosensory feedback by translating external sensor information, e.g., from a prosthetic hand, into electric stimulation patterns delivered to primary somatosensory cortex (S1) (Figure 1). Then I will discuss some of the motivation surrounding a principled biomimetic approach to sensory feedback

2.1 Bidirectional Brain-computer Interfaces

In recent years, there has been significant progress toward developing prostheses that restore movement of the arm and hand (Ajiboye et al., 2017; Bouton et al., 2016; Carmena et al., 2003; Collinger et al., 2013; Hochberg et al., 2012; Santhanam, Ryu, Yu, Afshar, & Shenoy, 2006; Velliste, Perel, Spalding, Whitford, & Schwartz, 2008) with demonstrations of up to 10 dimensions of simultaneous and continuous control (Wodlinger et al., 2015). This level of control allows the arm to be positioned and oriented in space, and finger movements to be combined into different functional grasp postures. Recently, intracortical BCIs have been combined with functional electric stimulation of muscles to restore arm or hand movements in monkeys (Ethier, Oby, Bauman, & Miller, 2012; Moritz, Perlmutter, & Fetz, 2008) as well as humans (Ajiboye et al., 2017; Bouton et al., 2016).

While these reports illustrate the progress that has been made in BCI for motor control, significantly less attention has been given to restoring tactile or cutaneous sensations, which can be crucial for grasping and manipulating objects. For simple tasks, tactile feedback can signal important changes in state, such as object contact (Roland S Johansson & Flanagan, 2009). Sensory feedback becomes even more crucial for tasks that require fine dexterity, such as lighting a match or orienting a key (Robles-De-La-Torre, 2006). Sensory and motor functions do not exist as distinct processes; rather our brains create complex motor plans and compare the desired outcome with sensory feedback to make appropriate adjustments (Wolpert, Ghahramani, & Jordan, 1995). These motor plans are the product of experience shaped by sensory feedback, which motivates the need for sensory feedback in clinical applications of BCI.

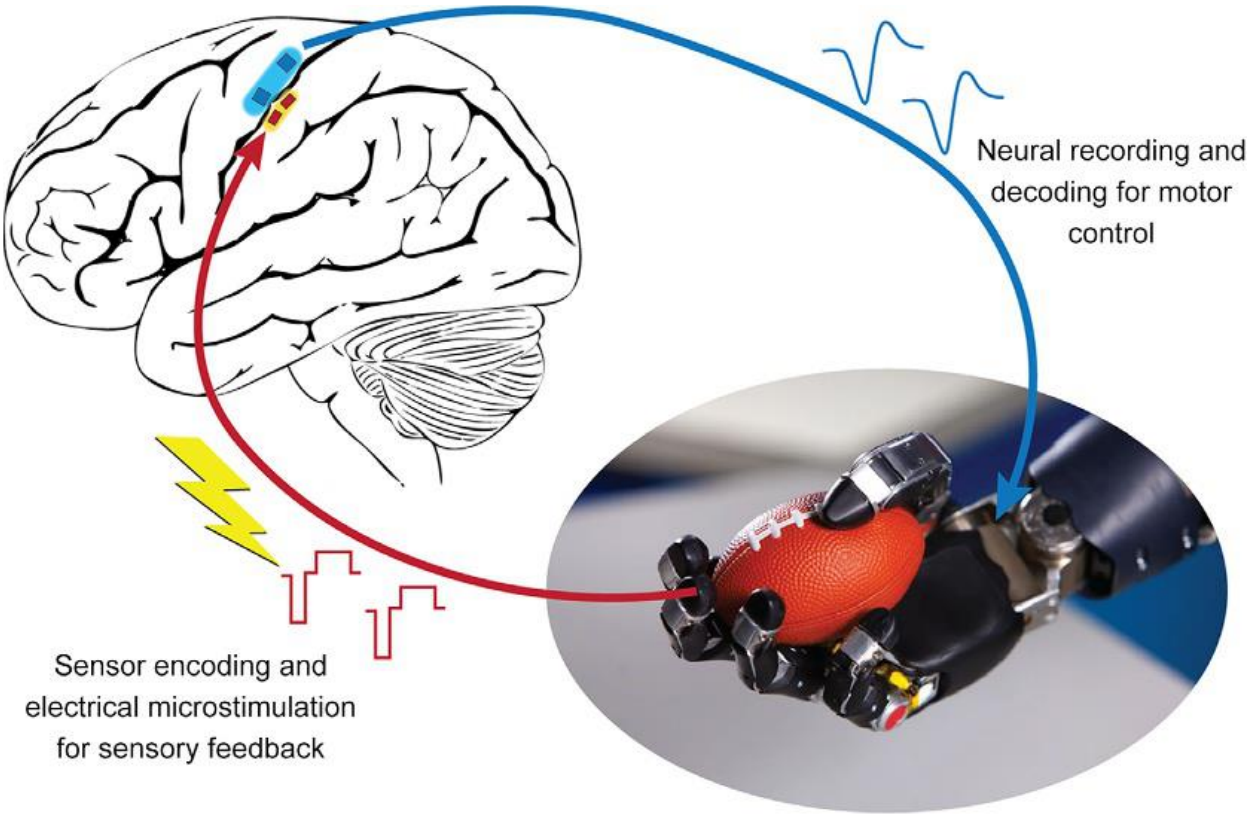

Figure 1. Bidirectional brain-computer interfaces A bidirectional BCI records neural activity to derive a control signal for an end effector, such as a robotic arm, while also providing sensory feedback by stimulating the brain based on sensor output from the end effector.

Clinical trials of implanted BCI systems have been informed by basic science efforts. Much of this work originated with patients undergoing brain monitoring for intractable epilepsy. Today, it has been expanded to individuals with spinal cord injuries who have been implanted with intracortical electrodes in primary somatosensory cortex as part of clinical trials to develop bidirectional BCIs. These implants are able to evoke sensations that feel like they originate from focal locations on the hand (S. N. Flesher et al., 2016) or arm (Armenta Salas et al., 2018). While evoked sensory percepts have naturalistic qualities, additional work is needed to optimally produce natural and useful sensations. Here, I will review the neuroscience of somatosensation, the history of cortical stimulation for somatosensation, current approaches to creating bidirectional BCIs, and biomimetic approaches to sensory feedback.

2.1.1 Importance of Sensory Feedback for Bidirectional BCIS

During grasping, somatosensory feedback provides critical cues about hand shape and object contact and release that shape the motor plan (Flanagan, Bowman, & Johansson, 2006; D. A. Nowak, Glasauer, & Hermsdörfer, 2013). This tactile information is multifaceted and includes the timing, magnitude, direction, and spatial distribution of forces applied to the skin from which information about surface shape and object friction can be determined (I Birznieks, Jenmalm, Goodwin, & Johansson, 2001; Gordon, Forssberg, Johansson, & Westling, 1991; P Jenmalm, Dahlstedt, & Johansson, 2000; P Jenmalm & Johansson, 1997). Sensory feedback informs motor plans for future interactions, but also allows for error corrections on a moment-by-moment basis (Gordon, Westling, Cole, & Johansson, 1993; Per Jenmalm, Schmitz, Forssberg, & Ehrsson, 2006; R S Johansson & Westling, 1988; Roland S Johansson & Flanagan, 2009).

Powerful examples of the importance of these sensory signals are found by observing the limitations in motor performance that occur in the face of sensory impairment. For example, when cutaneous afferents with receptive fields in the digits are anesthetized, manipulation of objects is impaired, leading to difficulties in reacting to unexpected loading conditions or moving grasped objects (Roland S. Johansson, Häger, & Bäckström, 2004; Monzée, Lamarre, & Smith, 2006).

One interesting case study of a person with chronic sensory impairment involves a man who was deafferented due to severe peripheral sensory neuropathy (Rothwell et al., 1982). This person could conduct instructed motor programs (including a hand orientation and force matching task) in a lab setting with almost no issues but had severe difficulties in performing daily tasks that required fine dexterous movement, such as buttoning a shirt or writing with a pen. Cases have also been reported of people losing proprioceptive feedback due to large diameter afferent degeneration that leads to severely compromised motor control, particularly without vision (Sainburg, Ghilardi,

Poizner, & Ghez, 1995; Sainburg, Poizner, & Ghez, 1993; Sanes et al., 1984). These observations demonstrate that somatosensory feedback is a crucial component of normal motor control: it is critical to perform normal reaching movements and to grasp and manipulate objects. Therefore, an important challenge for BCI development is to create technologies that can convey sensory information back to the user in a way that enables skilled movements and object manipulation. For those interested in further exploring the role of sensory feedback in motor control, we refer you to some excellent reviews (Flanagan et al., 2006; Roland S Johansson & Flanagan, 2009; R. Schmidt & Lee, 2005).

2.2 Neuroscience of Sensory Restoration

Developing technologies that interface with the nervous system to restore normal motor and sensory functions requires a strong understanding of the underlying neuroscience. Although developing a deeper understanding of somatosensory neuroscience is the focus of many research labs, there is much we currently know about the neural control of movement and somatosensation that can be applied to BCI technology.

2.2.1 Somatosensory Receptors and the Pathway to the Brain

The perception of touch originates in the periphery from the complex patterns of skin deformation and vibration detected by many types of peripheral receptors, including four types of cutaneous mechanosensitive receptors: Merkel disks, Meissner corpuscles, Pacinian corpuscles, and Ruffini endings. Each of these receptor types is typically associated with a particular function;

however, in normal interactions, simultaneous activation is common. Merkel disks, located in the basal epidermis, are typically associated with discrimination of the texture and spatial properties of a stimulus. Meissner corpuscles, located in the papillary dermis, are important for hand adjustment in the presence of slipping and respond to moderate frequency vibrations. Pacinian corpuscles, located in the hypodermis, are important for detection of high frequency vibratory sensations but are not sensitive to static forces. Ruffini endings, located in the reticular dermis, respond primarily to skin stretch and subsequently provide information regarding the direction of object motion and force. Merkel disks and Ruffini endings adapt slowly, meaning they fire for extended periods of time in the presence of a stimulus, while both Meissner corpuscles and Pacinian corpuscles adapt rapidly to stimuli and are unresponsive to sustained input. These receptors also have different densities in the glabrous skin of the human hand, with Meissner corpuscles and Merkel disks being most prominent in the fingers—especially the fingertips—the Pacinian corpuscles and Ruffini endings being broadly distributed throughout the hand, but at lower overall densities. For an in-depth review of these mechanoreceptors and their functions, see (K. O. Johnson, 2001)

Embedded in muscles and joints are a completely different set of mechanosensitive afferents that give rise to our proprioceptive sense. Proprioception—the ability to know where our limbs are in space—is conveyed primarily though muscle spindles and Golgi tendon organs within muscle bellies and tendons, respectively, and a variety of receptors within joints themselves. The muscle spindle is a remarkably complex sensory structure that is innervated by multiple classes of primary sensory afferents but is also under the control of a parallel motor system, known as the gamma motoneuron system. In broad terms, muscle spindles are sensitive to the length and change in length of muscles themselves, while the gamma motoneuron system regulates the gain of stretch

sensitivity. Golgi tendon organs are distributed in tendons, and produce output that is roughly proportional to the tension in the tendon. Finally, joint capsule receptors can produce output that is modulated by the joint angle, and often fire particularly vigorously near the extremes of the range of motion. The proprioceptive system and its role in perception and movement control is the subject of many recent review articles, which the reader can turn to for further information (Prochazka & Ellaway, 2012; Proske & Gandevia, 2009, 2012).

The axons of the primary afferent neurons innervating these peripheral receptors in the hand and arm form peripheral nerves, which ultimately enter the spinal cord through the cervical spinal nerves. The spinal nerves are divided into dorsal (posterior) and ventral (anterior) components (the Bell-Magendie law) with sensory afferents traveling in the dorsal component. The cell bodies of these primary afferent neurons are located in the dorsal root ganglia, an enlargement in the sensory root, most commonly located in the intervertebral foramina. The axons carrying touch and proprioceptive information then send projections into the spinal cord and synapse in various lamina of the spinal cord before ascending through the dorsal column–medial lemniscus pathway to a first synapse in the dorsal column nuclei. Second order neurons then project to the ventroposterolateral nucleus of the thalamus, which has outputs to the primary somatosensory cortex (S1) (Figure 2). Not all information that passes through these areas makes it to S1, and what does make it through is regulated by reciprocal projections from the cortex to intermediate parts of the pathway (Künzle, 1977; Nothias, Peschanski, & Besson, 1988). Sensory signals arriving through the spinal cord also project to the cerebellum via different spinal tracts and to other areas of the brain via different thalamic pathways. For a more detailed description of these sensory pathways, see (Patestas & Gartner, 2006).

2.2.2 Somatosensory Cortex

Sensations originating from specific locations on the body are projected to corresponding areas in S1, forming a somatotopic representation of the body (Kaas et al., 1981). This somatotopic representation is organized along the medial–lateral axis of the brain where the most medial areas of the postcentral gyrus correspond to legs, and moving laterally, progresses to the trunk, arms, hands, and face. Some parts of the body have a larger representation than others in S1, depending on the relative importance of that area and the number of receptors present in the periphery: an increased number of receptors corresponds to increased representation in the cortex that leads to finer two-point discrimination. As one might expect, the fingertips and hand representations are particularly large. In the rostral–caudal direction, S1 is divided into regions known as Brodmann's areas 1, 2, 3a, and 3b (Brodmann, 1909) (Figure 2). Each of these areas is associated with a distinct distribution of cells throughout the cortical layers, unique intra- and subcortical connections, and distinct functionality. Area 3a receives information about movement through large inputs from muscle spindles and thus plays a large role in proprioception (Mima et al., 1997). Areas 3b and 1 contain information about object structure and texture and are associated with tactile perception (Paul, Merzenich, & Goodman, 1972). Neurons in these areas likely receive convergent input from different populations of peripheral receptors (Saal & Bensmaia, 2014). Area 2 contains information about vibratory type sensations and likely contributes to the integrated processing of proprioceptive and tactile information (Pons & Kaas, 1986).

Due to the organization of the primary somatosensory cortex, only area 1 and perhaps portions of area 2 are easily visible on the surface of the brain. Device implantation is greatly simplified in these areas, although more challenging targets such as thalamus have also been

targeted (Heming, Sanden, & Kiss, 2010). Somatosensory cortex has six layers each with different attributed functions. Layer IV receives inputs from thalamus and thus may be the ideal target for stimulation that is designed to mimic sensory inputs arriving from the periphery, although, another possible target for stimulation is layer III, which primarily receives cortico-cortical inputs.

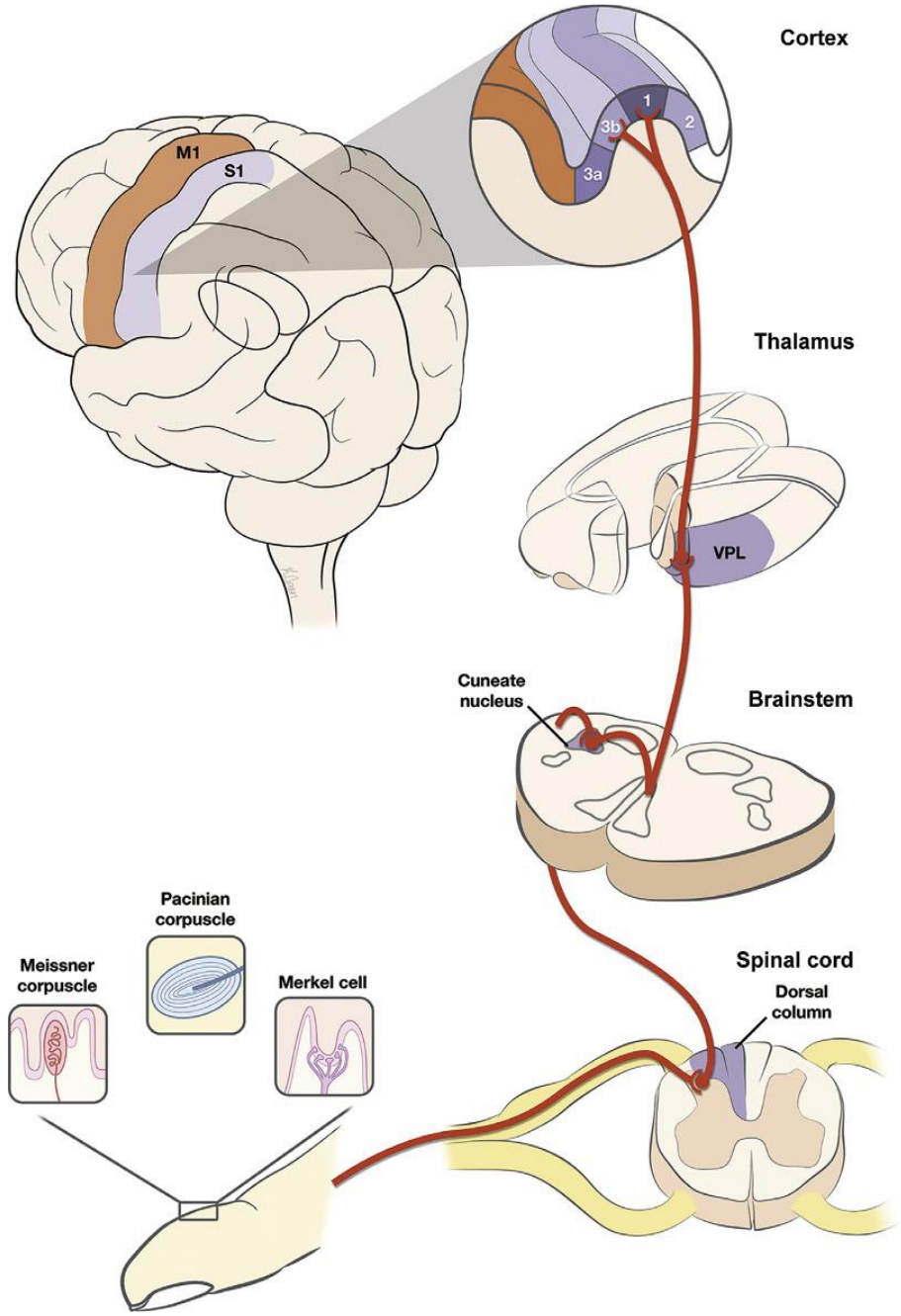

Figure 2. Sensory transduction from the finger to the brain. Peripheral mechanoreceptors in the fingertips send sensory information upstream through the spinal cord, brainstem, and thalamus to the primary somatosensory cortex. Somatosensory cortex is divided into four subregions, areas 3a, 3b, 1, and 2, each one of which possesses different functions based on the inputs from the periphery and computations performed. Image credit: Kenzie Green.

2.3 History of Human Cortical Stimulation

Much of the inspiration for attempting to restore conscious percepts through cortical stimulation in humans comes from the landmark findings of Wilder Penfield, a Canadian neurosurgeon who famously investigated the somatosensory and motor cortices in people with epilepsy using electric stimulation during invasive surgeries beginning in the 1930s (Penfield & Boldrey, 1937). While the surgeries were performed with clinical benefit in mind, namely to localize and remove brain tissue associated with seizure generation, the neuroscientific findings of these investigations were profound. Penfield and Boldrey clearly demonstrated that there was strong functional organization in the cortex and provided one of the earliest demonstrations that electric stimulation of the cortex could evoke neural activity, and ultimately elicit memories, movement, and conscious sensations. Although Penfield is widely recognized as having pioneered the clinical use of electric stimulation of the cortex, Fritsch and Hitzig had demonstrated that the brain was responsive to electrical stimulation in 1870 (Fritsch & Hitzig, 1870). Later on in the late 1920s, Foerster was able to evoke "phosphenes," or points of light, in the visual field of humans by stimulating the occipital lobe (Foerster, 1929). These findings inspired many groups, including the lab of Giles Brindley and Walpole Lewin, to investigate how electric stimulation could be applied to neuroscientific investigation. Brindley and Lewin implanted radio receivers connected to platinum stimulating electrodes on the surface of the visual cortex of a human (Brindley & Lewin, 1968). A transmitting coil was placed above the receiver and controlled the implanted stimulator, which induced phosphenes in a blind person. This experiment was a precursor to cortical visual prostheses that was taken up by Dobelle (W. H. Dobelle & Mladejovsky, 1974). Dobelle began studying stimulation of the visual system in the 1970s and published results of a

rudimentary visual prostheses in the year 2000 (W. Dobelle, 2000). In both systems, the electrodes were relatively large (0.5–2mm in diameter) and were placed on the surface of the visual cortex.

An alternative approach to surface stimulation is to place microwire electrodes directly into the cortex, which brings the active electrode region closer to the target neural populations deeper in the cortex around layer IV, which receives sensory input regions to the cortex from subcortical structures (Viaene, Petrof, & Sherman, 2011). In the 1990s, two experiments were conducted, first as intraoperative procedures (Bak et al., 1990) and then as a long-term implant (E. M. Schmidt et al., 1996)in which multiple microwire electrodes were placed into the visual cortex. These patients reported seeing phosphenes, but at much lower current intensities than were required for stimulation at the surface of the cortex. Ultimately, concerns about electrode–tissue safety, as well as technical and infrastructure challenges, ended this research and until very recently there were no further reports of long-term microstimulation in the human cortex.

Although Penfield reported on the organization of somatosensory cortex as early as 1937 (Penfield & Boldrey, 1937), it is only in recent efforts that this area has become the target for efforts to elicit somatosensory percepts in the context of neural prostheses. One significant reason for this is that cortical motor prostheses only started to be developed in the late 1990s, when it was demonstrated that an actuator could be controlled by motor cortex activity in rats (Chapin, Moxon, Markowitz, & Nicolelis, 1999). The first human trials of motor neural prostheses did not begin until the middle of the first decade of the 21st century (Hochberg et al., 2006). Motor BCI, along with robotic technology, has now advanced to the point that somatosensory feedback has the potential to play an important role in device performance.

2.4 Current Approaches in Human Bidirectional BCI

There are currently two categories of implanted electrodes that have been used in humans to elicit cutaneous sensations through electric stimulation of the cortex: those that are on the surface of the brain and those that penetrate the cortical surface. In both cases, these stimulation approaches use or adapt electrode technologies that are more commonly used for recording neural activity from the brain. Here, we highlight work on cortical stimulation that supports the development of bidirectional BCIs using each of these technologies and summarize several newer approaches to cortical stimulation that are being developed.

2.4.1 Cortical Surface Stimulation

Electric stimulation of the cortical surface is often associated with electrocorticography (ECoG), an electrophysiologic monitoring approach that uses electrodes placed on the surface of the brain, either above or below the dura mater. ECoG grids are most commonly used to monitor brain activity in people with intractable epilepsy and typically have electrodes that are 4−5 mmin diameter with 1 cm between electrode centers, although smaller electrodes and custom spacings have been used in research applications (Kramer et al., 2019; B. Lee et al., 2018; Wang et al., 2013). The ECoG electrodes consist of an array of platinum disc electrodes embedded in a silicon sheet. Since platinum is generally considered to be an acceptable material for stimulation (Cogan, 2008), these same electrode grids can also be used to stimulate the cortex. Clinically, electric stimulation through ECoG electrodes is normally used to map areas of the eloquent cortex prior to neurosurgical intervention (Borchers, Himmelbach, Logothetis, & Karnath, 2012).

Over the past 15 years, several research groups have leveraged the opportunity provided by having ECoG electrodes placed on the cortical surface to examine whether people can voluntarily modulate brain activity to control computers and devices (Cronin et al., 2016; Leuthardt, Schalk, Wolpaw, Ojemann, & Moran, 2004; Schalk et al., 2008; Vansteensel et al., 2016; Wang et al., 2013; Yanagisawa et al., 2012). More recently, attention has turned toward restoring cutaneous percepts by stimulation through these electrodes in mapping studies similar to those performed by Penfield decades ago. These experiments have been performed either as part of monitoring studies for intractable epilepsy (Caldwell et al., 2019; Collins et al., 2017; Cronin et al., 2016; L. A. Johnson et al., 2013; Kramer et al., 2019; B. Lee et al., 2018) or as part of a BCI study (Hiremath et al., 2017) (Figure 3).

One specific advantage of conducting these studies in humans is that we can record the verbal descriptions about how this kind of stimulation feels. In Penfield's studies, patients commonly described the evoked sensations as "buzzy" and covering large regions of the body (whole hand, arm, etc.). In more recent studies, (L. A. Johnson et al., 2013) reported that two subjects perceived qualitatively different sensations ("wind running down the hand" and "light rub or a light buzz") and the qualities of these sensations were not changed with variations in stimulus amplitude or frequency. However, (Hiremath et al., 2017) reported that the perceptual quality of the sensation evoked with stimulation on a high-density ECoG array could be changed by varying the pulse width, although the subject generally reported sensations that felt unnatural, with the larger pulse width generally corresponding to "electrical buzz" and the smaller pulse width generally corresponding to "tingling." Since then, similar reports in people undergoing epilepsy monitoring have confirmed that cortical surface stimulation tends to generate tingling or electrical feelings, with occasional reports that are more naturalistic such as "something brushing," "light

tapping," or a "feeling of movement." The location of the evoked sensation depends highly on electrode placement. Both standard and custom electrodes have been reported to evoke sensations over large areas of the hand or arm as well as more focal sensations covering 1 or 2 digits (L. A. Johnson et al., 2013).

Apart from the conscious sensations evoked by stimulation, these studies explored several other interesting phenomena relevant to bidirectional BCIs. First, electrodes that were near each other on the arrays tended to evoke sensations from the same regions of the body. Electrodes that were adjacent were difficult to discriminate spatially, and electrodes pairs separated by at least one intermediate electrode were easily discriminable spatially (Hiremath et al., 2017). Second, increases in stimulation frequency, amplitude, and pulse duration led to increases in the reported intensity of the evoked percepts (L. A. Johnson et al., 2013; B. Lee et al., 2018). Finally, another study was conducted in the epilepsy monitoring unit to investigate whether cortical stimulation could induce ownership over an artificial limb (Collins et al., 2017). To do this, the subject was shown an artificial limb, which was touched with a probe. A 500-ms pulse train was simultaneously delivered to the corresponding region of the brain. This process induced a sense of ownership over the artificial limb. However, when the stimulation was altered either by stimulating a mismatched projected field or delaying the cortical stimulation relative to the visual stimulus, the illusion of ownership decreased (Collins et al., 2017). Overall, these studies show that cortical stimulation through grids of electrodes placed on the surface of the brain have the potential to be used as a feedback source in bidirectional BCI applications aimed at restoring cutaneous percepts, although the quality and location of sensations is highly variable between participants and electrode locations.

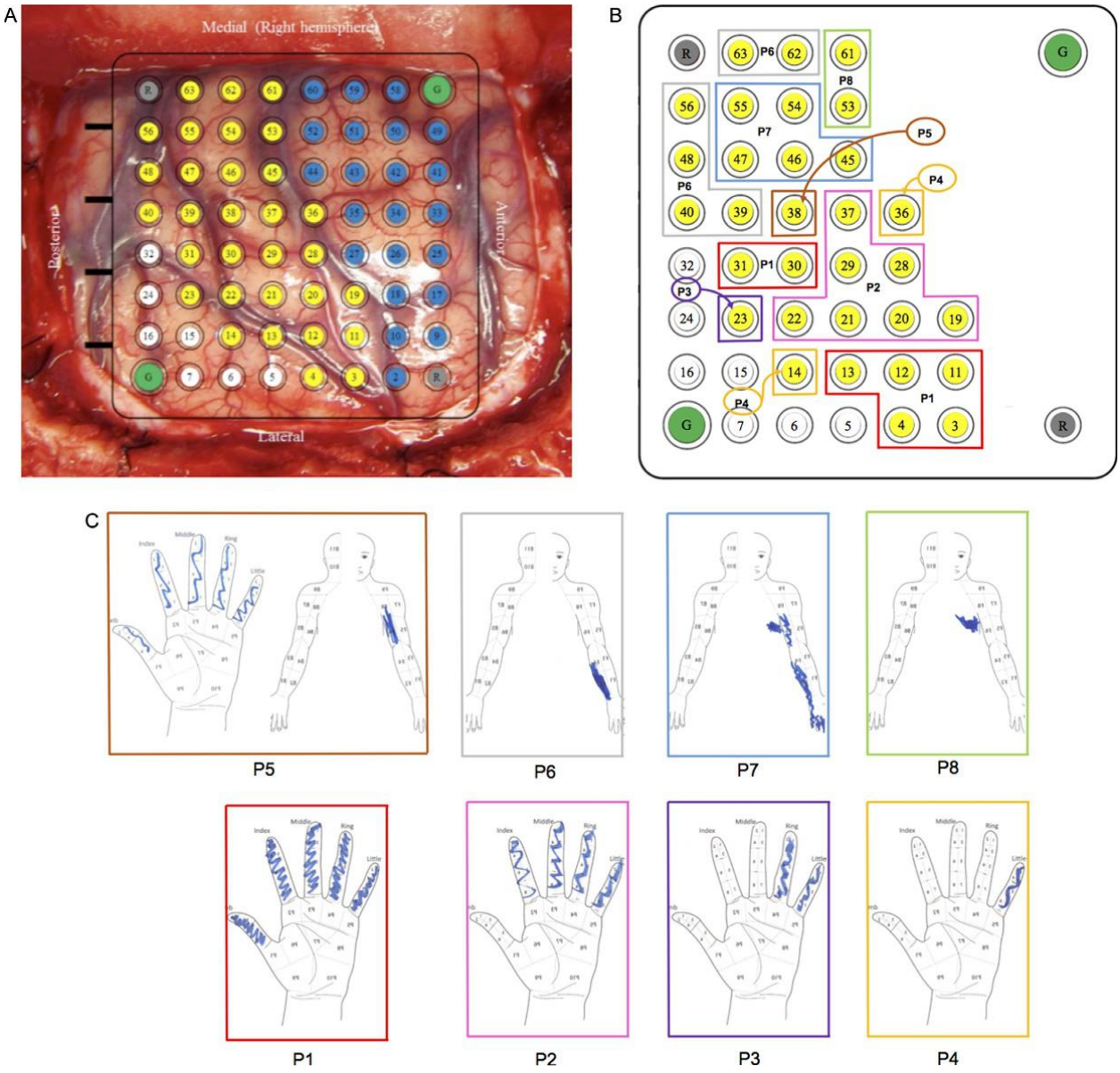

Figure 3: ECoG stimulation can drive sensation on the arms and hands. A) An ECoG grid was implanted subdurally (yellow circles correspond to electrodes in S1 and blue circles correspond to electrodes in M1) in a person with arm paralysis due to brachial plexus injury. B) Electrode groups that correspond to the eight patterns of evoked sensations as reported by the participant, which are shown in C). The white electrodes had no response to cortical stimulation. The sketches in C) were made by the participant using his right hand on a template. Adapted with permission from Hiremath SV, Tyler-Kabara EC, Wheeler JJ et al. (2017). Human perception of electrical stimulation on the surface of somatosensory cortex. PLoS One 12(5): 1–16.

2.4.2 Intracortical Microstimulation

Intracortical microstimulation (ICMS) is a more invasive approach to activating neurons and involves implanting the tips of microelectrodes within the cortex itself so that electrodes are close to the target neurons. This approach has a key potential advantage over stimulation of the cortical surface, since intracortical microelectrodes are typically close enough to neurons to record their activity, much smaller stimulation currents (typically $1–100 mA$) are required to activate these neurons. This in turn allows for the stimulation of very small volumes of tissue, resulting in the activation of nearby neurons (Armenta Salas et al., 2018; Bak et al., 1990; S. N. Flesher et al., 2016; Otto, Rousche, & Kipke, 2005; Tehovnik & Slocum, 2009) ICMS can thus have greater selectivity than surface stimulation, which is a potentially important criterion for restoring somatosensory capabilities to individual digits, or even components of the digits.

ICMS in the somatosensory cortex has been investigated for its potential to elicit tactile percepts in monkeys for several decades. In one landmark study, it was shown that monkeys could use mechanical stimulation of the digits or patterned ICMS that evoked percepts in the same digit equivalently in a frequency discrimination task (Romo, Hernández, Zainos, & Salinas, 1998) This suggested a direct relationship between percepts evoked by ICMS and natural tactile perception. Further studies have characterized the psychophysical characteristics of ICMS and demonstrated how amplitude, frequency, and pulse duration modulate detection thresholds in monkeys (S. Kim, Callier, Tabot, Tenore, & Bensmaia, 2015) Further, the ability to discriminate different parameters of stimulation produced characteristic psychometric curves described by sigmoidal functions relating variation of stimulation parameters to detection performance (Figure 4). The monkeys' ability to detect and discriminate different ICMS parameters has been exploited in several

experiments where monkeys made BCI cursor movements (O'Doherty, Lebedev, Hanson, Fitzsimmons, & Nicolelis, 2009)or reaching movements (Dadarlat, O'Doherty, & Sabes, 2014; Fitzsimmons, Drake, Hanson, Lebedev, & Nicolelis, 2007) cued by ICMS.

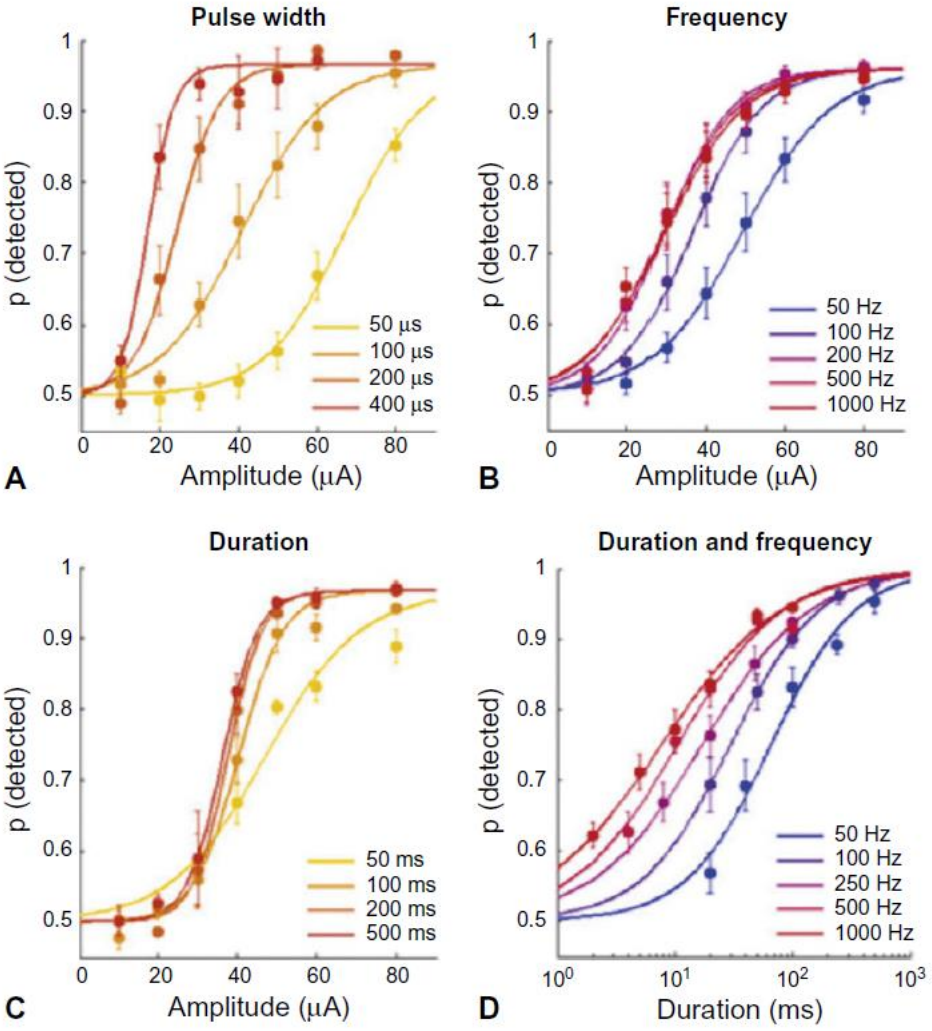

Figure 4: Characterization of various stimulus parameters for intracortical microstimulation and their effect on the ability to detect stimulation in monkeys. Adapted with permission from Kim S, Callier T, Tabot GA, et al. (2015). Behavioral assessment of sensitivity to intracortical microstimulation of primate somatosensory cortex. Proc Natl Acad Sci USA 112(49): 15202−15207.

One obvious limitation of ICMS in monkeys is that they cannot describe what these percepts feel like, nor can they easily be trained to report where on the body The sensation originates. To address these issues, to verify that the monkey findings hold true for humans, and to accelerate the development of bidirectional BCIs, our research group began a study of ICMS in humans. Microelectrode arrays were implanted in area 1 of S1 based on presurgical imaging with the goal of eliciting tactile sensations from the hand of a person with upper limb paralysis resulting from a spinal cord injury (S. N. Flesher et al., 2016). We were able to document what ICMS in S1 "feels like" for the first time and how these percepts mapped to the body surface. In our first participant, we found that stimulation across the implanted electrodes evoked sensations corresponding to the expected somatotopy in S1 (Figure 5). These sensations spanned the upper palmar region of the hand and parts of the index finger and were typically focal in nature. One of the expected limitations of intracortical microelectrodes was that the spatial coverage was limited due to the small size of the electrode arrays compared to the region of area 1 involved in tactile sensations from the hand.

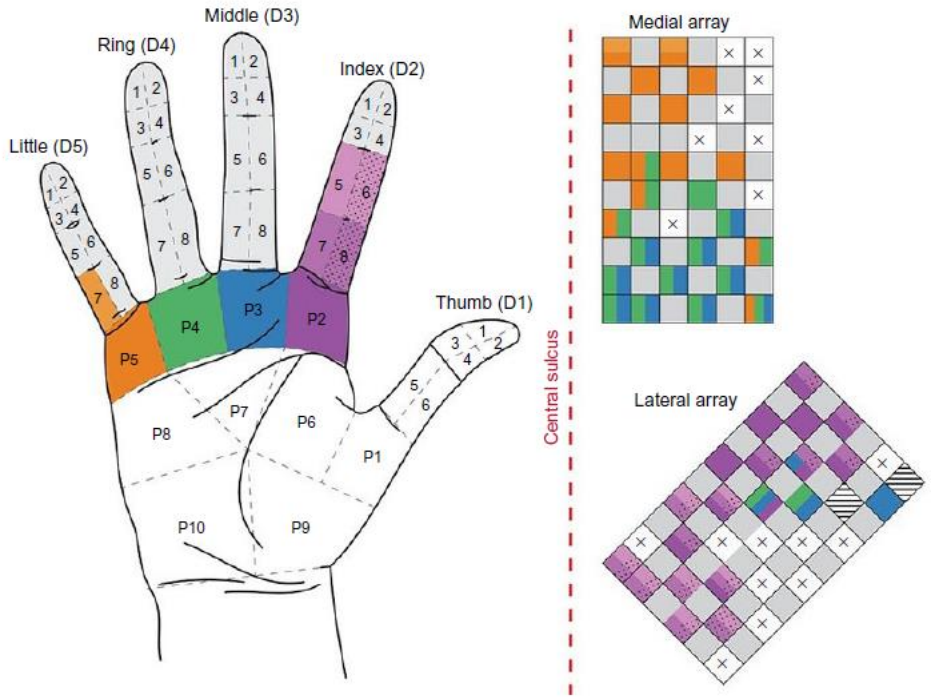

Figure 5: Intracortical microstimulation of area 1 can drive sensation on the hand. (A) The subject indicated the areas of perceived sensation based on the electrodes stimulated. Colored areas show all projected fields reported. (B) A representation of the 32-channel Utah array implants. The colored mapping corresponds to the individual channels with reported projected fields on the hand in (A). The correspondence of the electrodes with the projected fields of the hand aligned well with known somatotopy. Adapted with permission from Flesher SN, Collinger JL, Foldes ST, et al. (2016) Intracortical microstimulation of human somatosensory cortex. Sci Transl Med 8(361): 1–11.

Ultimately, there is a trade-off between the sensation specificity or focality, and the range over which these sensations can be generated. Recall that stimulation on the surface of the brain typically induces paresthetic "buzzing" sensations that are often experienced on an entire digit or even the whole hand and arm. Here, the participant reported feelings of "tingle," "pressure," "vibration," "touch," and "warmth," with "pressure" present in 36.9% of reports and "tingle" present in 79.2% of reports. Many of these sensations are described as "possibly" and "almost" natural, although we have found it difficult to precisely characterize how ICMS-induced percepts compare to natural sensations. One crucial finding of this work is that the projected fields of individual electrodes have remained essentially constant over time with no major variations since

the subject began to report sensations from them. Interestingly, the number of electrodes that elicit detectable sensations increased over the duration of the experiment (Figure 6). This is in contrast to previous studies of recording quality with intracortical electrodes, which have shown decreases over time (Dickey, Suminski, Amit, & Hatsopoulos, 2009; Downey, Schwed, Chase, Schwartz, & Collinger, 2018; Fraser & Schwartz, 2012; Tolias et al., 2007). Of course, the ability to stimulate nearby neurons may depend on factors that are different from the ability to record from a given electrode, which has not been rigorously quantified.

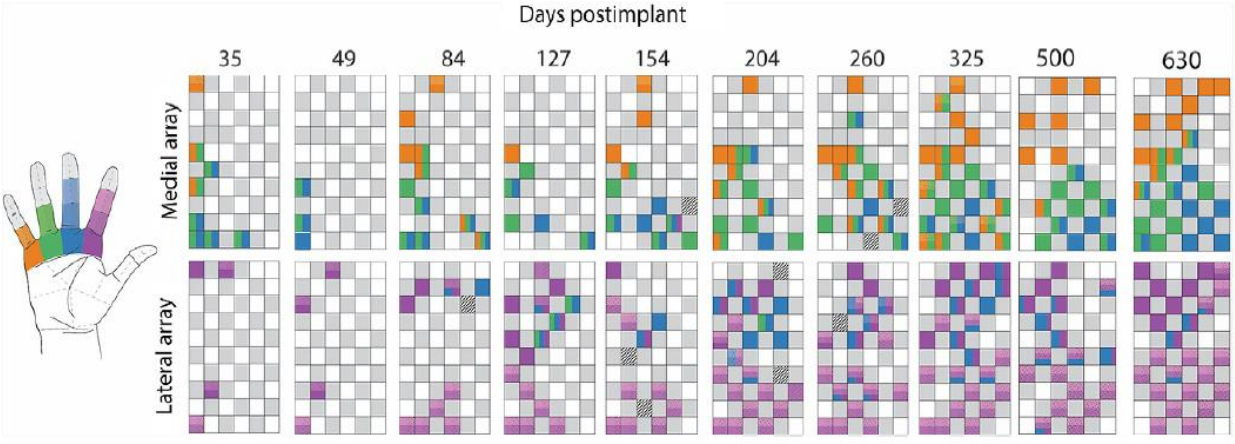

Figure 6: The number of electrodes able to evoke sensation increases over time. A human subject implanted with two microelectrode arrays in area 1 of somatosensory cortex showed an increase in the number of channels reported following an approximate logarithmic curve. The subject has shown no decline in reported channels after 6 months (unpublished results).

We also performed psychometric evaluations of ICMS as part of these human experiments. We measured the detection thresholds using a two-alternative forced choice task design and found a range of 15–88mA with a median of 34.8 mA across the electrodes (S. N. Flesher et al., 2016). We also found a highly linear relationship between current amplitude and the perceived intensity of the stimulus and found that the just noticeable difference (JND) in stimulus amplitude was 15mA. These results agree with reports from monkey experiments with identical stimulus

parameters although experiments in monkeys could not address questions about perceptual quality, such as perceived intensity. Overall, our experiments in a human participant have shown that focal, somewhat natural sensations coming from the hand can be evoked with ICMS and that the perceived intensity of the stimulus can be modulated with stimulation amplitude. This suggests that ICMS could be used to convey both the location and pressure of a contact event while remaining within a safe stimulus range.

Another group has also demonstrated the use of ICMS in human S1 for tactile feedback (Armenta Salas et al., 2018). Rather than eliciting sensations on the hand, this group primarily found sensations on the arms, which were sometimes proprioceptive in nature. The difference in results between these two participants is likely due to differences in array placement. The arrays in this participant were more medial than in our participant and also agreed with the expected somatotopy of the somatosensory cortex with the medial electrode array evoking more upper arm sensations and the lateral array evoking more forearm sensations. The study participant reported many naturalistic sensations, with the most common reported percepts being "squeeze" and "tap." One notable difference was a lack of reports of "tingle" sensations, which were common in our work. Variations in the perceptual quality of sensations could be related to the differences in array placement and the location of the evoked sensations. They may also highlight challenges with subjective evaluation of tactile perception, providing support for rigorous psychophysical quantification of somatosensory percepts. (Armenta Salas et al., 2018) confirmed prior reports in monkeys and humans that increases in stimulation amplitude led to increases in detectability and intensity. However, they also reported that increases in stimulation amplitude are more likely to evoke proprioceptive sensations than cutaneous sensations. One hypothesis was that the increase in stimulation amplitude activated a larger volume of tissue that included area 2 of the

somatosensory cortex, an area associated with proprioception. While some differences were noted in terms of the location and perceptual quality of the evoked sensation, both human studies demonstrate that ICMS can generate focal and naturalistic sensations even after chronic spinal cord injury.

Ultimately, a major goal of restoring somatosensory percepts is to improve BCI-controlled end effectors. At this point of time, the impact of ICMS-based feedback on BCI control in humans remains to be evaluated, although preliminary experiments have begun. In one experiment, the subject performed a finger discrimination task where sensor data from a robotic hand was used to drive ICMS of electrodes that evoked sensations in the corresponding fingers. The subject could distinguish which prosthetic finger was being touched 84% of the time with incorrect reports mostly occurring on adjacent fingers (S. N. Flesher et al., 2017).

Beyond restoring tactile percepts with ICMS, some labs are investigating the restoration of proprioceptive feedback as well. Although tactile information is important for fine dexterous movements (Roland S Johansson & Flanagan, 2009), proprioception is crucial to our ability to produce coordinated and graceful movements, particularly in the absence of vision. Area 3a is the primary cortical region receiving proprioceptive afferent projections from the thalamus and is located, rather inconveniently, at the fundus of the central sulcus. Given its location, it presents a difficult target for stimulation since commonly used multielectrode arrays, like the Utah array, cannot access this region. As a result, ICMS of area 3a has not been performed in humans. However, experiments in monkeys have shown that ICMS feedback in this area can improve performance on motor tasks (London, Jordan, Jackson, & Miller, 2008). In this experiment, monkeys performed a cursor movement task with a joystick and were trained to associate ICMS at two different frequencies with left and right movements. ICMS was shown to improve reaction

times for these cursor movement tasks. In another experiment, area 2, an area associated with both cutaneous and proprioceptive information, was stimulated to provide task-relevant proprioceptive feedback (Tomlinson & Miller, 2014). While these experiments attempted to leverage the biologic function of neurons in this cortical region, recreating natural input patterns though ICMS may not be necessary. This was elegantly demonstrated in an experiment in which information about hand position was encoded in the patterned activity of eight electrodes implanted in the somatosensory cortex (Dadarlat et al., 2014). Importantly, these electrodes were not placed in a region that intrinsically encoded proprioceptive information. Rather, the monkeys were trained to make novel associations between hand motion and stimulation so that they were ultimately able to perform the movement tasks with only ICMS feedback.

2.5 Alternative Approaches

While electric stimulation of the cortex is both an effective tool to probe the physiology of sensory perception and a method that is currently being developed to restore somatosensation in BCIs, electric stimulation techniques have several important limitations. Microelectrode implants are known to have a finite lifetime (C. A. Chestek et al., 2011; Kane et al., 2013)which means they may not provide a permanent solution to patients, or that electrodes may need to be replaced multiple times through multiple surgeries. Furthermore, electric stimulation activates many cells at once, in nonspecific and often nonphysiologic ways (Gaunt, Prochazka, Mushahwar, Guevremont, & Ellaway, 2006; Histed, Bonin, & Reid, 2009; L. G. Nowak & Bullier, 1998), even at very low stimulus currents (Tehovnik, 1996). However, it could be functionally critical to stimulate individual cells or small populations of cells to restore truly natural sensation. Finally,

electric stimulus artifacts and electrochemical safety at the electrode–tissue interface are nontrivial challenges that must be addressed in real systems and are uniquely associated with electric stimulation. Here, we briefly discuss several alternatives to electric stimulation of the cortex to restore somatosensation.

2.5.1 Optogenetics

Optogenetics broadly refers to the ability to observe and activate genetically modified cells using light. Green fluorescent protein (GFP) can be bound to other proteins resulting in a construct that is responsive to the presence of intracellular calcium (T.-W. Chen et al., 2013; Nakai, Ohkura, & Imoto, 2001). This effectively creates cells that fluoresce when they become active. In this way, image sensors can be used instead of electrodes to monitor the activity of populations of neurons. However, most excitement in the field has derived from the ability to activate neurons by shining light on them. Cells are genetically modified to express ion channels that are sensitive to specific wavelengths of light. Genetically identifiable cells can be targeted and either excited (Zhang, Wang, Boyden, & Deisseroth, 2006) or inhibited (Zhao et al., 2008) by shining light of different wavelengths. This ability to target specific types of cells and manipulate their behavior in real time provides a level of control that is not possible with electric stimulation. Further, stimulation artifacts that occur on recording electrodes during a stimulus pulse can largely be eliminated using optogenetic stimulation. As a result, optogenetic techniques have become widely used in neuroscientific investigation and could eventually provide an alternative to electric stimulation for brain-computer interface applications. For a review of optical neural interfaces, see (Warden, Cardin, & Deisseroth, 2014).

2.5.2 Magnetic Stimulation

Another potential alternative to activating cells using electric stimulation is to use rapidly changing magnetic fields, because this produces an electric field That can activate neurons. The most common magnetic stimulation method is transcranial magnetic stimulation (TMS), which is a noninvasive method that activates large populations of cells (Hallet, 2000). Typical TMS systems require large external apparatus and electrical coils on the head, so the application to bidirectional BCI is likely low at this point. However, recent developments of implantable magnetic stimulation systems offer several potential advantages over standard electric stimulation systems. Microcoils implanted in the cortex can create highly focal magnetic fields, which in turn elicit electric activity in nearby neurons (S. W. Lee, Fallegger, Casse, & Fried, 2016). At their simplest, these microcoils are a single continuous loop of conductive material, and have at least two unique properties. First, the magnetic field induces electric current in a specific direction, unlike monopolar electric stimulation, where the electric field radiates out uniformly from a point source electrode. For intracortical stimulation, this means that neurons with specific orientations can be preferentially activated. Second, with electric stimulation, irreversible redox reactions can occur when the voltage is too high at the electrode interface, which can lead to degradation of the electrode over time. With magnetic stimulation, the coil itself is fully insulated, so unwanted electrochemical reactions, which can be challenging to control in electric stimulation approaches, are completely eliminated.

2.5.3 Peripheral Nerve Stimulation

For some potential BCI users who have an intact spinal cord, such as amputees, it is possible to provide somatosensory feedback through peripheral nerve stimulation. Peripheral interfaces have the advantage of activating the sensory system at the most distal location, where the signals are more deterministic, and for which good models of afferent activation are being developed (Oddo et al., 2016; Saal, Harvey, & Bensmaia, 2015). At more central locations, sensory signals are transformed and become more complex, which could make it more difficult to create fully natural percepts. Peripheral nerve stimulation to elicit somatosensory percepts in amputees has been an active area of investigation for several decades (Clippinger, Avery, & Titus, 1974) and has recently seen a resurgence in interest. Using modern techniques, different groups have shown that sensory feedback through peripheral nerve stimulation can allow subjects to discriminate many unique projected fields (Davis et al., 2016; Tan et al., 2014). Combined with myoelectric prosthesis control, it also enables users to transfer objects (Clemente et al., 2019; Schiefer, Tan, Sidek, & Tyler, 2016; G Valle et al., 2018; Giacomo Valle et al., 2018; Wendelken et al., 2017) and modulate grasp force (Clemente et al., 2019; D'Anna et al., 2017; Raspopovic et al., 2014; G Valle et al., 2018; Giacomo Valle et al., 2018) without any visual or auditory feedback. For a more in-depth review of peripheral interfaces, see (Navarro et al., 2005) and (Micera & Navarro, 2009)

2.5.4 Thalamic Stimulation

Another possible approach to evoke somatosensory percepts is stimulation of the thalamus (Heming et al., 2010). Stimulation in the thalamus could enable perception in people with spinal

cord injuries, but also occurs at a lower computational level than cortical stimulation. Exploratory thalamic stimulation in humans undergoing implantation for deep brain stimulation showed that percepts could be elicited and that the projected field of the neurons stimulated were mostly consistent with their receptive fields (Heming et al., 2010). A variety of different percepts, including mechanical and tingle percepts have been reported, similar to those evoked through ICMS (S. N. Flesher et al., 2016). Despite the fact that the thalamus is located deep within the brain, thalamic stimulation has significant precedent as a clinical technique and it can evoke percepts in chronically implanted people (Heming et al., 2010).

2.6 Challenges to Implementing Bidirectional BCIs

It is clear that there is a need for BCIs that provide somatosensory feedback, and we have thus far described many of the current approaches to achieve this goal. However, there are several challenges that must be overcome to address the current limitations of bidirectional BCIs and accelerate clinical translation of this technology. Other reviews (Bensmaia & Miller, 2014; Gilja et al., 2011; Lega, Serruya, & Zaghloul, 2011; Ryu & Shenoy, 2009) have focused on the general challenges of translating BCI technologies to clinical practice, so here we focus on issues that are particularly important for bidirectional BCIs.

2.6.1 Stimulus artifact

Electric stimulation pulses generate rapidly changing electric fields centered around the electrode tips, which are sampled by any recording electrodes in the vicinity. Unfortunately, the

stimulation artifact voltage is usually much larger than action potentials themselves (sometimes orders of magnitude larger) and is detected as a spike on the recording electrodes. In addition, stimulation is typically delivered as a train of pulses, and as attempts to create sophisticated pulse trains on many electrodes simultaneously are developed, it rapidly becomes the case where there are no instances when stimulation is not occurring. Within the context of a BCI, this essentially eliminates the ability to record neural activity to provide a control signal. A challenge is that the stimulus artifact voltage often exceeds the input range of standard neural amplifiers, causing them to saturate. During this saturation period, it is theoretically impossible to recover any neural signal. In addition to recording the changing electric field in the implanted tissue, stimulus artifacts can also appear in the recorded signal through capacitive coupling between nearby electrode lead wires and other locations in the signal pathways.

Fortunately, there are many approaches to reducing the occurrence of artifacts including constraining or scheduling stimulus pulse timing. For experiments in which amplifiers are saturated, artifacts can be rejected through blanking or zeroing neural amplifier output during stimulus delivery (O'Doherty et al., 2011). When the amplifiers do not saturate, one can use template or high bit depth recordings to sample the entire artifact and enable signal extraction (Limnuson, Lu, Chiel, & Mohseni, 2014; Mena et al., 2017; O'Shea & Shenoy, 2018). However, there is not yet one best solution, and this practical problem remains a significant technical consideration for bidirectional BCIs and is an area of active development. Currently, the simplest approaches involve blanking, either by alternating recording and stimulation intervals (e.g., 50ms intervals) (O'Doherty et al., 2011), or by recording in between every stimulus pulse. A simple approach in which signal blanking is combined with digital filters is sufficient for control of a bidirectional BCI in humans, where the hardware is limited to that approved for human use (Weiss,

Flesher, Franklin, Gaunt, & Collinger, 2018). Blanking techniques, while technically simple and robust, have the significant disadvantage of impairing BCI performance since the amount of information used for decoding intent is reduced. More advanced techniques attempt to minimize the artifact itself and recover neural data during stimulation pulses (Culaclii, Kim, Lo, & Liu, 2016). As stimulation patterns become more advanced (e.g., variable frequency or multielectrode stimulation), these more sophisticated methods of artifact removal will almost certainly be required.

2.6.2 Electrode design and placement

Clinical BCI studies using intracortical microelectrode arrays have all used the NeuroPort arrays (more commonly known as Utah arrays), manufactured by Blackrock Microsystems (Salt Lake City,Utah) and have been conducted under Investigational Device Exemptions from the US Food and Drug Administration. These devices typically consist of 100 electrodes on a 10x10 grid with 400mm between each electrode. Each electrode projects 1.0–1.5mm from the silicon substrate (Maynard et al., 1997). Because of the design of these electrodes, they can only be implanted into brain regions that are easily accessible on the surface. Accessing deep structures, or cortical regions in a sulcus, is not possible with Utah arrays. As described previously, the only regions of human somatosensory cortex that are visible on the surface of the postcentral gyrus are area 1 and, possibly, area 2 (see Figure 2). Therefore, with current technology, only these regions can be used in a bidirectional BCI.

In our previous work, one person was implanted with two 60-channel microelectrode arrays in area 1 of somatosensory cortex (Flesher et al., 2016). The goal was to specifically target the finger region of area 1. However, these two arrays (2.4 x 4.0mm) were far smaller than the visible

portion of the postcentral gyrus that is responsive to input from the fingers (roughly 10-30mm). Stimulation through the electrodes evoked sensations on the palm near the base of the second through fifth digits, as well as on the proximal two segments of the second digit. Stimulation on adjacent electrodes often elicited distinct percepts, but the projected fields were located close to each other on the surface of the skin. Although the spatial specificity of sensations evoked with ICMS is far better than what has been reported in ECoG studies (Johnson et al., 2013; Hiremath et al., 2017), the percepts themselves cover a much smaller region of the skin. This highlights a current issue with ICMS: the microelectrode arrays are too small to elicit percepts across large areas. From these results, future electrodes will need to access much larger regions of the somatosensory cortex to provide broad coverage of the hand, especially the fingertips. Ultimately, it remains unknown what the ideal combination of spatial resolution and coverage is for stimulation, although broader coverage may be more desirable to restore at least some sensations from the entire hand and palm.

In addition to developing electrodes that can achieve broad, high-density coverage of cortical regions visible on the surface, progress on clinical electrodes that can access deeper structures will be necessary as well. Two areas important for touch and proprioception, areas 3a and 3b, are located in the fundus and posterior bank of the central sulcus, respectively. Suitable electrodes that have longer shanks are used in monkeys (Kipke et al., 2003; London et al., 2008; Dadarlat et al., 2014) but devices like these will need to be developed for human use in the future.

2.6.3 Biomimetic vs nonbiomimetic stimulation

There are two conceptual approaches to providing sensory feedback. In the first approach, stimulation is delivered in an arbitrary but principled manner that fundamentally ignores a biologic

framework. The subject, instead, learns to integrate the stimulus into their sensorimotor repertoire through adaptation or learning. The approach at the other end of the spectrum is to stimulate the brain in a manner that completely mimics normal physiologic activity. This biomimetic approach uses knowledge about the normal function of cortical neurons to inform stimulus encoding algorithms as well as electrode design and placement.

The learning-based, or nonbiomimetic, approach leverages the brain's ability to adapt and adjust to novel inputs to inform motor plans. Recently, it was demonstrated that monkeys could learn arbitrary mappings to inform movement as provided by ICMS of S1 (Dadarlat et al., 2014). The monkeys were able to use sensory feedback in this way to complete a target acquisition task to an unseen target. The inference from these experiments is that even if stimulation is delivered in a way that is fundamentally unnatural, intrinsic learning networks in the brain could enable a person to learn to appropriately discriminate different sensory information in a way that is useful. This is a similar approach to sensory substitution experiments where visual information is mapped to tactile stimulation of the back or tongue, and used as assistive devices for people with visual impairments (Bach-y-Rita & W. Kercel, 2003; White, Saunders, Scadden, Bach-Y-Rita, & Collins, 1970).

Being able to completely replicate the functionality of the intact nervous system would be ideal, as it would allow for complete recovery of function for patients and eliminate potentially long training sessions. This is a daunting and perhaps impossible challenge, but this general approach has been applied in peripheral nerve stimulation studies, where stimulus pulses are designed to mimic certain features of intact nerve function (Oddo et al., 2016; Saal & Bensmaia, 2015; Tan et al., 2014). Researchers are further investigating how this approach can be applied in the cortex for proprioception (Tomlinson & Miller, 2016) and cutaneous perception (Bensmaia &

Miller, 2014; Saal, Delhaye, Rayhaun, & Bensmaia, 2017). However, this approach requires a deep understanding of how cortical neurons respond to inputs and stimulation technology that has a high enough resolution to stimulate neurons in a biologically relevant manner. Recently, one group investigated the use of biomimetic pulse trains in the peripheral nervous system for restoration of touch (Giacomo Valle et al., 2018). Their study showed that using biomimetic pulse trains resulted in reports of more natural tactile sensations from the participants. They additionally reported that it improved performance on specific tasks and improved some aspects of device embodiment. No published work to date has investigated biomimetic principles in human cortical implants. It is encouraging that modulating stimulus amplitude can change the intensity of evoked sensations and that these sensations can feel like pressure and touch (Armenta Salas et al., 2018; S. N. Flesher et al., 2016). However, there remains significant room for improvement to evoke truly natural and biomimetic sensations via ICMS.

2.6.4 Electric stimulation safety

As with any developing technology, risks must be monitored and minimized. Bidirectional BCIs have similar risks for many devices using implanted electrodes, including localized tissue damage or infection. Many of these risks have been described extensively elsewhere(Bensmaia & Miller, 2014; Gilja et al., 2011; Lega et al., 2011; Ryu & Shenoy, 2009). However, a particular concern related to BCIs using ICMS is the potential for electrode and tissue damage caused by the stimulation itself. The electrochemistry at the electrode–tissue interface during stimulation pulses can damage both the electrode and the tissue (Cogan, 2008), ultimately leading to loss of electrode functionality. To mitigate the risk of damaging the electrode and surrounding tissue, stimulation parameters should be limited to those characterized as safe in previous animal studies (Kane et al.,

2013; S. Kim, Callier, Tabot, Gaunt, et al., 2015; D. McCreery, Pikov, & Troyk, 2010; Parker, Davis, House, Normann, & Greger, 2011; Torab et al., 2011). If the total charge delivered during a stimulation pulse exceeds safe limits, over time the electrode or surrounding neural tissue may be damaged (Agnew, Yuen, McCreery, & Bullara, 1986; D. B. McCreery, Bullara, & Agnew, 1986; Sandeep Negi, Bhandari, van Wagenen, & Solzbacher, 2010). Unfortunately, there are widely different estimates for what is considered a safe level of charge injection, which likely stem from differences in the details of the stimulation protocols used in different studies. However, many studies have used stimulation parameters within a range considered safe by at least a subset of additional studies and have reported no functional consequences of chronic ICMS (S. N. Flesher et al., 2016; Rajan et al., 2015; Romo, Hernández, Zainos, Brody, & Lemus, 2000; Romo et al., 1998; P. J. Rousche & Normann, 1999). Stimulation of up to 20 nC/phase has proven to be safe in long-term experiments in animals (K. H. Chen et al., 2014; Rajan et al., 2015) and humans (Armenta Salas et al., 2018; S. N. Flesher et al., 2016) if additional duty cycle and other precautions are observed. In our experiments (S. N. Flesher et al., 2016), we use asymmetric charge balanced pulses with a 200ms cathodic phase and a 400ms anodic phase, set at half the amplitude of the cathodic phase, separated by a 100ms interphase period. For these pulses, the cathodic phase amplitude can go up to 100mA while remaining under the 20 nC/phase limit.

Cortical stimulation also carries a risk of causing seizures, although this risk is low for the stimulation levels that are typically used in bidirectional BCIs. Screening for a personal or familial history of seizures may also be prudent at the early development stages for these devices. Another risk is that implanted devices could alter any residual or spared sensation that a person may retain. We have reported previously that after 6 months of ICMS, the detection thresholds on areas of the participant's skin that remained sensate after injury were unchanged (S. Flesher et al., 2017).

Nevertheless, as more implants are conducted, it will be critical to monitor any changes in participants′ spared sensations to document the effects of stimulation of the human cortex over long periods of time.

2.6.5 Outcome assessment

In humans, sensations evoked with electric stimulation can be documented through surveys and psychometric techniques designed to measure features including detection thresholds, perceived intensity, location, and perceptual quality (S. N. Flesher et al., 2016). Some of these factors can be documented easily and reliably, albeit through tedious and time-consuming experimental procedures. However, perceptual quality, essentially the question "What did it feel like?," can be more challenging to quantify (Hermansson, Fisher, Bernspång, & Eliasson, 2005; Light, Chappell, & Kyberd, 2002). A similar obstacle has been observed when using peripheral stimulation (Graczyk et al., 2016). Microneurographers have developed a lexicon to assess the effects of peripheral nerve stimulation on perception (Vallbo, Hagbarth, Torebjork, & Wallin, 1979), and the studies of Lenz (Lenz et al., 1993) and Kiss (Heming et al., 2010) have also provided structured methods to assess the perceptual qualities of electrically induced sensations. Nevertheless, accurately probing and documenting these sensations remains a challenge, one that depends significantly on the personality and introspectiveness of the individual reporting them. Additional tools to probe perceptual quality or perhaps a new way to frame the question of how electric stimulation "feels" will be necessary to make more progress in this area.

In addition to documenting the perceptual qualities of evoked sensations, we also need to consider the impact of restored sensation on motor performance and embodiment. For bidirectional

BCIs to be clinically viable, they need to demonstrate functional benefit. Some tests exist for evaluating prosthetic limb function (Hermansson et al., 2005; Light et al., 2002; Resnik et al., 2013); however, they were not designed or validated with sensory feedback in mind and thus may not be sensitive performance metrics. BCI studies have also used outcome assessments from rehabilitation, such as the Action Research Arm Test (ARAT) (Collinger et al., 2013; Yozbatiran, Der-Yeghiaian, & Cramer, 2008), to evaluate BCI performance. The ARAT assesses the subject's ability to pick up and transport objects of different shapes and sizes. Current robotic effectors can be limited when performance necessitates fine, dexterous movements that rely more heavily on sensory feedback. Some prosthetic control studies have begun to incorporate tasks that require handling of delicate objects or force coordination (Clemente et al., 2019; Raspopovic et al., 2014; Tan et al., 2014; G Valle et al., 2018; Giacomo Valle et al., 2018), but this remains an area of active research.

2.7 Conclusion

A great deal has been discovered about how to provide sensory feedback through a BCI in a safe manner to evoke localized and graded sensations. Early studies of bidirectional BCIs have shown favorable results in monkeys (Dadarlat et al., 2014; Fagg et al., 2007; O'Doherty et al., 2011) and work with human subjects in recent years has also been promising (Collins et al., 2017; S. N. Flesher et al., 2016; Hiremath et al., 2017; L. A. Johnson et al., 2013; B. Lee et al., 2018). Further studies will need to be conducted to both provide a greater understanding of the neurophysiologic basis of sensorimotor processes and to test the effectiveness of this technology.

3.0 General Methods

3.1 Participant and Implants

This study was conducted under an Investigational Device Exemption from the U.S. Food and Drug administration, approved by the Institutional Review Boards at the University of Pittsburgh (Pittsburgh, PA) and the Space and Naval Warfare Systems Center Pacific (San Diego, CA), and registered at ClinicalTrials.gov (NCT0189-4802). Informed consent was obtained before any study procedures were conducted. Two subjects, referred to as P2 and P3, were implanted with two microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT) in somatosensory cortex and two microelectrode arrays in the motor cortex. Each somatosensory electrode array consisted of 32 wired electrodes distributed throughout a 6x10 grid. All 60 electrodes were not wired due to technical constraints related to the total available number of electrical contacts. Electrode tips were coated with a sputtered iridium oxide film (SIROF) (S Negi, Bhandari, Rieth, & Solzbacher, 2010). Each motor electrode array consisted of 88 wired electrodes in P2 and 96 wired electrodes in P3 distributed throughout a 10x10 grid. Electrode tips in motor cortex were coated with platinum.

Participant P2 was 28 years old at the time of implant and had a C5 motor/C6 sensory ASIA B spinal cord injury. Results from this participant have been reported previously (S. N. Flesher et al., 2016)The stimulation return electrode was the titanium pedestal that was screwed into the skull.

Participant P3 was 28 years old at the time of implant and had a C6 ASIA B spinal cord injury. He received the same type of microelectrode arrays in the somatosensory cortex as P2. The

electrodes were also targeted to the hand region of area 1 of the somatosensory cortex using preoperative imaging and evoked sensations that he described as originating from his hand.

3.2 Stimulation Protocol

Stimulation was delivered using a CereStim C96 multichannel microstimulation system (Blackrock Microsystems, Salt Lake City, UT). Pulse trains consisted of cathodal phase first, current-controlled, charge-balanced pulses delivered at frequencies from 20-300 Hz and at amplitudes from 2-100 μA. The cathodal phase was 200 μs long, the anodal phase was 400 μs long, and the anodal phase was set to half the amplitude of the cathodal phase. The phases were separated by a 100 μs interphase period. At the beginning of each test session involving stimulation, we sequentially stimulated each electrode first at 10 μA and 100 Hz for 0.5 s and then at 20 μA and 100 Hz for 0.5 s. During these trials, the interphase voltage on each electrode was measured at the end of the interphase period, immediately before the anodal phase (Cogan, 2008). The voltage transients associated with each stimulation pulse were recorded using National Instruments data acquisition modules. Voltage traces were displayed in real time using LabView and saved to disk for analysis. Interphase voltage was measured as the voltage at the end of the interphase period immediately prior to the anodal phase for a given stimulation pulse. The total charge delivered to each electrode was calculated across all stimulation experiments using the charge delivered during the cathodal phase. If an electrode's measured interphase voltage was below -1.5 V, the electrode was disabled for the day. This step was performed to minimize stimulation on electrodes that might potentially experience high voltages, which could result in irreversible damage. Typically in P2, 2 to 10 electrodes were removed from the test set each day,

although this number increased over time. In P3, 0 to 4 electrodes were removed for each test day. The electrodes that were removed tended to change from day to day suggesting that the high interphase voltage was due to poor contact between the percutaneous connector and the stimulation cable. In P2, tactile sensations localized to the hand were elicited on 50-60 of the 64 electrodes with stimulation which increased over time (S. N. Flesher et al., 2016). All electrodes, except those exhibiting high interphase voltages, were stimulated at suprathreshold amplitudes, typically 60 μA, at least once a month during a monthly survey of elicited tactile sensations. Some electrodes were used more frequently for other tasks involving stimulation. We conducted experiments in P2 exclusively at the participant's home from Day 364 to 498 for reasons unrelated to the study. Experiments conducted in the home used a different set of hardware and were subject to different environmental noise characteristics than the laboratory. Stimulation experiments were not conducted during this time because our regulatory approvals dictated that stimulation may only be performed in the lab. However, neural recordings were made from electrodes implanted in somatosensory cortex during this time and those data are included in this manuscript. After implant Day 498, stimulation experiments continued both at home and in the laboratory after regulatory modifications had been approved.

3.3 Neural Recordings

At the beginning of each session for both participants, we recorded neural data while the participant was at rest with room noise minimized. These data were processed offline and used to assess signal quality. Neural signals were recorded using the NeuroPort data acquisition system (Blackrock Microsystems, Salt Lake City, UT) and were sampled at 30 kHz with a 750 Hz first

order high pass filter (Weiss et al., 2018). Each time the recorded voltage signal crossed a pre-defined threshold of -4.5 times the baseline root-mean-square on each electrode, the time of the crossing and a 48-sample (1.6 ms) snippet of the signal, starting 11 samples before the crossing, was saved for offline analysis.

3.4 Detection Thresholds

In participant P2, detection thresholds were calculated on at least two electrodes each day that stimulation was provided. One of these two was electrode 19 while the other electrode tested was taken sequentially from a list of seven electrodes (electrodes 8, 11, 28, 34, 40, 54, and 57). These electrodes were selected because they spanned both arrays and consistently generated perceptible sensations, but were otherwise arbitrarily chosen. In P3, six electrodes were chosen (2, 12, 16, 34, 46, 62) which were collected in pairs (one on the lateral and one on the medial each day). Detection thresholds were calculated using a three-down, one-up staircase method (Leek, 2001; Levitt, 1971). This involved a two-alternative forced choice task in which participant was presented with a stimulus pulse train during one of two 1-s intervals separated by a 1-s delay period and had to select which interval contained the pulse train. The amplitude of the stimulus was increased by 2 dB after an incorrect response and decreased by 2 dB after three correct responses. After five changes in direction, the trial was stopped and the threshold was calculated as the average of the last ten values before the end of the trial.

4.0 Stability of Electrodes With and Without Stimulation

This chapter is based on two manuscripts. The first is a first authorship manuscript currently available on medRxiv and under review at the Journal of Neural Engineering titled "Neural stimulation and recording performance in human somatosensory cortex over 1500 days" (C. L. Hughes, Flesher, et al., 2020). *The second manuscript is a second authorship manuscript currently in preparation in collaboration with Tracy Cui's lab with Kevin Woeppel as first author titled "Explant analysis of recording and stimulating Utah electrode arrays implanted in human cortex for brain-computer-interfaces."*

Objective: Intracortical microstimulation (ICMS) in somatosensory cortex can restore sensation to people with spinal cord injury or other conditions. One potential challenge for chronic ICMS is whether neural recording and stimulation can remain stable over many years. This is particularly relevant since the recording quality from implanted microelectrode arrays can degrade over time and limitations in stimulation longevity have been considered a potential barrier to the clinical use of ICMS. Our objective was to evaluate recording stability on intracortical stimulated sputtered iridium oxide (SIROF) and non-stimulated platinum electrodes in somatosensory and motor cortex in a human participant across a long period of implantation. Additionally, we measured how ICMS was able to evoke sensations over time.

Approach: In a study investigating intracortical implants for a bidirectional brain-computer interface, we implanted microelectrode arrays with SIROF tips in the somatosensory cortex of a human participant with a cervical spinal cord injury. We regularly stimulated these electrodes to evoke tactile sensations on the hand. Here, we quantify the stability of these electrodes in comparison to non-stimulated platinum electrodes implanted in the motor cortex over 1500 days

in two ways: recorded signal quality and electrode impedances. Additionally, we quantify the perceptual stability of ICMS-evoked sensations using detection thresholds.

Main results: We found that recording quality, as assessed by the number of electrodes with high-amplitude waveforms (> 100 μV peak-to-peak), peak-to-peak voltage, noise, and signal-to-noise ratio, generally decreased over time on stimulated SIROF and non-stimulated platinum electrodes. However, stimulated SIROF electrodes were much more likely to continue to record high-amplitude signals than non-stimulated platinum electrodes. Interestingly, the detection thresholds for stimulus-evoked tactile sensations decreased over time from a median of 31.5 μA at day 100 to 10.4 μA at day 1500, with the most substantial changes occurring between day 100 and 500.

Significance: These results provide evidence that ICMS in human somatosensory cortex can be provided over long periods of time without deleterious effects on recording or stimulation capabilities. In fact, the sensitivity to stimulation improved over time.

4.1 Introduction

As intracortical electrodes must be surgically implanted, microelectrode arrays need to function for long periods of time to be clinically practical. The stability of microelectrode arrays in motor cortex has been well studied in non-human primates (Barrese et al., 2013; C. Chestek et al., 2011; Suner, Fellows, Vargas-Irwin, Nakata, & Donoghue, 2005). Additionally, there are several reports on signal quality and stability for electrodes implanted in human motor cortex (Downey et al., 2018; Hochberg et al., 2006; Simeral, Kim, Black, Donoghue, & Hochberg, 2011). Although intersubject variability is high, signals can be reliably recorded for up to 3-5 years

when devices do not fail, although the quality of these recordings deteriorates over time. However, whether electrodes primarily used for intracortical microstimulation (ICMS) can record and stimulate effectively over clinically relevant timelines is uncertain, especially given that stimulation itself may have detrimental effects on the electrodes and the surrounding neural tissue (Agnew et al., 1986; Patrick J Rousche & Normann, 1998; Weber, Friesen, & Miller, 2012). This concern is particularly relevant for people, since implantation requires a craniotomy performed under general anesthesia.

Prior to the clinical results presented in this work, a series of experiments in non-human primates were performed to establish safe stimulation limits using microelectrodes arrays. These studies demonstrated that frequent microstimulation over six months did not appear to cause more damage to the cortex than what could be expected from implanting the devices themselves, that there were minimal effects on the characteristics of the electrode-tissue interface, and that that there were no detectable behavioral changes in the animals' abilities to perform dexterous behaviors that require somatosensory feedback (K. H. Chen et al., 2014). Other studies have also demonstrated that signal can be reliably recorded and sensations can be reliably evoked over long periods of time in animals when using stimulation amplitudes up to 300 μA (Callier et al., 2015; Davis et al., 2012; Patrick J Rousche & Normann, 1998). Despite the precautions taken in this study to use parameters that have proven effective in animals, it is necessary to demonstrate that these parameters are safe and effective in humans. Here, I present results on the stability of Utah microelectrode arrays used for ICMS in the somatosensory cortex of a human participant over 1500 days using these safety standards derived from non-human primate studies.

4.2 Methods

Data for this study were collected for the first 1500 days after implantation in P2. Typically, experiments were conducted three days a week. Experimental sessions were typically four-hours long, although stimulation was not used in every session or for all four hours. Across the 1500 implant days, experiment sessions were performed on 510 days, 378 of which involved stimulation. Additionally, a separate set of electrodes were implanted in P2 prior which were explanted 182 days after implant and had a small amount of charge injection. These electrodes were used for material analysis.

4.2.1 Stability Metrics

To quantify the stability of stimulated electrodes in somatosensory cortex, we measured recorded signal quality, electrode impedances, and stimulation detection thresholds over time. Signal quality and impedance were compared between stimulated electrodes and non-stimulated electrodes. Recording quality was evaluated using four metrics: (1) the number of high-amplitude recordings, (2) peak-to-peak voltage, (3) noise, and (4) signal-to-noise ratio. Ideally, a clinical device would be able to record many neurons with large peak-to-peak voltages, have low noise levels, and therefore, a high signal-to-noise ratio for the duration of the implant. Another key metric of electrode stability, particularly for stimulated electrodes, is the electrode impedance. Increases in the impedance could result in higher required voltages at the electrode-tissue interface for constant-current stimulation pulses, resulting in potentially irreversible reduction and oxidation reactions (Cogan, 2008). Therefore, it is necessary for electrode impedances to remain stable over the length of the implant. Finally, the ability to elicit sensations with ICMS must necessarily be

maintained. Detection thresholds are a measure of how well the participant can detect electrical stimulation. Changes in this parameter reflect the amount of charge that must be used to induce tactile percepts, and there is an upper limit to the amount of charge that can be safely applied (D. B. McCreery, Agnew, Yuen, & Bullara, 1990). Therefore, detection thresholds should not systematically increase over the length of implantation. Increasing thresholds may then result in an inability to evoke tactile percepts with parameters that have been shown to be safe.

4.2.2 Signal Quality

Neural activity recorded at rest was processed offline in MATLAB (Natick, MA) to measure the number of high-amplitude recordings, peak-to-peak voltage, noise, and signal-to-noise ratio (SNR) over time. The peak-to-peak voltage was calculated individually for every snippet. Only the snippets with peak-to-peak voltages within the top 2% on a given electrode were used for analysis. This method was used to isolate the largest neural recordings and provide an unbiased estimate of the capacity of each electrode to record signals. More typical single-unit based analysis, especially over the long time periods of this study, could be subject to biases introduced by manual spike sorting (Wood, Black, Vargas-Irwin, Fellows, & Donoghue, 2004). We therefore selected analysis methods that did not require spike sorting. The largest 2% of the snippets for each electrode were averaged and the peak-to-peak voltage was calculated. If the firing rate of all the snippets on any electrode was less than 1.67 Hz or the peak-to-peak voltage of the averaged signal was less than 30 μV, the electrode was excluded from analysis. We used 1.67 Hz because it ensured we would have at least two isolated waveforms for analysis when using only the top 2% of snippets across a minute of recording. Electrodes containing snippets which had peak-to-peak voltages over 100 μV were considered electrodes that contained high-amplitude

recordings. The noise metric was calculated as three times the standard deviation of the first five-time samples of all action potential snippets. As the first five values of each snippet capture time points prior to the threshold crossing event, they provided a metric for how much variance existed due to noise in the recordings. A similar method for calculating noise was used in a previous publication looking at motor unit stability (Downey et al., 2018). SNR was calculated as the magnitude of the peak of the averaged waveform divided by the calculated noise. The filter applied to the recorded neural data was changed at Day 200 from a fourth order 250 Hz highpass Butterworth filter to a first order 750 Hz high-pass Butterworth filter to reduce the effects of stimulus artifact. The increased cut-off frequency resulted in an overall decrease in noise and, therefore, an increase in SNR (Weiss et al., 2018). Because of this, we separated data into pre-and post- filter change epochs for all signal quality analysis. All reported statistical results for signal quality are from data collected after the filter change.

4.2.3 Impedances

Electrode impedances at 1 kHz were measured at the beginning and end of each test session for every electrode. Impedances were measured using the impedance mode built into the NeuroPort patient cable data acquisition system (Blackrock Microsystems, Salt Lake City, UT), which involves delivering a 1 kHz, 10 nA peak-to-peak sinusoidal current for 1-s to each implanted electrode. For our analysis, we only used impedance recordings from the beginning of the sessions. This is because post-session impedances are affected by the application of ICMS, although these values return to normal the following test session, as has been noted previously (K. H. Chen et al., 2014).

4.2.4 Material Stability

Prior to the implantation used to look at signal and sensation stability, the same participant (P2) was implanted with microelectrode arrays in the brain which were later explanted. P2 was originally implanted with two Pt microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT) in the left somatosensory cortex and two Iridium Oxide (IrOx) microelectrode arrays in the left posterior parietal cortex. Each Pt array in the somatosensory cortex consisted of 88 wired electrodes in a 10x10 grid while each IrOx array in the posterior parietal cortex consisted of 32 wired electrodes distributed throughout a 6x10 grid. After implantation, it was discovered that the implant locations were posterior to the intended sites. Following this, the pedestals were removed and a second implantation was performed two months later in the correct locations.

In these first set of implants in P2, seven test sessions across approximately one month involved microstimulation on the IrOx arrays. Stimulation was delivered using a CereStim R96 multichannel microstimulation system (Blackrock Microsystems, Salt Lake City, UT) with the same parameters described in the general methods.

The first set of implants were explanted on post-implant day 182. Following explantation, all arrays were removed from their wire bundles by clipping the wires proximal to the probe, washed with saline. The arrays were fixed 2 months post-implant, and one of the Pt arrays has visible tissue encapsulation and was imaged using TPM. Because these arrays were not immediately fixed, we did not perform immunostaining, and only characterized the collagen structure, which can be stable without the fixation. These arrays did not undergo the enzymatic cleaning procedure. All arrays were stored adhered to copper tape, tips up.

Explanted electrodes from P2 were first characterized by optical and two-photon microscopy to assess the degree of tissue encapsulation. For TPM, we used a two-photon laser

scanning microscope with a Bruker scan head (Prairie Technologies, Madison, WI), TI:sapphire laser tuned to 920 nm (Mai Tai DS; Spectra-Physics, Menlo Park, CA), light collection through non-descanned photomultiplier tubes (Hamamatsu Photonics KK, Hamamatsu, Shizuoka, Japan), and a 10x or 16x, 0.8 numerical aperture water immersion objective (Nikon Inc., Milville, NY). Laser power was maintained between 20-40 mW. For each electrode tip, Z-stacks were collected with filters to resolve second harmonic generation (SHG) at half the laser wavelength (~460nm), which enabled intrinsic imaging of collagen-I representing the meningeal encapsulation. Images along the length of the electrode shanks were collected as Z-stacks. Z-stack images were either collected at specific regions of interest, or in a grid at all locations across the face of the electrode array. Grid images were automated by the Prairie software with a 10% overlap between images. All image stitching and subsequent image processing was conducted with ImageJ software (NIH). Electrode integrity was characterized by scanning electron microscopy (SEM) and energy-dispersive x-ray spectroscopy (EDS). Samples were washed, dried under alcohol, and sputter-coated with 4nm Au/Pd. Images were taken by JSM 6335F electron microscope. EDS was taken by Zeiss Sigma 500VP, excluding Au and Pd from quantification.

Using the SEM images, a qualitative category of ‘non-degraded/unencapsulated’ or ‘degraded/encapsulated’ was assigned to each electrode based on the degree of damage to the tip or shank, or the level of encapsulation around the electrode. Degraded electrode tips were defined as having obvious and substantial surface defects in the metal coating, including pitting of the metal, flaking of the metal, and exposure of the underlying silicon. Degraded shanks were defined relative to the parylene insulation, with defects including insulation cracking along the shank, peeling of the insulation away from the shank near the tip, and other obvious defects in or below the insulation. These categories were compared to EDS images, confirming the presence/absence

of metalation at the tip (Pt/IrOx). Electrodes which could not be quantified, due to breakage during removal or gross encapsulation, were assigned a null score and excluded from analysis.

4.2.5 Data Analysis and Statistics

All statistical analysis was performed in MATLAB (Mathworks, Natick, MA). We tested for changes in signal quality, impedance, and detection thresholds over time using linear regression. Data points that had values more than three scaled median absolute deviations away from the median were excluded from analysis as outliers. Impedances and detection thresholds followed an exponential decay so the regressor, days post-implantation, was log-transformed prior to regression. Median data on stimulated electrodes in somatosensory cortex were compared to data on non-stimulated electrodes in motor cortex using ANCOVA. We used ANCOVA because it allowed us to assess significant differences between mean values on stimulated and non-stimulated electrodes by accounting for changes over time as a covariate, producing an ANCOVA adjusted means comparison. Additionally, we were able to assess the interaction of the two factors, time and stimulation condition, to determine if the changes over time were significantly different between stimulated and non-stimulated electrodes, producing an ANCOVA interaction term. The coefficients for slopes and interactions were considered to be significantly different than zero or from each other at the $P < 0.05$ level and highly significant at the $P < 0.001$ level. All p-values reported are for the coefficient of the regression slope unless otherwise indicated. For detection thresholds measured across all electrodes at specific time points, we analysed the differences between blocks using Kruskal-Wallis tests and Tukey's honestly significant difference (HSD) post-hoc tests. A non-parametric test was used because the detection data across electrodes were nonnormal at each time point, as determined with an Anderson-Darling test. We quantified the

spatial clustering of detection thresholds on the arrays using Moran's I which is a method to assess spatial autocorrelation (Moran, 1950). The weighting scheme considered only adjacent electrodes as neighbors. The significance for Moran's I was determined using a z-test comparison to the predicted outcome of a random distribution. For visual clarity, interquartile ranges (IQRs) shown in figures were smoothed with a ninepoint moving average filter with a triangular kernel.

Total charge delivered, minimum interphase voltages, and charge delivered after exceeding an interphase voltage of -0.6V were compared between electrodes that had received stimulation using Mann-Whitney tests. We used a non-parametric test because the data was determined to not be normally distributed using an Anderson-Darling test. We used a Fisher exact test to determine if there was a significant relationship between an electrode's material properties (undamaged or damaged) and the length of implantation or if it received stimulation (yes or no). We further quantified if there was a relationship between the charge injected, total and after exceeding and interphase voltage of -0.6V, on stimulated electrodes and their material properties (undamaged or damaged) using logistic regression.

4.3 Results

4.3.1 Recording Stability

We quantified recording quality using four metrics: the number of high-amplitude recordings, peak-to-peak voltage, noise, and signal-to-noise ratio. Overall, we found that all signal quality metrics decreased significantly over time for both the stimulated (somatosensory) and non-

stimulated (motor) electrodes. Importantly however, stimulated and non-stimulated electrodes were affected differently (Figure 7).

The number of electrodes with high-amplitude recordings decreased significantly over time on both non-stimulated motor and stimulated sensory electrodes ($P < 0.001$, linear regression, Figure 7A). Interestingly, the stimulated electrodes with high-amplitude recordings decreased less over time (slope = -5 electrodes/year) than the non-stimulated electrodes with high amplitude recordings (slope = -23 electrodes/year). This difference was highly significant ($P < 0.001$, ANCOVA interaction) and reflects a 47% loss of high-amplitude signals on stimulated electrodes and a 72% loss of high-amplitude signals on non-stimulated electrodes from Day 200 to 1500. Early in the study, between Days 200 and 300, we recorded high-amplitude signals on 30±3 electrodes in somatosensory cortex and 101±10 electrodes in motor cortex. Late in the study, between Days 1400 and 1500, we recorded high-amplitude signals on 17±4 electrodes in somatosensory cortex and 38±9 electrodes in motor cortex. It should be noted that we record from 64 electrodes in somatosensory cortex and 176 electrodes in motor cortex, which favors recording a larger number of high-amplitude electrodes in the motor cortex. These results together demonstrate that stimulated electrodes better maintained high amplitude recordings over time than non-stimulated electrodes.

There were also highly significant differences in the changes in the peak-to-peak voltages, noise, and SNR on stimulated and non-stimulated electrodes ($P < 0.001$, ANCOVA interaction). Interestingly, the peak-to-peak voltage on stimulated electrodes decreased less over time (slope = -10.6 μV/year, $P < 0.001$, linear regression, Figure 7B) than on the non-stimulated electrodes (slope = -14.2 μV/year, $P < 0.001$, linear regression, Figure 7B) and the stimulated electrodes maintained a higher adjusted mean peak-to-peak voltage ($P < 0.001$, ANCOVA adjusted means).

The noise on the stimulated electrodes also decreased less over time (slope = -1.0 μV/year, $P < 0.001$, Figure 7C) than on non-stimulated motor electrodes (slope = -2.9 μV/year, $P < 0.001$, Figure 7C) but the stimulated electrodes maintained a lower adjusted mean noise ($P < 0.001$, ANCOVA adjusted means).

This resulted in SNR decreasing more over time on stimulated electrodes (slope = -0.2 a.u./year, $P < 0.001$, Figure 3D) than on non-stimulated electrodes (slope = -0.1 a.u./year, $P < 0.001$, Figure 7D) due primarily to differences in how noise changed over time. This difference was highly significant ($P < 0.001$, ANCOVA interaction) and reflect a decrease in SNR of 23% on stimulated electrodes and 15% on non-stimulated electrodes from Day 200 to 1500. However, stimulated electrodes maintained a higher adjusted mean SNR than non-stimulated electrodes ($P < 0.001$, ANCOVA adjusted means). So, although the SNR decreased more over time on stimulated electrodes, a higher SNR was maintained throughout implantation than on non-stimulated electrodes. Early in the study, between Days 200 and 300, we recorded an SNR of 2.9±0.3 in somatosensory cortex and an SNR of 2.5±0.1 in motor cortex. Late in the study, between Days 1400 and 1500, the SNR had dropped by a small, but statistically significant amount to 2.4±0.5 in somatosensory cortex and 2.2±0.1 in motor cortex. This implies that significant differences in how SNR changed over time did not translate to practical differences in SNR, and in fact stimulated electrodes maintained higher SNR over time than non-stimulated electrodes.

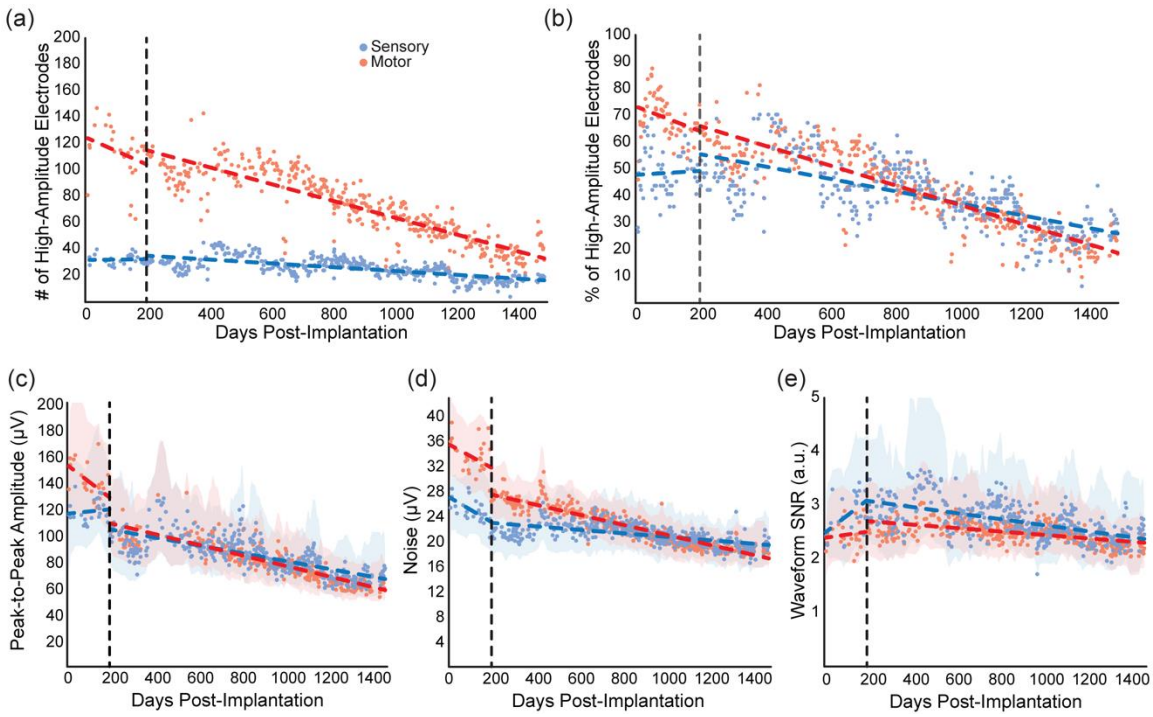

Figure 7: Signal quality over time. Blue points represent signal quality metrics from stimulated sensory electrodes and red points represent non-stimulated motor electrodes. Dotted lines represent regression before and after day 200. Shaded areas represent the smoothed interquartile range for each data set. The dotted vertical line marks day 200, when the filter order was changed. A) The number of high-amplitude recordings since implantation. Each point represents the number of electrodes with high-amplitude recordings. The thick solid lines show the percentage of electrodes that had high-amplitude recordings for each group with a corresponding y-axis on the right. B) Measured median peak-to-peak voltage since implantation in microvolts. C) Measured median noise since implantation in microvolts. D) Measured median signal-to-noise ratio since implantation.

To address the concern that charge itself might be associated with degradation in signal quality, we also investigated the signal quality metrics of a single electrode, electrode 19, which received the most stimulation of any electrode (Figure 8). The detection threshold for this electrode was tested during every stimulation session and this electrode was additionally the most commonly used electrode for bidirectional BCI tasks. Although the intersession variance was much larger for this single electrode than the median data, neither the peak-to-peak amplitude ($P = 0.92$, ANCOVA interaction, Figure 8A) nor SNR ($P = 0.22$, ANCOVA interaction, Figure 8C) were significantly different over time compared to all stimulated electrodes. However, the baseline noise decreased more on electrode 19 than the rest of the stimulated electrodes ($P < 0.001$, ANCOVA interaction,

Figure 8B). This resulted in an adjusted mean noise that was significantly lower and an adjusted mean SNR that was significantly higher ($P < 0.05$, ANCOVA adjusted means) than the adjusted mean of the median noise and SNR for all stimulated electrodes. Next, we compared electrode 19 to the non-stimulated electrodes in motor cortex and found that the magnitude of the decrease in noise on electrode 19 over time (the slope) was not significantly different than the decrease in the median noise on the non-stimulated electrodes over time ($P = 0.7786$, ANCOVA interaction). However, the noise itself on electrode 19 was significantly lower than the median noise on non-stimulated electrodes ($P<0.001$, ANCOVA adjusted means). Overall, the noise on stimulated electrodes decreased more quickly than the noise on non-stimulated electrodes. That this effect did not appear to be driven by the amount of stimulation (electrode 19 was no different than non-stimulated electrodes), suggests that other factors such as electrode material and impedance could have been the cause.

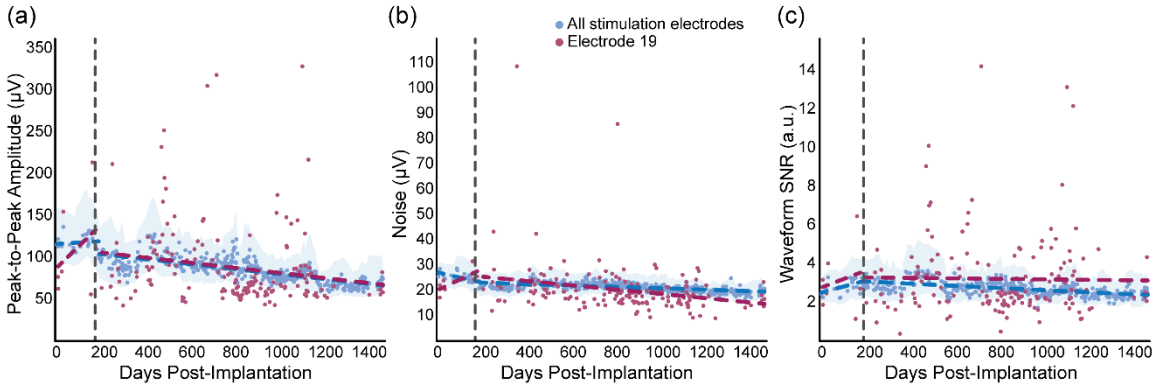

Figure 8: Signal quality on a single electrode that received the most stimulation. Data points for all the stimulated electrodes (blue) represent median values from test days. Data points for the single electrode (red) are the measured values for each metric on each day. Dotted lines show regression across all data. Shaded areas represent the smoothed interquartile range for each for all stimulated electrodes. The dotted vertical line marks day 200 when the filter order was changed. (**a**) Peak-to-peak voltage. (**b**) Background noise. (**c**) Signal-to-noise ratio.

4.3.2 Impedance Stability

There was a large increase in impedances at 1 kHz following implantation on both motor electrodes (median pre-implant impedance: 447.5 kOhms; median Day 7 impedances: 1396 kOhms) and sensory electrodes (median pre-implant impedance: 74.5 kOhms; median Day 7 impedances: 533 kOhms). We assessed whether there was any significant change in the electrode impedances following implantation over 1500 days using linear regression (Figure 9A). We found that there was a highly significant decrease in electrode impedance over time on both the stimulated and non-stimulated electrodes ($P < 0.001$). Additionally, there was a highly significant difference in the changes in impedance between stimulated and non-stimulated electrodes ($P < 0.001$, ANCOVA interaction) with a greater decrease in impedance over time on the non-stimulated electrodes. Over 1500 days, the impedance on the stimulated electrodes decreased by 79% while the non-stimulated electrode impedances decreased by 85%. It should be noted that the median impedances on the platinum electrodes in motor cortex were initially much higher than the SIROF electrodes in somatosensory cortex (S Negi et al., 2010). Impedance measurements on individual electrodes were often highly variable from day to day, making the comparison of individual electrodes to group median values impossible. Electrode 19, the most stimulated electrode, was one electrode with high intersession variance, making comparisons of its impedance to other stimulated or non-stimulated electrodes uninformative. We suspect that this was due to issues related to the specific connector and headstage used to measure impedances.

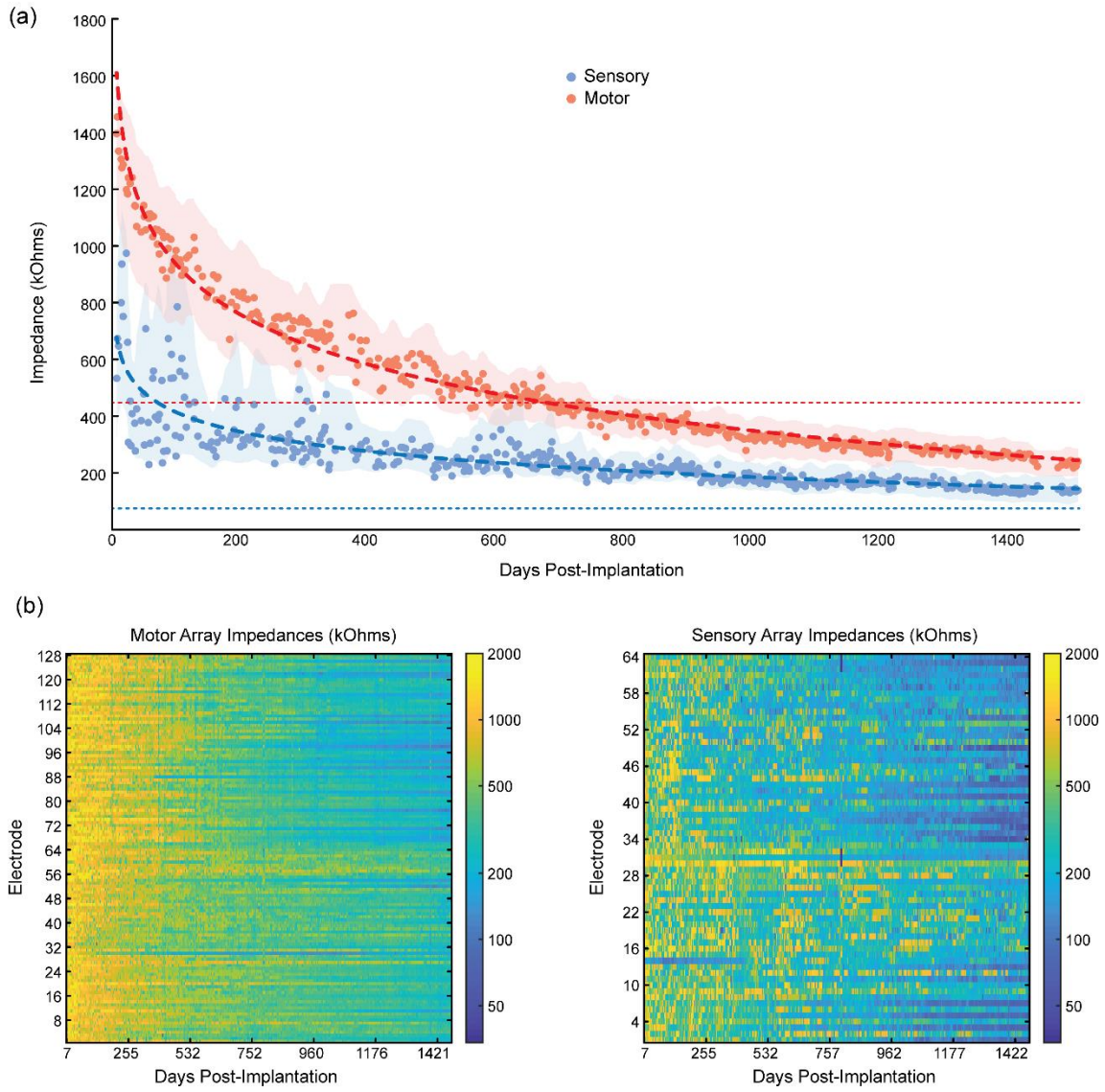

Figure 9: Electrode impedance over time. A) Plots for impedances of all electrodes plotted against days since implantation for the stimulated sensory array (blue) and the non-stimulated motor array (red). Each point represents the median impedance for the test day. Dotted lines represent the linear regression of the data with log-transformed days. Shaded areas represent the smoothed interquartile range for each data set. B) Heatmaps for impedances of all electrodes plotted against days since implantation for the motor array (left) and sensory array (right). Color maps were log transformed to better illustrate changes over time.

4.3.3 Detection Threshold Stability

Detection thresholds were measured in four different time ranges: near Day 100, Day 500, Day 1000, and Day 1500. Due to limits on the participant's time in the lab for each test session, these measurements were typically taken across multiple test sessions. Nearly all of the implanted electrodes (n=64) were tested within each time range with 54 electrodes tested around Day 100, 61 electrodes around Day 500, 58 electrodes around Day 1000, and 53 electrodes around Day 1500. Some electrodes were excluded from detection due to high voltages during the interphase period at the beginning of the test session. Surprisingly, we saw that over the course of the study, the median detection thresholds decreased by about two-thirds, from 31.5 μA at Day 100 (IQR: 22.8-49.6 μA), to 15.8 μA at Day 500 (IQR: 9.0-24.9 μA), 12.4 μA at Day 1000 (IQR: 8.1-18.0 μA), and 10.4 μA at Day 1500 (IQR: 7.4-16.6 μA) (Figure 10A). We found that detection thresholds around Day 100 were significantly higher than Days 500, 1000, and 1500 ($P < 0.001$, Kruskal-Wallis test with Tukey's HSD post-hoc test) but other sessions were not significantly different from each other ($P > 0.05$, Kruskal-Wallis Test with Tukey's HSD post-hoc test). We also assessed whether the detection thresholds were spatially organized on the arrays (Figure 10B) and found that for all test ranges except Day 100, there was significant clustering ($P < 0.05$, Moran's I with z-test). This indicates that for most of the implant duration, the detection thresholds were not randomly distributed across the array and electrodes with high thresholds tended to be near other electrodes with high thresholds. Finally, we measured the detection thresholds on a subset of electrodes more frequently throughout the study. These electrodes spanned the two sensory arrays but were otherwise chosen arbitrarily. Changes over time were quantified with regression of the individual electrode detection data using a log-transformed time axis. Of the eight tested electrodes, the detection threshold on four electrodes decreased significantly over time ($P <$

0.05, Figure 10C, indicated with *) while no electrode had significant increases. The analysis of the group data in Figure 10A showed that after Day 500 there was no further decreases in detection thresholds. To examine whether this was true on the eight electrodes where we had considerably more measurements, we performed linear regression for data collected after Day 500. We found that on five electrodes there was a significant change in detection thresholds after Day 500 ($P < 0.05$). Four of these were significant decreases in thresholds and one was a significant increase. However, these changes were all small, with slopes of -5.4, -4.2, -3.2, -2.2, and 2.0 μA/year.

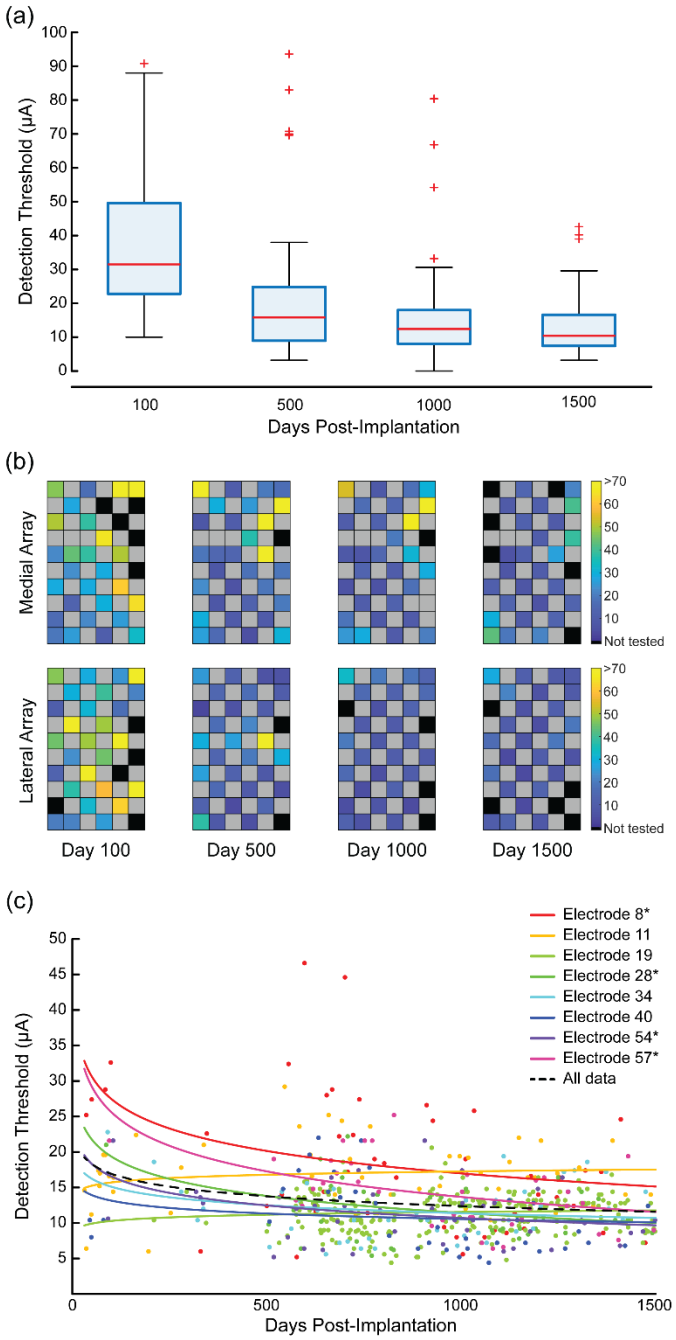

Figure 10: Detection thresholds for stimulated electrodes since implantation. A) Box plots for the median threshold values from each test range. The four time ranges are shown chronologically from left to right. B) The measured detection thresholds for each electrode plotted to the array as a heat map. Black spaces represent electrodes that were not tested. Grey spaces represent electrodes that were not wired due to technical constraints. The color bars show the detection threshold values in microamperes. C) The measured detection thresholds for eight electrodes are plotted over time. Each point represents the measured threshold for the given electrode and post-implant day.

4.3.4 Material Stability

Two IrOx arrays implanted in P2 posterior parietal cortex (prior to P2 implants in somatosensory cortex) received a low amount of total charge (all electrodes <160 μC). Each of the two stimulated IrOx arrays had 60 electrodes, half of which were used for stimulation. Preimplant optical images of the arrays did not show any variation between arrays. The stimulated electrode sites are arranged primarily in a checkerboard fashion. SEM shows that the lateral array had a high degree of tip and shank degradation (Figure 11A). Interestingly, tips and shanks showing visible damages appeared to coincide with the electrodes that were used for stimulation. Furthermore, EDS revealed that stimulated tips had lower iridium content than non-stimulated tips (Figure 11B). The loss of metallization for the lateral stimulating array occurred only on the electrodes used for stimulation. The medial array did not show this pattern (Figure 11C). The damage scores for each electrode tip and shank are summarized in the Figure 11D,E. The checkerboard pattern of damages of the lateral array is clearly seen, which correspond very well with arrangement of the stimulation electrodes. The medial stimulating array has overall much less observable material damage but more tissue encapsulation. Of the 62 electrodes used for stimulation on both arrays, 56 were analyzed, of which 23 had notable tip degradation, 21 of which were located on the lateral electrode array. Metal loss, and the corresponding decrease in iridium signal, was not observed on any non-stimulated electrodes.

Delivered charge and measured interphase voltages were compared to the material degradation. The amount of stimulation provided was quantified by both the total charge delivered and number of pulses delivered. Although the mean amount of charge injected on the lateral array was greater, it was not significantly different than the mean charge injected on the medial array

(Mann-Whitney test, $p = 0.22$). The medial array contained the three electrodes with the most charge delivered, none of which displayed observable material degradation.

Additionally, we found that there was a significant relationship between the total charge injected at voltages exceeding -0.6V (Figure 11G) and the tip score ($p = 0.025$, crit-$p = 0.034$, logistic regression) and shank category ($p = 0.023$, crit-$p = 0.034$, logistic regression) on the lateral stimulating array. There was no relationship between total charge injected at voltages less than -0.6V and tip category ($p = 0.60$, logistic regression) or shank category ($p = 1$, logistic regression) on the medial array.

When comparing the recording quality (Vpp) (Figure 11H) between the damaged and non-damaged electrodes on the two stimulation arrays after excluding the encapsulation sites, we found no significant differences.

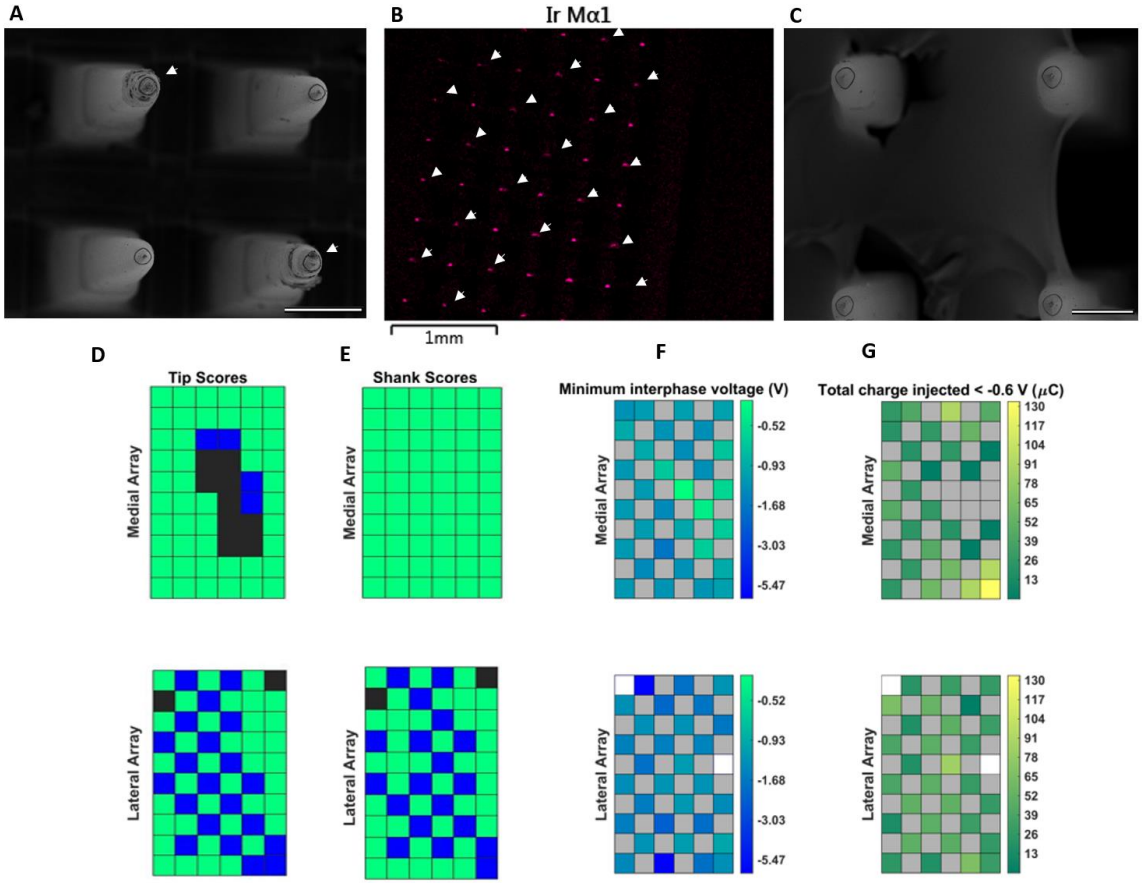

Figure 11: A small amount of charge caused damage on one of the implanted arrays but not the other. *SEM and EDS images here were provided by Kevin Woeppel from Tracy Cui's lab*. A) SEM image of the lateral array, indicating the stimulated electrodes with white arrows. B) EDS of the stimulating electrodes for the lateral array showing presence of iridium. White arrows indicating the stimulated sites. C) SEM image of the medial stimulating array tips. No differences were observed between the non-stimulated and stimulated tips on this array. D,E) Arrays showing the measured material properties on the stimulation arrays including tip categories (D) and shank categories (E). Green spaces show electrodes categorized as undamaged/unencapsulated, blue spaces show electrodes categorized as damage/encapsulated, and black spaces show electrodes that were excluded from analysis. F,G) Medial (top) and lateral (bottom) stimulating arrays showing (F) minimum interphase voltage (G) and total charge injected below -0.6V. The color bar for the minimum interphase voltages is log-transformed to emphasize differences between electrodes. Grey spaces indicate unwired electrodes. White spaces indicate wired electrodes that were never stimulated.

4.4 Discussion

Microstimulation in the somatosensory cortex of a person using SIROF-coated Utah microelectrode arrays can evoke detectable sensations for 1500 days. We found that stimulated electrodes maintained a higher SNR than non-stimulated electrodes throughout the length of the implant, although the SNR on stimulated electrodes declined at a faster rate. In fact, stimulated electrodes were far more likely to retain the capacity to record high-amplitude neurons after 1500 days than electrodes that had never been stimulated. Indeed, 50% of the stimulation electrodes recorded high-amplitude neurons within the first 100 days and 25% recorded high-amplitude neurons in the last 100 days, representing a 50% loss. However, on non-stimulated electrodes in the motor cortex, 70% recorded high-amplitude neurons within the first 100 days, but just 20% recorded high-amplitude neurons in the last 100 days, representing a 70% loss. Electrode impedances for stimulated electrodes had a significantly smaller decrease over time. Finally, and perhaps most importantly, stimulation detection thresholds continually decreased for 1500 days, indicating an improvement in the ability to elicit sensations with ICMS.

Additionally, we found that for electrodes implanted for a much shorter period of time, small amounts of current, particularly current at low voltages, could result in damage on some electrodes.

4.4.1 Stimulation Safety Limits

The safety limits on the stimulus parameters used in this study, such as pulse amplitude and frequency were based on a series of studies in non-human primates investigating the effects of stimulation on safety at the electrode tissue interface (K. H. Chen et al., 2014; S. Kim, Callier,

Tabot, Tenore, et al., 2015). However, these pulse parameters have not always been shown to be safe (Kane et al., 2013; D. B. McCreery et al., 1990; D. McCreery et al., 2010; Sandeep Negi, Bhandari, Rieth, van Wagenen, & Solzbacher, 2010; Sandeep Negi, Bhandari, van Wagenen, et al., 2010; Parker et al., 2011; Patrick J Rousche & Normann, 1998). Of particular note, a study of chronic microstimulation in the cat cortex showed that continuous stimulation at even at the low level of 4 nC/phase (equivalent to a stimulation amplitude of 20 μA with the 200 μs pulse width we used in this study), led to a loss of neurons around the electrode tips (D. McCreery et al., 2010). While we regularly exceeded this stimulation amplitude and use the full amplitude range up to 100 μA on implanted electrodes, we limited the duty cycle to a maximum of 15 seconds of continuous stimulation, at which point stimulation would be disabled for an equivalent amount of time. This may be why stimulation with these parameters did not lead to measurable deleterious effects on electrodes or evoked sensations.

4.4.2 Recording Signal Quality

It is well known that signal quality deteriorates on recording electrodes over long periods of time (Barrese et al., 2013; Bullard, Hutchison, Lee, Chestek, & Patil, 2019; C. Chestek et al., 2011; Downey et al., 2018; Suner et al., 2005). In this study, we found similar decreases in signal quality over time on both stimulated and non-stimulated electrodes. Importantly, across 1500 days we saw a 37% decrease in the peak-topeak voltage on the stimulated electrodes, while the peak-to-peak voltage on non-stimulated electrodes decreased by 46%. For comparison, Chestek et al. 2011 reported a 28.2% and 47% decrease in unit amplitude in two implanted non-human primates within the first two months after implant while Barrese et al. 2013 showed an average decrease in the signal amplitude of about 12% across 27 implanted non-human primates over 1000 days on

viable electrodes. However, about half of electrodes were excluded from analysis because they were considered not viable, meaning the peak-to-peak voltage fell below 40 μV. Our results are consistent with these and other studies showing that signal quality decreases over time.

However, interestingly we saw a significantly greater decrease in both the peak-to-peak voltage and the number of high-amplitude recordings on non-stimulated electrodes. These findings suggest that, at a minimum, ICMS did not additionally contribute to decreases in recording quality over time and may actually improve the longevity of high-amplitude recordings. Previous work has posited that stimulation can rejuvenate the electrode-tissue interface, resulting in increased SNR through an improvement in signal amplitude and decreased impedances (M. D. Johnson, Otto, & Kipke, 2005; Otto, Johnson, & Kipke, 2006). This rejuvenation effect could be related to the preservation of high amplitude recordings on stimulated electrodes that we observed.

However, our results showed a steeper decline in SNR over time on stimulated electrodes compared to non-stimulated electrodes, although the SNR itself was higher on stimulated electrodes than non-stimulated electrodes. Furthermore, we saw that the impedance on stimulated electrodes declined at a slower rate than the impedances on non-stimulated electrodes. Impedances however were difficult to compare between stimulated and non-stimulated electrodes since these electrodes contained different materials with different impedance properties, and stimulated electrodes maintained lower impedance values throughout. The previous work suggesting a rejuvenation effect was focused on the short-term effects of stimulation on signal properties, with a maximum tested duration of eight days. Changes in the signal and impedance over this time scale may not reflect expected changes over many years. Another substantial difference between the previous work and this current study is the stimulus protocol. In the previous work, stimulation was held constant at 1.5 V for four seconds, and this pulse was only delivered once prior to all

signal and impedance measurements. Here, our stimulus parameters consisted of more typical stimulation protocols, including charge-balanced biphasic pulses with an initial cathodic phase lasting 200 μs. Stimulus trains were delivered at a maximum of 300 Hz for up to 15 seconds at a maximum amplitude of 100 μA over many years. The substantial differences in our stimulus protocols makes it difficult to assess similarities or differences in the results.

4.4.3 Impedances

Impedances on electrodes have been shown to increase immediately after implantation but decrease over long periods of time (Barrese et al., 2013; Kane et al., 2013; Parker et al., 2011; Torab et al., 2011). Our results similarly showed an increase from pre-implant impedance values and then a decrease in impedances across the 1500 days of implantation. While the impedances of the non-stimulated electrodes implanted in the motor cortex had a significantly greater decrease than the stimulated electrodes in the somatosensory cortex, this effect is likely related to the difference material properties of the electrodes in these two locations. Sputtered iridium-oxide electrodes have significantly lower impedances than platinum electrodes as a result of their significantly larger surface area, due in large part to the sputtering deposition process (S Negi et al., 2010). As a result, the impedances on the stimulation electrodes were much lower than the platinum electrodes shortly after implantation and therefore did not have as much range to decrease. Nevertheless, these data demonstrate that over 1500 days, including nearly 378 days of ICMS, the electrode impedances were well within ranges suitable for microstimulation. Increasing impedances, potentially as a result of electrode damage resulting from stimulation itself, would result in higher voltages at the electrode-tissue interface which could damage tissue (Cogan, 2008), or exceed the compliance voltage limits of the stimulator itself. Although differences in the

changes over time were significant, the difference in the percent change between stimulated and non-stimulated electrodes was small and may not be practically meaningful.

4.4.4 Detection Thresholds

Perhaps the most supportive demonstration of the long-term utility of microstimulation in somatosensory cortex was the observation that that sensory percepts could be consistently evoked over the length of implantation, with detection thresholds decreasing over time. Non-human primate studies had demonstrated that sensations could be evoked over periods of months without behavioral deficits using stimulation parameters higher than those used in this experiment (S. Kim, Callier, Tabot, Gaunt, et al., 2015; D. B. McCreery et al., 1986; Romo et al., 2000, 1998). This is, however, the first time a human participant has been implanted and tested with this protocol and it is promising for bidirectional BCIs that percepts can be reliably evoked and that detection thresholds themselves decrease over long periods time. Detection of stimulation could improve over time for a variety of reasons.

As we mentioned previously, stimulation could possibly provide rejuvenating effects on neural tissue, which could result in more responsive neurons. Stimulation over many years could also possibly result in neural plasticity resulting in stronger sensitivity to stimulation (Jackson, Mavoori, & Fetz, 2006). Additionally, the participant's familiarity with the stimulus detection task could have resulted in increased behavioral sensitivity.

We also demonstrated that the detection thresholds were spatially clustered on the electrode arrays. There are several possible explanations for this effect. First, if the arrays were not perfectly perpendicular to the cortical surface, or if the cortical surface was curved under the electrode, individual electrode tips on different parts of the array could be at different depths in the cortex, a

factor which is known to have an effect on detection thresholds (DeYoe, Lewine, & Doty, 2005; Tehovnik & Slocum, 2009). Additionally, localized tissue reactions could potentially affect the microenvironment around individual electrodes (Grand et al., 2010) and adjacent electrodes or different locations in somatosensory cortex could be differentially responsive to stimulation. Further work is needed to explore the mechanisms of increased stimulus sensitivity as well as spatial clustering of thresholds.

4.4.5 Material Stability

We implanted two IrOx arrays into the posterior parietal cortex of P2, which were explanted 182 days after implant and received small amounts of charge. Here, we found that even this small amount of stimulation induced damage on one of the two devices. On the lateral array, de-metallization was visible under SEM and detected by EDS only on the stimulated electrodes, indicating that stimulation was the cause of the metal loss. The reason that stimulation caused material damage on the lateral array but not the medial array is unclear. One notable difference between the lateral and medial array is that the medial had higher degree of tissue encapsulation. This can be a result of a higher degree of vascular damage or less stable fixation *in vivo*. While the specific reason for this cannot be determined, this encapsulation resulted in subsequent decreases in impedance. The decrease in impedance then could have resulted in more positive voltage excursions during stimulation, decreasing the likelihood of material damage. Indeed, we found that the lateral array had more negative interphase voltages (mean = -1.7V) when compared to the medial array (mean = -1.1V).

More material damage was found on the lateral arrays which experienced higher average maximum cathodic interphase voltage amplitude. The interphase voltage is analogous to the

maximum cathodic electrode potential (E_{mc}) measured during charge injection limit (CIL) experiments performed *in vitro*. E_{mc} with values more negative than -0.6V (vs Ag/AgCl) are often considered to be unsafe due to irreversible water hydrolysis occurring at the electrode which could cause hydrogen gas production and pH increases (S Negi et al., 2010). Such reactions could lead to delamination of the IrOx coating even with a small number of pulses. We do not expect the median interphase voltage to be directly comparable to *in vitro* CIL measurements due to the two-electrode setup and increased variables introduced from the biological environment, but we expected the general relationship between voltage and interfacial reactions to hold. We found that the mean maximum voltage measured on both arrays exceeded -0.6V (mean lateral = -1.7 V, mean medial = -1.1 V) with the lateral array experiencing higher voltage excursion on average. Furthermore, we found a significant correlation between the charge injected below -0.6V and damage on the lateral stimulating array. These results indicate that stimulation, beyond a certain voltage threshold, may damage electrodes in a charge dependent manner.

It should be pointed out that some of the electrodes on the medial array experienced the highest voltage excursions but did not show material damage. One potential explanation is that the stimulation on the lateral array only weakened the adhesion of the IrOx coating and the coating was not fully stripped from the electrode until or after explantation. Alternatively, variations could also be a result of batch-to-batch difference in fabrication where the lateral array received poorly adhered IrOx coating. Notably, the electrodes damaged by stimulation did not perform significantly worse in recording than the undamaged electrodes from the Vpp point of view. This surprising result indicates that despite the IrOx delamination and insulation cracking, the electrode is capable of recording the neural signals.

The biocompatibility of IrOx coatings has been widely studied and validated for stimulation and recording applications (Cogan, 2008; S Negi et al., 2010; Sandeep Negi, Bhandari, Rieth, et al., 2010). In our results on signal quality and impedances, we didn't see additional degradation caused by stimulation. Based on our observations here, this could be because a) the material damage caused by stimulation is idiosyncratic, and stimulation didn't result in damage on these implanted arrays or b) material damage caused by stimulation had no effect on the electrode's ability to record or stimulate. Discerning between the two is difficult, as studying the *in vivo* properties of the electrodes in parallel with the material properties is not possible in humans. Analysis will need to be conducted on these arrays that received much higher levels of stimulation after explant. Additionally, further animal studies using the stimulus parameters used in our study and assessing damage and changes in recording over time could provide insight here.

4.4.6 Study Limitations

Although these results are supportive of the long-term utility of microstimulation in the somatosensory cortex as a component of implanted BCIs, we have only tested this in one participant. Future implantations will need to be similarly evaluated to determine if signal quality and detection thresholds are stable over long periods of time. Furthermore, this study gives a general overview of stability on electrodes that have been stimulated as compared to electrodes which have not been stimulated but does not delve deeply into how the amount of stimulation delivered on each electrode might impact signal quality, impedances, or detection thresholds. We have provided results for a single electrode which was stimulated much more frequently than any other electrode due to its involvement in many of our bidirectional BCI paradigms. Its signal quality over time did not deviate significantly from other stimulated electrodes except for noise,

which had greater decreases over time. Another possible limitation is that the stimulation delivered as part of this experiment may be much less than what would be provided in a deployable BCI system. However, as stated previously, we have not seen any notable differences between electrodes based on the amount of stimulation they have received. As mentioned previously, the electrodes that were provided stimulation were coated with iridium oxide while the electrodes that were not provided stimulation were coated with platinum. If there are differences in how these materials degrade over time regardless of stimulation, comparisons can be difficult to make. For better comparison, future implants should have iridium oxide coated tips on all electrodes. Another consideration is that stimulated electrodes were implanted in somatosensory cortex while non-stimulated electrodes were implanted in motor cortex. Neurophysiological differences in these two areas could possibly affect the results. For example, layer 5 of motor cortex contains large Betz cells while layer 4 of somatosensory cortex contains smaller pyramidal cells (Rivara, Sherwood, Bouras, & Hof, 2003). This difference in cell type is the likely cause of the initially high-amplitude signals recorded from motor cortex. Whether neuroanatomical differences in motor and somatosensory cortex could have differential effects on the response to microstimulation or the presence of implanted devices over many years is unknown. Additionally, the material analysis shown here is not related directly to the other metrics because the material stability was based on electrodes implanted for a much shorter period of time and receiving much less stimulation. Post-explant analysis will additionally need to be conducted on the second set of implants when they are removed for further analysis.

4.4.7 Conclusion

Overall, these findings indicate that electrodes receiving intracortical microstimulation in somatosensory cortex can maintain recording quality as well, if not better, than non-stimulated electrodes in motor cortex and continually elicit sensory percepts with stimulation over 1500 days. While this time frame may still be a relatively short in the context of a life-long implantation, demonstrating stability at these time points is a necessary step to support the continued development of these systems. Furthermore, we found idiosyncratic effects of stimulation on material integrity, where small amounts of stimulation were able to drive damage under certain circumstances. However, this material damage did not seem to correlate with recording quality. These findings are promising for the field of neural prostheses and specifically sensory restoration and indicate that implanted microelectrodes for sensory restoration is plausible for clinical application.

5.0 Signal Metrics and Evoked Sensations in a Second Participant

The previous chapter focused on stability metrics or both recording and stimulation in participant P2, who has been implanted for over 1500 days. Participant P3 has been implanted for much less time, making it more difficult to assess how recording quality, stimulation effects, and the interaction between them have changed over time. Nevertheless, here, we document these same data in P3 and report on several interesting and important differences. These same metrics will need to be measured over much longer periods of time for more direct comparison between both participants.

5.1 Methods

Data for this study were collected for 321 days after implantation in P3. Typically, experiments were conducted once or twice a week. Experimental sessions were typically three-hours long, although stimulation was not used in every session or for all three hours. Across the 321 implant days, experiment sessions were performed on 68 days, 32 of which involved stimulation.

5.1.1 Stability Metrics

To quantify the stability of stimulated electrodes in somatosensory cortex, we measured recorded signal quality, electrode impedances, and stimulation detection thresholds over time.

Signal quality and impedance were compared between stimulated electrodes and non-stimulated electrodes. Recording quality was evaluated using four metrics: (1) the number of high-amplitude recordings, (2) peak-to-peak voltage, (3) noise, and (4) signal-to-noise ratio.

5.1.2 Signal Quality

Neural activity recorded at rest was processed offline in MATLAB (Natick, MA) to measure the number of high-amplitude recordings, peak-to-peak voltage, noise, and signal-to-noise ratio (SNR) over time. The peak-to-peak voltage was calculated individually for every snippet. Only the snippets with peak-to-peak voltages within the top 2% on a given electrode were used for analysis. This method was used to isolate the largest neural recordings and provide an unbiased estimate of the capacity of each electrode to record signals. The largest 2% of the snippets for each electrode were averaged and the peak-to-peak voltage was calculated. If the firing rate of all the snippets on any electrode was less than 1.67 Hz or the peak-to-peak voltage of the averaged signal was less than 30 μV, the electrode was excluded from analysis. Electrodes containing snippets which had peak-to-peak voltages over 100 μV were considered electrodes that contained high-amplitude recordings. The noise metric was calculated as three times the standard deviation of the first five-time samples of all action potential snippets. SNR was calculated as the magnitude of the peak of the averaged waveform divided by the calculated noise. The filter used was fa first order 750 Hz high-pass Butterworth filter.

5.1.3 Surveys

Surveys were conducted on a regular basis in P3. During a survey, each enabled electrode was stimulated sequentially using a 1-s pulse train at 60 μA and 100 Hz. These parameters were selected because they were typically able to evoke sensations consistently while remaining well below our maximum stimulus current amplitude of 100 μA. Surveys were conducted to quantify stimulus-evoked tactile percepts. No visual or auditory cue was provided to the participant to indicate when stimulation was occurring. The participant was instructed to indicate when a sensation was detected, at which point progression through the trial was paused. The participant verbally reported when he detected a sensation, and the pulse train was repeated as many times as necessary for the participant to be able to accurately describe the location and quality of the sensation. A drawing of the hand was partitioned into different segments and the participant reported on which segments the sensation was felt. The participant also used a tablet and stylus to circumscribe the precise areas where sensation was felt on a map of the hand. The data presented here represents data collected from 11 surveys. Seven of these surveys were conducted on all available electrodes, four were only on conducted on a subset of electrodes.

5.2 Results

5.2.1 Projected Fields of Evoked Sensations

Electrodes were implanted in participant P3 based on preoperative imaging to try to target the fingers (Figure 12A). We measured the locations of sensations evoked by ICMS in P3 using a

tablet interface (Figure 12B). We found that electrodes on the lateral array generally evoked more sensations on the index finger, P2, and thumb regions. The electrodes on the medial array evoked more sensations on the middle finger, ring finger, and P5 region. This corresponds generally to known somatotopy, although it does not necessarily align with expectations based on preoperative imaging. Additionally, most sensations reported on the fingers were not on the tip of the fingers, which was the desired location of evoked sensations. We found that the number of electrodes which evoked sensation increased over time, with 27 electrodes evoking sensation on our first full survey (post-implant day 44) and 38 electrodes evoking sensation in our most recent full survey (post-implant day 293). If the number of electrodes with evoked sensation will continue to increase and if the projected fields on these individual electrodes will remain stable over time remains to be seen with more data collected over longer periods of time.

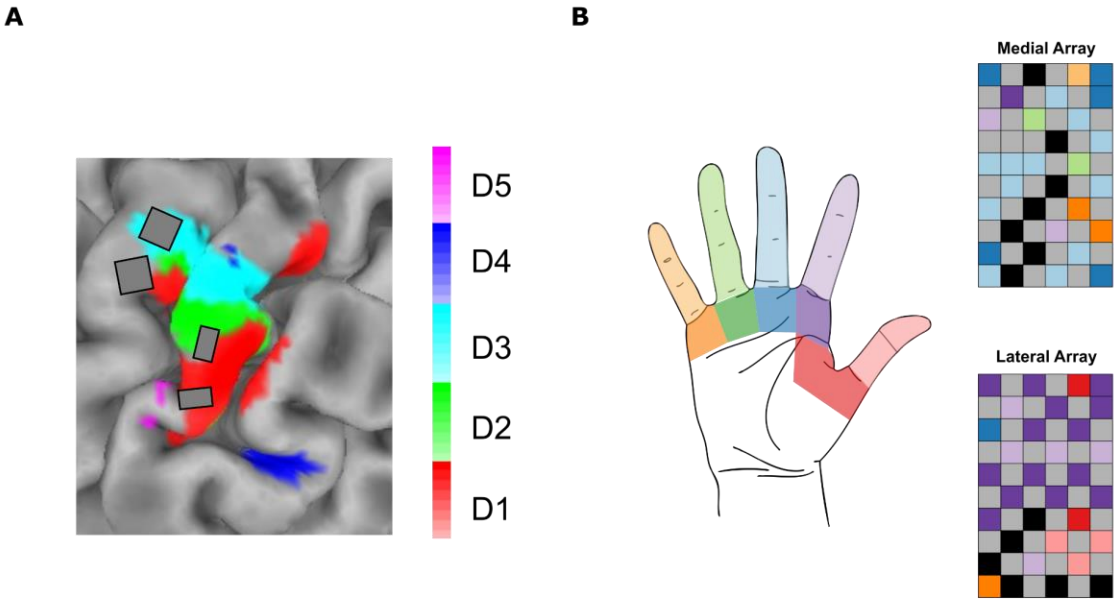

Figure 12: Implant locations and projected fields in P3. A) (Image provided by Fang Liu) Microelectrode array implant location mapped onto preoperative imaging. Each gray square represents a different microelectrode array. Each color represents the mapped sensation of a different digit (D1-D5). B) The most reported projected field location for each electrode from survey data.

5.2.2 Signal Stability

We looked at signal stability on both the stimulated arrays in somatosensory cortex and non-stimulated electrodes in motor cortex (Figure 13). We saw an initial increase across the first 65 days post-implant followed by a decrease on all electrode arrays. However, we saw a significantly larger decrease on the stimulated somatosensory electrodes in terms of high-amplitude recordings after day 65 (Figure 13A, $p < 0.001$, ANCOVA interaction). At Day 331, high amplitude recordings were made on 55% of motor electrodes but only 15% of sensory electrodes. However, the change in Vpp was not significantly different over time after day 65 (Figure 13B, $p = 0.44$, ANCOVA interaction) although motor electrodes maintained a higher Vpp overall. At Day 331, the median Vpp was 81.2 μV on motor electrodes and 53.6 μV on sensory electrodes. Interestingly the noise showed a significantly larger decrease on stimulated sensory electrodes as compared to non-stimulated motor electrodes (Figure 13C, $p = 0.0002$, ANCOVA interaction) which also resulted in a significant difference in how SNR changed over time (Figure 13D, $p = 0.0012$, ANCOVA interaction) where SNR on non-stimulated motor electrodes decreased more than SNR on stimulated sensory electrodes, although motor electrodes still maintained an overall higher SNR. At Day 331, motor electrodes had a median SNR of 2.83, while sensory electrodes had a median SNR of 2.45.

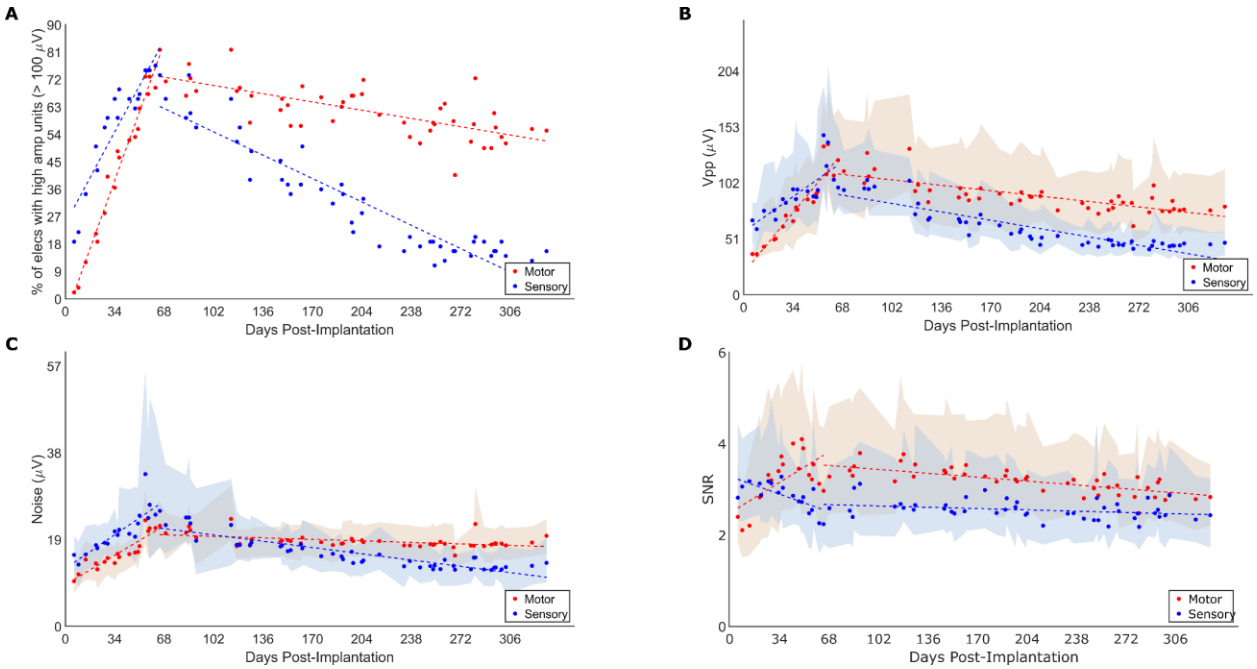

Figure 13: Signal stability in P3. Signal quality plots over 331 days of implant for participant P3 with electrode arrays divided into stimulated sensory arrays and non-stimulated motor array. Dotted lines represent linear regression of the data for either day 1 to 65 or day 65 to 331. Shaded areas represent interquartile ranges. A) The percent of electrodes with high amplitude waveforms. B) Median peak-to-peak voltage. C) Median noise. D) Median signal-to-noise ratio.

5.2.3 Detection Thresholds

We measured detection thresholds across all electrodes around day post-implant 100 and measured detection thresholds more continuously across a subset of six electrodes over time. We found that the median detection threshold across all electrodes was 18.8 µA at day 100 (Figure 14A). We also found that over the 331 days post-implant, electrodes that were measured continuously showed no change in thresholds for individual tested electrodes (Figure 14B, $p > 0.05$, linear regression) or for the median across all six tested electrodes ($p = 0.68$, linear regression).

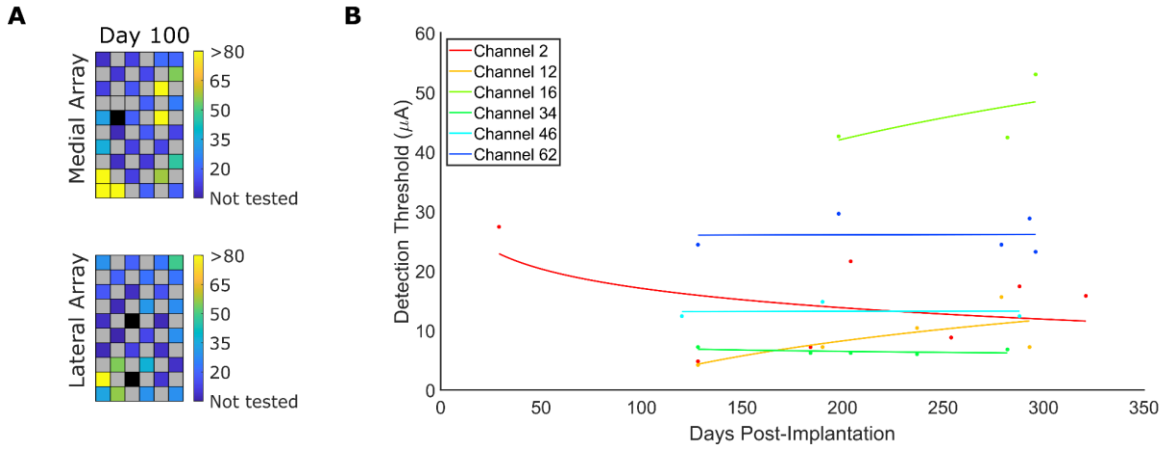

Figure 14: Detection thresholds in P3. Detection thresholds measured across all implanted electrodes around day post-implant 100. Colors represent the measured detection threshold, where the maximum threshold was cut-off at 80 µA. Gray squares represent unwired electrodes and black squares show electrodes that weren't tested. B) Detection thresholds over time for six electrodes that were tested more continuously up to day post-implant 331. Solid lines show log-transformed linear regression fits for the data.

5.3 Discussion

5.3.1 Signal Stability

We found interesting differences between P2 and P3 in terms of signal stability. Previously we found that the number of electrodes with high amplitude recordings decreased more over time on non-stimulated motor electrodes than stimulated sensory electrodes in P2. However, we saw the opposite effect in P3, where stimulated sensory electrodes showed much larger decreases in the number of high amplitude recordings. Interestingly, the percent of electrodes with high amplitude recordings on stimulated sensory electrodes was higher in P2 at Day 1500 (27%) than the percent of electrodes in P3 at Day 331 (16%). This effect was reversed for non-stimulated motor electrodes, where the percent was higher in P3 at Day 331 (55%) than P2 at Day 1500 (19%). The reason for these differences is difficult to know, but is unlikely a direct effect of stimulation, since P2 received much more stimulation over 1500 days than P3 did over 331 days. We also saw that the SNR decreased more over time on the non-stimulated motor electrodes than the stimulated sensory electrodes, although the motor electrodes maintained a higher SNR overall throughout (Figure 12). This again is the opposite of what was observed in P2, where the stimulated sensory electrodes showed more significant decreases over time but maintained a higher SNR throughout (Figure 7).

Although it is difficult to assess the reason for these opposite observations in both participants, there are some important differences to note. The first is that P2 had platinum electrodes implanted in motor cortex while P3 had iridium oxide arrays in motor cortex. Material differences could explain differences between the trends on the motor arrays over time. However, the trends in the motor cortex implants were actually more similar between participants, while

there were large deviations between the sensory electrodes, which were iridium oxide in both participants. It seems unlikely then that material differences explain our observations. Another important difference is that the signals recorded in P3 were collected using Cereplex E connectors while signals in P2 were collected with patient cables (Blackrock Microsystems). We have noted differences in both the signal amplitude and impedances recorded with Cereplex E connectors, which could be related to changes in signal over time. However, it seems that the Cereplex E connectors are unlikely to produce larger changes on a specific set of arrays, so it seems unlikely that this should affect differences between motor and somatosensory electrodes over time. The data reported here for P3 were also collected for a much shorter period of time. Although the trends in P3 still do not seem to match the trends in P2, we should observe the signal over a similar length of time for full comparison. Differences between participants then are difficult to explain and require further investigation in more participants.

5.3.2 Detection Threshold Stability

Detection thresholds in P2 showed a significant decrease from day post-implant 100 to day post-implant 500, but were stable after that point. Additionally, individual electrodes that were measured more continuously showed a significant decrease over time, with the most substantial changes occurring in the earlier post-implant days. In P3, we only collected all detection thresholds once at day 100 since they have not been implanted for a full 500 days. Interestingly, the median threshold measured at day 100 in P3 (18.8 μA) was more similar to the median threshold measured at day 500 in P2 (15.8 μA) than day 100 (31.5 μA). This may indicate that the thresholds in P3 dropped more quickly and are thus less likely to show significant decreases over time. However, our measurements in P3 are limited, particularly on the six electrodes we measured more

continuously which only have 4 to 7 measures total. We will have to continue to monitor the thresholds over time to understand how these trends compare across participants. However, the fact that the thresholds are low and stable in both participants is promising for the future application of these devices.

5.3.3 Projected Fields of Evoked Sensations

We found that the projected fields in P3 followed a general somatotopy, similar to what was observed in P2. Interestingly, in both participants, evoked sensations were mostly localized between the palmar regions and knuckles of the finger, although the arrays were implanted in a location with the goal of evoking finger-tip sensations. Other labs have previously reported finger-tip sensations from similar implants (Fifer et al. 2020). These findings may suggest that higher resolution imaging is needed to more consistently target finger-tip areas. In both participants, we also saw the number of electrodes that evoke sensation increase over time. In P2, we already had 28 electrodes that evoked sensation at day post-implant 44, while we only had 7 electrodes evoke sensation in P2 at day 49 post-implant. In P2, most electrodes evoked sensation by day post-implant 630. More data will need to be collected in P3 over time to see if the number of electrodes continues to increase and how stable projected fields are over time.

5.4 Conclusions

We found that results in P3 collected over a much shorter period of time had agreed with P2 in some ways but also possessed some important differences. We found that signal increased

over a short period of time followed by a more continuous drop in signal over time in both participants. However, there were differences in how the motor electrodes and somatosensory electrodes changed relatively in each participant. We found detection thresholds were low and stable over time in both participants, but P3 showed lower thresholds and more detectable electrodes earlier in the implant, while P2 showed large decreases in thresholds and increases in electrode evoking sensation in the first 500 days. Finally, we found that electrodes evoked sensations localized to the hand that followed a general somatotopy in both participants, although the specific locations of sensation were different. In order to fully understand how these trends behave over time, we will need to collect more data over longer periods of time in P3 and look at similar data in other participants for comparison.

6.0 Effects of Stimulus Parameters on Evoked Intensity and Quality

This chapter is taken directly from a first authorship manuscript currently available on bioRxiv and in revision at eLife titled "Perceptual responses to microstimulation frequency are spatially organized in human somatosensory cortex" (C. Hughes et al., 2020).

Microstimulation in the somatosensory cortex can evoke artificial tactile percepts and can be incorporated into bidirectional brain-computer interfaces (BCIs) to restore function after injury or disease. However, little is known about how stimulation parameters themselves affect perception. Here, we stimulated through microelectrode arrays implanted in the somatosensory cortex of human participants with cervical spinal cord injury and varied the stimulus amplitude, frequency and train duration. Increasing the amplitude and train duration increased the perceived intensity on all tested electrodes. Surprisingly, we found that increasing the frequency evoked more intense percepts on some electrodes but evoked less intense percepts on other electrodes. These different frequency-intensity relationships were divided into three groups which also evoked distinct percept qualities at different stimulus frequencies. Neighboring electrode sites were more likely to belong to the same group. These results support the idea that stimulation frequency directly controls tactile perception and that these different percepts may be related to the organization of somatosensory cortex, which will facilitate principled development of stimulation strategies for bidirectional BCIs.

6.1 Introduction

The behavioral effects of ICMS in somatosensory cortex have been studied in detail in non-human primates (NHPs) (Dadarlat et al., 2014; S. Kim, Callier, Tabot, Gaunt, et al., 2015; S. Kim, Callier, Tabot, Tenore, et al., 2015; Romo et al., 2000, 1998). However, animals are limited in their ability to perform certain psychophysical tasks. NHPs can learn to discriminate between two or more stimuli, and their ability to perform these tasks can provide insight into how stimulus parameters affect sensory perception. However, they can never describe the qualitative nature of the sensory percepts they are experiencing, nor can they be trained to perform more complex psychophysical tasks such as magnitude estimation. NHP studies can therefore lead to hypotheses about how stimulus parameters affect qualitative aspects of perception, but only human studies can investigate these directly.

Limited work has been conducted in humans using ICMS of somatosensory cortex to restore sensation (Armenta Salas et al., 2018; Fifer et al., 2020; S. N. Flesher et al., 2016). From these studies we know that ICMS can evoke tactile sensations that are perceived to originate from the hands (Fifer et al., 2020; S. N. Flesher et al., 2016) and arms (Armenta Salas et al., 2018) and that the stimulation locations in the cortex that elicit these percepts agree with known cortical somatotopy (Penfield & Boldrey, 1937). Participants reported naturalistic sensations such as “pressure” and “touch” (S. N. Flesher et al., 2016) as well as “squeeze” and “tap” (Armenta Salas et al., 2018), but the quality and naturalness varied between stimulated electrodes within each participant. Additionally, all studies found that increasing the stimulus current amplitude consistently increased the perceived intensity of the tactile percepts. The effect of stimulus pulse frequency has been less studied, although low frequencies may require higher amplitudes to evoke a detectable percept (Armenta Salas et al., 2018).

It has been frequently suggested that increasing the stimulus frequency increases the perceived intensity of a stimulus train. Increasing the pulse frequency of ICMS reduced the current amplitude required to evoke a detectable percept in NHPs (S. Kim, Callier, Tabot, Gaunt, et al., 2015; Romo et al., 2000, 1998) and rats (Butovas & Schwarz, 2007; Semprini, Bennicelli, & Vato, 2012). This was thought to indicate that increasing pulse frequency increased perceived intensity. Additionally, increasing amplitude biased NHPs (Callier, Brantly, Caravelli, & Bensmaia, 2020) and rats (Fridman, Blair, Blaisdell, & Judy, 2010) towards selecting stimulus trains as having higher frequencies, providing further evidence that increasing pulse frequency increases perceived intensity. Perceived intensity also increases as stimulation amplitude and frequency are increased in human peripheral nerves (Graczyk et al., 2016) and human visual cortex (E. M. Schmidt et al., 1996). This is also true for mechanical stimuli where perceived intensity increased with increasing vibration frequency in able-bodied human participants using tactile input to the hand (Hollins & Roy, 1996; Muniak, Ray, Hsiao, Dammann, & Bensmaia, 2007; Verrillo, Fraioli, & Smith, 1969). This implies that both electrical and tactile stimulation with higher frequency components are perceived as being more intense. Our goal here was to understand if this same principle applied to ICMS of human somatosensory cortex and to evaluate whether perceptual qualities were affected by changes in stimulus pulse frequency.

In ongoing experiments, we implanted microelectrode arrays into the motor and somatosensory cortices of two participants (referred to as P2 and P3) with cervical spinal cord injuries to evaluate the safety and efficacy of bidirectional BCIs and to study sensorimotor control in humans. In P2, we delivered ICMS to somatosensory cortex, which evoked tactile percepts that felt like they originated from the paralyzed hand (Flesher et al., 2016). However, the percepts themselves varied considerably, from more natural sensations, such as touch and pressure, to less

natural sensations, such as vibration and tingle. In order to represent more complex and intuitive tactile inputs with ICMS, it is critical that we understand how stimulus parameters directly affect sensation.

We are particularly interested in how stimulus parameters, such as current amplitude, pulse frequency, and train duration change the perceived intensity of tactile percepts. The ability to control perceived intensity in a bidirectional BCI will be essential, as modulated sensory feedback is crucial for object interaction (Roland S Johansson & Flanagan, 2009; D. A. Nowak et al., 2013). While grasp contact could be relayed by simple on-off stimulation, conveying grip force, which is essential for grasp stability, efficiency and precision (Godfrey, Bianchi, Bicchi, & Santello, 2016; D. A. Nowak, Glasauer, & Hermsdörfer, 2004; D. A. Nowak & Hermsdörfer, 2006), requires the ability to modulate the perceived intensity of a stimulus. We sought to assess the effects of changing the stimulus pulse frequency on several perceptual metrics in two participants, P2 and P3, and expected to see increases in the perceived intensity as the stimulus pulse frequency.

6.2 Methods

6.2.1 Magnitude Estimation

We assessed the effect of stimulus parameters on perceived intensity using a magnitude estimation task. To test the potential effect of pulse frequency on intensity in P2, pulse trains were delivered for 1 s at 60 µA with frequencies of 20, 40, 60, 80, 100, 150, 200, 250 and 300 Hz. Following each pulse train, the participant was asked to report the magnitude of the perceived intensity on a self-selected scale. The participant was instructed to use values such that a value

twice as large as a previous value was twice as intense, and a value half as large was half as intense. These values typically ranged from zero to six. Each set of stimulus pulse frequencies was presented six times, with the presentation order randomized in each block. The responses from the first block were not used in the analysis to allow the participant to establish a baseline for reporting for the session. Data collected on the same electrode over multiple sessions were aggregated for analysis. Data were connected with piecewise fits. We tested 29 total electrodes using this paradigm. Seven electrodes were tested in 3 to 6 sessions while 22 electrodes were tested in 1 to 2 sessions.

To increase the number of trials and decrease the time for data collection, we presented 20, 100, and 300 Hz at 80 μA in participant P3. We presented each frequency 21 times and removed the first trial. We found 22 of 23 tested electrodes showed a significant difference between intensities across tested frequencies (Friedman's test, $p < 0.05$). Data for each electrode was only collected once.

We also assessed the effect of changing the stimulus current amplitude on perceived intensity while the stimulus pulse frequency was held constant. The pulse frequency was set to 100 Hz, the train duration to 1 s, and the current amplitude ranged from 20 to 80 μA in 10 μA increments. Data were fit with a linear function. We tested nine electrodes for this paradigm. Finally, we assessed the effect of changing the stimulus train duration on perceived intensity. The stimulus pulse frequency and current amplitude were set to 100 Hz and 60 μA, respectively, and the train duration was set to 0.1, 0.2, 0.3, 0.4, 0.5, 0.75, 1, 1.5, and 2 s. Data were fit with a logistic function. We tested four electrodes for this paradigm. For current amplitude and train duration plots, the data were normalized to the median intensities of the set in which it was collected for visualization purposes.

To investigate the interaction between current amplitude and pulse frequency, we additionally tested frequency and amplitude pairs in P2. The train duration was set to 1 s, the current amplitude was set to 20, 50, or 80 μA, and the pulse frequency was set to 20, 100, or 300 Hz. All frequency and amplitude combinations were tested for each tested electrode six times, and the first trial was excluded from analysis. Each tested electrode was tested twice on two different test sessions, resulting in ten total trials for each frequency and amplitude pair. For analysis and plotting, we divided electrodes into the categories defined in the frequency magnitude estimation described previously. We tested two LFP electrodes, two IFP electrodes, and two HFP electrodes. We tested six electrodes for this paradigm, each measured twice.

6.2.2 Standard Detection Task

We conducted standard detection trials where the stimulus pulse frequency was changed while the stimulus current amplitude was held constant in P2. The current amplitude was set to 1.2X the detection threshold for each electrode measured at 100 Hz. The tested frequencies were 20, 100, and 300 Hz and each pulse frequency was presented 30 times. Pulse frequencies were interleaved randomly resulting in 90 trials per tested electrode. We tested four electrodes with this paradigm.

6.2.3 Surveys

Surveys were conducted once every month from the time the arrays were implanted in P2. During a survey, each enabled electrode was stimulated sequentially using a 1-s pulse train at 60 μA. These parameters were selected because they were typically able to evoke sensations

consistently while remaining well below our maximum stimulus current amplitude of 100 μA. In participant P2, surveys were conducted once a month at 100 Hz, but we collected additional surveys at 20 and 300 Hz. This resulted in 152 samples at 20 Hz, 621 samples at 100 Hz, and 85 samples at 300 Hz. Surveys were conducted to quantify stimulus-evoked tactile percepts. No visual or auditory cue was provided to the participant to indicate when stimulation was occurring. The participant was instructed to indicate when a sensation was detected, at which point progression through the trial was paused. The participant verbally reported when he detected a sensation, and the pulse train was repeated as many times as necessary for the participant to be able to accurately describe the location and quality of the sensation. A drawing of the hand was partitioned into different segments and the participant reported on which segments the sensation was felt. The participant also used a tablet and stylus to circumscribe the precise areas where sensation was felt on a map of the hand.

After the location of the percept was established, the participant reported the quality of the sensation using a list of predefined descriptors. The participant's response was documented by the experimenter and video recordings were also taken during all responses. If the participant felt that the sensation was not accurately described by the provided descriptors, his response was recorded, and the best approximation using the descriptors was used. The descriptors included a five-point scale for naturalness ranging from totally unnatural to totally natural, the location of the sensation on or below the skin surface, and an assessment of pain ranging from 0 to 10. The quality of the sensation was further assessed using the following descriptors: mechanical (touch, pressure, or sharp), movement (vibration or movement across the skin), temperature (warm or cool), and tingle (electrical, tickle, or itch). These descriptors were based on a previously described questionnaire (Heming et al., 2010). The participant could report multiple qualities for a single stimulus, and in

some cases, the subcategories (for example, electrical, tickle, or itch) could not be described. The participant also reported qualities that deviated from the descriptors. The participant developed four new descriptors that were not originally included, which often were combinations of the other descriptors. We attempted to reidentify these percepts in the context of a new questionnaire which was published during this study in consultation with the participant (L. H. Kim, McLeod, & Kiss, 2018). Three of these sensations were reidentified as "tapping," "buzzing," and "prick". One descriptor the participant reported, "sparkle," could not be reidentified with the new questionnaire. The participant described this percept as feeling like tapping that varied in intensity and moved around the projected field in a random manner. It should be noted that all percepts in our study were identified as tactile percepts and no proprioceptive sensations were evoked.

The survey data included in these analyses were collected during the same year as the frequency magnitude estimation data to ensure the evoked sensations were consistent across paradigms, which included data from post-implant days 630 to 962.

6.2.4 K-means Clustering

Electrodes were divided into three categories in P2 using k-means clustering using the reported intensity at 20, 100, and 300 Hz. Both silhouette and elbow analysis were used to validate that k = 3 was a suitable parameter choice for P2. We labeled the categories as Low Frequency Preference (LFP), Intermediate Frequency Preference (IFP), and High Frequency Preference (HFP) based on the frequency at which the maximum intensity occurred. Based on silhouette analysis, we found that data from P3 divided best into two clusters. We labeled these clusters as LFP and HFP in line with the classification from the P2.

Electrodes were additionally clustered based on the reported perceptual qualities at 20, 100 and 300 Hz in the P2. Each reported quality (of which there were 10) was summed across sessions and pulse frequencies for each electrode. The total number of reports for each quality was then divided by the maximum number of reports for any electrode, so that each quality was represented by number between zero and one and contributed equally to the clustering of each electrode. No dimensionality reduction was used and electrodes were clustered within the 10 dimensions of reported qualities.

6.2.5 Data Analysis and Statistics

All quantification and statistical analyses were done in MATLAB (Mathworks, Natick, MA). Sample sizes are listed in the methods for each experiment. A power analysis was not conducted to determine the number of replicates for each experiment. The number of repetitions for psychophysics experiments were based on commonly used values. Electrodes that elicited clearly perceptible sensations and showed a significant change in perception with a change in a parameter were collected across multiple sessions to determine if effects were consistent over time.

For all statistical tests, we determined whether to use parametric or non-parametric tests based on the normality of the data as assessed with an Anderson-Darling test. If the data were significantly different than normal, then we used non-parametric tests. Any time multiple comparisons were made, we used the Benjamini-Hochberg procedure to correct for multiple comparisons which resulted in a critical p-value that was used as a cut-off. If no values were significant, then the critical p-value returned is 0 and not reported and no values are considered significant. For any tests that required post-hoc comparisons, we used Tukey's HSD test.

For magnitude estimation data, we used Friedman's test to assess significant differences between the intensity responses at different pulse frequencies as well as differences between electrode responses across days. Friedman's test also allowed us to compare significant effects of pulse frequency on intensity across multiple sessions by excluding experimental day as a cofactor. When comparing the same electrode across sessions, we compared intensity responses with the same tested pulse frequency and corrected for multiple comparisons. We compared differences in the median intensity of electrodes within each category using a Kruskal-Wallis test.

For detection data, we used an ANOVA to assess significant differences in the detection accuracy at different pulse frequencies.

For quality data obtained from surveys, we used Fisher's exact test to evaluate if there was a relationship between the categorization of each electrode and the perceptual qualities evoked on the electrode. Contingency tables were developed for each descriptor and responses were row-divided by the three categories (LFP, IFP, and HFP) and column-divided by the presence or absence of the quality. Each category was compared pairwise. Fisher's exact test was used instead of a chi-squared because the sample sizes for each group were relatively small.

To test if there was spatial clustering of the effects of frequency on perceived intensity across the array, we adopted a technique used in geographic information systems, where they are described as Local Indicators of Spatial Association (LISA) (Anselin, 1995). We quantified the number of electrodes that had an adjacent electrode with the same frequency response category and divided this by the total number of adjacent electrodes to obtain a fraction. We then randomly distributed the categorized electrodes on two simulated arrays with the same tested electrode locations. We conducted this simulation 100,000 times and compared the output values of this random simulation to the observed values. A pseudo p-value was obtained by comparing the total

number of simulations that had a fraction greater than or equal to the observed fraction, which indicates the probability of obtaining our observed value by chance.

For all statistics, we considered $p < 0.05$ to be significant.

6.3 Results

6.3.1 Effects of Frequency on Perceived Intensity are Electrode Dependent

In participants P2 and P3, we delivered ICMS trains through individual electrodes and asked the participant to report the perceived intensity on a self-selected scale, which typically ranged from 0 to 6. We found that increasing the stimulus current amplitude and train duration consistently increased the perceived intensity of the evoked sensations on all tested electrodes (Figure 15).

However, we found that the relationship between stimulus frequency and perceived intensity was electrode-dependent (Figure 16). We delivered a 60 μA stimulus train for 1 s at pulse frequencies ranging from 20 to 300 Hz in P2. On some electrodes, percept intensity increased with stimulus pulse frequency. However, on over half of the tested electrodes, the opposite effect occurred; stimulus trains with low pulse frequencies (20-100 Hz) were perceived as being the most intense and the intensity *decreased* as the stimulus pulse frequency *increased*.

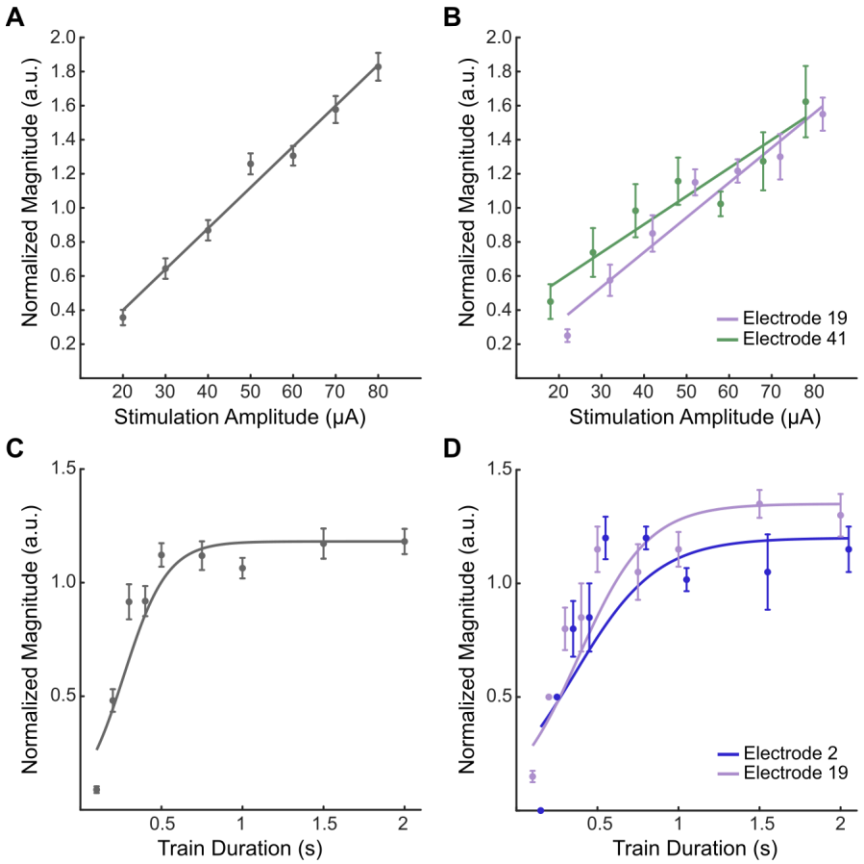

Figure 15: Increases in current amplitude and train duration consistently drive increases in perceived intensity. A-B) Normalized intensity as a function of current amplitude for all nine tested electrodes A), and for two individual electrodes B). The data were fit with a linear function. C-D) Normalized intensity as a function of train duration for all four tested electrodes C) and two individual electrodes D). The data were fit with a logistic function. In all panels, data points are the median reported intensity at each stimulus parameter. Samples were normalized to the median intensity value for each test. Error bars show the standard error. Note that the Y-axes are scaled differently for each panel for clarity. Colors represent different electrodes as indicated by the legends. Data points for individual electrodes are jittered slightly on the x-axis for visualization.

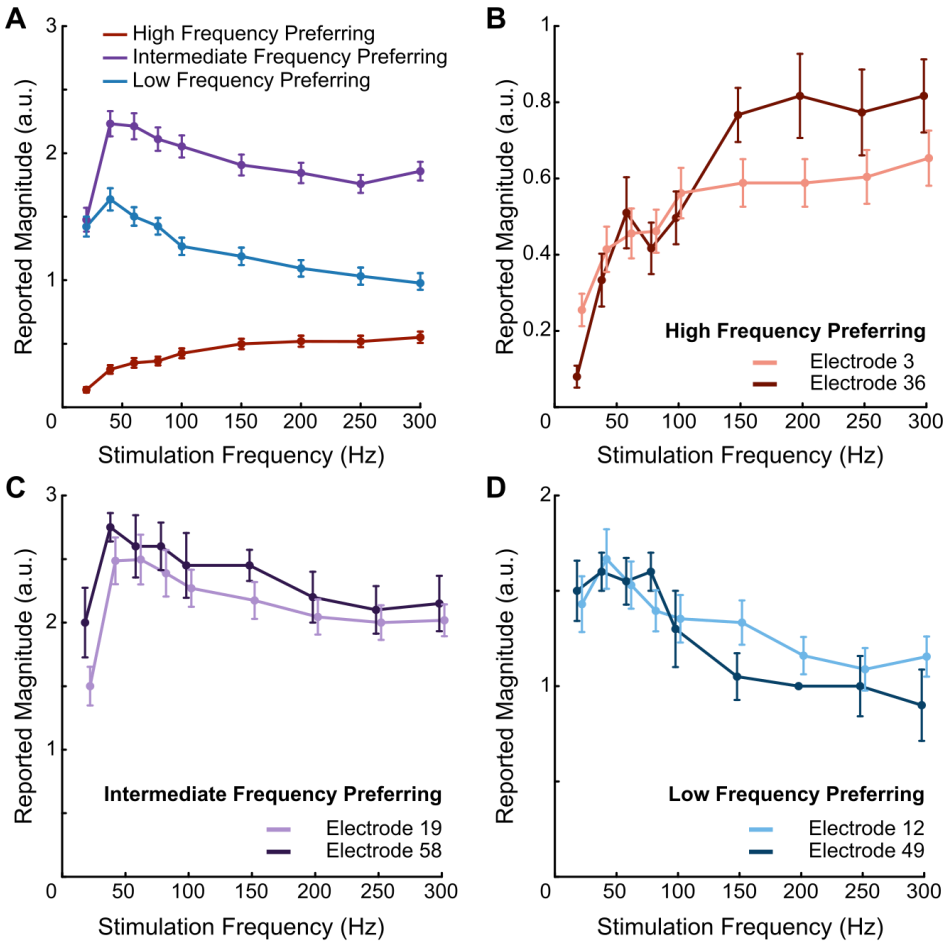

Figure 16: Pulse frequency drives electrode specific changes in intensity which can be grouped into categories. A) K-means clustering for data from P2. Each point represents the median intensity of a different tested electrode. Data were divided into three groups as indicated by the color. B) K-means clustering for data from P3. Each point represents the median intensity of a different tested electrode. Data were divided into two groups as indicated by the color. C) Perceived intensity for each aggregated frequency preference group in P2. Different colors represent different categories. Each data point shows the mean intensity response of all of the electrodes in a given category. Points are connected with piecewise fits. D) Perceived intensity for each aggregated frequency preference group in P3.

We used k-means clustering to separate electrodes into three categories in P2 based on the reported percept intensity at 20, 100, and 300 (Figure 17): electrodes with the highest intensity response at 20 Hz (Figure 17B), electrodes with the highest intensity responses at 100 Hz (Figure 17C), and electrodes with the highest intensity response at 300 Hz (Figure 17D). For simplicity, we refer to these groups based on the pulse frequency range at which the maximal intensity occurred: High Frequency Preferring (HFP), Intermediate Frequency Preferring (IFP), and Low Frequency Preferring (LFP) electrodes.

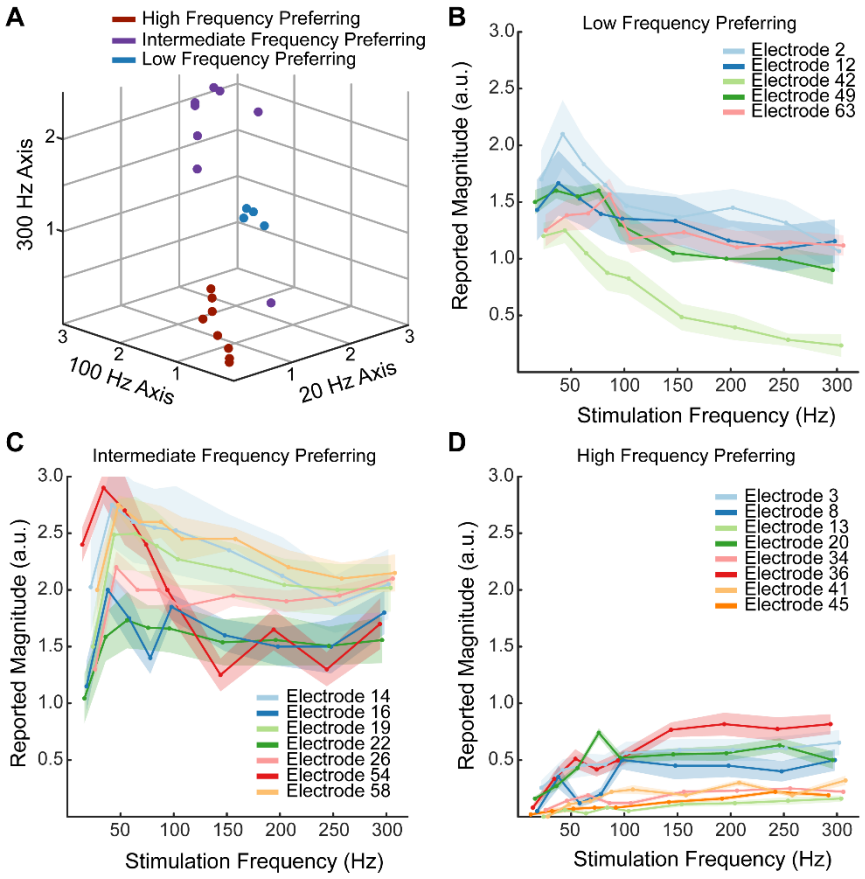

Figure 17: Electrodes divide into three categories based on their frequency-intensity relationships. A) K-means clustering of individual electrodes based on intensity responses at 20, 100, and 300 Hz. Individual data points are the median intensities at each frequency across all repetitions. B-D) Perceived intensity responses at different frequencies for all electrodes classified as low-frequency preferring B), intermediate-frequency preferring C), and high-frequency preferring D). Shaded regions show the smoothed standard error for each electrode.

In P2, seven electrodes were tested in multiple sessions (3 to 6 per electrode) to determine whether the relationships between pulse frequency and perceived intensity were consistent across sessions (Figure 18). The perceived intensities reported on all electrodes that were tested in three or more sessions changed by statistically significant amounts as the stimulus pulse frequency changed ($p < 0.001$, Friedman test). The reported intensities at each frequency on these electrodes did not change significantly across test days ($p > 0.05$, Friedman test). An additional 22 electrodes were tested in one or two sessions. Of the 29 electrodes tested in total, 20 electrodes exhibited intensities that changed by statistically significant amounts as the stimulus frequency changed ($p < 0.02$, Friedman test). Of these 20 electrodes, five were classified as low-frequency preferring, seven were classified as intermediate-frequency preferring, and eight were classified as high-frequency preferring.

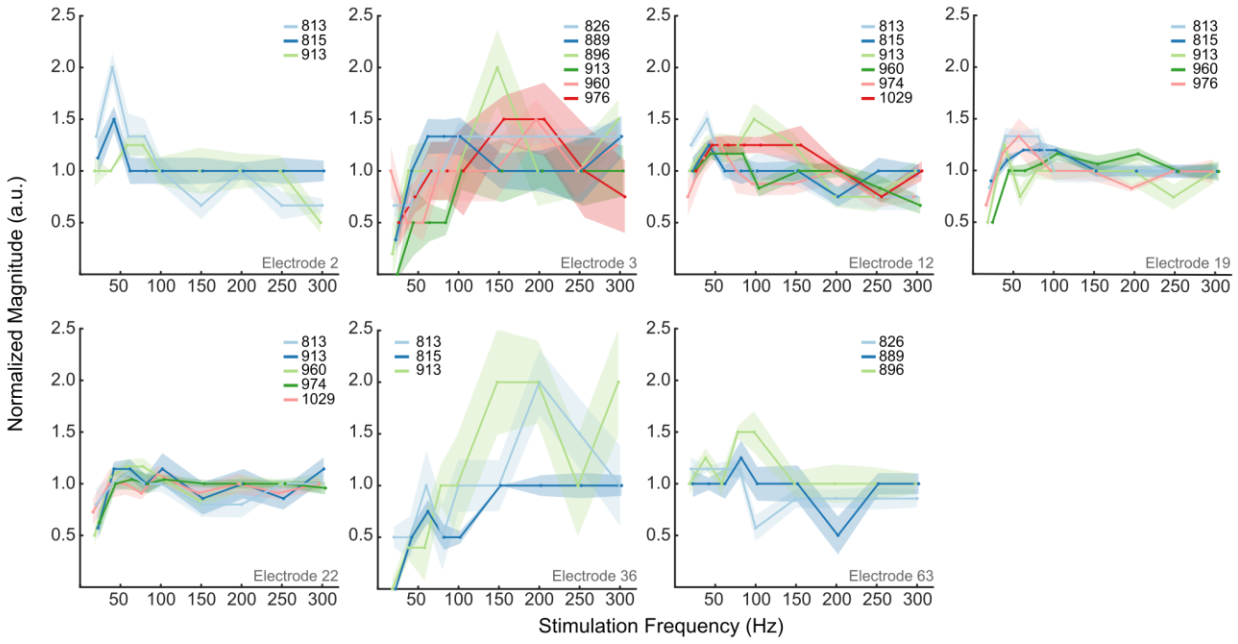

Figure 18: Electrodes maintain same frequency-intensity relationships over time. Plots of magnitude estimation results on all electrodes tested three or more times. Each set of points and the corresponding fit indicate a single post implant date, as indicated in the legend. Data from each test session were normalized by the median intensity. Different colors show different post-implant dates in each plot as indicated by the legend. Shaded regions show the smoothed standard error.

In participant P3 we tested 23 electrodes at 80 μA and three different frequencies (20, 100, and 300 Hz) (Figure 19). The perceived intensity changed by statistically significant amounts on 22 electrodes as the stimulus frequency changed ($p < 0.05$, Friedman Test). There were similar electrode specific effects, where some electrodes evoked the highest intensity percepts at the highest frequencies and others had the highest intensity at the lowest frequencies (Figure 19A). Using the same clustering approach, the data divided into two clusters, which were most similar to the LFP and HFP categories. Fifteen electrodes were classified as HFP and seven were classified as LFP (Figure 19B).

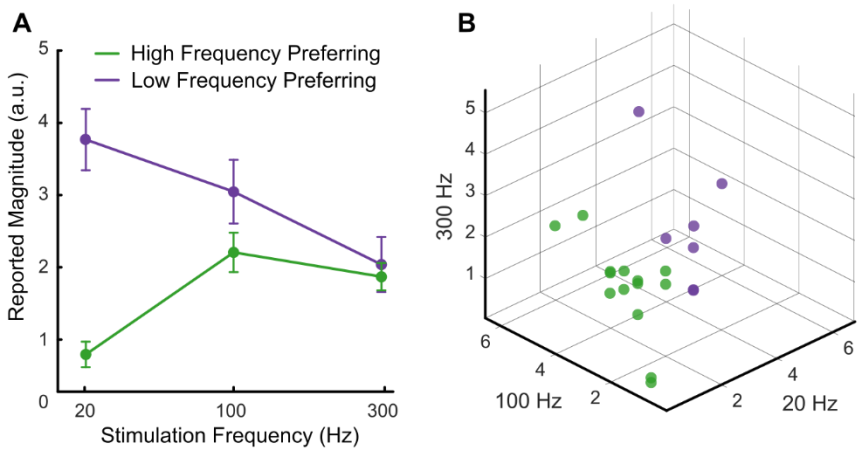

Figure 19: Electrode specific frequency-intensity relationships and spatial clustering generalize to a second participant. A) The mean intensity response across two frequency preference groups. Each data point represents the mean intensity response at the given frequency. The error bars represent the standard error of the mean. The points are connected with piecewise fits. B) K-means clustering of individual electrodes based on intensity responses at 20, 100, and 300 Hz. Individual data points are the median intensities at each frequency across all repetitions. Some points may overlap due to having the same median intensities.

6.3.2 Frequency-intensity Relationships are Preserved Across Suprathreshold Amplitudes

We measured whether the frequency-intensity relationships were affected by stimulus current amplitude. If the frequency-intensity relationships were dependent on the current amplitude, this result might reflect idiosyncratic recruitment effects of ICMS. Therefore, in P2 we presented stimulus trains at three current amplitudes (20, 50, and 80 μA) and three pulse frequencies (20, 100, and 300 Hz), which spanned the range of detectable and safe parameters, and asked the participant to report the perceived intensity of the evoked percepts. There were no significant differences in the shape of the frequency-intensity relationships for the three electrode groups at 50 and 80 μA after controlling for changes in median intensity caused by increasing current amplitude ($p = 0.21$-0.99 Friedman's test, Figure 20). The reported intensity on low-frequency preferring electrodes peaked at 20 Hz at both current amplitudes ($p = 0.02$, Kruskal-Wallis, Figure 20A), whereas the reported intensities of intermediate-frequency preferring electrodes peaked at 100 Hz for both current amplitudes ($p < 0.001$, Kruskal-Wallis, Fig. 20B) and the reported intensity on high-frequency preferring electrodes peaked at 300 Hz for both current amplitudes ($p < 0.001$, Kruskal-Wallis, Fig. 20C). Interestingly, when we decreased the current amplitude to 20 μA, which was close to the detection threshold for most electrodes, increasing the pulse frequency from 20 to 100 Hz evoked more intense percepts for all electrode groups ($p < 0.05$, Kruskal-Wallis, Figure 20A,B,C, 20 μA). There were highly significant differences between the shape of the frequency-intensity relationships for all groups at 20 μA versus 50 or 80 μA ($p < 0.001$, Friedman's test) even after controlling for changes in the median intensity caused by

increasing current amplitude. At 20 μA, the percept intensity was very low, making magnitude estimation akin to a detection task.

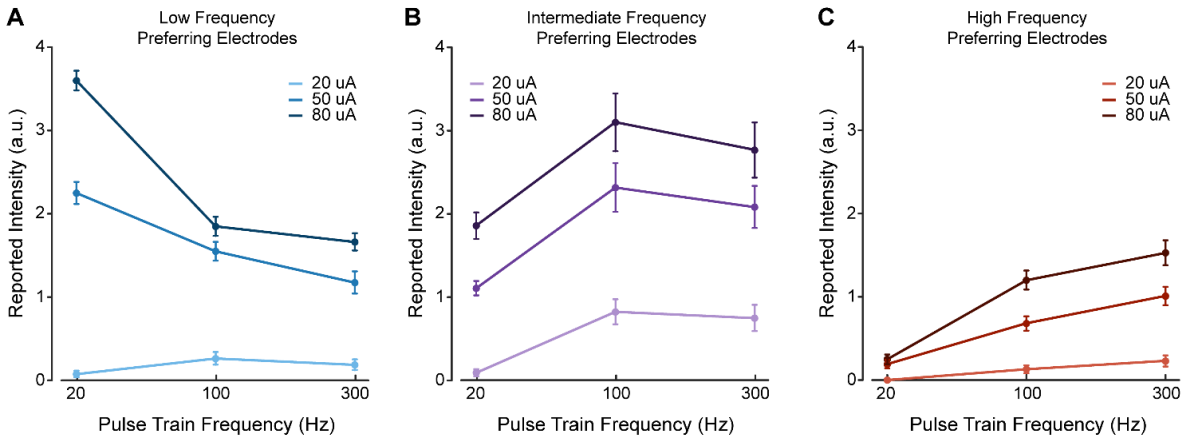

Figure 20: Stimulus current amplitude does not change the relationship between pulse frequency and intensity at suprathreshold amplitudes. Magnitude estimation data for different current amplitudes and pulse frequencies. Data were aggregated across electrodes by their category, where each plot shows a different category of electrodes. Perceived intensity values for A) LFP electrodes, B) IFP electrodes, and C) HFP electrodes at different current amplitudes and pulse frequencies. Different colored bars represent different current amplitudes. Error bars indicate the standard error across electrodes. We tested two LFP electrodes, three IFP electrodes, and two HFP electrodes which were each tested twice in different sessions.

6.3.3 High Frequency Stimuli are Detected More Reliably at Perithreshold Amplitudes

Our observation that higher stimulus pulse frequencies can evoke less intense percepts at suprathreshold stimulus current amplitudes differs from predictions made from non-human primate studies; higher frequencies can evoke detectable percepts at lower amplitudes in NHPs, which led to predictions that frequency always leads to higher perceived intensities (S. Kim, Callier, Tabot, Gaunt, et al., 2015; Romo et al., 2000, 1998). These detection threshold experiments suggest that increasing the stimulus frequency should generally evoke more intense percepts. However, the effect of changing ICMS parameters on perceived intensity cannot be tested directly

in NHPs. Indeed, we found that the perceived intensity at the lowest tested currents always increased when the frequency increased from 20 to 100 Hz (Figure 20A,B,C, 20 μA), but that this effect was not always maintained at higher current amplitudes (Figure 20A,B, 50 and 80 μA). To explicitly compare our results to NHP work, we performed a detection task in P2 in which the current amplitude was set to perithreshold levels and the pulse frequency was varied between 20, 100, and 300 Hz. We found that at 300 Hz, the interval containing the stimulus train was correctly identified 80% of the time across all tested electrodes (Figure 21). Similarly, when the pulse frequency was set to 100 Hz, the mean detection accuracy was 72%. In contrast, when the pulse frequency was set to 20 Hz, the mean detection accuracy was just 42%, which was not significantly different than chance levels of 50% ($p = 0.14$, one-sample t-test). Detection accuracies at 100 Hz and 300 Hz were significantly higher than the detection accuracy at 20 Hz ($p < 0.05$, ANOVA) but were not significantly different than each other ($p = 0.66$, ANOVA). These results are consistent with the observations in NHPs but demonstrate a dichotomy between detection and intensity evaluation: detection thresholds are not necessarily predictive of perceived intensity and predictions about subjective measures of perception may be difficult to make in animals.

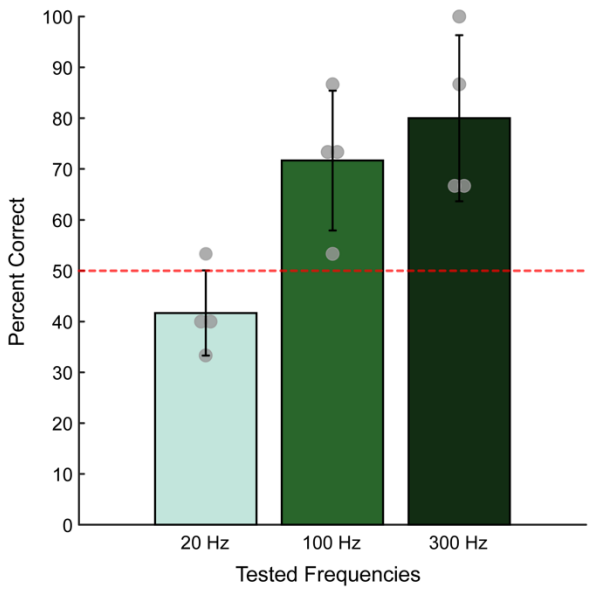

Figure 21: Higher pulse frequencies always improved detection at perithreshold current amplitudes. Bar plots showing the probability of correctly identifying the window containing a stimulus train with different pulse frequencies at a fixed perithreshold current amplitude (6-16 μA). Each bar represents the mean detection accuracy at each pulse frequency on four tested electrodes. The error bar indicates the standard deviation. The grey dots show the individual electrode performance accuracies. Chance performance was 50% and is indicated with the red dotted line.

6.3.4 Frequency-intensity Relationships are Associated with Different Perceptual Qualities

One advantage of studying somatosensation in humans is the ability to document the sensory qualities evoked by stimulation. We found that there were significant differences in the qualities evoked on electrodes belonging to different categories defined by the effect of pulse frequency on intensity in P2 (Figure 22A). Additionally, the sensory qualities for electrodes in each group were differentially modulated by pulse frequency (Figure 22B).

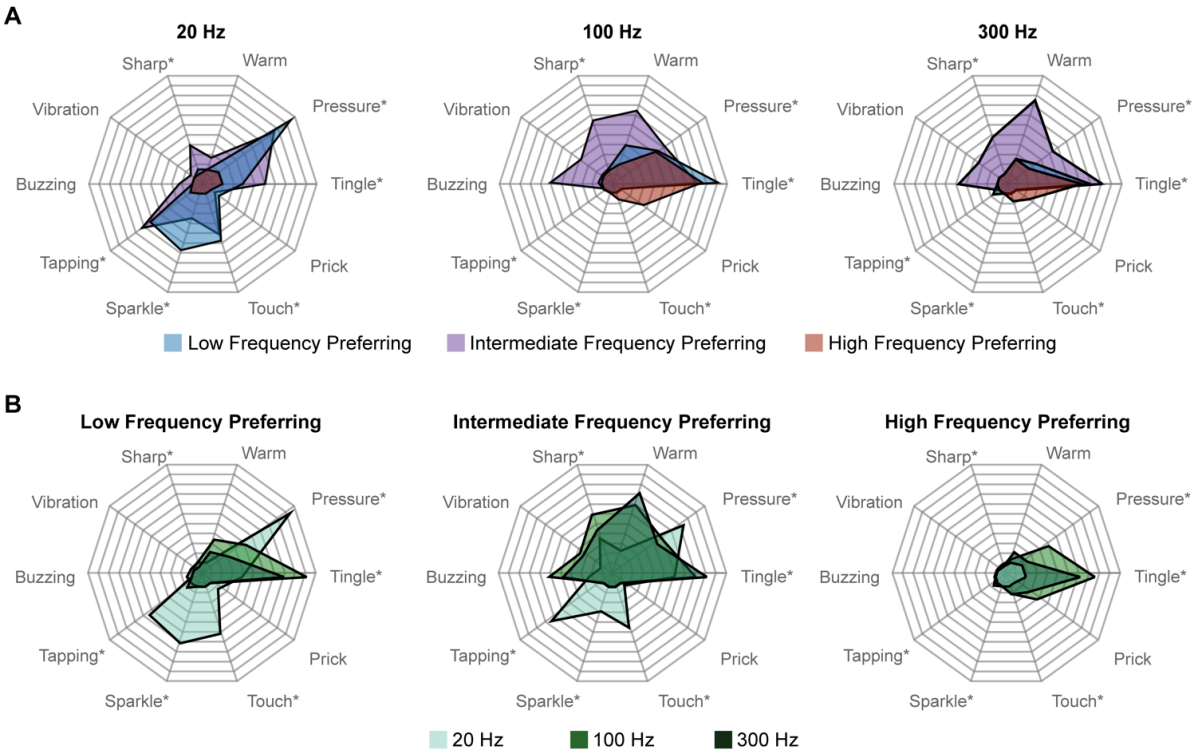

Figure 22: Perceptual qualities are associated with specific electrode categories and stimulus pulse frequencies. Radar plots showing the distribution of reported qualities at different pulse frequencies for each electrode category. A) Percepts sorted by pulse frequency. Electrode categories are indicated with different colors. B) Percepts sorted by electrode categories. Pulse frequencies are indicated with different colors. In each plot, qualities on which there was a significant difference between categories, as determined with Fisher's exact test, are marked with an asterisk.

At 20 Hz, we found that LFP and IFP electrodes evoked percepts with pressure, tapping, sparkle, and touch qualities. These qualities were not evoked on HFP electrodes at any frequency. At this low stimulation frequency, HFP electrodes were generally not detectable, resulting in few reports of any percepts. At 100 Hz, IFP electrodes evoked percepts with buzzing, vibration, and sharp qualities. LFP and HFP electrodes never evoked these qualities when stimulated at 100 Hz. HFP electrodes also evoked sensations of touch and prick at 100 Hz that never occurred on LFP or IFP electrodes at any frequency. However, these qualities occurred on less than 30% of trials on HFP electrodes. At 300 Hz, the responses were similar to those at 100 Hz except that all electrode categories evoked less pressure.

We also clustered electrodes based on the verbal reports of percept quality at all frequencies (Figure 23). Interestingly, these clusters were remarkably similar to those based on intensity responses at different frequencies. That these electrode categories were nearly identical when created using completely different data sets–perceptual qualities and perceived intensities–strongly suggests that these two features are measures of the same underlying properties of the neurons recruited by stimulation.

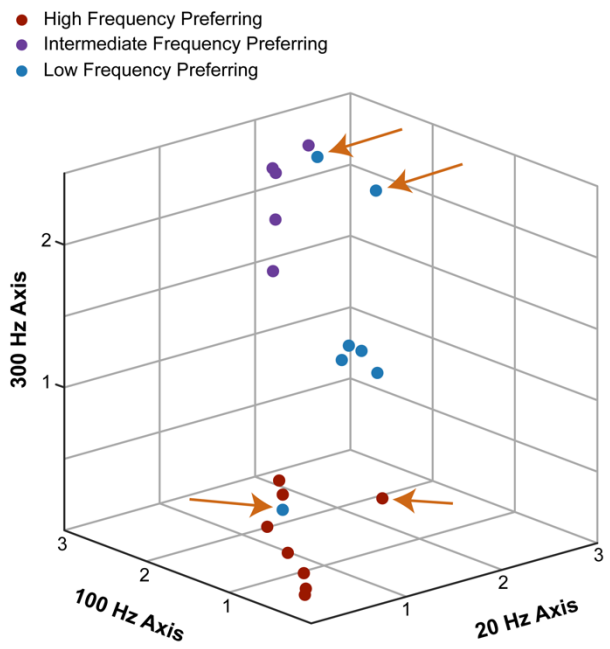

Figure 23: Clustering by evoked qualities results in nearly identical clusters to those identified from perceived intensity. Individual electrodes are plotted on the same axes as shown in Figure 17. The data were clustered in a ten-dimensional quality space and then plotted in the three-dimensional frequency-intensity space. Clusters are labeled based on the three categories defined by frequency-intensity responses. For example, the blue point in the lower portion of the figure represents an electrode that shared similar frequency-intensity properties with other high frequency preferring electrodes but shared qualities that were similar to low frequency preferring electrodes. However, the majority of the electrodes were identified as being in the same clusters regardless of whether the clustering was performed on quality or frequency-intensity data. Electrodes that were classified differently between quality and frequency-intensity data are indicated with orange arrows.

6.3.5 Perceptual Responses are Spatially Clustered in Somatosensory Cortex

Finally, we asked whether the categorization of an electrode, which corresponds to its frequency-intensity responses and evoked perceptual qualities, was related to its location in cortex. We compared the observed spatial occurrence of electrode category with a simulation that randomly assigned each category to one of the tested electrode locations while maintaining the same number of electrodes in each category. In P2, there was significant clustering of electrodes in the same category (Figure 24A) across arrays (pseudo-p = 0.00017). This was particularly apparent on the lateral array. In P3, LFP electrodes only occurred on one of the arrays which resulted in significant levels of clustering across the arrays (p = 0.0045, LISA, Figure 25).

While we found a strong overlap with projected field location and frequency preference, we observed that in some cases, clusters of electrodes from different categories evoked percepts from the same region of the hand (Figure 24B). For example, LFP, IFP, and HFP electrodes elicited sensations on the palmar region beneath the middle and ring fingers. As a result, percepts from a single region of the hand, such as the index finger, could be evoked by electrodes that generated multiple response types.

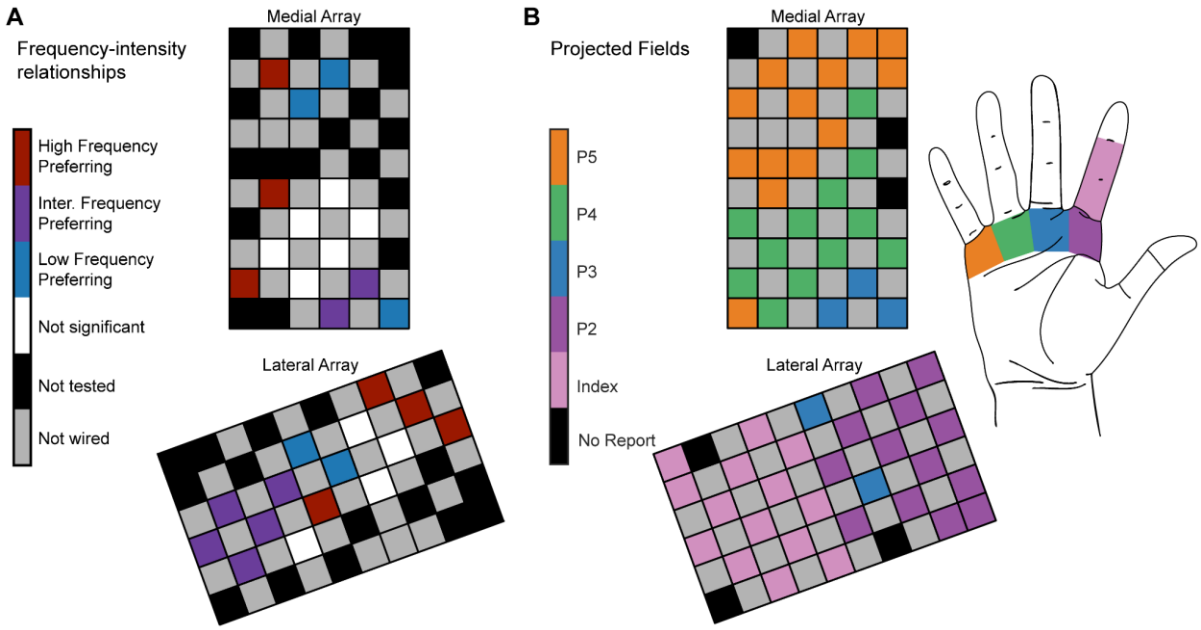

Figure 24: Electrode location is significantly related to electrode categorization. A) Map of the medial electrode array (top) and lateral electrode array (bottom) implanted in somatosensory cortex and the distribution of the frequency preference categorizations. The electrode arrays were implanted close to the central sulcus with the left edge of the medial array being approximately parallel to the central sulcus. The arrays are oriented to reflect the implant orientation. Colored squares represent different types of electrodes as indicated by the color bar. B) The projected field locations for each tested electrode. The label for each electrode corresponds to the most reported projected field for each electrode on all 100-Hz surveys taken in the same year as the magnitude estimation data.

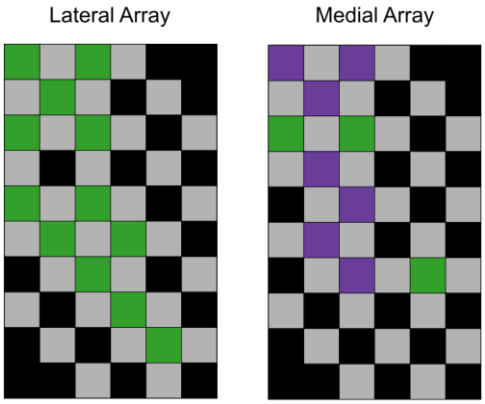

Figure 25: The spatial mapping of the two groups on the arrays for P3. Spatial clustering was significant across the arrays ($p = 0.0045$, LISA). Gray square represents unwired electrodes and black squares represent untested electrodes.

6.4 Discussion

We found that ICMS frequency alters the perceived intensity (Figure 17) and quality (Figure 22) in an electrode-specific manner. Further, we found that electrodes with similar intensity responses and qualities clustered spatially in somatosensory cortex (Figure 24). This implies that the observed electrode-specific relationships between frequency and perception are not caused by random factors and are instead related to the underlying structure of the cortex.

6.4.1 Neural Populations Preferentially Respond to Different Stimulus Frequencies

Intracortical microstimulation at the maximum amplitudes used in this study can directly activate neurons up to 2 mm away from the electrode tip, but most activation occurs less than 500 µm from the electrode tip (Overstreet et al., 2013; Stoney, Thompson, & Asanuma, 1968). At intermediate amplitudes (e.g. 50-60 µA) direct activation primarily occurs within 200-300 µm of the electrode tip. Stimulation can also recruit passing axons which can project to far away areas, resulting in sparse, distributed activation of the cortex (Histed et al., 2009; Michelson, Eles, Vazquez, Ludwig, & Kozai, 2019). Using optical imaging, clusters of neurons with similar responses extend from 0.2 to 1 mm in squirrel monkeys (Friedman, Chen, & Roe, 2004) while electrophysiological recordings have measured similar effects over 0.5 to 1 mm in the mediolateral direction and multiple millimeters in the rostrocaudal direction in macaque monkeys (Sur, Wall, & Kaas, 1984). These spatial scales over which function varies are similar to the expected recruitment distances from ICMS, supporting the idea that different perceptual or frequency responses may be linked to activating different functional groups of neurons.

Electrophysiology (Mountcastle, Talbot, Sakata, & Hyvärinen, 1969; Sur, Wall, & Kaas, 1981; Sur et al., 1984) and optical (L. M. Chen, Friedman, Ramsden, LaMotte, & Roe, 2001; Friedman et al., 2004) recordings have shown organized neural populations in the somatosensory cortex that are sensitive to tactile input with specific frequency content. These experiments promoted the idea of submodality separation in the cortex in which the activity of cortical neurons is primarily driven by input from either rapidly adapting Meissner corpuscles (RAs), slowly adapting Merkel cells (SAs), or Pacinian Corpuscles (PCs). However, many cortical neurons receive heterogeneous input from multiple classes of mechanoreceptors (Pei, Denchev, Hsiao, Craig, & Bensmaia, 2009; Reed et al., 2010; Saal & Bensmaia, 2014), leading to neurons that exhibit both sustained and transient responses. Therefore, the different effects of stimulus frequency on intensity and perception are unlikely to arise from activating inputs representing specific tactile subpopulations (e.g. SAs, RAs, or PCs), but by how a local region of somatosensory cortex can respond to different stimulus frequencies, consistent with the concept of the cortex encoding different frequency features (Prsa, Morandell, Cuenu, & Huber, 2019).

The idea that somatosensory cortex is organized for feature encoding is supported by human psychophysics experiments where frequency perception was dependent on specific spiking patterns and not on the types of mechanoreceptor that were activated (Ingvars Birznieks et al., 2019). Similarly, individual cells in mouse cortex are preferentially activated by different mechanical stimulation frequencies (Prsa et al., 2019). In those same experiments, the frequency preference of the neural population tended towards higher frequencies when the indentation depth decreased, similar to our results that higher frequencies were perceived as being more intense when the ICMS amplitude was decreased (Figure 18). Together, these results suggest that the somatosensory cortex receives convergent input from different mechanoreceptors and is organized

for feature-selective encoding, which results in different preferential responses to ICMS frequency and different evoked qualities.

6.4.2 Possible Mechanisms for Heterogeneous Perceptual Responses to Stimulus Frequencies in Cortex

The effects observed in this study must be related to different cellular responses to stimulation in different regions of the cortex. In fact, different stimulation frequencies in mouse somatosensory cortex can alter the activation of neurons far away from the source of stimulation (Michelson et al., 2019). Specifically, high pulse frequencies lead to rapid habituation of neurons far away from the electrode while low pulse frequencies can maintain activation of these same neurons. This reduced activity in neurons far away from the could lead to decreases in perceived intensity and changes in percept quality in a way that depends on electrode location and local neural populations.

A potential mechanism to explain electrode-dependent responses are varying distributions of inhibitory and excitatory neurons. The presence of more inhibitory neurons in a local region could result in stronger inhibitory drive at higher frequencies, resulting in more robust responses to low frequency stimuli. Indeed, recruitment of inhibitory Martinotti cells in the somatosensory cortex of rats increases as the duration and frequency of presynaptic action potentials increase (Kapfer, Glickfeld, Atallah, & Scanziani, 2007; Silberberg & Markram, 2007). Further, rostrocaudal heterogeneity of inhibition has been documented in rat olfactory cortex (Large et al., 2018; Luna & Pettit, 2010). Whether such organization exists in human somatosensory cortex remains to be seen.

Short term plasticity (Tsodyks & Markram, 1997) at synapses driven by stimulation may also explain the observed effects. If a synapse is unable to resupply neurotransmitter at a rate faster than the stimulus frequency, transmitter release at the synapse could become depressed. In this scenario, neurons would be unable to recruit other neurons in synchrony with stimulation, which could result in lower recruitment and lower perceived intensity. If cells in somatosensory cortex have different time constants for transmitter recovery, this could serve as a mechanism for frequency filtering (Rosenbaum, Rubin, & Doiron, 2012). Elucidating the precise mechanisms underlying observed frequency responses in cortex will require further studies in animal models.

6.4.3 Human Perception of ICMS Reveals New Insights that Could Not Be Predicted from Non-Human Primate Studies

Higher stimulus pulse frequencies decreased the current amplitude required to detect a stimulus train in NHPs (S. Kim, Callier, Tabot, Gaunt, et al., 2015). It was predicted then that higher stimulus frequencies would increase the perceived intensity of a stimulus train. Similar to these animal studies, we found that higher frequencies improved the detectability of stimulus trains at perithreshold amplitudes. However, at suprathreshold current amplitudes, increasing the frequency did not always produce higher perceived intensities. A question that emerges then is whether the prediction of increasing intensities at higher frequencies can be reconciled with our observations of decreased intensities at higher frequencies on a subset of the electrodes.

In other NHP experiments, animals were trained to identify which of two intervals contained the higher frequency stimulus train, regardless of current amplitude, to determine if changes in frequency could be perceived independently of changes in amplitude (Callier et al., 2020). Increasing the amplitude always biased the animals towards selecting a stimulus train as

having a higher frequency. However, animals were still able to distinguish between changes in amplitude and frequency on some electrodes. In our experiments, LFP and IFP electrodes, which generated high intensity percepts at low frequencies, often evoked percepts with highly salient qualities, such as tapping or buzzing. The presence of these qualities at some frequencies and not others (Figure 22) would allow the participant to distinguish between increases in amplitude, which only increases the percept intensity, and increases in frequency, which changes the percept quality and intensity (Figure 17). On electrodes without highly salient frequency-dependent qualities, such as the high-frequency preferring electrodes, it would be difficult to disambiguate changes in amplitude and frequency.

However, an important difference between our study and the NHP studies is that many electrodes in our study evoked less intense percepts as the pulse frequency increased, which was not observed in NHPs. The reason for this is unclear, and it may be related to the larger frequency range explored in this study or even the electrode location in the cortex. However, animals cannot directly report the perceived intensity of a set of stimuli on an open scale, as is commonly done in humans. Rather, perceived intensity, as well as other subjective aspects of perception such as quality and naturalness, must be inferred from other experimental paradigms, which makes it difficult to assess how ICMS affects subjective aspects of perception in animals. This demonstrates that human experiments are crucial to understanding how ICMS modulates tactile perception, particularly for subjective evaluation of experience.

6.4.4 Limitations of Study

There are several limitations associated with this work. First, most of these experiments were conducted in a single participant with a chronic implant. Different participants, with different

timelines of injury preceding implant, could potentially respond differently to stimulation, particularly if the electrodes are implanted in a different part of the somatosensory cortex. However, the repeatability of our findings suggest that these effects were at least not due to day-to-day variations. Additionally, we found electrode-specific frequency effects, including LFP electrodes, that were spatially clustered in a second participant. This suggests that changing frequency will affect intensity and perception similarly in other participants. One important difference in the second participant was that we only observed LFP relationships on a single array.

The participants had limited residual sensation in their hands, which made it difficult to measure responses in cortex to tactile indentation. Comparing perceptual responses to ICMS with cortical responses to tactile indentation could help better relate these findings to previous studies in monkeys. Additionally, it is notable that due to spinal cord injury there may be reorganization of cortex (R. Chen, Cohen, & Hallett, 2002; Freund et al., 2011; Henderson, Gustin, Macey, Wrigley, & Siddall, 2011; Wrigley et al., 2009). However, recent work has argued that measured remapping may be simply driven by the uncovering of pre-existing latent activity, corresponding instead to homeostasis (Makin & Bensmaia, 2017; Muret & Makin, 2021). The ability to elicit sensations with ICMS years after injury is supportive of this idea (Armenta Salas et al., 2018; Fifer et al., 2020; S. N. Flesher et al., 2016).

Another potential confound is that perceived intensity can change throughout a session. Because we used pseudo-randomized presentations of different stimulus parameters to ensure that electrodes were not tested in the same order, and excluded the first block of trials from analysis for each set for magnitude estimation, we believe that this phenomenon did not affect our results.

Our results are consistent with the idea that somatosensory cortex is organized in a way that represents different features in different locations, however, there are several limitations that

should be considered. First, the electrodes covered just a small region of somatosensory cortex, and with a limited spatial resolution, limiting the ability to create detailed maps. Second, we divided electrodes into three groups for participant P2 and two groups for participant P3. This categorical division arose from considering the frequency-intensity relationships and the unique perceptual qualities reported for the electrodes in each group. Categorical divisions are commonly used to describe neural responses in the cortex, including somatosensory cortex (Friedman et al., 2004; Sur et al., 1981, 1984). However, neurons receive convergent input from multiple sub-type modalities (Dicarlo, Johnson, & Hsiao, 1998; Saal & Bensmaia, 2014) and it is possible that the responses to stimulation may divide into more than three groups or fall on a spectrum of different frequency preferences with no discrete categories. More data will need to be collected across additional participants and regions of somatosensory cortex to see if these patterns persist. Third, we do not know if electrodes across the array are in different layers of cortex. Different layers of cortex may drive different perceptual responses with the same input. However, if this were the case, this would still reflect important functional differences in cortex which need to be understood for bidirectional BCIs.

Finally, a challenge for developing mechanistic explanations of these observations is that there are few neuroscientific tools that we can use to further probe these effects in a human. Because of this, addressing the neurophysiological mechanisms of these frequency responses is difficult in a human participant and further investigation of these properties in animal models is needed.

6.4.5 Implications for Prostheses

Stimulus amplitude linearly modulates intensity, while frequency has non-monotonic and electrode specific effects on intensity and percept quality. To signal changing the intensity of a tactile input, amplitude should be used and not frequency. Other potential options also exist to modulate intensity that were not explored in this paper, including pulse width modulation and multielectrode stimulation. Future studies should assess the efficacy of these parameters.

Knowing that different electrodes encode different perceptual features can inform our approach to creating a functional bidirectional BCI in two primary ways. First, these results may help identify electrodes that have perceptual or intensive properties that are relevant to the task being performed. Certain electrodes are more likely to represent specific perceptual qualities, and these electrodes could be selectively used depending on the type of tactile input to the prosthetic device.

Second, these results suggest that electrode-specific stimulation encoding schemes would be particularly useful. In the peripheral nervous system, biomimetic approaches to stimulation using models such as TouchMime have been used (George et al., 2019; Okorokova et al., 2018; Giacomo Valle et al., 2018). In the cortex, combining these biomimetic models with electrode selection based on measured feature-preferences may yield more natural percepts. For example, electrodes that represent “tapping” sensations could receive large amplitude transients, signaling the onset and offset transients, while electrodes that do not evoke this sensation could receive low amplitude, tonic stimulation, signaling maintained contact. Another promising future direction is to use machine learning methods to categorize the feature-preferences of different electrodes more quickly and accurately. These methods could ultimately improve the usefulness of somatosensory

feedback, in turn improving the performance of bidirectional BCIs and ultimately improving the quality of life for people living with paralysis.

7.0 Changing Interpulse Spacings Alone Can Change Tactile Perception of Microstimulation

This chapter is taken directly from a first authorship manuscript published as a conference proceeding for IEEE NER 2021 titled "Changes in interpulse spacing changes tactile perception of microstimulation in human somatosensory cortex" (C. L. Hughes & Gaunt, 2021).

Stimulus frequency modulates percepts evoked by microstimulation in the somatosensory cortex. However, it is not known how the timing of individual pulses affects perception. Here, we stimulated through microelectrode arrays implanted in the somatosensory cortex of a human participant with a cervical spinal cord injury and measured the participant's ability to discriminate microstimulation trains with different frequencies. We also tested the participant's ability to discriminate trains with the same number of pulses but different interpulse spacings. We found that the participant could discriminate the full range of tested frequencies on half of tested electrodes. On electrodes in which the participant could discriminate frequencies, the performance was always better at the lower frequencies. Additionally, on half of tested electrodes, the participant was able to discriminate trains that had the same number of pulses but different interpulse spacings. Finally, we tested the point of subjective equivalence for a train with shifted interpulse spacings compared to a fixed frequency train. We found that increases in interpulse spacings with the same number of pulses resulted in a decrease in perceived frequency. These findings demonstrate that the interpulse spacings can modulate perception of microstimulation and suggests that the encoding of stimulus timing may be important for providing sensory feedback in a bidirectional BCI.

7.1 Introduction

I found in the previous chapter that stimulus frequency modulates percepts evoked by microstimulation in the somatosensory cortex. However, I did not investigate directly how the timing of individual pulses impacts perception.

In at least one study, the effect of varying interpulse timing on perception was investigated using vibratory mechanical stimuli delivered to the hand of people (Ingvars Birznieks & Vickery, 2017; Ng et al., 2018). Changing the interpulse spacings while maintaining the same number of pulses shifted the perceived frequency of the stimuli. This shift in perceived frequency was described as a function of the interpulse spacings, where larger interpulse spacings results in lower perceived frequencies (Ng et al., 2018). We wanted to know if changes in the interpulse spacing of an ICMS train delivered to somatosensory cortex could drive changes in tactile perception like those that occurred using mechanical stimuli of the hand.

7.2 Methods

7.2.1 Pulse Train Design for Interpulse Spacings

To test how trains with fixed-frequencies compared to trains with variable interpulse spacings, we designed multiple trains with the same number of pulses but shifted every other pulse by 5 ms, 10 ms, 15 ms, or 20 ms (Figure 26).

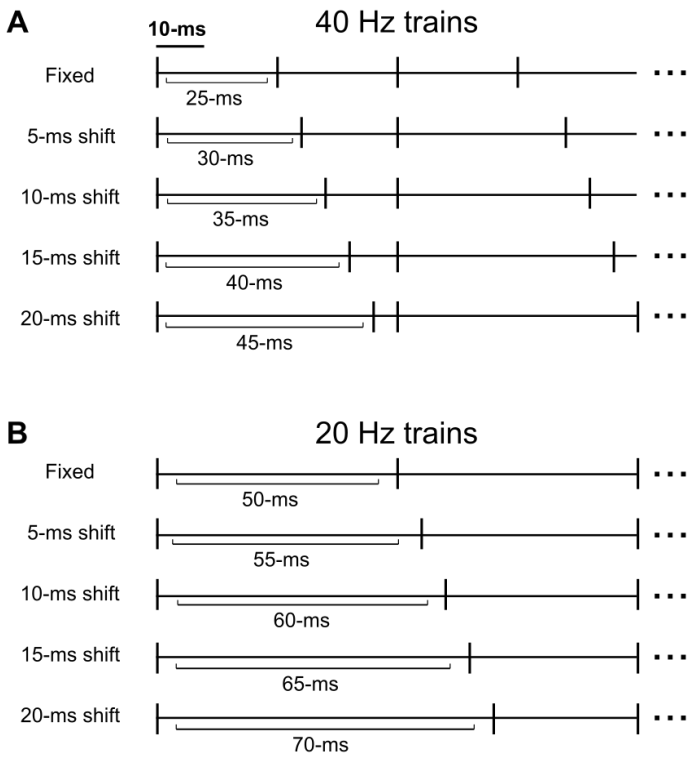

Figure 26: Representations of the shifted ICMS pulse trains. We started with a fixed train of either 40 Hz A) or 20 Hz B) and then created shifted trains in which we shifted every other pulse by 5-ms, 10-ms, 15-ms, or 20-ms to produce four comparison trains. Each train is 1000-ms but here we show a 100-ms sample of the 40-Hz trains and a 200-ms sample of the 20-Hz trains. Each small dash represents a stimulus pulse.

7.2.2 Frequency Discrimination

Just-noticeable differences (JNDs) were determined using a two-alternative forced choice task (2AFC). P2 was instructed to focus on a fixation cross on a screen located in front of him. Two 1-s long windows separated by a 1-s long period were indicated by a change in color of the fixation cross. Stimulation was presented at the reference frequency during one of these intervals and stimulation at a comparison frequency was presented on the other interval. The order of the reference and comparison frequency was varied randomly by trial and the selection of comparison frequencies was block randomized. P2 was asked to select the higher frequency. Because

stimulation frequency does not have consistent perceptual effects across all electrodes, the participant was presented with the reference and two comparison values before the experiment to familiarize him with how changes in frequency were expected to impact perception. We tested two reference frequencies and two sets of corresponding comparison frequencies. The low frequency reference was 20 Hz which had corresponding comparison values of 21, 22, 23, 24, 26, 28, 30, 36, 40, and 60 Hz. The high frequency reference was 250 Hz which had corresponding comparisons of 210, 170, 150, 130, 110, 90, 70, 50, and 30 Hz. We chose the ranges based on preliminary data which showed much better discrimination at lower frequency ranges. Just noticeable differences were calculated as the point at which the participant was expected to be 75% accurate based on logistic regression. Weber fractions were calculated as the JND divided by the reference frequency.

7.2.3 Same-different Task

We determined JNDs for shifts in the interpulse spacings using a 2AFC same-different task. Using a similar setup as previously described, the participant was asked to indicate if the two stimulus trains presented in each time interval were the same or different. The reference train was always a fixed-frequency 40 Hz train, while the comparison train was one of the corresponding shifted trains of 5-ms, 10-ms, 15-ms, or 20-ms (Figure 26). The order in which each comparison was tested was varied randomly. 30 trials of each set contained the reference and the comparison, while another 30 trials contained the reference twice. The proportion correct was calculated using the following equation:

$$PC = \frac{pH + (1 - pF)}{2}$$

Where PC represents the proportion correct, pH represents the probability of a "hit" (the trains were different and the participant indicated they were different) and pF represents the probability of a "false alarm" (the trains were the same and the participant indicated they were different).

7.2.4 Point of Subjective Equivalence

We determined the point of subjective equivalence (PSE) using a 2AFC. Using the same design, the participant was asked which of two stimulus trains had the highest frequency. The order of the reference and comparison frequency was varied randomly by trial and the selection of comparison frequencies was block randomized. The reference value was either a 40 Hz fixed frequency train or the 40 Hz 20-ms shifted train. The comparison values were always fixed-frequency trains of 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, and 42 Hz. Each comparison was presented 10 times (resulting in 120 total trials per electrode). Because frequency leads to electrode specific perceptual effects, the participant was presented with three comparison values (20 Hz, 30 Hz, and 42 Hz) spanning the entire frequency range before the experiment to familiarize him with how changes in frequency were expected to affect perception.

7.3 Results

7.3.1 Frequency Discrimination is Better at Lower Frequencies

The participant performed a two-alternative forced choice task in which they had to select the higher frequency train between a fixed-frequency reference of either 20 Hz or 250 Hz and a series of fixed-frequency comparison values. We found that the participant performed the task well on half of the tested electrodes (Figure 27, top), however, on the other half of tested electrodes, we were not able to calculate a JND. On these electrodes, the behavior was non-linear (Figure 27, bottom). On electrodes in which the participant could perform the task normally, we found that the participant was better able to distinguish frequencies near the low frequency reference of 20 Hz (mean JND = 12.2 Hz) than near the high frequency reference of 250 Hz (mean JND = 127.7 Hz) (Figure 27). This difference is expected based on Weber's law. However, we found that the Weber fractions also differed between the low frequency reference and the high frequency reference, with values of 0.61 and 0.51 respectively, although the Weber fractions were not significantly different between the two groups ($p = 0.45$, t-test).

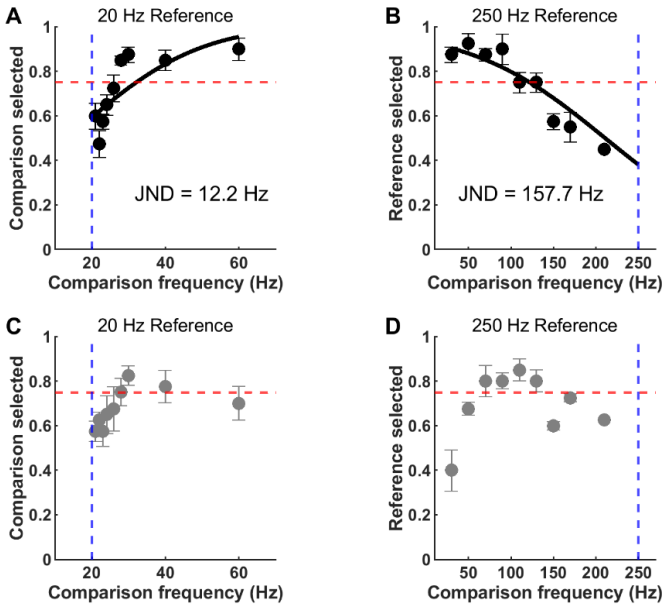

Figure 27: Frequency discrimination is better at lower frequencies. Average fraction of trials in a frequency discrimination task in which the comparison was selected with a 20 Hz reference (A,C) and the reference was selected with a 250 Hz reference (B,D). Electrodes were separated based on if they followed a traditional logistic relationship (A,B) or not (C,D). Each data point represents the mean across 4 tested electrodes each with 10 trials The black line shows the logistic regression to the mean data. The error bars show the standard error. The just-noticeable difference is selected as the point where the logistic regression passes 0.75, indicating 75% accuracy. The dotted red lines indicate the point of JND and the dotted blue lines mark the reference frequency.

7.3.2 Changes in Interpulse Spacings Affect Perception

The participant performed a same-different task comparing a fixed frequency train of 20 or 40 Hz to the corresponding shifted trains (Figure 28). We found that the participant perceived differences in the fixed and shifted trains on half of tested electrodes. On these electrodes, we found that the JND was a 15-ms shift for the 20 Hz trains and a 17-ms shift for the 40 Hz trains (Figure 28).

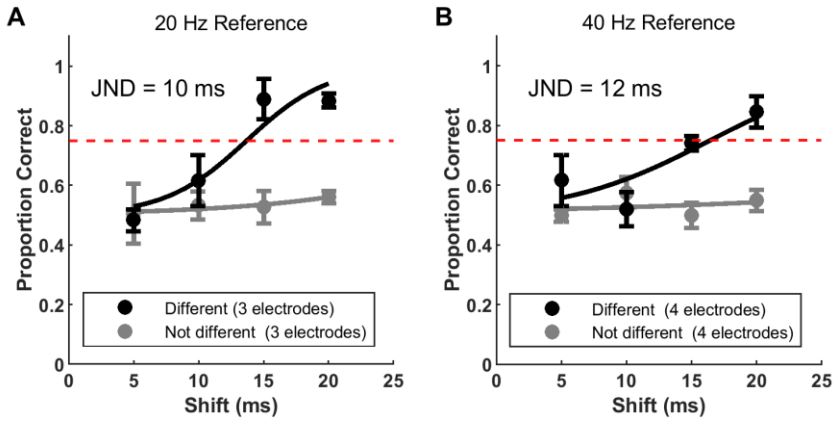

Figure 28: Pulse shifts alone can alter tactile perception. Average proportion correct for the same-different task at each comparison frequency for 20 Hz (A) and 40 Hz (B). The black data points represent the average on electrodes on which there was a perceptible difference, while the grey data points represent the average on electrodes on which there was not a perceptible difference. The proportion correct is calculated based on the hits and false alarms as described by Equation 1. Each data point represents the mean across 3 (A) or 4 (B) tested electrodes each with 10 trials The black and grey lines show the logistic regression of the average data sets. The error bars indicate the standard deviation across the tested electrodes included. The red line indicates the JND of 0.75.

7.3.3 Increasing the Interpulse Spacing Reduces the Perceived Frequency

The participant performed a two-alternative forced choice task in which he had to select the train that was perceived as being higher in frequency. We found that increasing the interpulse spacings resulted in a lower perceived frequency (Figure 29). The 40-Hz fixed frequency train had an average PSE of 39 Hz across four tested electrodes, while the 20-ms shifted train had a PSE of 31 Hz.

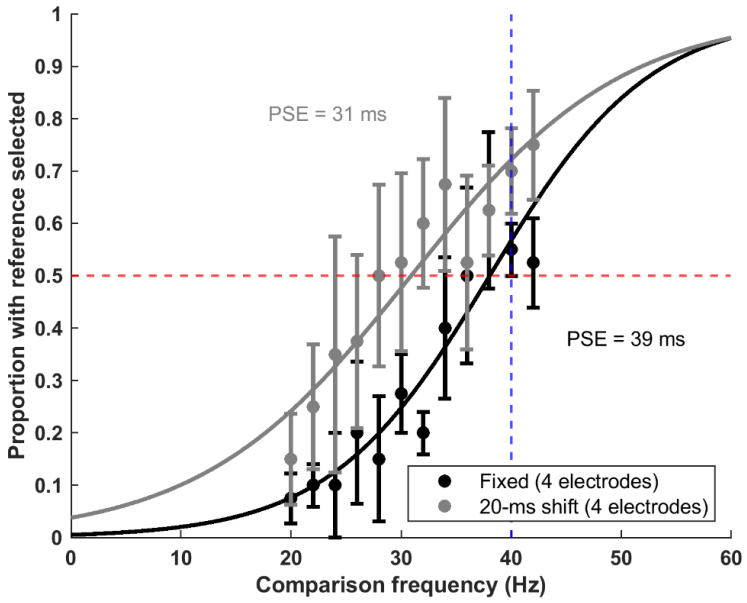

Figure 29: Pulse shifts change the perceived frequency. Average proportion of trials on which the reference was selected as having a higher frequency. The colors indicate which reference train is shown as indicated by the legend. Each data point represents the mean across 4 tested electrodes each with 10 trials. The error bars represent the standard error. The solid lines show the logistic regression for each data set. The point of subjective equivalence (PSE) was considered to be the point where the regression passed 0.5.

7.4 Discussion

7.4.1 Frequency Discrimination Ability Depends on the Stimulated Electrode and Selected Frequency Range

We found that the participant was able to discriminate frequencies in the low and high frequency range on half of tested electrodes. On the other half of electrodes, we found that the participant could discriminate frequencies across a short range, but non-linearities in the perception across the tested frequency range resulted larger differences in frequency resulting in counterintuitive decreases in performance (Figure 27). These results likely relate to our previous

results, in which we found non-linearities in the perceptual responses to frequencies on some electrodes, which were spatially clustered in the somatosensory cortex (C. Hughes et al., 2020).

On electrodes in which the participant could discriminate frequencies, low frequencies had smaller JNDs than high frequencies, which is expected based on Weber's law. However, we also found that the Weber fractions in these two regimes were different, although this difference was not statistically significant from our data. Differences in Weber fractions could indicate different mechanisms are being used to discriminate low and high frequency stimuli. Indeed, the brain may use rate codes for higher frequency tactile stimuli and timing codes for low frequency stimuli (Harvey, Saal, Dammann, & Bensmaia, 2013; Saal et al., 2015). This property has also been observed in auditory perception, where low frequency and high frequency tones have different Weber fractions (Ungan & Yagcioglu, 2014). In fact, the frequency characteristics of touch and audition are linked (Yau, Olenczak, Dammann, & Bensmaia, 2009). This may then implicate a fundamental motif of sensory processing, in which different frequency domains are processed through different mechanisms. However, more data would be needed to substantiate this claim.

7.4.2 Interpulse Spacing Affects Tactile Perception

We found that even while maintaining the same number of pulses, shifting individual pulses changed perception on half of the tested electrodes. We believe that the reason only half of tested electrodes showed some significant difference in perception is related to the organization of cortex as we previously described, where some areas of cortex, and corresponding electrodes, are not sensitive to the timing of stimuli and are more generally sensitive to the rate. On the electrodes which were sensitive to changes in timing, we found similar JNDs of 15-ms and 17-ms with 20 and 40 Hz references. The minimum shift needed to drive a change in perception then may be

consistent across frequencies. If this is true, it would additionally imply that for frequencies higher than 67 Hz, changes in interpulse spacings would not produce perceptible differences, since the minimum space between pulses for higher frequencies is larger than 15-ms. This may indicate a transition from using a temporal code to a rate code in the cortex.

7.4.3 Larger Interpulse Spacings Bias Tactile Perception

We found that by shifting pulses, the perceived frequency decreased. Shifting every other pulse results in half of the interpulse spacings becoming larger, and the other half becoming smaller. Since the perceived frequency decreased, the larger interpulse spacings must bias the perception more than the smaller interpulse spacings. This aligns with previous findings using mechanical indentations of the human hand (Ingvars Birznieks & Vickery, 2017; Ng et al., 2018). In these studies, it was demonstrated that the larger interpulse spacings of vibratory stimuli decreased the PSE. Our results show that ICMS works in a similar way to normal tactile input, providing further evidence that there is a correspondence between the brain's processing of normal tactile input and ICMS.

7.4.4 Limitations and Implications

All results obtained here were in one participant. This will need to be investigated further in other human participants to know if the effects are generalizable. Although these results show that interpulse spacing alone can influence tactile perception, the details underlying these effects require further investigation. We only manipulated pulse timing in one way, in which every other pulse is shifted by a set amount. Other trains that involve more stochastic changes in timing or

other patterns were not tested here and may influence perception in different ways. We know from previous work that there are spatially dependent effects of ICMS frequency, but electrode dependent relationships were not explored here. We also have observed previously that frequency can affect perceptual quality (C. Hughes et al., 2020), but how interpulse spacings impact quality was not explored here. Furthermore, values for JNDs and PSEs were obtained based on average data, but it is hard to assess if these values are generalizable given the data set. We hope these results will inspire further more detailed studies to understand how interpulse spacings impacts tactile perception. We believe this will be important in the design of sensory feedback algorithms moving forward. Our results imply that encoding algorithms will need to consider the interpulse spacings in an electrode dependent manner to optimally provide sensory feedback.

8.0 Continuous, High Frequency Microstimulation of Human Somatosensory Cortex Habituates Evoked Sensations

This chapter is taken directly from a first authorship manuscript which is currently in preparation. Bidirectional brain-computer interfaces (BCIs) have the potential to restore functional movement and sensation to people with spinal cord injury. However, if stimulation evoked perception diminished over time, then sensory feedback would not be very useful for a clinically implanted device. Here, we document decreases in the intensity of evoked perception with stimulation and find that sensation are typically extinguished within a minute of continuous stimulation. Intermittent stimulation paradigms however result in changes in intensity that never lead to complete extinction. These results imply then that intermittent stimulation paradigms may provide a better way to encode sensation for clinical applications by maintaining perceptible sensation over long periods of time.

8.1 Introduction

Habituation refers to the diminishment or extinction of sensation as continuous stimulation is provided. This effect has been documented with stimulation of peripheral nerves for tactile perception (Graczyk, Delhaye, Schiefer, Bensmaia, & Tyler, 2018) as well as ICMS of the visual cortex for vision restoration (E. M. Schmidt et al., 1996). However, whether or not habituation occurs with ICMS of somatosensory cortex has not been previously demonstrated.

For a bidirectional BCI to benefit people who are implanted, it will need to provide reliable feedback during every day motor control. For example, a person may want to drink from a cup of coffee using their BCI. If the sensation of holding the cup habituated within a short period of time, the person may become unable to tell if they are holding the cup or not without visual input. In order then to practically apply sensory feedback for bidirectional BCI applications, we will need to design a feedback system that doesn't result in habituation of sensation. The goal of this paper was to document and understand habituation of perceived intensity with ICMS of somatosensory cortex and to investigate methods to reduce this effect to produce a better bidirectional BCI for clinical implementation.

8.2 Methods

8.2.1 Continuous Stimulation Habituation Protocol

P2 used an analog slider to indicate changes in intensity over time while receiving continuous stimulation. The analog slider began in the highest possible position which indicated the starting intensity, which read as 0.97-1 units. We considered the intensity to have changed from baseline when the participant moved the slider to be below 0.95 units. We considered the sensation to be completely extinguished when the slider had been moved to less than 0.05 units. Recordings were taken up to 15-s after stimulation was ceased to measure any further changes in intensity following cessation of stimulation.

For burst-modulated stimulation, we delivered pulse trains of 100 Hz at 60 μA to single electrodes. To maintain stimulation over long periods of time, we used burst modulation with small

intermittent delays in stimulation. We tested three different burst modulation paradigms: 100-ms, 200-ms, and 500-ms (Figure 30B). Each of these burst modulations consisted of a burst of stimulation followed by a period of no stimulation of equal size. For example, 100-ms of 100 Hz stimulation followed by 100-ms of no stimulation. We delivered 60-s of stimulation for each of these burst modulations on 10 electrodes.

For fully continuous stimulation, we delivered pulse trains of 20, 100, and 300 Hz at 60 µA to single electrodes (Figure 30A). We delivered 15-s of stimulation for 20 and 100 Hz and 5-s of stimulation for 300 Hz on 4 electrodes.

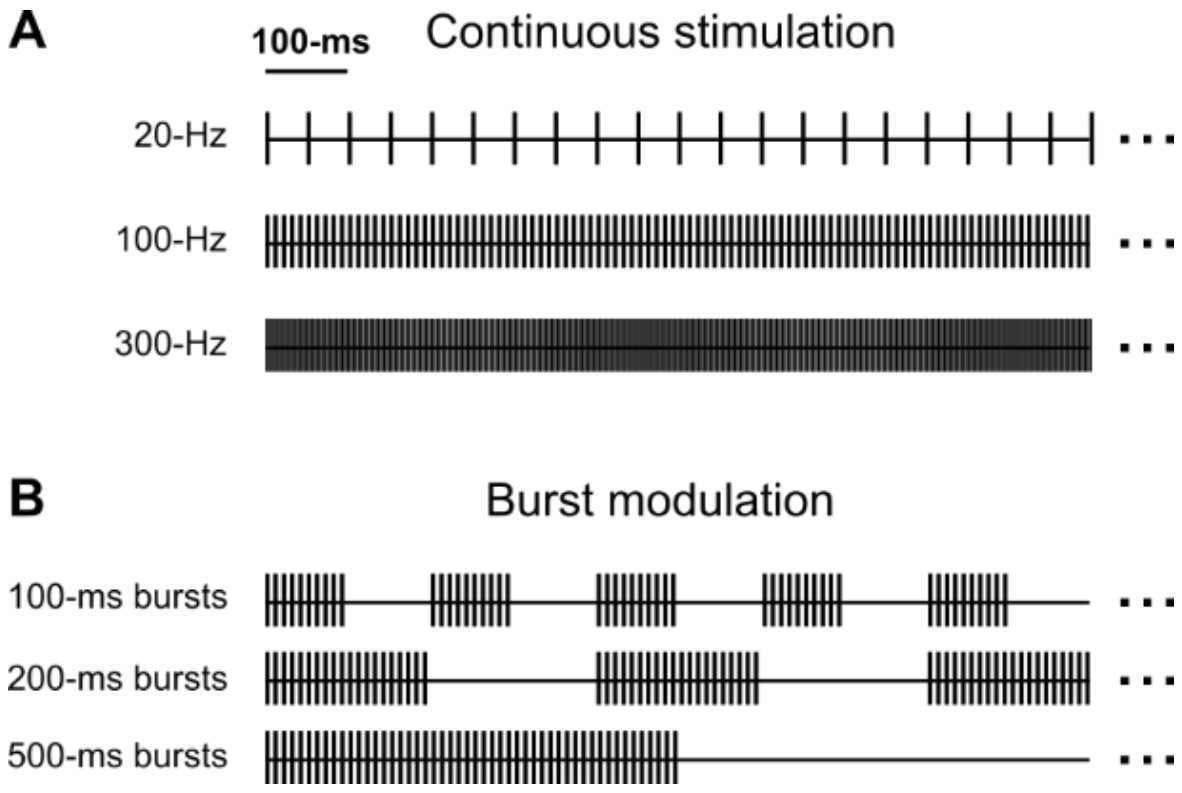

Figure 30: Pulse trains used for continuous habituation paradigms. Each line small line represents an individual pulse. We show a 1-s sample of each train. A) Continuous frequency trains. These trains were delivered for 5-s for the 300-Hz train and 15-s for the 20 and 100-Hz trains. B) Burst modulated trains. These trains were all delivered for a full 60-s.

8.2.2 Intermittent Stimulation Habituation Protocol

P2 received 1-s of stimulation at 60 µA followed by 4-s of no stimulation for 50 repetitions to measure changes in intensity over time. For each 1-s pulse train, the participant reported the perceived intensity on a self-selected scaled, which typically ranged from 0.1-2. Following 200-s of 1-s on 4-s off stimulation, P2 received 1-s on 60-s off stimulation for another 5 repetitions. This was used to assess any recovery in intensity over time following longer rest periods.

Seven electrodes were tested twice with the intermittent paradigm at 100 Hz to measure differences in habituation over time between electrodes. Four electrodes were tested four times with the intermittent paradigm at 20, 100, and 250 Hz to measure differences in habituation as a function of frequency.

8.2.3 Detection Habituation Protocol

Detection thresholds were determined the two-alternative forced choice task described in the GENERAL METHODS section.

Following the first detection task, the participant received 15-s of ICMS at 60 µA and 100 Hz followed by 15-s of no ICMS for 240-s. The detection task described previously was then repeated to find a new threshold.

8.2.4 Statistics and Data Analysis

All statistical analysis was conducted in MATLAB. To find if electrodes habituated more quickly under different burst modulations or frequencies for continuous stimulation, we compared

the times at which intensity began to drop between paradigms using Friedman's test. The time at which intensity began to drop was considered to be when the intensity fell below 0.95. Electrodes were organized by row and paradigm was organized by column for the Friedman test. To understand how intensity decreased as a function of frequency for the intermittent stimulation paradigm, we compared the difference between the intensity measured on the first repetitions and the intensity measured on the last repetition of the habituation paradigm using Friedman's test. Repeated measures were organized by row and stimulus frequency was organized by column for the Friedman test. We repeated this analysis for recovery by comparing the intensity measured on the last repetitions of the habituation paradigm and the intensity measured on the last repetition of the recovery paradigm. To find out if the ability to detect stimulation changed with long periods of stimulation, we compared the detection thresholds measured before and after a long period of continuous stimulation using a Wilcoxon rank-sum test.

8.3 Results

8.3.1 Continuous Stimulation Extinguishes Sensation Over Time

We delivered continuous burst-modulated ICMS to the somatosensory cortex of our participant for 60-seconds. Because fully continuous stimulation is limited to 15-s in our protocol, we had to use burst-modulation to stimulate for 60-s. We tested burst modulations of 100-ms, 200-ms, and 500-ms (Figure 30B). We found that stimulation for 60-s with any burst modulation on 26/29 tests led to complete extinction of sensation (Figure 31A). The time at which intensity began

to habituate on tested electrodes was not significantly different between burst paradigms ($p=0.12$, Friedman's test).

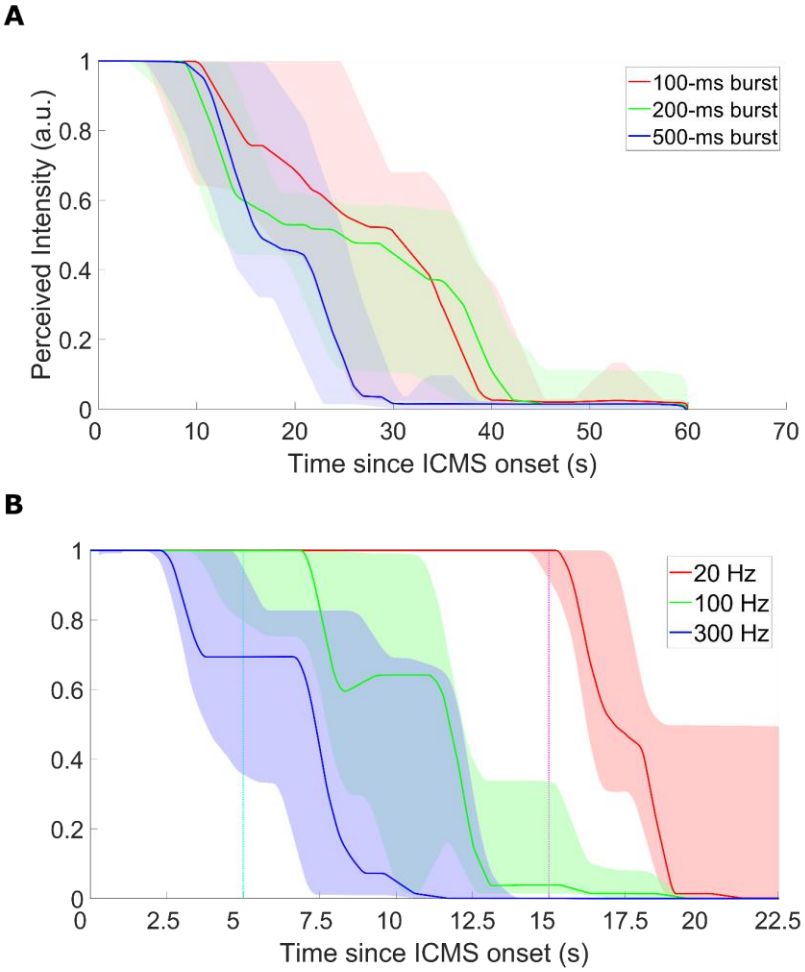

Figure 31: Continuous burst-modulated stimulation extinguishes perceived intensity across 60-s. The participant indicated the perceived intensity of ICMS with an analog slider. The slider always started at the top position, corresponding to a value of 1 and the participant moved the slider to indicate changes in perceived intensity. Each line represents the smoothed median intensity value across all tested electrodes for a given burst length, as indicated by the legend. The shaded regions represent the smoothed IQR across all tested electrodes for the given burst length. A) Continuous burst-modulated stimulation across 60-s. B) Completley continuous stimulation across 5 or 15-s. The cyan dotted line indicates the end of stimulation for the 300 Hz train. The magenta dotted line indicated the end of stimulation for 20 and 100 Hz.

8.3.2 Continuous Stimulation at Higher Frequencies Results in Faster Habituation

We delivered fully continuous stimulation for 15-seconds at 20 and 100 Hz on 4 electrodes (Figure 30A). We additionally delivered 5-s of continuous stimulation at 300 Hz. We found that the time at which intensity began to habituate on tested electrodes was significantly different between different stimulus frequencies ($p=0.018$, Friedman's test, Figure 31B). 300 Hz stimulation resulted in the fastest change from baseline, with the median elicited intensity falling to 58% (IQR: 24-85%) of the baseline intensity at 5-s of stimulation. The median electrode didn't elicit any changes in intensity at 20 Hz (median: 99.8%, IQR: 99.8-99.9%) or 100 Hz (median: 99%, IQR: 59-99%) within 5-s of stimulation. 100 Hz stimulation elicited intensity changes on the median electrode after 7-s and fell to 2.7% (IQR: 1.5-13.8%) of the baseline intensity at 15-s of stimulation. 20 Hz stimulation, however, did not result in any change in intensity within 15-s of stimulation on the median electrode (median: 99%, IQR: 83-99%).

8.3.3 Intensity of Intermittent Stimulation Changes in an Electrode Specific Manner that Never Results in Extinction

We delivered an intermittent stimulation protocol, consisting of 1-s of fully continuous stimulation followed by 4-s of no stimulation, for 50 repetitions on seven electrodes. We then delivered an intermittent stimulation protocol consisting of 1-s of fully continuous stimulation followed by 60-s of no stimulation for an additional 5 repetitions to test for recovery of intensity. We found that no electrode on which this protocol was conducted ever showed complete extinction of sensation (Figure 32). Additionally, most electrodes showed some decrease in intensity during the habituation paradigm and some increase in intensity during the recovery paradigm (Figure

32B). However, how intensity changed over time was found to be electrode specific. While most electrodes showed some habituation over the habituation protocol, some tested electrodes changed more dramatically. Two of the tested electrodes consistently decreased by more than 90% of the initial measured intensity (Electrode 36 and 64), while one tested electrode showed no change in intensity (Electrode 22). The median intensity decrease for the habituation paradigm was 62% of the initial intensity. Additionally, 5 of the 6 tested electrodes that showed habituation showed recovery of intensity during the recovery paradigm with longer interstimulus intervals. The median intensity increase on habituated electrodes across the recovery period was 112% of the intensity measured at the end of the habituation paradigm. We tested each electrode with the same protocol on two separate sessions. We found that the habituation that occurred on each electrode and the relative magnitude between electrodes was similar between sessions. However, the average magnitude of intensity values used by the participant changed between sessions (Average intensity S1 = 1.84, Average intensity S2 = 1.17).

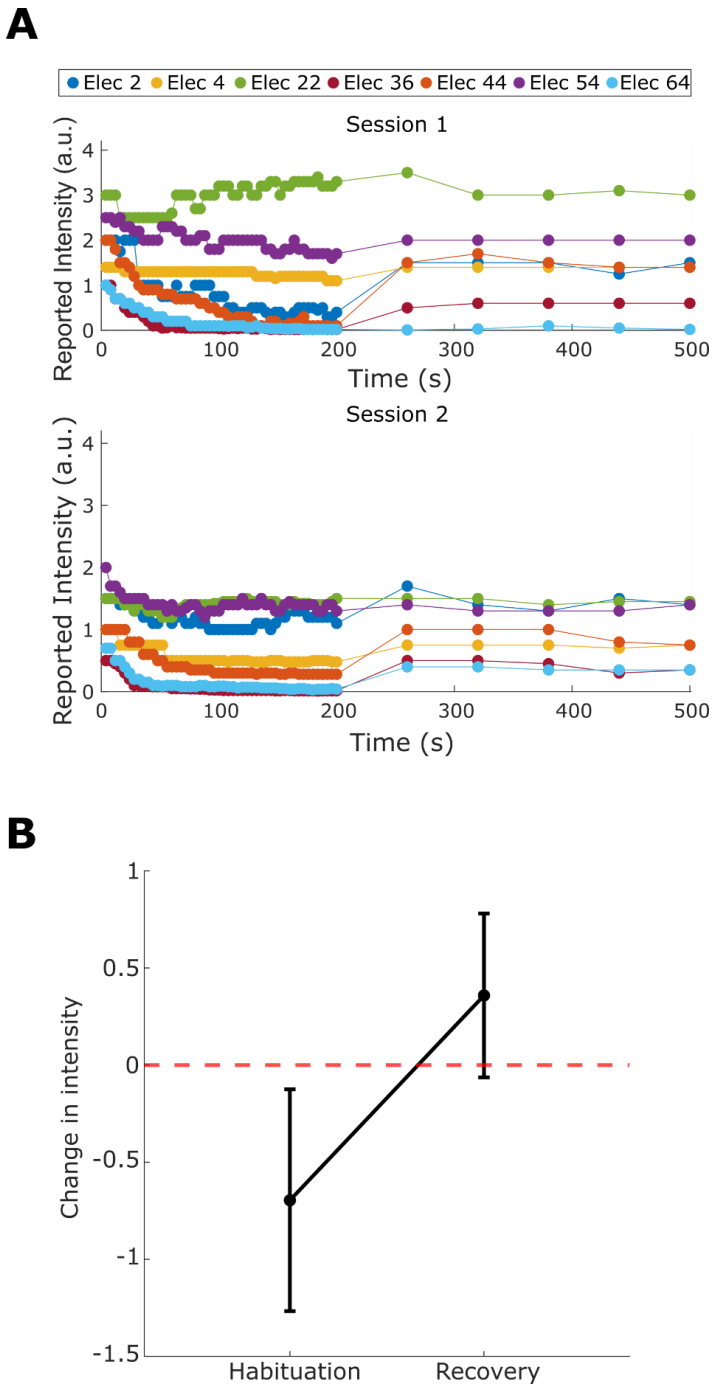

Figure 32: Intermittent stimulation lowered intensity over time which recovered with longer interstimulus delays. A) Each tested electrode was given stimulation for 1-s at 100 Hz every 5-s for 200-s and then was stimulated for 1-s every 60-s for 300-s. The participant indicated the perceived intensity for each stimulus train. Colored dots represent the intensity value measured at each time point. The color indicates the tested electrode as indicated by the legend. The top plot shows the first session on which each electrode was tested and the bottom plot shows the second session on which each electrode was tested. B) The change in intensity for habituation was the difference between the intensity at 200-s and 1-s and for recovery was the difference between the intensity at 500-s and 200-s. Black dots represent the average change across all tested electrodes and the error bar represents the standard deviation.

8.3.4 Intensity of Intermittent Stimulation Decreases by a Fixed Electrode-Specific Amount Across All Tested Frequencies

We repeated the habituation paradigm on four electrodes at 20 Hz, 100 Hz, and 250 Hz. These three frequencies represent a low, intermediate, and high frequency within our stimulus range. Consistent with previous findings (C. Hughes et al., 2020), we found that frequency had electrode specific effects on evoked intensity, where one electrode elicited the highest intensity at the lowest frequency while the other three electrodes elicited the highest intensity at the highest frequency (Figure 33A). Despite these differences, the amount the intensity decreased during the habituation paradigm and recovered during the recovery paradigm was consistent across frequencies for each tested electrode (Friedman test, $p > 0.05$, Figure 33B). However, if we measure habituation as a percentage of initial intensity, lower intensity percepts habituated and recovered more.

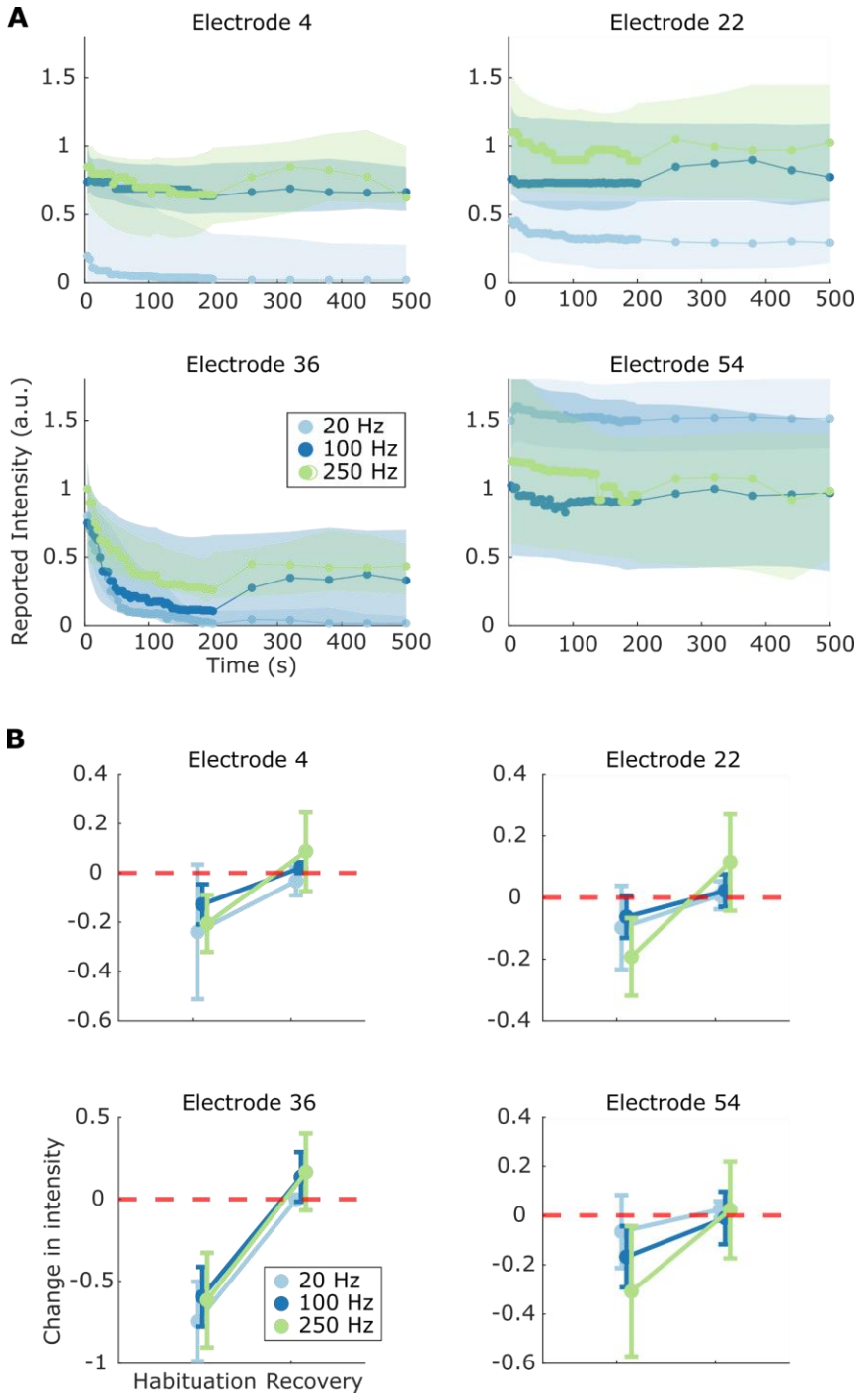

Figure 33: Different frequencies of intermittent stimulation result in similar magnitudes of habituation and recovery. A) Each tested electrode was given stimulation for 1-s every 5-s for 200-s and then was stimulated for 1-s every 60-s for 300-s at 20, 100, and 250 Hz. The participant indicated the perceived intensity for each stimulus train. Colored dots represent the median intensity value measured at each time point across 4 test sessions. Shaded regions indicate the minimum and maximum value range across 4 test sessions. The color indicates the tested frequency as indicated by the legend. Each plot shows the results for a different tested electrode. B) The change in intensity for habituation was the difference between the intensity at 200-s and 1-s and for recovery was the difference between the intensity at 500-s and 200-s. Colored dots represent the mean difference across 4 test sessions. Error bars indicate the standard deviation across 4 test sessions. The red dotted line indicates no change in intensity.

8.3.5 Detection of Stimulation was Not Significantly Changed with Continuous Stimulation

To test if the ability to detect stimulation was affected by long periods of continuous stimulation, we measured detection thresholds using a dynamic detection task. We then delivered 4 minutes of stimulation with 15-seconds on followed by 15-s off, which is the maximal length of time we can continuously deliver stimulation. We then remeasured detection thresholds. Across 12 tested electrodes, we found no significant difference in the thresholds measured before and after 4 minutes of stimulation ($p=0.12$, Wilcoxon rank sum test) with a median threshold increase of 1.3 μA following continuous stimulation.

8.4 Discussion

8.4.1 Continuous Stimulation at High Frequencies Leads to Extinction of Sensation

We found that fully continuous and burst-modulated stimulation at high frequencies, such as 100 and 300 Hz, resulted in habituation and eventually extinction of sensation. Interestingly this contrasts with studies done in the peripheral nervous system, where it was found that pulse frequency had no significant impact on the rate of habituation (Graczyk et al., 2018).

Low frequency stimulation across 15-s never resulted in habituation. However, due to protocol limitations, we could not stimulate continuously longer than this, so it is difficult to know if very low frequency stimulation would result in habituation over long periods of time. Using low frequency stimulation may provide other barriers for bidirectional BCIs. Specifically, it has been demonstrated that low frequencies have effects on perceived intensity and quality which are

electrode specific (C. Hughes et al., 2020). Inconsistency in the intensity and quality of the evoked sensation may be undesirable for bidirectional BCI application. For example, evoking qualities of "tapping" or "sparkle" would be undesirable for object grasping. Therefore, low frequency stimulation likely doesn't provide a practical means to provide consistent sensations.

8.4.2 Intermittent Stimulation Resulted in Electrodes Specific Changes in Intensity Over Long Periods of Stimulation but Never Resulted in Extinction

Intermittent stimulation allowed for sensation to be evoked over much longer periods of time than we found with continuous stimulation. Sensation never extinguished over 200-s of high-frequency stimulation with an intermittent paradigm. Intermittent stimulation did however result in habituation of intensity, which was electrode specific. Similar to previous findings in visual cortex (E. M. Schmidt et al., 1996), many electrodes exhibited some recovery of intensity with longer intermittent stimulation times. For bidirectional BCI use, it might make sense then to select electrodes that do not demonstrate habituation over long period of times. However, the electrode-specific habituation observed might relate to other important aspects of evoked sensation. We have previously documented electrode-specific effects of frequency on intensity as well as the electrode-specific presence of specific sensory qualities (C. Hughes et al., 2020). It may be the case then that, rather than completely excluding electrodes that exhibit fast habituation, these electrodes should be used in specific circumstances, such as signaling onset and offset of object contact.

Intermittent stimulation provides a further benefit for BCI applications. Continuous stimulation currently can only be provided for 15-s with 20 or 100 Hz, and only 5-s with 300 Hz. While burst modulation provides one method to continuously provide stimulation over long

periods of times, we found that burst modulation completely extinguished sensation. Intermittent stimulation, or in other words providing stimulation at only task-dependent points, then can provide a method to provide continuous evoked sensation over long periods of time given current safety guidelines.

8.4.3 Detection Thresholds of Stimulation were Not Impacted by Long Periods of Stimulation

Although we found both continuous and intermittent stimulation affected the perceived intensity, we did not find any significant effect on measured detection thresholds. This does not agree with previous literature in the peripheral nervous system, where detection thresholds were significantly increased after continuous stimulation (Graczyk et al., 2018). Furthermore, this doesn't intuitively agree with our findings on habituation of perceived intensity. The expectation would be that, if intensity decreased, detection thresholds should increase. However, we have demonstrated previously that detection and intensity perception do not necessarily go hand in hand (C. Hughes et al., 2020). Therefore, knowing that stimulation decreases intensity does not mean it will always increase thresholds.

However, a potential confound with this experiment is the method for evaluating detection thresholds results in 1-s of stimulation followed by a delay of typically 5-10 seconds for 2-5 minutes. The protocol then is similar to the protocol that we use for intermittent stimulation, which itself drives habituation. This would mean that the first detection task could drive habituation, which may mean the threshold measured is not an accurate representation of detection prior to habituation. Furthermore, the detection task could similarly allow for some recovery from the 4 minutes of continuous stimulation during the second detection task since there are longer delays

between stimulation. Unfortunately, any task used to calculate detection thresholds would require the delivery of stimulation, making the effect of stimulation on thresholds difficult to determine. Previous experiments in the peripheral nervous system addressed the recovery problem by delivering bursts of the conditioning stimulus during the second detection task (Graczyk et al., 2018). However, this makes it difficult to determine if the conditioning stimulus increased the detection thresholds or the intermittent bursts are affecting the participant's ability to perform detection. Given that we never observed complete recovery of intensity following our intermittent habituation paradigm, we don't believe that recovery during the detection task should play a significant role in measured detection thresholds if the conditioning stimulus increased the detection thresholds.

9.0 Biomimetic Amplitude Modulation Improves Naturalness and Intuitiveness of Evoked Percepts

This chapter is taken directly from a first authorship manuscript which is currently in preparation. Intracortical microstimulation (ICMS) is a method to restore sensation through direct interface with the brain. Previous work has demonstrated that ICMS can evoke sensations of the arm and hand and improve brain-computer interface control. However, sensations evoked were often unnatural and varying in quality, which is not desirable for a clinical implant. Here, we investigate if biomimetic modulation of pulse trains can change evoked qualities and improve the evoked naturalness and intuitiveness of sensations. We built two pulse trains based on neural activity recorded in non-human primates that modulated the frequency or the amplitude. The biomimetic frequency train did not consistently change the quality or naturalness and had electrode specific effects. We found that the biomimetic amplitude modulated train resulted in increases in naturalness and intuitiveness of sensation across many electrodes and increased the report of more natural "poke" sensations. Additionally, biomimetic amplitude modulation resulted in decreases in the projected field size of evoked percepts. These results imply that biomimetic modulation may provide a method to improve the naturalness and focality of evoked percepts.

9.1 Introduction

One possible method to improve upon sensory feedback is biomimetic modulation (Bensmaia, 2015; Fagg et al., 2007; George et al., 2019; Giacomo Valle et al., 2018). Biomimetic

modulation refers to modulating the pulse trains in a way that more closely resembles normal neural activity. Previous work has investigated the cortical activation of non-human primate cortex using tactile indentation of the hand (Callier et al., 2018). From these studies, models were developed to simulate population neural activity (Saal et al., 2017)and from this a program was developed to produce biomimetic trains (Okorokova et al., 2018). This model was used successfully in peripheral stimulation to improve the naturalness and function of a bidirectional peripheral device (Giacomo Valle et al., 2018). In this previous work, both frequency and amplitude modulation of stimulation contributed to an improvement in perceived naturalness. However, this method has not previously been evaluated for cortical stimulation. It is known that cortical stimulation and peripheral stimulation differ in terms of how parameters affect perception. In particular, it has previously been shown that increase in frequency consistently increase intensity of evoked percepts in peripheral nerve stimulation (Graczyk et al., 2016). However, we previously found frequency to have electrode specific effects on perceptions for cortical stimulation (C. Hughes et al., 2020). Therefore, evaluating if biomimetic amplitude and frequency modulation could improve the naturalness of ICMS will be important to understand how we can best implement a bidirectional brain-computer interface.

Here, we investigated how biomimetic modulation of pulse trains impacted the perceived naturalness and intuitiveness of stimulation in two participants with electrodes implanted in somatosensory cortex.

9.2 Methods

9.2.1 Pulse Train Design

We designed multiple ICMS pulse trains based on fixed parameters, biomimetic modulation, or linear modulation. All trains used in these tasks are 1-s in length, except for the duration discrimination task in which the durations were changes for the purpose of the task. Fixed trains refer to pulse trains that had a constant amplitude and frequency throughout the full 1-s duration. Three types of biomimetic trains were used in this study: biomimetic frequency, biomimetic amplitude, or TouchMime trains. The biomimetic frequency train varied the timing of pulses based on the threshold crossings of a recorded neural unit from a non-human primate during hand stimulation while keeping the amplitude constant (Figure 34A, top). The biomimetic amplitude trains varied the amplitude of stimulation based on the recorded firing rate of a population of neurons in non-human primate cortex during hand stimulation while keeping the frequency constant (Figure 34A, bottom). The TouchMime trains were produced by feeding in different mechanical indentation profiles into TouchMime (Okorokova et al., 2018) and normalizing the output to the desired ICMS amplitude range (Figure 39). The linear trains were produced by using the same mechanical indentation profiles and converting them directly to ICMS trains by normalizing to the desired amplitude range.

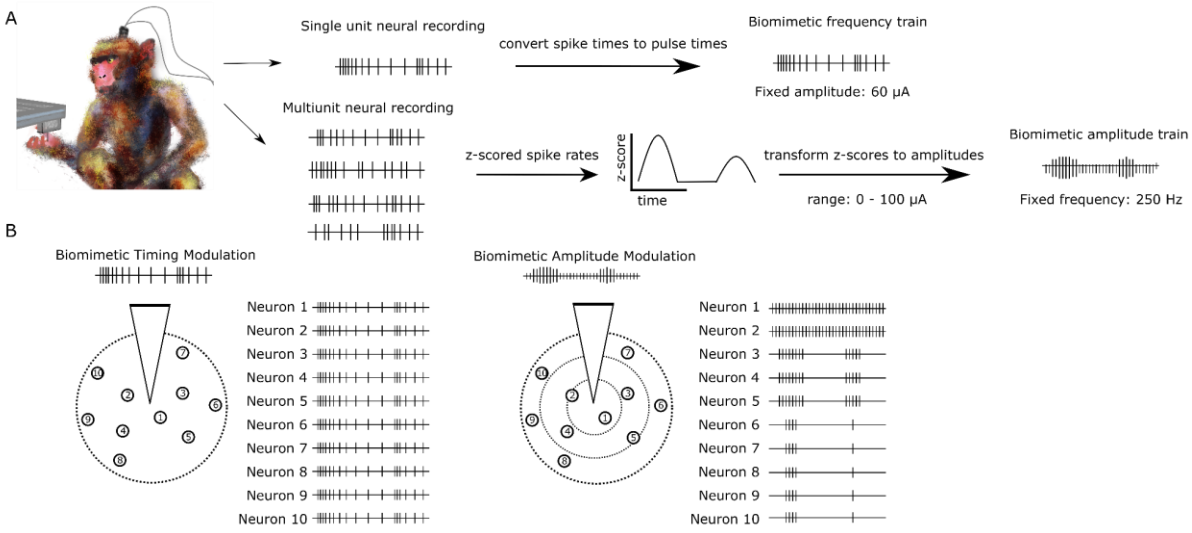

Figure 34: Biomimetic trains were produced from non-human primate neural data. A) Neural data was recorded from non-human primates while they received mechanical indentation to the hand. We built two trains from this neural activity: biomimetic timing (top) and biomimetic amplitude (bottom). B) The theoretical effects of each biomimetic train. Biomimetic timing trains should recruit the same population of neurons over time with a biomimetic time profile. Biomimetic amplitude trains should recruit different neurons throughout the train, with more neurons recruited during the onset and offset transients

9.2.2 Naturalness Discrimination

The participant received stimulation on two intervals separated by an intertrain delay. On each interval, the participant received a biomimetic train or a comparison, in random order. The comparisons were fixed trains of 20, 100, or 250 Hz. The biomimetic trains consisted of either the biomimetic frequency or biomimetic amplitude train (Figure 34A). We additionally conducted additional tests with comparing the biomimetic amplitude train to a 200-ms fixed train (Figure 38), and a biomimetic timing train (Figure 34A). After receiving each stimulation, the participant had to choose the interval that they believed contained the more natural evoked percept. For the purposes of this task, we defined natural as "something that could be experienced in every-day life

with normal tactile input." Each comparison was provided 30 times on each tested electrode. Selection was considered to be significantly different based on the binomial test for each comparison.

For experiments in which intensity matching was used, we used a method of adjustment (Kingdom & Prins, 2013). Prior to the naturalness discrimination, we would play the biomimetic train and then the reference and ask the participant which was more intense. Based on the participant's selection, we would either increase or decrease the amplitude of the reference by 10 μA. We would repeat this procedure until the participant indicated that the intensities of the train were the same.

9.2.3 Duration Discrimination

The participant received stimulation on two intervals separated by an intertrain delay. On each interval, the participant received a biomimetic amplitude train or a comparison, in random order. The comparisons were fixed trains of 250 Hz, 60 μA, and 0.2-1.2 s. Presentation of different train durations was block randomized. After receiving each stimulation, the participant had to choose the interval that they believed contained the longer duration of stimulation. Each comparison was provided 10 times on each tested electrode, resulting in 60 trials per set. All electrodes were collected twice except for electrode 3, which was not retested due to a high interphase voltage during the second set of data collection. The results were pooled across tested electrodes and fit with logistic regression. The point-of-subjective equivalence was the point where the logistic fit crossed 50%.

9.2.4 Intuitiveness Discrimination

The participant received mechanical indentation with amplitude and rates of 0.5mm at 10mm/s, 2mm at 5mm/s, 2mm at 10mm/s, and 2mm at 50mm/s. These values were used in reference to prior literature in non-human primates (Callier et al., 2018). Following this, the participant received stimulation on two intervals separated by an intertrain delay. Each interval contained either a TouchMime train or a linear encoded train that corresponded to the presented mechanical train, and the order was randomized (Figure 39A). The participant was instructed to choose the ICMS interval that contained the evoked percept that felt most like the mechanical input. Each triplet of trains was presented 30 times in a block randomized fashion for each tested electrodes, resulting in a total of 120 trials per electrode. Breaks were taken every 40 trials. Differences in selection were pooled across tested electrodes and were considered to be significant based on a Wilcoxon rank-sum test.

All trains were intensity matched prior to the experiment using a dynamic intensity matching task. In this task, the participant received stimulation on two intervals separated by an intertrain delay. Each interval contained either a TouchMime train or a linear encoded train, and the order was randomized. The participant would indicate which interval contained the more intense evoked percept. The amplitude of the linear train would then be increased or decreased by 2 μA based on the response. The linear train could be varied to have maximum amplitudes of 20-80 μA. If either of these limits were reached, the intensity matching would stop and the corresponding amplitude would be used as the matched amplitude for intuitiveness discrimination. Otherwise, after ten changes in direction of the amplitude changes, the experiment would stop and the matched amplitude would be determined with Bruceton analysis (Dixon & Mood, 1948).

9.3 Results

To test the impact of biomimetic modulation on perception, we created two types of pulse trains: biomimetic frequency modulated and biomimetic amplitude modulated (Figure 34). Both trains were built based on neural activity recorded from the cortex of a non-human primate (Callier et al., 2018). For the biomimetic frequency modulated train, we used the recorded threshold crossings of a single recorded unit. The ICMS pulse train then had a fixed amplitude and each pulse occurred at the same time point as the recorded thresholds crossings. This resulted in high frequency transients during the "onset" and "offset" events of the tactile indentation. For the biomimetic amplitude modulated train, we used the recorded population activity. The ICMS pulse train had a fixed frequency and the amplitude was modulated based on the total recorded firing rate. This resulted in large amplitude transients during the "onset" and "offset" events of the tactile indentation.

9.3.1 Biomimetic Frequency Modulation had Electrode Specific Effects on Naturalness

We began by testing the impact of biomimetic frequency modulation on perceived naturalness. To test this, we compared biomimetic timing trains to fixed frequency trains of 20, 100, and 250 Hz using a two-alternative forced choice (2AFC) task for naturalness. The participant was asked to select the pulse train they perceived as being more natural. We found that the biomimetic timing trains did not generally improve the naturalness but instead had electrode specific effects (Figure 35). We found he chose the biomimetic trains more on 13 comparisons, chose the non-biomimetic trains on 13 comparisons, and still on 16 comparisons there was no significant difference, resulting in a biomimetic selection percentage of 31%. On some electrodes,

it was noted that the participant perceived very natural "tapping" sensations at 20 Hz, which aligns with previous findings (C. Hughes et al., 2020). When the participant selected the biomimetic stimulation, it was reported to feel more like a "poke." Most often, both fixed and biomimetic modulated stimulation resulted in "tingle" and were not perceptibly different in terms of naturalness.

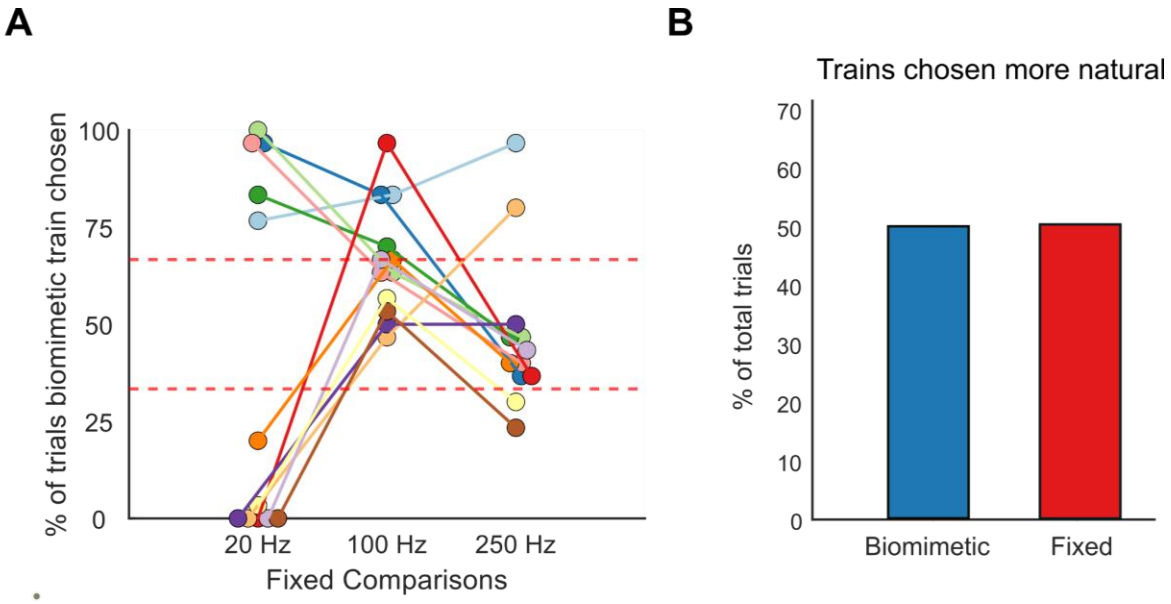

Figure 35: Biomimetic frequency trains drive electrodes specific effects. A) The percent of trials on which biomimetic frequency trains were chosen for each comparison on each tested electrode. Each color represented a different tested electrode. Solid lines connect the same electrode tested across different parameters. The red dotted lines mark bounds for significance according to the binomial test, where points above the top line or below the bottom line are significant. B) The percent of total trials on which the biomimetic frequency trains or fixed trains were chosen.

9.3.2 Biomimetic Amplitude Modulation Resulted in More General Increases in Perceived Naturalness

We next tested the impact of biomimetic amplitude modulation on perceived naturalness. We again compared the trains to fixed frequency and fixed amplitude trains. We found a more

general increase in the perceived naturalness of stimulation (Figure 36A,B). We found he chose the biomimetic trains more on 21 comparisons, chose the non-biomimetic trains on 14 comparisons, and still on 4 comparisons there was no significant difference, resulting in a biomimetic selection of 54% and a non-biomimetic selection of 36%. Similar to the previous experiment, we found that some electrodes evoked intense "tapping" sensations at 20 Hz which was still perceived as more natural than the biomimetic stimulation. Additionally, on four tested electrodes, the intensity was low, which resulted in the participant selecting the train that was more intense. If these electrodes are removed, the preference for biomimetic trains becomes even more pronounced, with a biomimetic selection of 70%.

To account for this confound of intensity, we repeated these experiments on a subset of electrodes, which were selected to include both high and low intensity electrodes, and preceded the discrimination experiment with an intensity matching paradigm. When the intensities were matched prior to the experiment, the participant selected the biomimetic amplitude trains more frequently (Figure 36C,D). With this paradigm, the biomimetic trains were selected on 16 comparisons, the non-biomimetic trains were selected on 5 comparisons, and on 6 comparisons there was no significant difference, resulting in a biomimetic selection of 59% and a non-biomimetic selection of 19%. This indicates that when accounting for intensity effects, the biomimetic trains made the quality of sensation more natural.

To quantify the effect size of the change in naturalness, we delivered biomimetic amplitude modulated trains on every electrode and asked the participant to report the quality and naturalness of the evoked sensation. We compared these results with our standard surveys, in which we delivered 100 Hz, 60 μA pulse trains on each electrode. We found that the median reported naturalness significantly increased from 5.2 to 5.4 ($p = 7.97e-6$, Wilcoxon rank-sum test, Figure

37A). Surprisingly, we found the qualities reported were largely similar, except that the biomimetic trains had significantly more reports of "poke/prick" ($p = 7.13e-5$, Fisher's Exact Test, Figure 37B) where reports of poke increased from 3% for the standard survey to 15% for the biomimetic survey. Additionally, there was a significant decrease in reports of "warm" ($p = 0.038$, Fisher's Exact Test) where reports decreased from 30% for the standard survey to 23% for the biomimetic survey. We additionally found that biomimetic stimulation evoked more focal percepts ($p = 3.6e-6$, Wilcoxon rank-sum test, Figure 37C). We saw a decrease in the median projected field size from 6132 pixels^2 for the standard stimulation to 3876 pixels^2 for biomimetic stimulation.

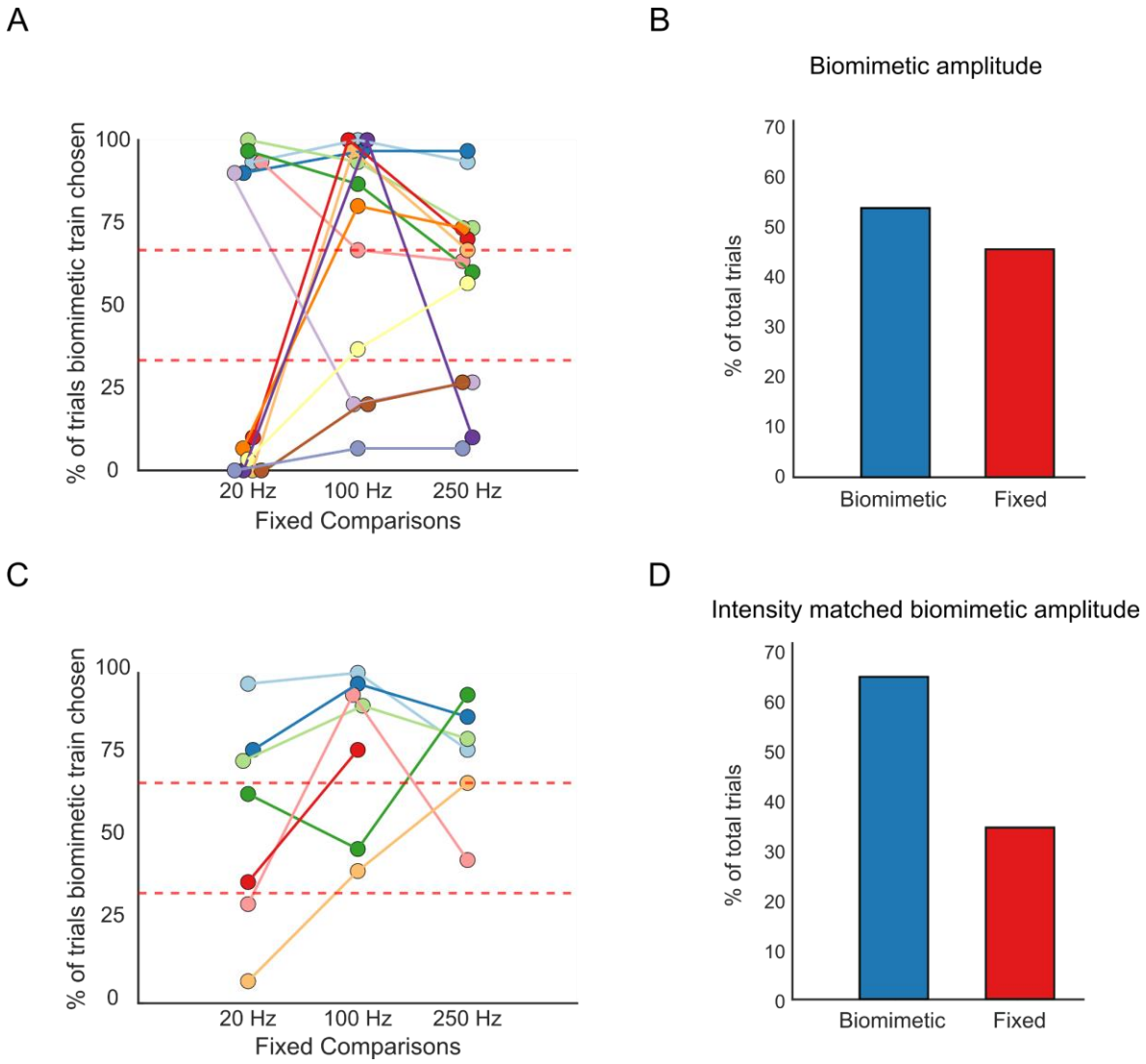

Figure 36: Biomimetic amplitude trains result in more general increases in naturalness over fixed trains. A) The percent of trials on which biomimetic frequency trains were chosen for each comparison on each tested electrode. Each color represented a different tested electrode. Solid lines connect the same electrode tested across different parameters. The red dotted lines mark bounds for significance according to the binomial test, where points above the top line or below the bottom line are significant. B) The percent of total trials on which the biomimetic chosen for each comparison on each tested electrode when fixed trains were intensity matched. B) The percent of total trials on which the biomimetic amplitude trains or fixed trains were chosen when fixed trains were intensity matched.

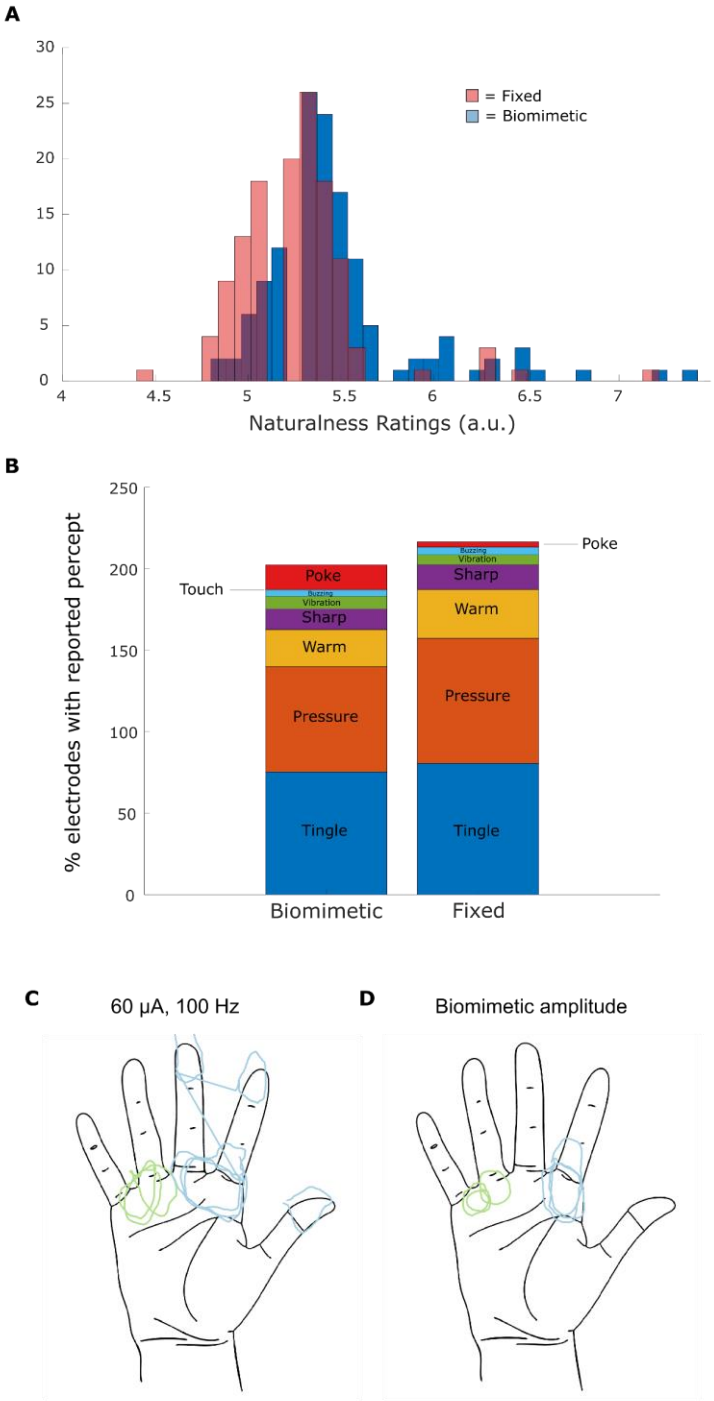

Figure 37: Comparison of sensations evoked by biomimetic and fixed stimulation. A) A histogram of the reported natrualness for the 60 uA, 100 Hz surveys and the biomimetic amplitude surveys. Biomimetic amplitude surveys had a significantly higher naturalness with a median of 5.4 vs 5.2 for the 60 uA survey. B) Stacked bar plots showing a comparison of the perceptual qualities evoked. Biomimetic amplitude surveys had significantly more reports of "Poke" and significantly less reports of "Warm." C) Example of the projected fields of two electrodes for the 60 uA survey (left) and the biomimetic amplitude survey (right). Biomimetic amplitude stimulation showed significantly smaller projected fields.

9.3.3 Biomimetic Amplitude Modulated Trains were Perceived as More Natural and Longer than Short Fixed Trains

Many of the biomimetic amplitude modulated trains were reported as feeling like "short pokes." Based on this description, we wondered if shorter pulse trains could similarly produce more natural sensations. We compared 200-ms fixed parameter trains to biomimetic amplitude modulated trains and found that the evoked naturalness was similar between the trains (Figure 24A), although the biomimetic amplitude trains were still selected more frequently (Figure 38B).

This result implied that the biomimetic amplitude train might evoke shorter sensations, which were perceived as more natural than longer durations. We thought that only the onset transient might be perceived, resulting in the perceptions of a 100-200 ms train. To check if this was true, we used a duration discrimination task, in which we compared the biomimetic amplitude modulated train to fixed amplitude trains of 0.2-1.2 s. We found that the point of subjective equivalence was 0.97-s (Figure 38C). This indicated then that the biomimetic amplitude train was not perceived to be shorter than the 1-second duration, but still maintained a quality and naturalness similar to a short duration train.

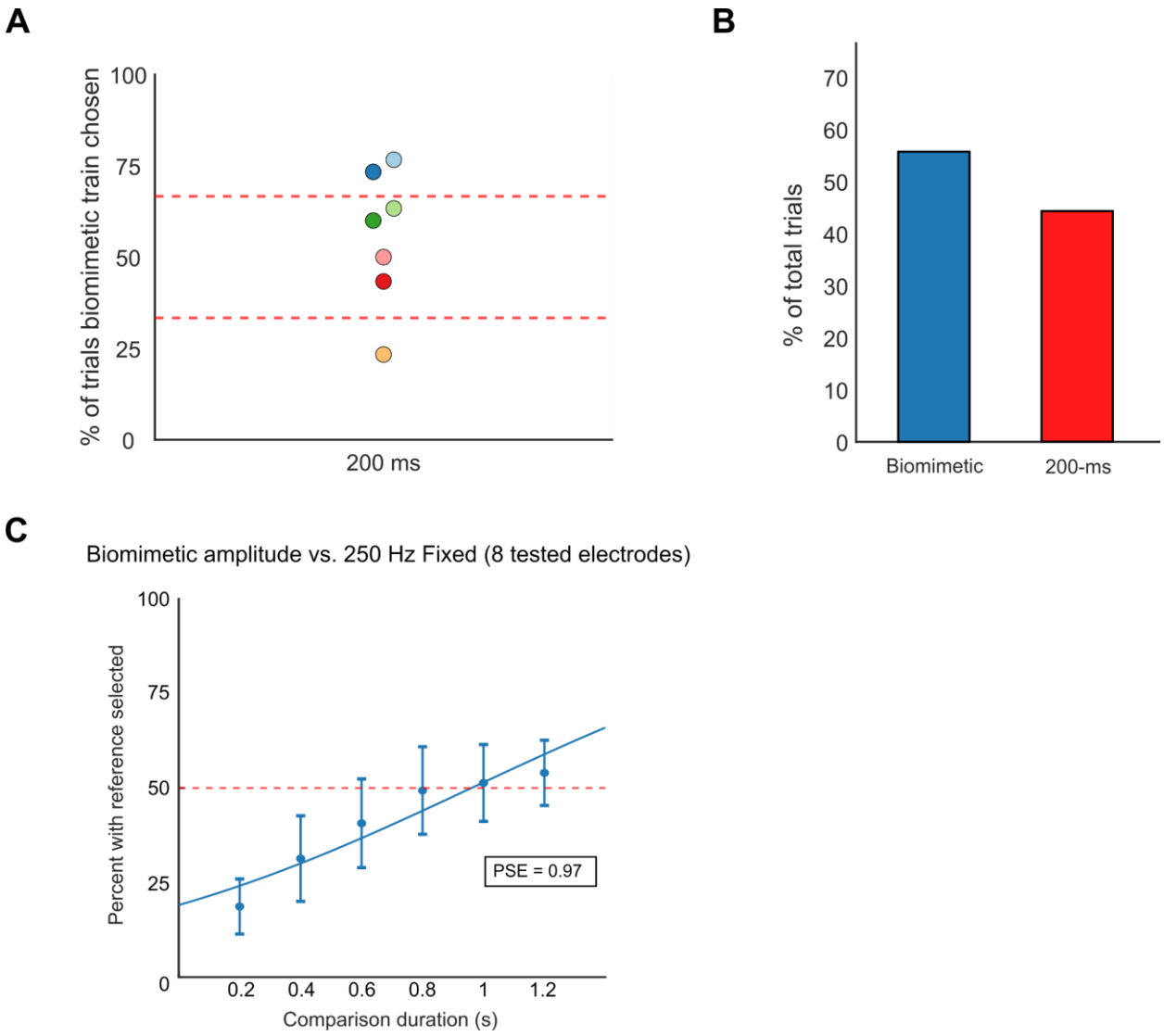

Figure 38: Biomimetic amplitude trains drive more natural and longer sensations than short trains. A) The percent of trials on which biomimetic amplitude trains were chosen over 200-ms fixed trains for each comparison on each tested electrode. Each color represented a different tested electrode. Solid lines connect the same electrode tested across different parameters. The red dotted lines mark bounds for significance according to the binomial test, where points above the top line or below the bottom line are significant. B) The percent of total trials on which the biomimetic amplitude trains or 200-ms fixed trains were chosen. C) The percent of trials on which the fixed reference train was selected as longer compared to the biomimetic amplitude train. Each point represents the mean across 8 tested electrodes. The error bar shows the standard error. The line represents a logistic regression fit. The point-of-subjective equivalence was selected as the point where the logistic fit crossed 50%.

9.3.4 TouchMime Generated Trains More Intuitively Felt like Mechanical Indentation than Trains Built with Linear Encoding

In order to provide biomimetic feedback for bidirectional brain-computer interfaces, we need a model that can flexibly transform touch into sensory feedback. Using recorded neural activity, as we have in the previous experiments, would not allow for on-the-fly transformations. TouchMime is a model based on real recorded neural activity designed to produce stimulus trains based on different force input profiles (Okorokova et al., 2018). We generated an ICMS pulse train using a simple ramp-and-hold function, representing a mechanical indentation (Figure 39A). We found that the ICMS pulse train produced this way was not discriminable from the biomimetic amplitude train in a naturalness discrimination task. This established that TouchMime trains could produce similar percepts to trains built from real neural activity.

We wanted to then understand if this biomimetic encoding with the TouchMime model would feel more intuitively like normal mechanical indentation. To test this, we delivered mechanical indentation of different amplitudes and rates to the lower palmar region of the participant's hand, which still contained intact sensation. Following mechanical indentation, the participant then received two intervals of ICMS trains, one of which contained a biomimetic train corresponding to the provided mechanical indentation and the other contained a linear encoded train. The participant was asked to indicate which train felt more intuitively like the presented mechanical indentation. We found that the participant was more likely to select the biomimetic train, and this bias was more pronounced at the higher rates and amplitudes (Figure 39B).

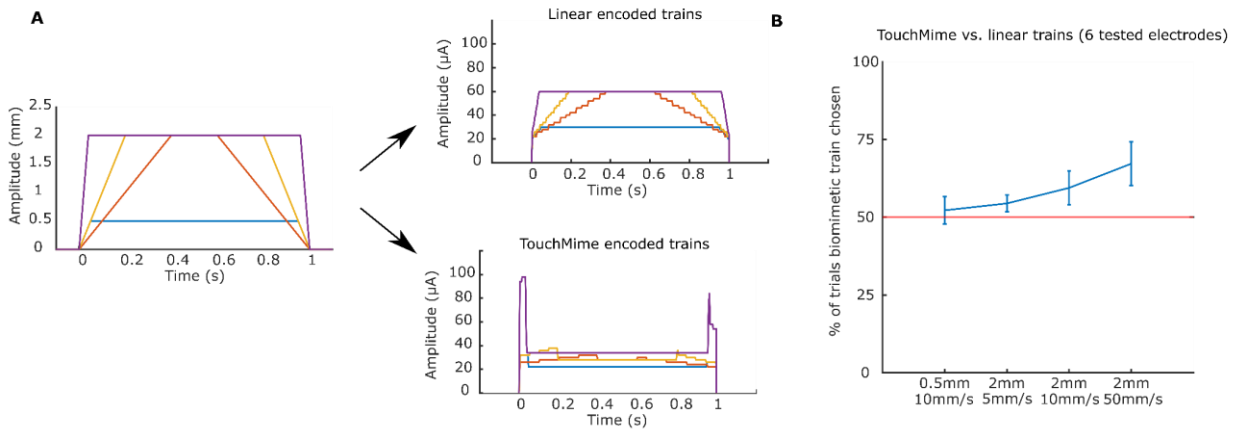

Figure 39: TouchMime encoded trains result in percepts that feel more intuitively like mechanical indentation than linear encoded trains. A) ICMS trains were built from mechanical force profiles using either linear encoding (top) or TouchMime (bottom). For linear encoded trains, force profiles were simply normalized to the desired amplitude range. For TouchMime encoded trains, force profiles were fed into TouchMime and the output was normalized to the desired amplitude range. B) A picture of the mechanical indenter set up. The participant's arm was strapped in and the mechanical indentation was applied to the lower palmar region of the hand. C) An outline of the paradigm. A mechanical indentation preceded each trial. This mechanical input was followed by an ICMS and linear train corresponding to the presented amplitude and rate of indentation. The participant then selected the interval that contained the stimulation that felt more like the mechanical input. D) The percent of trials on which TouchMime trains were chosen to feel more like the mechanical indentation that linear trains. Each point represents the mean percent of trials selected across six tested electrodes. The error bars represent the standard error.

9.4 Discussion

In this paper, we found that biomimetic amplitude modulation led to general increases in both naturalness and intuitiveness while biomimetic frequency modulation led to more electrode specific effects. Previous literature on biomimetic approaches in the peripheral nervous system showed that both amplitude and frequency modulation could lead to more natural percepts and modulation of both together resulted in the most natural percepts (George et al., 2019; Giacomo Valle et al., 2018). However, it has also been shown that frequency has more consistent effects in the peripheral nervous system. In particular, higher frequencies lead to higher intensities of evoked percepts. However, we have previously demonstrated that frequency has non-monotonic effects

on intensity and quality in the cortex (C. Hughes et al., 2020). Therefore, biomimetic frequency modulation having electrode specific effects is not very surprising.

Previously we found that amplitude had more consistent effects on intensity but didn't affect quality (C. Hughes et al., 2020). Because of this, it is a bit surprising that biomimetic amplitude modulation would produce more consistent effects on quality and naturalness. However, previously we only ever investigated one-second trains with fixed amplitudes. The key for biomimetic amplitude modulation may be varying amplitude over time as a function of the input. Indeed, in theory modulating amplitude over time should change the area of activated tissue as a function of the input (Figure 36B) whereas fixed amplitude stimulation would recruit all neurons with the same profile over time. It may be the case then that short transient activation of neurons is key to promoting more natural percepts. This agrees with the finding that short durations produce similarly natural percepts (Figure 38). However, biomimetic encoding of stimulation allows for more natural percepts perceived for longer durations.

Even though biomimetic amplitude modulation was able to improve the naturalness consistently in one participant, the effect size was not very large. Percepts on average went from a self-selected rating of 5.2 to 5.4. ICMS with current Utah electrodes recruits large swaths of tissue in synchrony which may deviate from normal activity in the cortex. In particular, many different neuronal cell types exist in the somatosensory cortex, some of which are inhibitory neurons that help regulate the activity of the network. Being able to target specific cell types might be necessary for more natural sensations. Although biomimetic amplitude modulation can change this by giving recruited neurons different profiles over time, it is likely that more targeted stimulation will be needed to produce fully natural percepts. This will require interventions with newer technologies that can better isolate individual neurons of specific subtypes

Aside from improving upon the naturalness and intuitiveness of stimulation, biomimetic modulation has other desirable qualities. For the same force profile, biomimetic stimulation results in less overall charge injection. Previous studies in animal models have shown that larger amounts of charge injection can lead to degradation of electrodes over time (D. B. McCreery et al., 1990; P. J. Rousche & Normann, 1999). Although we have not yet seen any decline in signal quality or ability to evoke sensations over time as a function of stimulation (C. L. Hughes, Flesher, et al., 2020) it is possible that this can play a role over very long periods of time. Injecting less charge then may result in better longevity for electrodes.

Another current concern with using stimulation for a take-home device is the habituation of evoked percepts, as described in the previous chapter. Previously, we have found that completely continuous stimulation can result in extinction of any sensation within a minute. This means that maintaining contact with objects for longer than a few seconds could potentially result in the loss of an ability to detect objects. However, we found that by providing small amounts of stimulation with appropriate spacing in between never results in complete extinction of sensation for many minutes. Because biomimetic encoding involves stimulating for small periods of time indicating grasp onset and offset events, it can potentially result in increased efficacy of the devices over time, allowing users to maintain perception of grasp contact.

Although we showed the stimulation improves the naturalness and intuitiveness, we did not evaluate here how this encoding scheme might affect functional use of a BCI. Previous work from our lab has shown that using stimulation can increase performance with a BCI (S. N. Flesher et al., 2021). From these results, we found that the most important aspect of stimulation seems to be that it signals grasp contact, allowing the participant to more confidently proceed in moving it. Because biomimetic feedback provides stronger information about object contact, we believe that

it can be useful for this kind of task. However, we don't expect necessarily that biomimetic feedback would improve performance on tasks such as object identification or discrimination, where differences in the objects is typically signaled by changes in the amplitude. In fact, current biomimetic stimulation approaches could be limiting for these kinds of tasks, as it limits the range over which amplitude can be varied.

For future work, biomimetic feedback should be evaluated in the context of functional bidirectional BCI control. Biomimetic amplitude modulation may be able to improve use of a BCI in the context of normal daily life tasks, such as maintaining contact with a cup. However, the fact that we have consistently found electrode specific effects of frequency may imply that the timing of stimulus trains needs to be personalized to individual electrodes and participants, based on identified features. Even though these approaches may ultimately make current technologies more useful, functional, and long-lasting, likely we will need further developments in the underlying technology to produce fully natural and functional sensory feedback.

10.0 Conclusions and Future Work

10.1 Stimulated Electrodes are as Stable as Non-stimulated Electrodes Despite Potential Damage

I found that standard Utah arrays are surprisingly robust over time with stimulation. I found no significant difference in the recording quality over time between stimulated and non-stimulated electrodes. Additionally, I found that the ability to detect stimulation only ever showed improvements over time. These results seem to indicate that even with large amounts of current injected over long periods of time, Utah arrays can continue to be effective in decoding neural activity and restoring sensation. However, we did still see declines over time in signal quality on both stimulated and non-stimulated electrodes. This could be due to deterioration of the insulation on implanted electrodes, which may ultimately lead to failure of the implanted devices. Newer technologies should focus on designing materials that can maintain better recording quality over time.

Additionally, we found that the even small amounts of stimulation could result in demetallation of electrode tips under certain conditions. It is possible that the metal itself remains intact with the electrode until the array is explanted, resulting in an ability to continuously record signal and stimulate despite these material changes. It may also be the case that, although we haven't seen any additional issues with recording or due to stimulation, we could experience sudden failure at a later time point. Methods that reduce stimulation then, and specifically methods that reduce stimulation at low voltages, could potentially reduce electrode damage and produce better electrode longevity.

10.2 Pulse Timing is Important for Tactile Perception

More of my work has focused on the question of tactile perception with stimulation. I found that fixed amplitude and train durations lead to predictable effects on intensity and quality, but frequency had electrode specific effects. These electrode specific effects were predictive of both the intensity and quality of the evoked percepts and clustered spatially in cortex. These results seem to relate directly to previous findings that the frequency of tactile input is organized in somatosensory cortex of non-human primates (Friedman et al., 2004; Sur et al., 1984) However, we found that even when the cortex is directly stimulated and all mechanoreceptors and peripheral nerves are bypassed, the cortex still shows preferential responses. This implies that the cortical response is not the consequence of submodality separation in cortex, but rather the cortex is itself organized for stimulus feature encoding. Additionally, we found that just changing the time between pulses could result in perceptual changes on some electrodes. This indicates that the cortex is not simply responsive to the overall frequency/rate of stimulation, but the timing of the pulses is itself important, which aligns with previous findings for vibrotactile stimulation (I Birznieks et al., 2001; Ingvars Birznieks & Vickery, 2017; Ng et al., 2018). Together, these results seem to indicate that the somatosensory cortex is organized for frequency feature processing, where some populations are sensitive to the timing of pulses and specifically use an encoding scheme that involves the time between pulses. For future BCI applications then, stimulation will likely need to be delivered on an electrode dependent basis, where some electrodes might receive frequency modulated stimulation, while others do not.

10.3 Intermittent or Low Frequency Stimulation Paradigms can Evoke Percepts Continuously Over Time

I also found that continuous stimulation resulted in decreases in the intensity of evoked percepts, and often complete extinction of sensations. Intermittent stimulation paradigms, however, were able to evoke percepts over long periods of time, although there were electrode specific effects on intensity. By providing intermittent stimulation, we can continue to evoke percepts over long periods of time, which will be necessary for the practical application of a bidirectional BCI. Although we didn't collect data to directly compare habituation effects with frequency preference, it is possible that these electrode specific effects are correlated. Future experiments will need to explore this, but it may also be the case then that these habituation effects should be considered for electrode specific stimulus encoding.

10.4 Biomimetic Encoding can Improve Naturalness and Intuitiveness and May Decrease Habituation and Electrode Damage

One method of encoding that resolves all of the aforementioned issues is biomimetic encoding. Biomimetic encoding would provide large amplitude transients during contact events or changes in force and low amplitude currents during maintained contact. This is similar to what has been observed in non-human primate cortex during normal tactile perception(Callier et al., 2018). Additionally, this is the kind of output produced by TouchMime for input force profiles (Okorokova et al., 2018). This method of stimulus encoding would result in overall less charge injection. If stimulation, and specifically stimulation at lower voltages, can result in damage to the

electrode over time, delivering less stimulation in shorter intervals may allow for better electrode longevity. Additionally, biomimetic modulation of pulse trains can be provided in an electrode specific manner, so that electrodes that are identified to be more sensitive to timing can receive stimulation in which biomimetic timing is modulated. Or alternatively, some electrode may only receive stimulation during the onset transients (similar to RA type fibers) while other electrodes, that are less prone to habituation, can receive continuous stimulation throughout object contact (similar to SA type fibers). Finally, by providing more transient stimulation, we can reduce the overall effects of habituation, resulting in a better ability to elicit sensation continuously.

I also found here that in one participant, biomimetic amplitude modulation resulted in more focal, natural, and intuitive sensations. All these results together imply that biomimetic modulation of pulse trains can result in more robust and functional tactile percepts for a bidirectional BCI.

10.5 Future Approaches

Although I found that biomimetic approaches improved naturalness and intuitiveness in a single participant, it only improved naturalness in a small but significant manner. This is likely because of limitations in the technology. Standard Utah arrays are limited in their resolution of recruitment. Even small current amplitudes result in the recruitment of many neurons simultaneously. But we know that for normal somatosensory activation, neurons are not all simultaneously active and neurons in the same vicinity can show different activation patterns. Additionally, there are many different neural types that likely play different roles in the processing of sensory input (excitatory, inhibitory, non-neuronal elements). Therefore, to provide stimulation

that completely mimics normal neural activity, we will likely need newer technologies that can better target individual neurons with different stimulus patterns.

Additionally, all the biomimetic work here was done in a single participant. We will need to test how these principles extend to other participants to know if this approach will provide a more general way to improve upon the sensory feedback we provide.

Finally, in this work, we did not apply these findings directly to bidirectional BCI tasks. Although the results we found are suggestive that biomimetic approaches might be beneficial in a multitude of ways, we won't know if there is any improvement in function until we apply these principles to a BCI task. We have found previously that stimulation can improve BCI control by decreasing the time it takes to grasp an object (S. N. Flesher et al., 2021). Biomimetic encoding would most likely be useful in the context of these tasks, where large onset and offset transients provide strong signals of object contact, which could improve the participants confidence in their grasp and further decrease timing. Other tasks such as object identification tasks, in which the participant has to identify objects based on sensory feedback, are less likely to be changed by biomimetic modulation, which actually could reduce the overall range of amplitudes available to divide objects.

To test of biomimetic feedback resolves issues of habituation, likely the tasks would require continuous performance over long periods of time. With normal habituation effects, we might expect performance to deteriorate more over time, while maintained perception should result in better maintained performance.

Finally, if we want to evaluate the effects of biomimetic stimulation on electrode longevity, this will require separate participants receiving linear and biomimetic encoding used for many

years and post-explant analysis of arrays. This is a much harder phenomenon to investigate in humans and might be more easily investigated in animal models.

Bibliography

Abbasi, A. A., Estebanez, L., Goueytes, D., Lassagne, H., Shulz, D. E., & Ego-Stengel, V. (2020). Cortical closed-loop brain-machine interface requires biomimetic sensory feedback. *BioRxiv*, 2019.12.12.873794. https://doi.org/10.1101/2019.12.12.873794

Agnew, W. F., Yuen, T. G. H., McCreery, D. B., & Bullara, L. A. (1986). Histopathologic evaluation of prolonged intracortical electrical stimulation. *Experimental Neurology*, *92*(1), 162–185. https://doi.org/10.1016/0014-4886(86)90132-9

Ajiboye, A. B., Willett, F. R., Young, D. D. R., Memberg, W. W. D. W., Murphy, B. A., Miller, J. P., … Kirsch, R. F. (2017). Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *The Lancet*, *389*(10081), 1821–1830. https://doi.org/10.1016/S0140-6736(17)30601-3

Anselin, L. (1995). Local Indicators of Spatial Association—LISA. *Geographical Analysis*, *27*(2), 93–115. https://doi.org/10.1111/j.1538-4632.1995.tb00338.x

Armenta Salas, M., Bashford, L., Kellis, S., Jafari, M., Jo, H., Kramer, D., … Andersen, R. A. (2018). Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation. *ELife*, (7), e32904. https://doi.org/10.7554/eLife.32904

Bach-y-Rita, P., & W. Kercel, S. (2003). Sensory substitution and the human–machine interface. *Trends in Cognitive Sciences*, *7*(12), 541–546. https://doi.org/10.1016/j.tics.2003.10.013

Bak, M., Girvin, J. P., Hambrecht, F. T., Kufta, C. v., Loeb, G. E., & Schmidt, E. M. (1990). Visual sensations produced by intracortical microstimulation of the human occipital cortex. *Medical & Biological Engineering & Computing*, *28*(3), 257–259. https://doi.org/10.1007/BF02442682

Barrese, J. C., Rao, N., Paroo, K., Triebwasser, C., Vargas-Irwin, C., Franquemont, L., & Donoghue, J. P. (2013). Failure mode analysis of silicon-based intracortical microelectrode arrays in non-human primates. *Journal of Neural Engineering*, *10*(6), 066014. https://doi.org/10.1088/1741-2560/10/6/066014

Bensmaia, S. J. (2015). Biological and bionic hands : natural neural coding and artificial perception. *Philosophical Transactions Royal Society, B*, *370*(figure 1), 20140209. https://doi.org/10.1098/rstb.2014.0209

Bensmaia, S. J., & Miller, L. E. (2014). Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nature Reviews Neuroscience*, *15*(5), 313–325. https://doi.org/10.1038/nrn3724

Birznieks, I, Jenmalm, P., Goodwin, a W., & Johansson, R. S. (2001). Encoding of direction of fingertip forces by human tactile afferents. *Journal of Neuroscience*, *21*(20), 8222–8237. https://doi.org/21/20/8222 [pii]

Birznieks, Ingvars, McIntyre, S., Nilsson, H. M., Nagi, S. S., Macefield, V. G., Mahns, D. A., & Vickery, R. M. (2019). Tactile sensory channels over-ruled by frequency decoding system that utilizes spike pattern regardless of receptor type. *ELife*. https://doi.org/10.7554/eLife.46510

Birznieks, Ingvars, & Vickery, R. M. (2017). Spike Timing Matters in Novel Neuronal Code Involved in Vibrotactile Frequency Perception. *Current Biology*, *27*(10), 1485-1490.e2. https://doi.org/10.1016/j.cub.2017.04.011

Borchers, S., Himmelbach, M., Logothetis, N., & Karnath, H. O. (2012). Direct electrical stimulation of human cortex - the gold standard for mapping brain functions? *Nat Rev Neurosci*, *13*(1), 63–70. https://doi.org/10.1038/nrn3140

Bouton, C. E., Shaikhouni, A., Annetta, N. V., Bockbrader, M. A., Friedenberg, D. A., Nielson, D. M., … Rezai, A. R. (2016). Restoring cortical control of functional movement in a human with quadriplegia. *Nature*, *533*(7602), 247–250. https://doi.org/10.1038/nature17435

Brindley, G. S., & Lewin, W. S. (1968). The sensations produced by electrical stimulation of the visual cortex. *The Journal of Physiology*, *196*(2), 479–493. https://doi.org/10.1113/jphysiol.1968.sp008519

Brodmann, K. (1909). Vergleichende Lokalizationslehre der Grosshirnrinde in ihren Prinzipien Dargestellt auf Grund der Zellenbaues. *Barth*. Retrieved from https://scholar.google.com/scholar?q=brodmann+1909&btnG=&hl=en&as_sdt=0%2C39

Bullard, A. J., Hutchison, B. C., Lee, J., Chestek, C. A., & Patil, P. G. (2019). Estimating Risk for Future Intracranial, Fully Implanted, Modular Neuroprosthetic Systems: A Systematic Review of Hardware Complications in Clinical Deep Brain Stimulation and Experimental Human Intracortical Arrays. *Neuromodulation*, ner.13069. https://doi.org/10.1111/ner.13069

Butovas, S., & Schwarz, C. (2007). Detection psychophysics of intracortical microstimulation in rat primary somatosensory cortex. *European Journal of Neuroscience*, *25*(7), 2161–2169. https://doi.org/10.1111/j.1460-9568.2007.05449.x

Caldwell, D. J., Cronin, J. A., Wu, J., Weaver, K. E., Ko, A. L., Rao, R. P. N., & Ojemann, J. G. (2019). Direct stimulation of somatosensory cortex results in slower reaction times compared to peripheral touch in humans. *Scientific Reports*, *9*(1), 3292. https://doi.org/10.1038/s41598-019-38619-2

Callier, T., Brantly, N. W., Caravelli, A., & Bensmaia, S. J. (2020). The frequency of cortical microstimulation shapes artificial touch. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(2), 1191–1200. https://doi.org/10.1073/pnas.1916453117

Callier, T., Schluter, E. W., Tabot, G. A., Miller, L. E., Tenore, F. v., & Bensmaia, S. J. (2015). Long-term stability of sensitivity to intracortical microstimulation of somatosensory cortex. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2560/12/5/056010

Callier, T., Suresh, A. K., & Bensmaia, S. J. (2018). Neural Coding of Contact Events in Somatosensory Cortex. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhy337

Carmena, J. M., Lebedev, M. A., Crist, R. E., O'Doherty, J. E., Santucci, D. M., Dimitrov, D. F., … Nicolelis, M. A. L. (2003). Learning to Control a Brain–Machine Interface for Reaching and Grasping by Primates. *PLoS Biology*, *1*(2), e42. https://doi.org/10.1371/journal.pbio.0000042

Chapin, J. K., Moxon, K. A., Markowitz, R. S., & Nicolelis, M. A. L. (1999). Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nature Neuroscience*, *2*(7), 664–670. https://doi.org/10.1038/10223

Chen, K. H., Dammann, J. F., Boback, J. L., Tenore, F. v, Otto, K. J., Gaunt, R. A., & Bensmaia, S. J. (2014). The effect of chronic intracortical microstimulation on the electrode–tissue interface. *Journal of Neural Engineering*, *11*(2), 026004. https://doi.org/10.1088/1741-2560/11/2/026004

Chen, L. M., Friedman, R. M., Ramsden, B. M., LaMotte, R. H., & Roe, A. W. (2001). Fine-scale organization of SI (area 3b) in the squirrel monkey revealed with intrinsic optical imaging. *Journal of Neurophysiology*, *86*(6), 3011–3029. https://doi.org/10.1152/jn.2001.86.6.3011

Chen, R., Cohen, L. G., & Hallett, M. (2002). Nervous system reorganization following injury. *Neuroscience*. https://doi.org/10.1016/S0306-4522(02)00025-8

Chen, T.-W., Wardill, T. J., Sun, Y., Pulver, S. R., Renninger, S. L., Baohan, A., … Kim, D. S. (2013). Ultrasensitive fluorescent proteins for imaging neuronal activity. *Nature*, *499*(7458), 295–300. https://doi.org/10.1038/nature12354

Chestek, C. A., Gilja, V., Kaufman, M. T., Rivera-Alvidrez, Z., Ryu, S. I., Nuyujukian, P., … Shenoy, K. v. (2011). Long-term stability of neural prosthetic control signals from silicon cortical arrays in rhesus macaque motor cortex. *Journal of Neural Engineering*, *8*(4), 045005. https://doi.org/10.1088/1741-2560/8/4/045005

Chestek, C., Gilja, V., Nuyujukian, P., Foster, J. D., Fan, J., Kaufman, M. T., … Shenoy, K. v. (2011). Long-term stability of neural prosthetic control signals from silicon cortical arrays in rhesus macaque motor cortex. *Journal of Neural Engineering*, *8*(4), 045005. https://doi.org/10.1088/1741-2560/8/4/045005

Clemente, F., Valle, G., Controzzi, M., Strauss, I., Iberite, F., Stieglitz, T., … Cipriani, C. (2019). Intraneural sensory feedback restores grip force control and motor coordination while using a prosthetic hand. *Journal of Neural Engineering*, *16*(2). https://doi.org/10.1088/1741-2552/ab059b

Clippinger, F. W., Avery, R., & Titus, B. R. (1974). A sensory feedback system for an upper-limb amputation prosthesis. *Bulletin of Prosthetics Research*, 247–258. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4462906

Cogan, S. F. (2008). Neural Stimulation and Recording Electrodes. *Annual Review of Biomedical Engineering*, *10*(1), 275–309. https://doi.org/10.1146/annurev.bioeng.10.061807.160518

Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., Weber, D. J., … Schwartz, A. B. (2013). High-performance neuroprosthetic control by an individual with tetraplegia. *The Lancet*, *381*(9866), 557–564. https://doi.org/10.1016/S0140-6736(12)61816-9

Collins, K. L., Guterstam, A., Cronin, J., Olson, J. D., Ehrsson, H. H., & Ojemann, J. G. (2017). Ownership of an artificial limb induced by electrical brain stimulation. *Proceedings of the National Academy of Sciences*, *114*(1), 166–171. https://doi.org/10.1073/pnas.1616305114

Cronin, J. A., Wu, J., Collins, K. L., Sarma, D., Rao, R. P. N., Ojemann, J. G., & Olson, J. D. (2016). Task-Specific Somatosensory Feedback via Cortical Stimulation in Humans. *IEEE Transactions on Haptics*, *9*(4), 515–522. https://doi.org/10.1109/TOH.2016.2591952

Culaclii, S., Kim, B., Lo, Y.-K., & Liu, W. (2016). A hybrid hardware and software approach for cancelling stimulus artifacts during same-electrode neural stimulation and recording. *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 6190–6193. IEEE. https://doi.org/10.1109/EMBC.2016.7592142

Dadarlat, M. C., O'Doherty, J. E., & Sabes, P. N. (2014). A learning-based approach to artificial sensory feedback leads to optimal integration. *Nature Neuroscience*, *18*(1), 138–144. https://doi.org/10.1038/nn.3883

D'Anna, E., Petrini, F. M., Artoni, F., Popovic, I., Simanić, I., Raspopovic, S., & Micera, S. (2017). A somatotopic bidirectional hand prosthesis with transcutaneous electrical nerve stimulation based sensory feedback. *Scientific Reports*, *7*(1). https://doi.org/10.1038/s41598-017-11306-w

Davis, T. S., Parker, R. A., House, P. A., Bagley, E., Wendelken, S., Normann, R. A., & Greger, B. (2012). Spatial and temporal characteristics of V1 microstimulation during chronic implantation of a microelectrode array in a behaving macaque. *Journal of Neural Engineering*, *9*(6), 065003. https://doi.org/10.1088/1741-2560/9/6/065003

Davis, T. S., Wark, H. A. C. C., Hutchinson, D. T., Warren, D. J., O'Neill, K., Scheinblum, T., … Greger, B. (2016). Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. *Journal of Neural Engineering*, *13*(3), 036001. https://doi.org/10.1088/1741-2560/13/3/036001

DeYoe, E. A., Lewine, J. D., & Doty, R. W. (2005). Laminar variation in threshold for detection of electrical excitation of striate cortex by macaques. *Journal of Neurophysiology*, *94*(5), 3443–3450. https://doi.org/10.1152/jn.00407.2005

Dicarlo, J. J., Johnson, K. O., & Hsiao, S. S. (1998). Structure of receptive fields in area 3b of primary somatosensory cortex in the alert monkey. *Journal of Neuroscience*, *18*(7), 2626–2645. https://doi.org/10.1523/jneurosci.18-07-02626.1998

Dickey, A. S., Suminski, A., Amit, Y., & Hatsopoulos, N. G. (2009). Single-Unit Stability Using Chronically Implanted Multielectrode Arrays. *Journal of Neurophysiology*, *102*(2). Retrieved from http://jn.physiology.org/content/102/2/1331.short

Dixon, W. J., & Mood, A. M. (1948). A Method for Obtaining and Analyzing Sensitivity Data. *Journal of the American Statistical Association*, *43*(241), 109–126. https://doi.org/10.1080/01621459.1948.10483254

Dobelle, W. (2000). Artificial vision for the blind by connecting a television camera to the visual cortex. *ASAIO Journal*, *46*(1), 3–9. Retrieved from http://journals.lww.com/asaiojournal/Abstract/2000/01000/Artificial_Vision_for_the_Blind_by_Connecting_a.2.aspx

Dobelle, W. H., & Mladejovsky, M. G. (1974). Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. *The Journal of Physiology*, *243*(2), 553–576. https://doi.org/10.1113/jphysiol.1974.sp010766

Downey, J. E., Schwed, N., Chase, S. M., Schwartz, A. B., & Collinger, J. L. (2018). Intracortical recording stability in human brain-computer interface users. *Journal of Neural Engineering*, *15*(4), 046016. https://doi.org/10.1088/1741-2552/aab7a0

Ethier, C., Oby, E. R., Bauman, M. J., & Miller, L. E. (2012). Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature*, *485*(7398), 368–371. https://doi.org/10.1038/nature10987

Fagg, A. H., Hatsopoulos, N. G., de Lafuente, V., Moxon, K. A., Nemati, S., Rebesco, J. M., … Miller, L. E. (2007). Biomimetic Brain Machine Interfaces for the Control of Movement. *Journal of Neuroscience*, *27*(44). Retrieved from http://www.jneurosci.org/content/27/44/11842.short

Fifer, M. S., McMullen, D. P., Thomas, T. M., Osborn, L. E., Nickl, R., Candrea, D., … Tenore, F. v. (2020). Intracortical microstimulation of human fingertip sensations. *MedRxiv*. https://doi.org/10.1101/2020.05.29.20117374

Fitzsimmons, N. A., Drake, W., Hanson, T. L., Lebedev, M. A., & Nicolelis, M. A. L. (2007). Primate Reaching Cued by Multichannel Spatiotemporal Cortical Microstimulation. *Journal of Neuroscience*, *27*(21), 5593–5602. https://doi.org/10.1523/JNEUROSCI.5297-06.2007

Flanagan, J. R., Bowman, M. C., & Johansson, R. S. (2006). Control strategies in object manipulation tasks. *Current Opinion in Neurobiology*, *16*(6), 650–659. Retrieved from papers2://publication/uuid/7F1515FD-3F17-433D-AAE1-CCE3598EBE91

Flesher, S., Downey, J., Collinger, J., Foldes, S., Weiss, J., Tyler-Kabara, E., … Gaunt, R. (2017). Intracortical Microstimulation as a Feedback Source for Brain-Computer Interface Users. In *Proceedings of the 6th International Brain-Computer Interface Meeting* (pp. 43–54). https://doi.org/10.1007/978-3-319-64373-1_5

Flesher, S. N., Collinger, J. L., Foldes, S. T., Weiss, J. M., Downey, J. E., Tyler-Kabara, E. C., … Gaunt, R. A. (2016). Intracortical microstimulation of human somatosensory cortex. *Science Translational Medicine*, *8*(361), 1–11. https://doi.org/10.1126/scitranslmed.aaf8083

Flesher, S. N., Collinger, J. L., Weiss, J. M., Hughes, C., Bensmaia, S. J., Boninger, M. L., & Gaunt, R. A. (2017). Restoring Touch through Intracortical Microstimulation of Human Somatosensory Cortex. *New Generation of Circuits and Systems (NGCAS)*. Retrieved from https://ieeexplore.ieee.org/abstract/document/8052300/

Flesher, S. N., Downey, J. E., Weiss, J. M., Hughes, C. L., Herrera, A. J., Tyler-Kabara, E. C., … Gaunt, R. A. (2021). A brain-computer interface that evokes tactile sensations improves robotic arm control. In *Science*.

Foerster, O. (1929). Beitrage zur Pathophysiologie der Sehbahn und der Sehsphare. *J. Psychol. Neurol.*, *39*, 463–485. Retrieved from https://scholar.google.com/scholar?q=FOERSTER%2C+0.+%281929%29.+Beitriige+zur+Pathophysiologie+der+Sehbahn+und+der+Sehsphare.+J.+Psychol.+Neurol.%2C+Lpz.+39%2C+463-485.&btnG=&hl=en&as_sdt=0%2C39

Fraser, G. W., & Schwartz, A. B. (2012). Recording from the same neurons chronically in motor cortex. *Journal of Neurophysiology*, *107*(7). Retrieved from http://jn.physiology.org/content/107/7/1970.short

Freund, P., Weiskopf, N., Ward, N. S., Hutton, C., Gall, A., Ciccarelli, O., … Thompson, A. J. (2011). Disability, atrophy and cortical reorganization following spinal cord injury. *Brain*. https://doi.org/10.1093/brain/awr093

Fridman, G. Y., Blair, H. T., Blaisdell, A. P., & Judy, J. W. (2010). Perceived intensity of somatosensory cortical electrical stimulation. *Experimental Brain Research*, *203*(3), 499–515. https://doi.org/10.1007/s00221-010-2254-y

Friedman, R. M., Chen, L. M., & Roe, A. W. (2004). Modality maps within primate somatosensory cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(34), 12724–12729. https://doi.org/10.1073/pnas.0404884101

Fritsch, G., & Hitzig, E. (1870). Über die elektrische Erreg- barkeit des Grosshirns. *Arch Anat Physiol Wiss Med*, *37*, 300–332. Retrieved from http://ci.nii.ac.jp/naid/10010878972/

Gaunt, R. A., Prochazka, A., Mushahwar, V. K., Guevremont, L., & Ellaway, P. H. (2006). Intraspinal microstimulation excites multisegmental sensory afferents at lower stimulus levels than local alpha-motoneuron responses. *Journal of Neurophysiology*, *96*(6), 2995–3005. https://doi.org/10.1152/jn.00061.2006

George, J. A., Kluger, D. T., Davis, T. S., Wendelken, S. M., Okorokova, E. v., He, Q., … Clark, G. A. (2019). Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Science Robotics*, *4*(32). https://doi.org/10.1126/scirobotics.aax2352

Gilja, V., Chestek, C. A., Diester, I., Henderson, J. M., Deisseroth, K., & Shenoy, K. v. (2011). Challenges and Opportunities for Next-Generation Intracortically Based Neural Prostheses. *IEEE Transactions on Biomedical Engineering*, *58*(7), 1891–1899. https://doi.org/10.1109/TBME.2011.2107553

Godfrey, S. B., Bianchi, M., Bicchi, A., & Santello, M. (2016). Influence of force feedback on grasp force modulation in prosthetic applications: A preliminary study. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, *2016-Octob*, 5439–5442. https://doi.org/10.1109/EMBC.2016.7591957

Gordon, A. M., Forssberg, H., Johansson, R. S., & Westling, G. (1991). Integration of sensory information during the programming of precision grip: comments on the contributions of size cues. *Experimental Brain Research*, *85*(1), 226–229. https://doi.org/10.1007/BF00230004

Gordon, A. M., Westling, G., Cole, K. J., & Johansson, R. S. (1993). Memory representations underlying motor commands used during manipulation of common and novel objects. *Journal of Neurophysiology*, *69*(6), 1789–1796. Retrieved from http://jn.physiology.org/content/69/6/1789.short

Graczyk, E. L., Delhaye, B. P., Schiefer, M. A., Bensmaia, S. J., & Tyler, D. J. (2018). Sensory adaptation to electrical stimulation of the somatosensory nerves. *Journal of Neural Engineering*, *15*(4), 046002. https://doi.org/10.1088/1741-2552/aab790

Graczyk, E. L., Schiefer, M. A., Saal, H. P., Delhaye, B. P., Bensmaia, S. J., & Tyler, D. J. (2016). The neural basis of perceived intensity in natural and artificial touch. *Science Translational Medicine*, *8*(362), 362ra142 LP-362ra142. https://doi.org/10.1126/scitranslmed.aaf5187

Grand, L., Wittner, L., Herwik, S., Göthelid, E., Ruther, P., Oscarsson, S., … Ulbert, I. (2010). Short and long term biocompatibility of NeuroProbes silicon probes. *Journal of Neuroscience Methods*, *189*(2), 216–229. https://doi.org/10.1016/j.jneumeth.2010.04.009

Hallet, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, *406*(6792), 147–150. https://doi.org/10.1038/35018000

Harvey, M. A., Saal, H. P., Dammann, J. F., & Bensmaia, S. J. (2013). Multiplexing Stimulus Information through Rate and Temporal Codes in Primate Somatosensory Cortex. *PLoS Biology*, *11*(5). https://doi.org/10.1371/journal.pbio.1001558

Heming, E., Sanden, A., & Kiss, Z. H. T. (2010). Designing a somatosensory neural prosthesis: Percepts evoked by different patterns of thalamic stimulation. *Journal of Neural Engineering*, *7*(6). https://doi.org/10.1088/1741-2560/7/6/064001

Henderson, L. A., Gustin, S. M., Macey, P. M., Wrigley, P. J., & Siddall, P. J. (2011). Functional reorganization of the brain in humans following spinal cord injury: Evidence for underlying changes in cortical anatomy. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2717-10.2011

Hermansson, L. M., Fisher, A. G., Bernspång, B., & Eliasson, A. C. (2005). Assessment of Capacity for Myoelectric Control: A new Rasch-built measure of prosthetic hand control. *Journal of Rehabilitation Medicine*, *37*(3), 166–171. https://doi.org/10.1080/16501970410024280

Hiremath, S. v., Tyler-Kabara, E. C., Wheeler, J. J., Moran, D. W., Gaunt, R. A., Collinger, J. L., … Wang, W. (2017). Human perception of electrical stimulation on the surface of somatosensory cortex. *PLoS ONE*, *12*(5), 1–16. https://doi.org/10.1371/journal.pone.0176020

Histed, M. H., Bonin, V., & Reid, R. C. (2009). Direct Activation of Sparse, Distributed Populations of Cortical Neurons by Electrical Microstimulation. *Neuron*, *63*(4), 508–522. https://doi.org/10.1016/j.neuron.2009.07.016

Hochberg, L. R., Bacher, D., Jarosiewicz, B., Masse, N. Y., Simeral, J. D., Vogel, J., … Donoghue, J. P. (2012). Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*, *485*(7398), 372–375. https://doi.org/10.1038/nature11076

Hochberg, L. R., Serruya, M. D., Friehs, G. M., Mukand, J. A., Saleh, M., Caplan, A. H., … Donoghue, J. P. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*, *442*(7099), 164–171. https://doi.org/10.1038/nature04970

Hollins, M., & Roy, E. A. (1996). Perceived Intensity of Vibrotactile Stimuli: The Role of Mechanoreceptive Channels. *Somatosensory & Motor Research*, *13*(3–4), 273–286. https://doi.org/10.3109/08990229609052583

Hughes, C., Flesher, S., Weiss, J., Boninger, M., Collinger, J., & Gaunt, R. (2020). Perceptual responses to microstimulation frequency are spatially organized in human somatosensory cortex. *Biorxiv.Org*. https://doi.org/10.1101/2020.07.16.207506

Hughes, C. L., Flesher, S. N., Weiss, J. M., Downey, J. E., Collinger, J. L., & Gaunt, R. A. Neural stimulation and recording performance in human somatosensory cortex over 1500 days. , medRxiv § (2020).

Hughes, C. L., & Gaunt, R. A. (2021). Changes in interpulse spacing changes tactile perception of microstimulation in human somatosensory cortex. *10th International IEEE EMBS Conference on Neural Engineering*, 1–4.

Hughes, C. L., Herrera, A., Gaunt, R., & Collinger, J. (2020). Bidirectional brain-computer interfaces. *Handbook of Clinical Neurology*, *168*, 163–181.

Jackson, A., Mavoori, J., & Fetz, E. E. (2006). Long-term motor cortex plasticity induced by an electronic neural implant. *Nature*, *444*(7115), 56–60. https://doi.org/10.1038/nature05226

Jenmalm, P, Dahlstedt, S., & Johansson, R. S. (2000). Visual and tactile information about object-curvature control fingertip forces and grasp kinematics in human dexterous manipulation. *Journal of Neurophysiology*, *84*(6), 2984–2997. Retrieved from http://jn.physiology.org/content/84/6/2984.short

Jenmalm, P, & Johansson, R. S. (1997). Visual and somatosensory information about object shape control manipulative fingertip forces. *Journal of Neuroscience*, *17*(11), 4486–4499. Retrieved from http://www.jneurosci.org/content/17/11/4486.short

Jenmalm, Per, Schmitz, C., Forssberg, H., & Ehrsson, H. H. (2006). Lighter or heavier than predicted: neural correlates of corrective mechanisms during erroneously programmed lifts. *Journal of Neuroscience*, *26*(35), 9015–9021. https://doi.org/10.1523/JNEUROSCI.5045-05.2006

Johansson, R S, & Westling, G. (1988). Coordinated isometric muscle commands adequately and erroneously programmed for the weight during lifting task with precision grip. *Experimental Brain Research*, *71*(1), 59–71. https://doi.org/10.1007/BF00247522

Johansson, Roland S, & Flanagan, J. R. (2009). Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nature Reviews Neuroscience*, *10*(5), 345–359. https://doi.org/10.1038/nrn2621

Johansson, Roland S., Häger, C., & Bäckström, L. (2004). Somatosensory control of precision grip during unpredictable pulling loads. *Experimental Brain Research*, *89*(1), 204–213. https://doi.org/10.1007/bf00229017

Johnson, K. O. (2001). The roles and functions of cutaneous mechanoreceptors. *Current Opinion in Neurobiology*, *11*(4), 455–461. https://doi.org/10.1016/S0959-4388(00)00234-8

Johnson, L. A., Wander, J. D., Sarma, D., Su, D. K., Fetz, E. E., & Ojemann, J. G. (2013). Direct electrical stimulation of the somatosensory cortex in humans using electrocorticography electrodes: a qualitative and quantitative report. *Journal of Neural Engineering*, *10*(3), 036021. https://doi.org/10.1088/1741-2560/10/3/036021

Johnson, M. D., Otto, K. J., & Kipke, D. R. (2005). Repeated voltage biasing improves unit recordings by reducing resistive tissue impedances. *IEEE Transactions on Neural Systems*

and Rehabilitation Engineering, *13*(2), 160–165. https://doi.org/10.1109/TNSRE.2005.847373

Kaas, J. H., Nelson, R. J., Sur, M., Merzenich, M. M., Schmitt, F. O., Worden, F. G., & Dennis, S. G. (1981). Organization of somatosensory cortex in primates. *The Organization of the Cerebral Cortex*, (10), 237–261. Retrieved from https://scholar.google.com/scholar?q=Organization+of+somatosensory+cortex+in+primates&btnG=&hl=en&as_sdt=0%2C39

Kane, S. R., Cogan, S. F., Ehrlich, J., Plante, T. D., McCreery, D. B., & Troyk, P. R. (2013). Electrical performance of penetrating microelectrodes chronically implanted in cat cortex. *IEEE Transactions on Biomedical Engineering*, *60*(8), 2153–2160. https://doi.org/10.1109/TBME.2013.2248152

Kapfer, C., Glickfeld, L. L., Atallah, B. V., & Scanziani, M. (2007). Supralinear increase of recurrent inhibition during sparse activity in the somatosensory cortex. *Nature Neuroscience*, *10*(6), 743–753. https://doi.org/10.1038/nn1909

Kim, L. H., McLeod, R. S., & Kiss, Z. H. T. (2018). A new psychometric questionnaire for reporting of somatosensory percepts. *Journal of Neural Engineering*, Vol. 15. https://doi.org/10.1088/1741-2552/aa966a

Kim, S., Callier, T., Tabot, G. a, Gaunt, R. A., Tenore, F. v, & Bensmaia, S. J. (2015). Behavioral assessment of sensitivity to intracortical microstimulation of primate somatosensory cortex. *Proceedings of the National Academy of Sciences*, *112*(49), 15202–15207. https://doi.org/10.1073/pnas.1509265112

Kim, S., Callier, T., Tabot, G. A., Tenore, F. v., & Bensmaia, S. J. (2015). Sensitivity to microstimulation of somatosensory cortex distributed over multiple electrodes. *Frontiers in Systems Neuroscience*, *9*(April), 47. https://doi.org/10.3389/fnsys.2015.00047

Kingdom, F., & Prins, N. (2013). Psychophysics: A Practical Introduction. In *Journal of Chemical Information and Modeling* (Vol. 53).

Kramer, D. R., Kellis, S., Barbaro, M., Salas, M. A., Nune, G., Liu, C. Y., … Lee, B. (2019). Technical considerations for generating somatosensation via cortical stimulation in a closed-loop sensory/motor brain-computer interface system in humans. *Journal of Clinical Neuroscience*, *63*, 116–121. https://doi.org/10.1016/j.jocn.2019.01.027

Künzle, H. (1977). Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. *Experimental Brain Research*, *30*(4), 481–492. https://doi.org/10.1007/BF00237639

Large, A. M., Vogler, N. W., Canto-Bustos, M., Friason, F. K., Schick, P., & Oswald, A. M. M. (2018). Differential inhibition of pyramidal cells and inhibitory interneurons along the rostrocaudal axis of anterior piriform cortex. *Proceedings of the National Academy of*

Sciences of the United States of America, *115*(34), E8067-E8076A. https://doi.org/10.1073/pnas.1802428115

Lee, B., Kramer, D., Armenta Salas, M., Kellis, S., Brown, D., Dobreva, T., … Andersen, R. A. (2018). Engineering Artificial Somatosensation Through Cortical Stimulation in Humans. *Frontiers in Systems Neuroscience*, *12*. https://doi.org/10.3389/fnsys.2018.00024

Lee, S. W., Fallegger, F., Casse, B. D. F., & Fried, S. I. (2016). Implantable microcoils for intracortical magnetic stimulation. *Science Advances*, *2*(12). Retrieved from http://advances.sciencemag.org/content/2/12/e1600889

Leek, M. R. (2001). Adaptive procedures in psychophysical research. *Perception and Psychophysics*, *63*(8), 1279–1292. https://doi.org/10.3758/BF03194543

Lega, B. C., Serruya, M. D., & Zaghloul, K. A. (2011). Brain-machine interfaces: electrophysiological challenges and limitations. *Critical Reviews in Biomedical Engineering*, *39*(1), 5–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21488812

Lenz, F. A., Seike, M., Richardson, R. T., Lin, Y. C., Baker, F. H., Khoja, I., … Gracely, R. H. (1993). Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. *Journal of Neurophysiology*, *70*(1). Retrieved from http://jn.physiology.org/content/70/1/200.short

Leuthardt, E. C., Schalk, G., Wolpaw, J. R., Ojemann, J. G., & Moran, D. W. (2004). A brain–computer interface using electrocorticographic signals in humans. *Journal of Neural Engineering*, *1*(2), 63–71. https://doi.org/10.1088/1741-2560/1/2/001

Levitt, H. (1971). Transformed Up-Down Methods in Psychoacoustics. *The Journal of the Acoustical Society of America*, *49*(2B), 467–477. https://doi.org/10.1121/1.1912375

Light, C. M., Chappell, P. H., & Kyberd, P. J. (2002). Establishing a standardized clinical assessment tool of pathologic and prosthetic hand function: Normative data, reliability, and validity. *Archives of Physical Medicine and Rehabilitation*, *83*(6), 776–783. https://doi.org/10.1053/apmr.2002.32737

Limnuson, K., Lu, H., Chiel, H. J., & Mohseni, P. (2014). Real-time stimulus artifact rejection via template subtraction. *IEEE Transactions on Biomedical Circuits and Systems*, *8*(3), 391–400. https://doi.org/10.1109/TBCAS.2013.2274574

London, B. M., Jordan, L. R., Jackson, C. R., & Miller, L. E. (2008). Electrical Stimulation of the Proprioceptive Cortex (Area 3a) Used to Instruct a Behaving Monkey. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *16*(1), 32–36. https://doi.org/10.1109/TNSRE.2007.907544

Luna, V. M., & Pettit, D. L. (2010). Asymmetric rostro-caudal inhibition in the primary olfactory cortex. *Nature Neuroscience*, *13*(5), 533–535. https://doi.org/10.1038/nn.2524

Makin, T. R., & Bensmaia, S. J. (2017). Stability of Sensory Topographies in Adult Cortex. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2017.01.002

McCreery, D. B., Agnew, W. F., Yuen, T. G. H., & Bullara, L. (1990). Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *IEEE Transactions on Biomedical Engineering*, *37*(10), 996–1001. https://doi.org/10.1109/10.102812

McCreery, D. B., Bullara, L. A., & Agnew, W. F. (1986). Neuronal activity evoked by chronically implanted intracortical microelectrodes. *Experimental Neurology*, *92*(1), 147–161. https://doi.org/10.1016/0014-4886(86)90131-7

McCreery, D., Pikov, V., & Troyk, P. R. (2010). Neuronal loss due to prolonged controlled-current stimulation with chronically implanted microelectrodes in the cat cerebral cortex. *Journal of Neural Engineering*, *7*(3), 036005. https://doi.org/10.1088/1741-2560/7/3/036005

Mena, G. E., Grosberg, L. E., Madugula, S., Hottowy, P., Litke, A., Cunningham, J., … Paninski, L. (2017). Electrical stimulus artifact cancellation and neural spike detection on large multi-electrode arrays. *PLoS Computational Biology*, *13*(11), e1005842. https://doi.org/10.1371/journal.pcbi.1005842

Micera, S., & Navarro, X. (2009). Chapter 2 Bidirectional Interfaces with the Peripheral Nervous System. *International Review of Neurobiology*, *86*, 23–38. https://doi.org/10.1016/S0074-7742(09)86002-9

Michelson, N. J., Eles, J. R., Vazquez, A. L., Ludwig, K. A., & Kozai, T. D. Y. (2019). Calcium activation of cortical neurons by continuous electrical stimulation: Frequency dependence, temporal fidelity, and activation density. *Journal of Neuroscience Research*, *97*(5), 620–638. https://doi.org/10.1002/jnr.24370

Mima, T., Ikeda, A., Terada, K., Yazawa, S., Mikuni, N., Kunieda, T., … Shibasaki, H. (1997). Modality-specific organization for cutaneous and proprioceptive sense in human primary sensory cortex studied by chronic epicortical recording. *Electroencephalography and Clinical Neurophysiology - Evoked Potentials*, *104*(2), 103–107. https://doi.org/10.1016/S0168-5597(96)96142-0

Monzée, J., Lamarre, Y., & Smith, A. M. (2006). The Effects of Digital Anesthesia on Force Control Using a Precision Grip. *Journal of Neurophysiology*, *89*(2), 672–683. https://doi.org/10.1152/jn.00434.2001

Moran, P. A. P. (1950). Notes on Continuous Stochastic Phenomena. *Biometrika*, *37*(1/2), 17. https://doi.org/10.2307/2332142

Moritz, C. T., Perlmutter, S. I., & Fetz, E. E. (2008). Direct control of paralysed muscles by cortical neurons. *Nature*, *456*(7222), 639–642. https://doi.org/10.1038/nature07418

Mountcastle, V. B., Talbot, W. H., Sakata, H., & Hyvärinen, J. (1969). Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination. *Journal of Neurophysiology*, *32*(3), 452–484. https://doi.org/10.1152/jn.1969.32.3.452

Muniak, M. A., Ray, S., Hsiao, S. S., Dammann, J. F., & Bensmaia, S. J. (2007). The Neural Coding of Stimulus Intensity: Linking the Population Response of Mechanoreceptive Afferents with Psychophysical Behavior. *Journal of Neuroscience*, *27*(43), 11687–11699. https://doi.org/10.1523/jneurosci.1486-07.2007

Muret, D., & Makin, T. R. (2021). The homeostatic homunculus: rethinking deprivation-triggered reorganisation. *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2020.08.008

Nakai, J., Ohkura, M., & Imoto, K. (2001). A high signal-to-noise Ca(2+) probe composed of a single green fluorescent protein. *Nature Biotechnology*, *19*(2), 137–141. https://doi.org/10.1038/84397

Navarro, X., Krueger, T. B., Lago, N., Micera, S., Stieglitz, T., & Dario, P. (2005). A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems. *Journal of the Peripheral Nervous System*, *10*(3), 229–258. https://doi.org/10.1111/J.1085-9489.2005.10303.X

Negi, S, Bhandari, R., Rieth, L., & Solzbacher, F. (2010). In vitro comparison of sputtered iridium oxide and platinum-coated neural implantable microelectrode arrays. *Biomedical Materials*, *5*(1), 015007. https://doi.org/10.1088/1748-6041/5/1/015007

Negi, Sandeep, Bhandari, R., Rieth, L., van Wagenen, R., & Solzbacher, F. (2010). Neural electrode degradation from continuous electrical stimulation: Comparison of sputtered and activated iridium oxide. *Journal of Neuroscience Methods*, *186*(1), 8–17. https://doi.org/10.1016/j.jneumeth.2009.10.016

Negi, Sandeep, Bhandari, R., van Wagenen, R., & Solzbacher, F. (2010). Factors affecting degradation of sputtered iridium oxide used for neuroprosthetic applications. *Proceedings of the IEEE International Conference on Micro Electro Mechanical Systems (MEMS)*, 568–571. https://doi.org/10.1109/MEMSYS.2010.5442438

Ng, K. K. W., Birznieks, I., Tse, I. T. H., Andersen, J., Nilsson, S., & Vickery, R. M. (2018). Perceived frequency of aperiodic vibrotactile stimuli depends on temporal encoding. *International Conference on Human Haptic Sensing and Touch Enabled Computer Application*, *10893 LNCS*, 199–208. https://doi.org/10.1007/978-3-319-93445-7_18

Nothias, F., Peschanski, M., & Besson, J.-M. (1988). Somatotopic reciprocal connections between the somatosensory cortex and the thalamic Po nucleus in the rat. *Brain Research*, *447*(1), 169–174. https://doi.org/10.1016/0006-8993(88)90980-8

Nowak, D. A., Glasauer, S., & Hermsdörfer, J. (2004). How predictive is grip force control in the complete absence of somatosensory feedback? *Brain*, *127*(1), 182–192. https://doi.org/10.1093/brain/awh016

Nowak, D. A., Glasauer, S., & Hermsdörfer, J. (2013). Force control in object manipulation-A model for the study of sensorimotor control strategies. *Neuroscience and Biobehavioral Reviews*, *37*(8), 1578–1586. https://doi.org/10.1016/j.neubiorev.2013.06.003

Nowak, D. A., & Hermsdörfer, J. (2006). Predictive and reactive control of grasping forces: On the role of the basal ganglia and sensory feedback. *Experimental Brain Research*, *173*(4), 650–660. https://doi.org/10.1007/s00221-006-0409-7

Nowak, L. G., & Bullier, J. (1998). Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. II. Evidence from selective inactivation of cell bodies and axon initial segments. *Experimental Brain Research*, *118*(4), 489–500. https://doi.org/10.1007/s002210050305

Oddo, C. M., Raspopovic, S., Artoni, F., Mazzoni, A., Spigler, G., Petrini, F., … Micera, S. (2016). Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans. *ELife*, *5*, e09148. https://doi.org/10.7554/eLife.09148

O'Doherty, J. E., Lebedev, M. A., Hanson, T. L., Fitzsimmons, N. A., & Nicolelis, M. A. L. (2009). A brain-machine interface instructed by direct intracortical microstimulation. *Frontiers in Integrative Neuroscience*, *3*(SEP), 20. https://doi.org/10.3389/neuro.07.020.2009

O'Doherty, J. E., Lebedev, M. A., Ifft, P. J., Zhuang, K. Z., Shokur, S., Bleuler, H., & Nicolelis, M. A. L. (2011). Active tactile exploration using a brain-machine-brain interface. *Nature*, *479*(7372), 228–231. https://doi.org/10.1038/nature10489

Okorokova, E. v., He, Q., & Bensmaia, S. J. (2018). Biomimetic encoding model for restoring touch in bionic hands through a nerve interface. *Journal of Neural Engineering*, *15*(6). https://doi.org/10.1088/1741-2552/aae398

O'Shea, D. J., & Shenoy, K. v. (2018). ERAASR: An algorithm for removing electrical stimulation artifacts from multielectrode array recordings. *Journal of Neural Engineering*, *15*(2), 026020. https://doi.org/10.1088/1741-2552/aaa365

Otto, K. J., Johnson, M. D., & Kipke, D. R. (2006). Voltage pulses change neural interface properties and improve unit recordings with chronically implanted microelectrodes. *IEEE Transactions on Biomedical Engineering*, *53*(2), 333–340. https://doi.org/10.1109/TBME.2005.862530

Otto, K. J., Rousche, P. J., & Kipke, D. R. (2005). Microstimulation in auditory cortex provides a substrate for detailed behaviors. *Hearing Research*, *210*(1–2), 112–117. https://doi.org/10.1016/j.heares.2005.08.004

Overstreet, C. K., Klein, J. D., & Helms Tillery, S. I. (2013). Computational modeling of direct neuronal recruitment during intracortical microstimulation in somatosensory cortex. *Journal of Neural Engineering*, *10*(6), 066016. https://doi.org/10.1088/1741-2560/10/6/066016

Parker, R. A., Davis, T. S., House, P. A., Normann, R. A., & Greger, B. (2011). The functional consequences of chronic, physiologically effective intracortical microstimulation. *Progress in Brain Research*, *194*, 145–165. https://doi.org/10.1016/B978-0-444-53815-4.00010-8

Patestas, M., & Gartner, L. (2006). Ascending sensory pathways. *A Textbook of Neuroanatomy*, 118-133. Retrieved from https://scholar.google.com/scholar?q=Ascending+sensory+pathways+patestas&btnG=&hl=en&as_sdt=0%2C39

Paul, R. L., Merzenich, M., & Goodman, H. (1972). Representation of slowly and rapidly adapting cutaneous mechanoreceptors of the hand in brodmann's areas 3 and 1 of Macaca Mulatta. *Brain Research*, *36*(2), 229–249. https://doi.org/10.1016/0006-8993(72)90732-9

Pei, Y. C., Denchev, P. V., Hsiao, S. S., Craig, J. C., & Bensmaia, S. J. (2009). Convergence of submodality-specific input onto neurons in primary somatosensory cortex. *Journal of Neurophysiology*, *102*(3), 1843–1853. https://doi.org/10.1152/jn.00235.2009

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, *60*(4), 389–443. https://doi.org/10.1093/brain/60.4.389

Pons, T. P., & Kaas, J. H. (1986). Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: A correlative anatomical and electrophysiological study. *The Journal of Comparative Neurology*, *248*(3), 313–335. https://doi.org/10.1002/cne.902480303

Prochazka, A., & Ellaway, P. (2012). Sensory Systems in the Control of Movement. In *Comprehensive Physiology*. Hoboken, NJ, USA: John Wiley & Sons, Inc. https://doi.org/10.1002/cphy.c100086

Proske, U., & Gandevia, S. C. (2009). The kinaesthetic senses. *The Journal of Physiology*, *587*(17), 4139–4146. https://doi.org/10.1113/jphysiol.2009.175372

Proske, U., & Gandevia, S. C. (2012). The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiological Reviews*, *92*(4), 1651–1697. https://doi.org/10.1152/physrev.00048.2011

Prsa, M., Morandell, K., Cuenu, G., & Huber, D. (2019). Feature-selective encoding of substrate vibrations in the forelimb somatosensory cortex. *Nature*. https://doi.org/10.1038/s41586-019-1015-8

Rajan, A. T., Boback, J. L., Dammann, J. F., Tenore, F. v, Wester, B. A., Otto, K. J., … Bensmaia, S. J. (2015). The effects of chronic intracortical microstimulation on neural tissue and fine

motor behavior. *Journal of Neural Engineering*, *12*(6), 066018. https://doi.org/10.1088/1741-2560/12/6/066018

Raspopovic, S., Capogrosso, M., Petrini, F. M., Bonizzato, M., Rigosa, J., di Pino, G., … Micera, S. (2014). Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Science Translational Medicine*, *6*(222), 222ra19. https://doi.org/10.1126/scitranslmed.3006820

Reed, J. L., Qi, H. X., Zhou, Z., Bernard, M. R., Burish, M. J., Bonds, A. B., & Kaas, J. H. (2010). Response properties of neurons in primary somatosensory cortex of owl monkeys reflect widespread spatiotemporal integration. *Journal of Neurophysiology*, *103*(4), 2139–2157. https://doi.org/10.1152/jn.00709.2009

Resnik, L., Adams, L., Borgia, M., Delikat, J., Disla, R., Ebner, C., & Walters, L. S. (2013). Development and evaluation of the activities measure for upper limb amputees. *Archives of Physical Medicine and Rehabilitation*, *94*(3). https://doi.org/10.1016/j.apmr.2012.10.004

Rivara, C. B., Sherwood, C. C., Bouras, C., & Hof, P. R. (2003). Stereologic characterization and spatial distribution patterns of Betz cells in the human primary motor cortex. *Anatomical Record - Part A Discoveries in Molecular, Cellular, and Evolutionary Biology*, *270*(2), 137–151. https://doi.org/10.1002/ar.a.10015

Robles-De-La-Torre, G. (2006). The importance of the sense of touch in virtual and real environments. *IEEE Multimedia*, *13*(3), 24–30. https://doi.org/10.1109/MMUL.2006.69

Romo, R., Hernández, A., Zainos, A., Brody, C. D. C. D., & Lemus, L. (2000). Sensing without touching: psychophysical performance based on cortical microstimulation. *Neuron*, *26*(1), 273–278. https://doi.org/10.1016/S0896-6273(00)81156-3

Romo, R., Hernández, A., Zainos, A., & Salinas, E. (1998). Somatosensory discrimination based on cortical microstimulation. *Nature*, *392*(6674), 387–390. https://doi.org/10.1038/32891

Rosenbaum, R., Rubin, J., & Doiron, B. (2012). Short term synaptic depression imposes a frequency dependent filter on synaptic information transfer. *PLoS Computational Biology*, *8*(6). https://doi.org/10.1371/journal.pcbi.1002557

Rothwell, J. C., Traub, M. M., Day, B. L., Obeso, J. A., Thomas, P. K., & Marsden, C. D. (1982). Manual motor performance in a deafferented man. *Brain*, *105*(3), 515–542. https://doi.org/10.1093/brain/105.3.515

Rousche, P. J., & Normann, R. A. (1999). Chronic intracortical microstimulation (ICMS) of cat sensory cortex using the utah intracortical electrode array. *IEEE Transactions on Rehabilitation Engineering*, *7*(1), 56–68. https://doi.org/10.1109/86.750552

Rousche, Patrick J, & Normann, R. A. (1998). Chronic recording capability of the Utah Intracortical Electrode Array in cat sensory cortex. *Journal of Neuroscience Methods*, *82*(1), 1–15. https://doi.org/10.1016/S0165-0270(98)00031-4

Ryu, S. I., & Shenoy, K. v. (2009). Human cortical prostheses: lost in translation? *Neurosurgical Focus*, *27*(1), E5. https://doi.org/10.3171/2009.4.FOCUS0987

Saal, H. P., & Bensmaia, S. J. (2014). Touch is a team effort: Interplay of submodalities in cutaneous sensibility. *Trends in Neurosciences*, *37*(12), 689–697. https://doi.org/10.1016/j.tins.2014.08.012

Saal, H. P., & Bensmaia, S. J. (2015). Biomimetic approaches to bionic touch through a peripheral nerve interface. *Neuropsychologia*, *79*, 344–353. https://doi.org/10.1016/j.neuropsychologia.2015.06.010

Saal, H. P., Delhaye, B. P., Rayhaun, B. C., & Bensmaia, S. J. (2017). Simulating tactile signals from the whole hand with millisecond precision. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(28), E5693–E5702. https://doi.org/10.1073/pnas.1704856114

Saal, H. P., Harvey, M. A., & Bensmaia, S. J. (2015). Rate and timing of cortical responses driven by separate sensory channels. *ELife*, *4*. https://doi.org/10.7554/elife.10450

Sainburg, R. L., Ghilardi, M. F., Poizner, H., & Ghez, C. (1995). Control of limb dynamics in normal subjects and patients without proprioception. *Journal of Neurophysiology*, *73*(2), 820–835. Retrieved from http://jn.physiology.org/content/73/2/820.short

Sainburg, R. L., Poizner, H., & Ghez, C. (1993). Loss of proprioception produces deficits in interjoint coordination. *Journal of Neurophysiology*, *70*(5), 2136–2147. Retrieved from http://jn.physiology.org/content/70/5/2136.short

Sanes, J. N., Mauritz, K.-H. H., Evarts, E. v, Dalakast, M. C., Chut, A., Dalakas, M. C., & Chu, A. (1984). Motor deficits in patients with large-fiber sensory neuropathy. *Proceedings of the National Academy of Science*, *81*(3), 979–982. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6322181

Santhanam, G., Ryu, S. I., Yu, B. M., Afshar, A., & Shenoy, K. V. (2006). A high-performance brain–computer interface. *Nature*, *442*(7099), 195–198. https://doi.org/10.1038/nature04968

Schalk, G., Miller, K. J., Anderson, N. R., Wilson, J. A., Smyth, M. D., Ojemann, J. G., … Leuthardt, E. C. (2008). Two-dimensional movement control using electrocorticographic signals in humans. *Journal of Neural Engineering*, *5*(1), 75–84. https://doi.org/10.1088/1741-2560/5/1/008

Schiefer, M., Tan, D., Sidek, S. M., & Tyler, D. J. (2016). Sensory feedback by peripheral nerve stimulation improves task performance in individuals with upper limb loss using a

myoelectric prosthesis. *Journal of Neural Engineering*, *13*(1), 016001. https://doi.org/10.1088/1741-2560/13/1/016001

Schmidt, E. M., Bak, M. J., Hambrecht, F. T., Kufta, C. v., O'Rourke, D. K., & Vallabhanath, P. (1996). Feasibility of a visual prosthesis for the blind based on intracortical micro stimulation of the visual cortex. *Brain*, *119*(2), 507–522. https://doi.org/10.1093/brain/119.2.507

Schmidt, R., & Lee, T. (2005). *Motor control and learning: A behavioral emphasis*. Retrieved from http://www.pelinks4u.org/bookreviews/media_1011.htm

Semprini, M., Bennicelli, L., & Vato, A. (2012). A parametric study of intracortical microstimulation in behaving rats for the development of artificial sensory channels. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 799–802. https://doi.org/10.1109/EMBC.2012.6346052

Silberberg, G., & Markram, H. (2007). Disynaptic Inhibition between Neocortical Pyramidal Cells Mediated by Martinotti Cells. *Neuron*, *53*(5), 735–746. https://doi.org/10.1016/j.neuron.2007.02.012

Simeral, J. D., Kim, S. P., Black, M. J., Donoghue, J. P., & Hochberg, L. R. (2011). Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *Journal of Neural Engineering*, *8*(2), 025027. https://doi.org/10.1088/1741-2560/8/2/025027

Stoney, S. D., Thompson, W. D., & Asanuma, H. (1968). Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulating current. *Journal of Neurophysiology*, *31*(5), 659–669. https://doi.org/10.1152/jn.1968.31.5.659

Suner, S., Fellows, M., Vargas-Irwin, C., Nakata, G. K., & Donoghue, J. P. (2005). Reliability of Signals From a Chronically Implanted, Silicon-Based Electrode Array in Non-Human Primate Primary Motor Cortex. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *13*(4), 524–541. https://doi.org/10.1109/tnsre.2005.857687

Sur, M., Wall, J. T., & Kaas, J. H. (1981). Modular segregation of functional cell classes within the postcentral somatosensory cortex of monkeys. *Science*, *212*(4498), 1059–1061. https://doi.org/10.1126/science.7233199

Sur, M., Wall, J. T., & Kaas, J. H. (1984). Modular distribution of neurons with slowly adapting and rapidly adapting responses in area 3b somatosensory cortex in monkeys. *Journal of Neurophysiology*, *51*(4), 724–744. https://doi.org/10.1152/jn.1984.51.4.724

Swanson, O. K., & Maffei, A. (2019). From hiring to firing: Activation of inhibitory neurons and their recruitment in behavior. *Frontiers in Molecular Neuroscience*, *12*. https://doi.org/10.3389/fnmol.2019.00168

Tan, D. W., Schiefer, M. A., Keith, M. W., Anderson, J. R., Tyler, J., & Tyler, D. J. (2014). A neural interface provides long-term stable natural touch perception. *Science Translational Medicine*, *6*(257), 257ra138-257ra138. https://doi.org/10.1126/scitranslmed.3008669

Tehovnik, E. J. (1996). Electrical stimulation of neural tissue to evoke behavioral responses. *Journal of Neuroscience Methods*, *65*(1), 1–17. https://doi.org/10.1016/0165-0270(95)00131-X

Tehovnik, E. J., & Slocum, W. M. (2009). Depth-dependent detection of microampere currents delivered to monkey V1. *European Journal of Neuroscience*, *29*(7), 1477–1489. https://doi.org/10.1111/j.1460-9568.2009.06695.x

Tolias, A. S., Ecker, A. S., Siapas, A. G., Hoenselaar, A., Keliris, G. A., & Logothetis, N. K. (2007). Recording Chronically From the Same Neurons in Awake, Behaving Primates. *Journal of Neurophysiology*, *98*(6). Retrieved from http://jn.physiology.org/content/98/6/3780.short

Tomlinson, T., & Miller, L. (2014). Multi-electrode stimulation in somatosensory area 2 induces a natural sensation of limb movement. *Neuromodulation*, *17*(5), e114. Retrieved from https://insights.ovid.com/neuromodulation/nmodl/2014/07/000/multi-electrode-stimulation-somatosensory-area/166/00128017

Tomlinson, T., & Miller, L. E. (2016). Toward a proprioceptive neural interface that mimics natural cortical activity. *Advances in Experimental Medicine and Biology*, *957*, 367–388. https://doi.org/10.1007/978-3-319-47313-0_20

Torab, K., Davis, T. S., Warren, D. J., House, P. A., Normann, R. A., & Greger, B. (2011). Multiple factors may influence the performance of a visual prosthesis based on intracortical microstimulation: Nonhuman primate behavioural experimentation. *Journal of Neural Engineering*, *8*(3), 035001. https://doi.org/10.1088/1741-2560/8/3/035001

Tsodyks, M. V., & Markram, H. (1997). The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(2), 719–723. https://doi.org/10.1073/pnas.94.2.719

Ungan, P., & Yagcioglu, S. (2014). Significant variations in Weber fraction for changes in inter-onset interval of a click train over the range of intervals between 5 and 300 ms. *Frontiers in Psychology*, *5*(DEC). https://doi.org/10.3389/fpsyg.2014.01453

Vallbo, A. B., Hagbarth, K. E., Torebjork, H. E., & Wallin, B. G. (1979). Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiological Reviews*, *59*(4). Retrieved from http://physrev.physiology.org/content/59/4/919.short

Valle, G, D'Anna, E., Strauss, I., Mazzoni, A., Iberite, F., Granata, G., … Micera, S. (2018). Comparison of linear frequency and amplitude modulation for intraneural sensory feedback

in bidirectional hand prostheses. *Scientific Reports*, *8*(1), 1–13. https://doi.org/10.1038/s41598-018-34910-w

Valle, Giacomo, Mazzoni, A., Iberite, F., D'Anna, E., Strauss, I., Granata, G., … Micera, S. (2018). Biomimetic Intraneural Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis. *Neuron*, *100*(1), 37–45. https://doi.org/10.1016/j.neuron.2018.08.033

Vansteensel, M. J., Pels, E. G. M., Bleichner, M. G., Branco, M. P., Denison, T., Freudenburg, Z. v., … Ramsey, N. F. (2016). Fully Implanted Brain–Computer Interface in a Locked-In Patient with ALS. *New England Journal of Medicine*, *375*(21), 2060–2066. https://doi.org/10.1056/NEJMoa1608085

Velliste, M., Perel, S., Spalding, M. C., Whitford, a S., & Schwartz, a B. (2008). Cortical control of a robotic arm for self-feeding. *Nature*, *453*(June), 1098–1101. https://doi.org/10.1038/nature06996

Verrillo, R. T., Fraioli, A. J., & Smith, R. L. (1969). Sensation magnitude of vibrotactile stimuli. *Perception & Psychophysics*, *6*(6), 366–372. https://doi.org/10.3758/BF03212793

Viaene, A. N., Petrof, I., & Sherman, S. M. (2011). Synaptic properties of thalamic input to layers 2/3 and 4 of primary somatosensory and auditory cortices. *Journal of Neurophysiology*, *105*(1), 279–292. https://doi.org/10.1152/jn.00747.2010

Wang, W., Collinger, J. L., Degenhart, A. D., Tyler-Kabara, E. C., Schwartz, A. B., Moran, D. W., … Boninger, M. L. (2013). An Electrocorticographic Brain Interface in an Individual with Tetraplegia. *PLoS ONE*, *8*(2), e55344. https://doi.org/10.1371/journal.pone.0055344

Warden, M. R., Cardin, J. A., & Deisseroth, K. (2014). Optical Neural Interfaces. *Annual Review of Biomedical Engineering*, *16*(1), 103–129. https://doi.org/10.1146/annurev-bioeng-071813-104733

Weber, D. J., Friesen, R., & Miller, L. E. (2012). Interfacing the somatosensory system to restore touch and Proprioception: Essential considerations. *Journal of Motor Behavior*. https://doi.org/10.1080/00222895.2012.735283

Weiss, J. M., Flesher, S. N., Franklin, R., Gaunt, R. A., & Collinger, J. L. (2018). Artifact-free recordings in human bidirectional brain–computer interfaces. *Journal of Neural Engineering*, *16*(1), 016002. https://doi.org/10.1088/1741-2552/aae748

Wendelken, S., Page, D. M., Davis, T., Wark, H. A. C., Kluger, D. T., Duncan, C., … Clark, G. A. (2017). Restoration of motor control and proprioceptive and cutaneous sensation in humans with prior upper-limb amputation via multiple Utah Slanted Electrode Arrays (USEAs) implanted in residual peripheral arm nerves. *Journal of NeuroEngineering and Rehabilitation*, *14*(1), 121. https://doi.org/10.1186/s12984-017-0320-4

White, B. W., Saunders, F. A., Scadden, L., Bach-Y-Rita, P., & Collins, C. C. (1970). Seeing with the skin. *Perception & Psychophysics*, *7*(1), 23–27. https://doi.org/10.3758/BF03210126

Wodlinger, B., Downey, J. E., Tyler-Kabara, E. C., Schwartz, A. B., Boninger, M. L., & Collinger, J. L. (2015). Ten-dimensional anthropomorphic arm control in a human brain−machine interface: difficulties, solutions, and limitations. *Journal of Neural Engineering*, *12*(1), 016011. https://doi.org/10.1088/1741-2560/12/1/016011

Wolpert, D. M., Ghahramani, Z., & Jordan, M. I. (1995). An internal model for sensorimotor integration. *Science*, *269*(5232), 1880–1882. https://doi.org/10.1126/science.7569931

Wood, F., Black, M. J., Vargas-Irwin, C., Fellows, M., & Donoghue, J. P. (2004). On the variability of manual spike sorting. *IEEE Transactions on Biomedical Engineering*, *51*(6), 912–918. https://doi.org/10.1109/TBME.2004.826677

Wrigley, P. J., Press, S. R., Gustin, S. M., Macefield, V. G., Gandevia, S. C., Cousins, M. J., … Siddall, P. J. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*. https://doi.org/10.1016/j.pain.2008.10.007

Yanagisawa, T., Hirata, M., Saitoh, Y., Kishima, H., Matsushita, K., Goto, T., … Yoshimine, T. (2012). Electrocorticographic control of a prosthetic arm in paralyzed patients. *Annals of Neurology*, *71*(3), 353–361. https://doi.org/10.1002/ana.22613

Yau, J. M., Olenczak, J. B., Dammann, J. F., & Bensmaia, S. J. (2009). Temporal Frequency Channels Are Linked across Audition and Touch. *Current Biology*, *19*(7), 561–566. https://doi.org/10.1016/j.cub.2009.02.013

Yozbatiran, N., Der-Yeghiaian, L., & Cramer, S. C. (2008). A Standardized Approach to Performing the Action Research Arm Test. *Neurorehabilitation and Neural Repair*, *22*(1), 78–90. https://doi.org/10.1177/1545968307305353

Zhang, F., Wang, L.-P., Boyden, E. S., & Deisseroth, K. (2006). Channelrhodopsin-2 and optical control of excitable cells. *Nature Methods*, *3*(10), 785–792. https://doi.org/10.1038/nmeth936

Zhao, S., Cunha, C., Zhang, F., Liu, Q., Gloss, B., Deisseroth, K., … Feng, G. (2008). Improved expression of halorhodopsin for light-induced silencing of neuronal activity. *Brain Cell Biology*, *36*(1–4), 141–154. https://doi.org/10.1007/s11068-008-9034-7