ROLE OF THE PRIMATE BASAL GANGLIA IN SACCADIC EYE MOVEMENTS

by

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Role of the primate basal ganglia in saccadic eye movements

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The basal ganglia are critical for motor behavior, and a well-known deficit of basal ganglia disorders is the loss of voluntary control over movements. Many studies on the role of basal ganglia in saccadic eye movements have focused on the caudate and substantia nigra pars reticulata (SNr). It has remained unclear, however, whether neurons in other nuclei of the basal ganglia are active during oculomotor behavior and, if they are, whether their activity is preferential for voluntary saccades. We ventured beyond the caudate-SNr pathway to study the globus pallidus externa (GPe) and interna (GPi).

First we recorded from neurons in GPe and GPi (and for comparison, in SNr) in monkeys that made memory-guided saccades. Neurons in all three structures had activity synchronized with saccade generation, visual stimulation, or reward. GPe activity was strongly visual-related while GPi activity was more reward-related. The distribution of signals in GPe, but not GPi, resembled that found in SNr. Response fields of neurons in all three structures were more spatially tuned early in trials (during visual and saccadic events) than later in trials (during reward).

In our second study, we examined whether saccade-related activity in GPe and GPi was preferentially active for voluntary saccades as defined in two ways: made in the absence of visual stimulation and made in the absence of instructions. We designed tasks that covered all

four permutations of presence or absence of visual stimulation and instruction, and analyzed neuronal activity associated with the same vectors of saccades across all the tasks. For about half of the saccade-related neurons in all three structures, saccade-related activity varied with task context. The most prominent factor accounting for differential saccade-related activity was instructional context. Surprisingly, we found *higher* activity for instructed saccades. Preferential activity for non-instructed (highly voluntary) tasks was rare in individual neurons and absent at the population level.

We conclude that GPe and GPi, in addition to SNr, may contribute to oculomotor behavior, and that none of these structures are preferentially active for voluntary saccades. Both of these results provide new views on the role of basal ganglia in eye movements.

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PREFACE

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1.0 INTRODUCTION

The basal ganglia (Fig. 1A) are an ensemble of subcortical nuclei that are well preserved throughout vertebrate species and regarded as critical for controlling movements. The nuclei consist of the caudate and putamen, the globus pallidus externa (GPe), the globus pallidus interna (GPi), the subthalamic nucleus (STN) and the substantia nigra pars reticulata (SNr). The caudate and putamen, collectively called the striatum, are two of the major input nodes of basal ganglia. They receive information from various regions of cerebral cortex and subsets of thalamic regions. The main output nodes of the basal ganglia are the GPi and SNr. Signals received by the striatum are transmitted either directly to the GPi and SNr ("direct" pathways) or indirectly to those two nodes through GPe and STN ("indirect" pathways). In addition to striatum, the STN can act as an input station as well; it receives projections from motor related cortical areas (Fig. 1B; (Coizet 2009; Feger et al. 1994; Hartmann-von Monakow et al. 1978; Lanciego 2004; Mena-Segovia et al. 2004; Nambu et al. 2002).

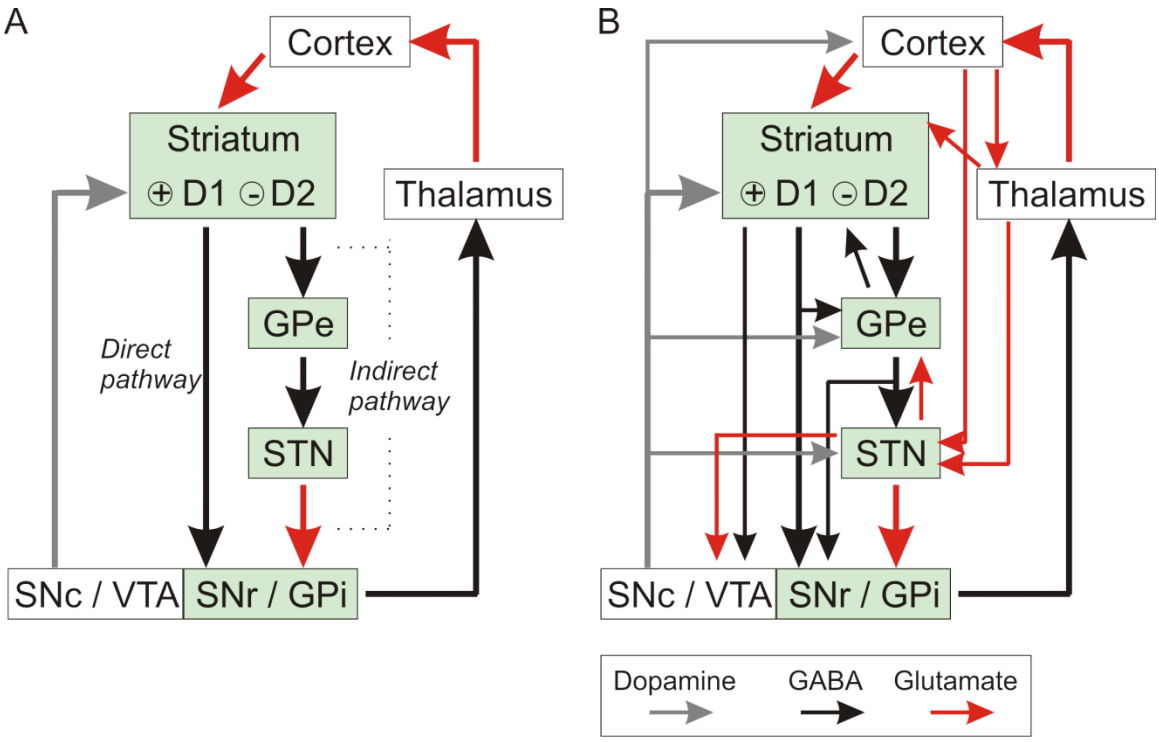

Figure 1: Basal ganglia nuclei and their connectivity

Connections between basal ganglia (green) nuclei and outside structures. A) Classical summary of the basal ganglia and its direct and indirect pathways. The striatum consists of two input nuclei, caudate and putamen. These nuclei contain projection cells that express D1 or D2 dopaminergic receptors. The binding of dopamine on D1 receptors excites striatal cells of the direct pathway (+) while binding on D2 receptors inhibits striatal cells of the indirect pathway (-). B) Details of the intrinsic and extrinsic connectivity (modified from Redgrave et al. 2010). Major pathways (reproduced from panel A) are shown in thick lines while sparse pathways and connectivity through collaterals are represented by thin lines. See *Section 1.1.1* for details.

The study of the basal ganglia in the relation to movement control dates back to late nineteenth century when David Ferrier suggested that the corpus striatum (which at the time referred rather indistinctly to the striatum, the globus pallidus, and associated white matter tracts) plays a role in "automatic or sub-voluntary (movement) integration" (Ferrier 1876; Finger 1994). Later, in the early twentieth century, the basal ganglia started to be implicated in various

movement disorders by clinical observation of patients with lesions (Carpenter et al. 1950; Denny-Brown 1962; Martin and McCaul 1959; Purdon Martin 1927; Purdon Martin and Alcock 1934; Wilson 1925; 1912). Those observations were mostly made for skeletal movements, and were followed up by single neuron recording studies (for review of early work see DeLong et al. 1990). The first investigations into the role of basal ganglia in eye movements were published in a series of papers in the early 1980's (Hikosaka and Wurtz 1985a; b; 1983a; 1983b; 1983c; 1983d).

Hikosaka and Wurtz investigated neurons in substantia nigra pars reticulata (SNr) and their functional relation to the superior colliculus (SC), a critical midbrain oculomotor region. Using electrophysiological recordings and pharmacological manipulations they found that neurons in SNr transiently release the SC from tonic inhibition just before saccade initiation. This gating is accomplished by a pause in the fairly high spontaneous firing rate of the SNr's (GABAergic) projection neurons. This disinhibition of the SC in turn promotes a burst of spiking which, a few synapses later, leads to contraction of the eye muscles. Hikosaka and Wurtz (1983c) also reported that neurons in the SNr show varied degrees of modulation for comparable saccades (i.e., similar vectors) made in different behavioral contexts. Especially, they claimed that SNr neurons projecting to the SC showed greater modulation for saccades to remembered targets ("memory-guided" saccades) than for visually-guided saccades (Hikosaka and Wurtz 1985b). Hikosaka and Wurtz (1983a,b,c) found a variety of other signals carried by pauses in SNr activity as well, such as visual responses and putative working memory signals.

Inspired by the seminal findings of Hikosaka and Wurtz, followup studies described in more detail the pathway involving SNr and SC as well as the caudate, which projects to the SNr. In the SNr, in addition to the neurons that carry signals in decreases of activity, neurons were

found that increase their activity in relation to visual target onset and/or saccade initiation (Basso et al. 2005; Handel and Glimcher 1999; Shin and Sommer 2010). Moreover, it was reported that many neurons in SNr are modulated in relation to reward and target selection (Basso and Wurtz 2002; Sato and Hikosaka 2002). In the caudate, electrical stimulation just after saccade onset (presumably mimicking a dopaminergic "reward" signal) facilitated saccades (Nakamura and Hikosaka 2006a), and injections of D1 and D2 antagonists modulated the effects of reward biases on saccadic reaction times (Nakamura and Hikosaka 2006b). That pair of studies implies that the caudate contributes to an integration of sensorimotor and reinforcement signals. All together, the caudate-SNr-SC pathway is now considered to play a central role in eye movement behavior.

What about other pathways in basal ganglia? Are they also involved in saccadic eye movements? A second direct pathway runs from putamen to GPi, and indirect pathways course through the GPe. There has been growing evidence that GPe and GPi contribute to oculomotor behavior. Deep brain stimulation and pallidotomy in human GPi are known to affect eye movements (Blekher et al. 2000; Fawcett et al. 2005; O'Sullivan et al. 2003; Straube et al. 1998). In addition to these clinical reports, recent laboratory studies using monkeys have suggested the involvement of pallidal neurons in saccadic movements. Kato and Hikosaka (1995) first described saccade-related activity in GPe, which is a logical candidate for contributing to saccades due to its projections to SNr. The participation of GPe in oculomotor behavior was further suggested by the above-mentioned pharmacological manipulation of dopaminergic receptors in caudate (Nakamura and Hikosaka, 2006b), since one class of those receptors (D2) is found predominantly on neurons that project to GPe in primates (Bergson et al. 1995; Gerfen et al. 1990; Hersch et al. 1995; Levey et al. 1993). The Hikosaka group also reported that GPi has

oculomotor effects to the extent that it provides reward-related signals to the lateral habenula (lHB) during a reward-biased eye movement task (Hong and Hikosaka 2008). Finally, a recent study reported that some pallidal neurons have peri-saccadic activity that is enhanced when monkeys look away from a visual target as opposed to toward a target ("antisaccade task"; Yoshida and Tanaka 2009a). All of this recent evidence is pointing toward a new view that caudate and SNr are not the sole oculomotor regions of basal ganglia; GPe and GPi may contribute to eye movements as well.

Previous studies of oculomotor-related neurons in GPe and GPi examined specific types of signals (mainly saccade-related) during specific tasks (e.g., antisaccade and reward bias tasks), but there has been no general, quantitative assessment of the signal content carried by pallidal neurons in basic oculomotor tasks. Also, there has been no systematic investigation of pallidal saccade-related activity in different behavioral contexts (e.g., during highly constrained saccadic tasks as opposed to during spontaneous scanning). Finally, there has not been any direct comparison between the oculomotor activity in globus pallidus and SNr. Thus, three important questions about the role of pallidal neurons in the visuomotor control remained unanswered. First, what exactly are the characteristics of visual-saccadic signals in GPe and GPi? Second, do those signals vary with behavioral context? And third, how do visual-saccadic signals in GPe and GPi compare with those in the more well-known SNr? These are the three questions that prompted my dissertation research.

1.1 THE BASAL GANGLIA

1.1.1 The Anatomy of the Basal Ganglia

The major input region of the basal ganglia is the striatum, composed of the caudate and putamen. The caudate receives inputs mainly from associative cortical and thalamic areas including eye movement related regions, while the putaman receives inputs mainly from somatomotor related cortical and thalamic areas. Major projection cells in both structures are medium-spiny neurons (MSNs). They are GABAergic and make up the majority of the striatal population. A smaller portion of striatal cells are cholinergic or GABAergic interneurons. Depending on where they project, striatal projection neurons can be divided into two groups: striatonigral and striatopallidal MSNs. Striatonigral MSNs project to the output nodes of the basal ganglia (SNr or GPi) and thus contribute to the monosynaptic direct pathways, while striatopallidal MSNs project to GPe and thus contribute to the polysynaptic indirect pathways. Signals from the GPe reach the GPi or SNr monosynaptically or via an excitatory relay in the STN.

In addition to their projection areas, the two populations of striatal MSNs are distinct in the receptors and substances that they express. Striatonigral MSNs co-express dopamine D1 receptors, substance P, and dynorphin, and are excited by dopamine. Striatopallidal MSNs co-express dopamine D2 receptors and enkephalin and are inhibited by dopamine (Gerfen and Wilson 1996; Schultz 1998). Models of dual modulation by dopamine of the direct versus indirect pathways are based on these distinctive characteristics of each group of MSNs (Albin et al. 1989; DeLong 1990; Mink 1996).

The conceptual separation of ‘direct versus indirect pathway’ has its anatomical basis described above, but recent anatomical evidence suggests updates to the model (Fig. 1B; (Redgrave et al. 2010). The first pieces of revisionist evidence concerned the position and connectivity of the GPe and STN. Traditionally, the nuclei were viewed only as sequential nodes (GPe to STN) in the indirect pathways. Recently, however, it was reported that the GPe (Smith et al. 1998) and the STN (Parent and Hazrati 1995; Parent and Parent 2007) have connectivity with all other basal ganglia nuclei through direct projections or collaterals, including a reciprocal connection from STN to GPe (Miwa et al. 2001; Shink et al. 1996; Smith et al. 1998). Second, the striatonigral MSNs which give rise to the direct pathways also affect GPe via sparse collateral fibers (Matamales 2009; Wu et al. 2000). Third, the STN is not only a relay node of the indirect pathway, but also it receives direct cortical input that bypasses striatum and GPe (Hartmann-von Monakow et al. 1978; Nambu et al. 2002; Lanciego et al. 2004; Feger et al. 1994; Coizet et al. 2009; Mena-Segovia et al. 2004). It is now generally accepted that the “textbook” idea of the basal ganglia in which all pathways arise from striatum and exit through GPi/SNr is a simplification. Nevertheless the direct and indirect pathways are important, major pathways through the basal ganglia, and my focus will be on them in this dissertation.

The connections between basal ganglia and distinctive cortical and subcortical areas form loops that are topographically organized and fairly segregated (Fig. 2; Alexander, (Alexander et al. 1986; McHaffie et al. 2005). These parallel-running loops carry sensorimotor, associative, and limbic information from distinct cortical areas, through the basal ganglia, and back to cerebral cortex via thalamus (Alexander et al. 1986).

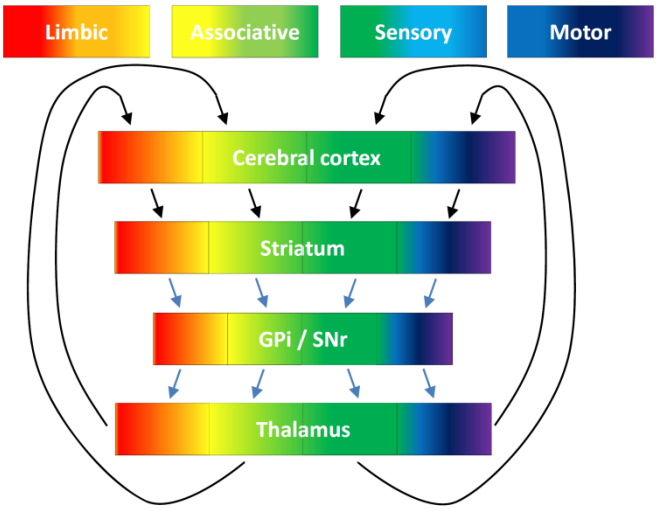

Figure 2: Cortex-basal ganglia-thalamus loops

Separate channels of information enter the striatum and remain distinct all the way through the basal ganglia nuclei, into thalamus, and back to cortex, thus forming segregated loops. Modified from Alexander (1995).

Another major extrinsic input to the basal ganglia is dopaminergic, arising from the SNc and VTA. These dopaminergic afferents reach all of the basal ganglia nuclei and thus influence signal processing throughout the basal ganglia complex. The most prominent dopaminergic inputs, however, terminate in the striatum. Dopaminergic inputs are known to be topographic as well (Matsuda 2009).

1.1.2 Efferent and Afferent Regions of the GPe, GPi, SNr, and STN

Globus pallidus externa and interna Positioned at the center of the basal ganglia, the GPe receives input from the striatum, STN, and SNc, and projects to virtually all of the basal ganglia nuclei. The GPi receives inputs mostly from putamen but also from the STN, GPe, and SNc. The efferent targets of GPi are ventral anterior (VA) and ventromedial (VM) thalamic regions and

brainstem motor related areas including the pedunculopontine tegmental nucleus (PPN), nucleus lateralis oralis and lHB. The GPi neurons that affect cortex via thalamus or project to brainstem motor areas are known to be different from the neurons providing inputs to lHB (Parent et al. 2001).

Substantia nigra pars reticulata The SNr is interdigitated with the other nigral area, the SNc. The SNc and SNr are spatially close but have distinct afferents and efferents. The SNr mainly receives inputs from caudate, especially the part posterior to the anterior commissure that receives inputs from eye movement related cortical areas (frontal eye field, FEF (Parthasarathy et al. 1992; Stanton et al. 1988); supplementary eye field, SEF (Shook et al. 1991); and lateral intraparietal area, LIP (Selemon and Goldman-Rakic 1985) and association cortex (dorsolateral prefrontal cortex; Selemon and Goldman-Rakic 1985; Yeterian and Pandya 1991). The SNr also receives inputs from the eye movement related parts of the STN and GPe, the VA and ventrolateral (VL) thalamus, the SC, and the SNc. The SNc receives inputs from various areas including the striatum and lHB (Herkenham and Nauta 1977), and it projects to all basal ganglia nuclei.

Subthalamic nucleus Unlike other basal ganglia nuclei, neurons in STN are glutamatergic and therefore cause excitation downstream (Nakanishi et al. 1987). The areas providing inputs to STN are GPe (Shink et al. 1996), frontal cortical areas (Carpenter and Jayaraman 1990; Hartmann-von Moakow et al. 1978; Nambu et al. 1996), and the dopamine system (SNc, VTA; Bjorklund and Dunnett 2007; Cragg et al. 2004). Neurons in the STN innervate basal ganglia nuclei GPe, GPi, and SNr, plus the SNc (Kita and Kitai 1987; Parent and Smith 1987). The monosynaptic projection from the cortex to STN facilitates fast conduction of signals to GPi and SNr (thus called “hyperdirect” pathways; Hartmann-von Monakow et al. 1978; Nambu et al.

2002; Lanciego et al. 2004; Feger et al. 1994; Coizet et al. 2009; Mena-Segovia et al. 2004). Very recent studies have reported that the STN sends a direct projection to the thalamus (Rico et al. 2010) and is the source of a disynaptic pathway to the cerebellum (Bostan et al. 2010).

1.1.3 Basal Ganglia Neurophysiology in the Relation to Eye Movements

Among the various basal ganglia networks described above, three major pathways have been thought to contribute to saccadic behavior due to their termination in SNr: 1) the direct pathway from the caudate to the SNr; 2) the indirect pathway from the caudate to SNr via GPe and STN; 3) the hyperdirect pathway from cortex to STN to SNr. An important difference between these pathways is the overall "sign" of their influence on downstream structures (e.g., the SC). Cortical inputs (glutamatergic) excite striatal projection neurons (GABAergic), leading to transient inhibition downstream. Hence one "sign reversal" (from excitation to inhibition) has occurred. Beyond striatum, more sign reversals occur due to transient inhibition of GABAergic neurons with high baseline firing rates. The pauses disinhibit those neurons' efferent targets, causing rebound excitation or allowing for expression of excitatory inputs. The net effect of the direct pathway (caudate then SNr) is a dual sign reversal or excitatory influence. In other words, a burst of activity in cortex, mediated by the direct pathway, promotes a burst of activity in the SC. The net effect in the indirect pathway (caudate, GPe, and SNr plus the sign-neutral, excitatory STN) is a triple sign reversal or inhibitory influence. The hyperdirect pathway through STN features a single sign reversal at the SNr, which again results in inhibition downstream. This overall story is complicated by the fact that some neurons in SNr and GPe do not signal events with pauses from baseline, but rather with increases in firing rate from baseline. The net signs of each pathway (direct: positive; indirect and hyperdirect: negative) are good heuristics and useful for

"back of the envelope" calculations of the effects of manipulating each pathway, but they are first approximations only.

1.1.4 The Functional Role of the Basal Ganglia in Eye Movements

The basal ganglia have been implicated in various aspects of eye movement control including selecting the relevant saccade based on expected reward, learning and performing sequences of saccades, forming oculomotor habits, generating voluntary saccades, and modulating certain kinematics of saccades. In the following sections, experiments on these putative functional roles of the globus pallidus and SNr will be reviewed.

1.1.5 GPi and SNr

The GPi and SNr are similar in terms of signal processing. Output neurons in the SNr and GPi are GABAergic (Di Chiara et al. 1979; Uno and Yoshida 1975; Yoshida and Omata 1979) and exhibit high baseline firing rates (DeLong and Georgopoulos 1981). Thus they impose strong tonic inhibition over brain areas that receive projections from them (e.g., thalamus). The basal ganglia control motor behavior through modulations of this tonic influence. The modulations take the form of inhibition or disinhibition, depending on whether the SNr or GPi activity decreases or increases relative to baseline (Anderson and Horak 1985; Shin and Sommer 2010; Hikosaka and Wurtz 1983a). There is phylogenic evidence for similarities between the SNr and GPi as well: in some mammals they form a single structure. The general view is that the two structures have similar functional roles in principle, but different topological organizations and functional domains.

Traditionally, the GPi has been thought to be exclusively involved in skeletal motor behavior by preferentially influencing areas of motor cortex and skeletal motor generating brainstem structures (Nambu 2007). Involvement of GPi in controlling movement has been demonstrated by single unit recording (Anderson 1977; DeLong 1971), inactivation (Beaubaton et al. 1981; Hore and Vilis 1980; Inase et al. 1996; Kato and Kimura 1992; Mink and Thach 1991b; Wenger et al. 1999), lesions (Horak and Anderson 1984a; Mink and Thach 1991b), and stimulation (Horak and Anderson 1984b). Some neurons in the arm related zone of GPi (and GPe) encode arm movement kinematics (i.e., movement vector; Turner et al. 1995) and are known to be modulated by behavioral context (Turner and Anderson 2005).

Although it has been known that the GPi is critical for skeletal motor behavior, this does not rule out a role for it in oculomotor behavior. The visuosaccadic properties of its neurons simply had not been studied in a systematic way before I began my work.

The SNr is best known for its involvement in the eye movement system, a conclusion reached through a long line of research initiated by the studies of Hikosaka and Wurtz as discussed above. As mentioned above, Hikosaka and Wurtz found a variety of oculomotor-related signals in the SNr, all carried in pauses of activity. Later it was shown that some SNr neurons carry signals in firing rate increases as well (Basso and Liu 2007; Handel and Glimcher 2000; Shin and Sommer 2010). For most of the SNr visual- and saccade-related neurons of either valence, response fields are centered in the contralateral hemifield. The neurons are found mainly in the dorsolateral part of the SNr (Hikosaka and Wurtz 1983a), and many can be activated antidromically by stimulation in SC (Hikosaka and Wurtz 1983d). Inactivation of the SNr (with the $GABA_A$ agonist muscimol) causes involuntary saccades to the contralateral side (Hikosaka and Wurtz 1985b), and stimulation of the SNr disrupts saccades, causing larger

deficits for memory-guided saccades than for visually-guided saccades (Liu and Basso 2008). These causal studies, taken together with the early finding that SNr neurons seem preferentially modulated by memory-guided saccades (Hikosaka and Wurtz 1985b), has led to the general conclusion that the SNr contributes primarily to producing voluntary saccades. Supporting this view, it has been reported that SNr pauses are correlated with important aspects of willful behavior such as expectation of reward (Sato and Hikosaka 2002) and covert selection of spatial goals for movement (Basso and Wurtz 2002).

The functional dichotomy between GPi (skeletomotor) and SNr (oculomotor) has been challenged recently (reviewed at the start of this Introduction). As with the "direct vs. indirect pathway" dichotomy, it may be useful as a rule of thumb to consider GPi and SNr functionally distinct, but the emerging evidence (including data presented in this dissertation) suggests that researchers and clinicians who study the basal ganglia should consider a more nuanced view.

1.1.6 GPe

The GPe has been explored with the use of various methods including single unit recording (Anderson and Turner 1991; Brotchie et al. 1991a; 1991b; DeLong 1990; Hamada et al. 1990; Mink 1996), excitotoxic lesions (Mink and Thach 1991b), and microinjection of pharmacological agents (Crossman et al. 1988; Crossman et al. 1984; Inase et al. 1996; Matsumura et al. 1995). These studies focused on limb and body movements, and cumulatively they confirmed a role for GPe in movement control. The general finding was that, functionally, GPe is similar to GPi. Most previous studies studied GPe and GPi in relation to skeletal motor behavior and found no differences in peri-movement activity between them (e.g., Mitchell et al. 1987; Turner and Anderson 1995, 2005). However, it has been known that at least one basic

neurophysiological property is different between the structures. GPe projection neurons with high baseline firing have frequent, long pauses (hundreds of ms; Elias et al. 2007) while neurons in GPi show much more regular firing (Arkadir et al. 2004; DeLong 1971; Galvan et al. 2005). The functional impact of the long GPe pauses is a matter of debate. For example, DeLong, (1971) found no correlation with specific behaviors or events but Elias et al. (2007) found correlations with behavioral events such as button pressing or reward delivery in a subset of neurons.

The main projection of GPe is to the STN, a connection that is reciprocal (Nauta and Mehler 1966). The STN, in turn, projects to both GPi and SNr (indirect pathway, Nauta and Cole 1978). Even with the anatomically known projection from the oculomotor region in caudate to the GPe, there were only a few previous studies that examined the primate GPe during visuosaccadic behavior, as reviewed at the start of this Introduction (Kato and Hikosaka 1995; Nakamura and Hikosaka 2006a; b; Yoshida and Tanaka 2009a).

My overall conclusion from consideration of all this previous work was that it is timely and necessary to record from both segments of globus pallidus with an extensive battery of purely saccadic tasks (no concurrent reaching or other skeletal movements) and to compare the results with identically collected recordings in SNr of the same monkeys.

1.2 EYE MOVEMENTS

Eye movements are an advantageous model system to study basal ganglia circuitry for several reasons. They are relatively simple in that they involve only six muscles and do not require consideration of factors such as inertia and joints. There is a rich history of study into the

mechanical aspects and neural mechanisms underlying eye movements. Finally, monkeys make eye movements frequently and tirelessly while engaging in decision making and other cognitive processes as they select where to look next. Hence eye movements are attractive to exploit as behavioral reports in cognitive neuroscience studies.

1.2.1 Types of Eye Movements

There are five basic types of eye movements: vestibular-ocular reflex (VOR), optokinetic response (OKN), vergence, smooth pursuit, and saccades. They are generated within different neuronal circuits that converge on common canonical mechanisms in the brain stem. The first three movements, VOR, OKN, and vergence, are not volitional. VOR is a reflex triggered by the vestibular system that stabilizes the eyes as the head moves. OKN is generated when the head remains stationary and large fields move across the retina; it is controlled ultimately by vestibular-oculomotor circuits. Vergence eye movements are disconjugate rotations of the eyes to re-align gaze on objects near or far from the current plane of focus, and are controlled primarily by the oculomotor nucleus (Büttner-Ennever and Horn 1997).

The last two types of eye movements, smooth pursuit and saccades, can be made voluntarily. They are eye movements used to bring the location/object of interest onto the fovea (saccades), or keep it there (smooth pursuit). Smooth pursuit is a steady rotation of the eyes to follow a moving object. This type of eye movement was not studied in my dissertation work, so for brevity I will not review it further. Saccadic eye movements are rapid eye movements, occurring 2-3 times per second. When made in a visually structured environment, they enable swift, high acuity analysis of the scene's details. But they do not require visual input and can be made entirely at will, for example in the dark. The system underlying saccadic eye movements is

one of the most extensively studied systems in the primate brain. Visual information courses through both the parvocellular and magnocellular retinogeniculostriate pathways into extrastriate cortex where it then reaches a few major saccade related cortical areas: the FEF, SEF, and LIP (Schall 1997). Saccade-related signals are then sent to the SC and other brainstem saccade generating areas via direct projections or more circuitously, via the basal ganglia. How the signals may travel within basal ganglia circuits was reviewed in detail above.

1.2.2 Saccadic Eye Movements Made in Standard, Instructed Tasks

Various cognitive functions can be tested by simple saccadic eye movement tasks. In the following paragraphs, the most commonly used saccadic eye movement tasks will be reviewed.

Visually-Guided Task and Express Saccades A visually-guided saccade task usually requires the animal to fixate a central spot, which then either disappears shortly before a peripheral visual target appears (gap version), disappears together with the appearance of the peripheral target (no gap version), or remains visible after peripheral target onset (overlap version). In all three cases the cue to move is target onset. The overlap task can be modified such that the cue to move, instead, is fixation spot disappearance, which can be delayed for an arbitrarily long time. In humans and non-human primates, decreased saccadic reaction times are commonly elicited in the gap version compared to all other versions of the task (e.g., Saslow 1967) and this effect is called the ‘gap effect’. In fact, many studies have reported saccades in the gap version of the task that have essentially reflexive latencies: 90-120 ms for human (Fischer and Ramsperger 1984) and 70-90 ms for monkeys (Fischer and Boch 1983; Pare and Munoz 1996). Such saccades, known as ‘express saccades’, emphasize the highly reactive, sensory-driven nature of these tasks. Visually-guided saccade tasks have been widely used to characterize

basic visuosaccadic activity throughout cortical and subcortical regions (e.g., FEF, Schall 1991; SNr, Hikosaka and Wurtz 1983a; SC, Wurtz and Goldberg 1972a,b). A detailed description of the visually-guided saccade task used in my work is provided in *Section 3.2*.

Antisaccade Task The antisaccade task is designed to dissociate the location of a visual target and the vector of a saccade. The monkey fixates and a target appears, following any of the versions of the visually-guided saccade task. But the animal must suppress a reactive saccade toward the target and, instead, look away from it (Munoz and Everling 2004). The antisaccade task therefore involves the generation of a saccade to an instructed, but blank, location. A complicating factor in interpreting results from the antisaccade task is that the animal must also suppress a competing, visually-guided movement. Patients with damage to frontal cortex are especially deficient at this task; they cannot help but make saccades toward the visual stimulus (Everling and Fischer 1998; Guitton et al. 1985). The task has been widely used in non human primate studies in conjunction with single unit recordings in cerebral cortex (Amador et al., 1998; Gottlieb and Goldberg, 1999; Schlag-Rey et al., 1997; see also Munoz and Everling (2004) for review) and globus pallidus (Yoshida and Tanaka 2009a), pharmacological manipulation in globus pallidus (Yoshida and Tanaka 2009a), and electrical stimulation in caudate (Watanabe and Munoz 2010). I did not use the antisaccade task in my work, but understanding this task is important for the purpose of comparing my results to the findings of previous studies that did use it.

Memory-guided Saccade Task The memory-guided saccade task requires an animal to remember a target location that is flashed only briefly and followed by a delay period before a cue to move is provided. The target is therefore unavailable at the moment of saccade initiation, and the animal must make its saccade to its remembered location. A detailed description of the

memory-guided saccade task used in my work is provided in *Section 2.2* and *3.2*. This paradigm has two main benefits in the investigation of neurons. First, the delay period provides temporal separation between visual target presentation and saccade initiation, thus enabling an investigator to distinguish between neuronal activities related to those events. Second, the task requires spatial working memory, a straightforward cognitive function of great interest. Because of these benefits, memory-guided saccade tasks have been used in many studies of the basal ganglia (Hikosaka and Wurtz 1983a,b,c, 1985a,b; Yoshida and Tanaka 2009a; Shin and Sommer 2010).

1.2.3 Scanning Saccades

The types of saccadic tasks described above have been invaluable in the laboratory, but have little relevance to real life. Most of our everyday saccades are made to look around rich visual scenes. The study of natural saccades using realistic stimuli (e.g., scenes and common objects) was first accomplished by Yarbus (1967). He concluded that depending on the distribution of complex objects in a natural scene, some portions of the scene attract more saccades than others. In other words, scanning saccades are not random, but are highly voluntary and sensitive to cognitive influences. Since then, behavioral studies of scanning saccades made in natural contexts have been performed often in humans (e.g., Hayhoe and Ballard 2005; Jovancevic-Misic and Hayhoe 2009) but only rarely in monkeys, especially concurrent with neuronal recording (Burman and Segraves 1994; Phillips and Segraves 2009). There are inherent challenges in the study of scanning saccades. If one uses a busy natural image, one can evoke from many neurons of the visual-saccadic system visual responses related to specific features (e.g., color, contrast) in the scene, and those visual responses may be modulated strongly by the intentions of the animal where to look next (Burman and Segraves 1994; Phillips and Segraves

2009). The neuronal responses can be difficult to interpret. A simpler, sparser scene provides for much more control, but still a second problem remains: how to reward the monkey. A "trial" can last a significantly long time, up to many seconds or minutes. If reward is delivered at the very end, the animal's motivational state might be low early in a trial, thus affecting saccadic parameters and, in all likelihood, the firing rates of many neurons. But if one delivers reward during the scan, it interrupts the animal's natural scanning behavior. Scanning tasks must be well designed and analyzed to account for these issues. To minimize any unknown visual and cognitive influences on the data, some studies have evoked scanning saccades with arrays of identical visual spots as the visual stimuli (Desrochers et al. 2010; Richards et al. 1994; Sommer 1994; 1997). There is little one can do, however, to keep reward rates the same as for the more traditional laboratory paradigms (e.g., the memory-guided saccade task). The best strategy in my view is to analyze post-hoc whether any measured values (such as firing rate) change as trials proceed to their reward phase.

Given that saccades can be made in the dark, another option for minimizing visual confounds is to remove the stimuli altogether. Tasks that involve saccades made to a featureless field or in the dark are especially useful for neurophysiologists. A couple of previous recording studies in the SNr have collected data while monkeys made saccades in the dark (Hikosaka and Wurtz, 1983c) or with visual features minimized (dimly lit room; Handel and Glimcher, 2000). Paradoxically, neurons in SNr hardly responded at all. While on the face of it this seems like a refutation of the dominant hypothesis that the SNr is preferentially active for voluntary saccades, I was not convinced. There was still a confounding factor in those studies: reward schedules. In the studies mentioned above, the spontaneous saccades were not rewarded at all. Nor was there a well defined goal for the monkey. Both factors (lack of reward and aimless task) could, it seemed

to me, contribute to the weak firing rates found in SNr neurons. When I designed my scanning tasks and analyzed my results, I kept these concerns in mind.

The complexities associated with interpreting scanning tasks are a reminder that the concept of "voluntary movement" can be difficult to define. Indeed, the definition seems to vary from study to study. Overall in the literature I have encountered two general operational definitions of voluntary movement. Actions may be considered voluntary if they are made without 1) sensory input or 2) instruction (Haggard 2008; Passingham 1987). In my view, thorough studies of voluntary movements should take both definitions into account. Further discussions of these two definitions, plus a description of how I designed my experiments around them, are presented in *Section 3.0*.

1.2.4 Eye Movements in Basal Ganglia Disease

One way to infer the function of a brain structure is to examine the changed behavior in individuals for whom the structure is damaged or diseased. In the case of basal ganglia, such patients include those with Parkinson's, Huntington's diseases, or Tourette's syndrome. For more than a century, investigators have noticed that there are deficits in eye movements in basal ganglia disorders. Well known problems include the paucity of spontaneous saccadic eye movements in Parkinson's disease (Cooke et al. 1978; Glickstein and Stein 1991) and the impaired suppression of reflexive saccades toward newly occurring sensory stimuli in Huntington's disease (Bates et al. 2002). Indeed, abnormality of saccades is considered one of the first signs of Parkinson's disease and has been used as a diagnostic criterion (Hikosaka et al. 2000).

Eye Movements in Parkinson's Disease The types of saccadic eye movements studied in Parkinson's patients have been as follows: Predictive saccades, visually-guided and other sensory driven saccades, memory-guided saccades, antisaccades, self-paced saccades, saccades to oddball targets, and sequenced saccades. In most studies, visually-guided saccades were fairly intact in terms of kinematics of saccades in moderate and advanced Parkinson's patients (i.e., comparable velocity, amplitude of saccades to those in normal) with some characteristic changes such as increase in frequency of breaking fixation and decrease latency of saccade onset (i.e., more express saccades; Chan et al. 2005; Crawford et al. 1989a; Crawford et al. 1989b; Kitagawa et al. 1994; Muller et al. 1994; Vidailhet et al. 1994). Those results imply that reactive saccades are intact, and perhaps even disinhibited such that they are difficult to suppress, in Parkinson's disease.

In tasks for which saccades are less determined by sensory context, and more dependent on voluntary and cognitive behavior, various results have been reported. The general consensus has been, however, that there is a deficit in making voluntary saccades. During memory-guided saccade tasks, when compared to a healthy control group, Parkinson's patients showed significant reductions in mean gain, resulting smaller, multi-step saccades while other parameters of the saccades were unchanged (Crawford et al., 1989b). In a task requiring memory of a multi-step sequence for making saccades, the patients showed increased errors in sequence order and greater spatial displacement between target locations and saccade endpoints. Eye movements have been examined as well in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated monkeys (Kato et al. 1995; Kori et al. 1995; Schultz et al. 1989a; Schultz et al. 1989b). MPTP treatment mimics Parkinson's disease by destroying dopamine neurons in the midbrain dopamine system (Pifl et al. 1991; Schultz et al. 1989a). Deficits in spontaneous and memory-guided

saccades (decrease in velocity, frequency of spontaneous saccades, increase in latency) were prominent. The effects were contralateral to the lesion side in unilaterally treated animals.

Eye Movements in Huntington's Disease and Tourette's Syndrome In Huntington's disease and Tourette's syndrome, the most prominent deficits include involuntary movements of body parts (Bates et al. 2002; Peterson et al. 1999). Despite the fact that the initial causes of Parkinson's disease, Huntington's diseases and Tourette's syndrome are different, all of the disorders involve damage to the basal ganglia and, more interestingly, similar deficits in eye movements (Hikosaka 2007) suggesting a common underlying problem in eye movement generation. Briefly, an inability to suppress reactive saccades, delays in initiation of memory-guided saccades, and increased errors in voluntary (i.e., memory-guided saccade or antisaccade) are commonly observed in patients with Huntington's disease (Lasker and Zee 1997) or Tourette's syndrome (Nomura et al. 2003).

Albeit important and valuable, the data from clinical studies have limitations in helping understand the basal ganglia function. First, in diagnosed Parkinsonian patients, in addition to the basal ganglia, many other brain areas undergo massive change due to the degeneration of dopaminergic inputs. In Huntington's disease, neuronal degeneration starts in the basal ganglia and the frontal cortex early on, but it eventually becomes widely spread in the brainstem as well (Barr et al. 1978; Simmons et al. 1986; Vonsattel et al. 1985). Therefore, behavioral and neuronal characteristics in Parkinson's or Huntington's diseases are unlikely to be solely attributable to malfunction in the basal ganglia. For example, prefrontal cortical areas, not the basal ganglia per se, are known to mediate working memory (Goldman-Rakic 1995) in delayed saccade tasks and suppression of visually-trigged saccades in antisaccade tasks (Everling and Munoz 2000; Sato et al. 2003). Thus dysfunctional characteristics in Parkinson's and

Huntington's patients may be due to secondary damage in prefrontal cortex, which receives dense inputs from both basal ganglia and midbrain dopamine systems. Also, abnormalities in behavior and of neurons in affected areas vary as the process of pathological plasticity progresses, so the degree of disease severity should be considered to interpret the patient data correctly. This idea is supported by the observation that some impairments (e.g., deficits in antisaccades) are found in advanced Parkinson's disease but not in mild forms of the disease (Chan et al. 2005). Finally, systematic investigation on neuronal data from Parkinson's patients is somewhat rare, although much has been accomplished with the MPTP primate model of the disease. The overall conclusion from single neuron recordings in the MPTP model is that basal ganglia output in the GPi seems elevated (Filion and Tremblay 1991; Miller and DeLong 1987), neuronal activity in primary motor cortex (M1) becomes more synchronous and bursty (Goldberg et al. 2002), and neurons in supplementary motor area (SMA) cortex show changes in neuronal responses to visual cues as well as irregular activity. It should be noted that some of the cortical effects found in MPTP-treated monkeys could be due to direct reduction of dopaminergic innervations to cortex rather than due to basal ganglia-mediated disruption of cortical function. The only study, to my knowledge, that evaluated the simultaneous relationship between basal ganglia and cortical deficits in MPTP-treated monkeys has only recently concluded and is unpublished (thesis work of Chan VS, 2011; personal communication). Neuronal activity during impaired eye movements in MPTP monkeys has not been studied yet, to my knowledge.

1.3 SUMMARY AND AIMS

The monkey saccadic eye movement system has served as a useful animal model for understanding the role of basal ganglia in the control of movements. Detailed descriptions of signal processing within the basal ganglia and how the basal ganglia influence downstream areas were characterized in detail first for the caudate-SNr-SC pathway. Various other aspects of movement control such as learning, memory, and selection of targets have been studied for the caudate and SNr. Beyond this classic work, a growing body of evidence from clinical and neurophysiological studies has begun to implicate GPe and GPi in eye movement control. And a larger debate, on the preferential role of basal ganglia in the initiation of voluntary movements, is still ongoing.

In my dissertation work, I made an attempt to clarify what I see as the main outstanding issues related to basal ganglia control of eye movements: the role of GPe and GPi, and the hypothesized preferential role in voluntary movements.

Aim 1: *Determine the extent to which GPe and GPi activity is related to saccades*

I investigated the new hypothesis that neurons in GPe and GPi carry eye movement related signals. I recorded from single cells in GPe and GPi while monkeys performed eye movement tasks. For comparison, I also recorded from the SNr in the same monkeys.

Aim 2: *Determine whether oculomotor activity in basal ganglia varies with task context*

I investigated whether saccade-related activity in GPe and GPi depends on behavioral context, especially in relation to voluntary action. I designed a battery of tasks that featured varying levels of sensory guidance and instruction, from highly constrained to as free as possible in a laboratory

setting. I tested whether neuronal activity for the same vectors of saccades differed between the tasks. Again for comparison, I performed the same experiments on SNr neurons from the same monkeys.

2.0 ACTIVITY OF NEURONS IN PRIMATE GLOBUS PALLIDUS DURING OCULOMOTOR BEHAVIOR COMPARED WITH THAT IN SUBSTANTIA NIGRA PARS RETICULATA

2.1 INTRODUCTION

The basal ganglia are important for the control of movements (DeLong 1971; Hikosaka et al. 2000; Hikosaka and Wurtz 1989; Mink 1996). Detailed anatomy was reviewed in *Section 1.0.* Briefly, the basic layout is that the striatum receives inputs from cerebral cortex, signals are processed through various pathways, and signals exit through the GPi and SNr (Graybiel and Ragsdale 1979; Niijima and Yoshida 1982). A direct pathway from caudate to SNr contributes to saccadic eye movements (Fig. 3A, blue line at right; Handel and Glimcher 2000; 1999; Hikosaka et al. 1989a; 1989b; Hikosaka et al. 2000; Hikosaka and Wurtz 1985b; 1983a; 1983b; 1983c; 1983d). A second direct pathway runs from putamen to GPi (Fig. 3A, blue line at left), and indirect pathways course through the GPe (Fig. 3A, orange lines). The SNr, GPi, and GPe are similar in having high spontaneous firing rates and inhibitory influences. We ventured beyond the classic caudate-SNr pathway to systematically examine the activity of GPe and GPi neurons during oculomotor behavior.

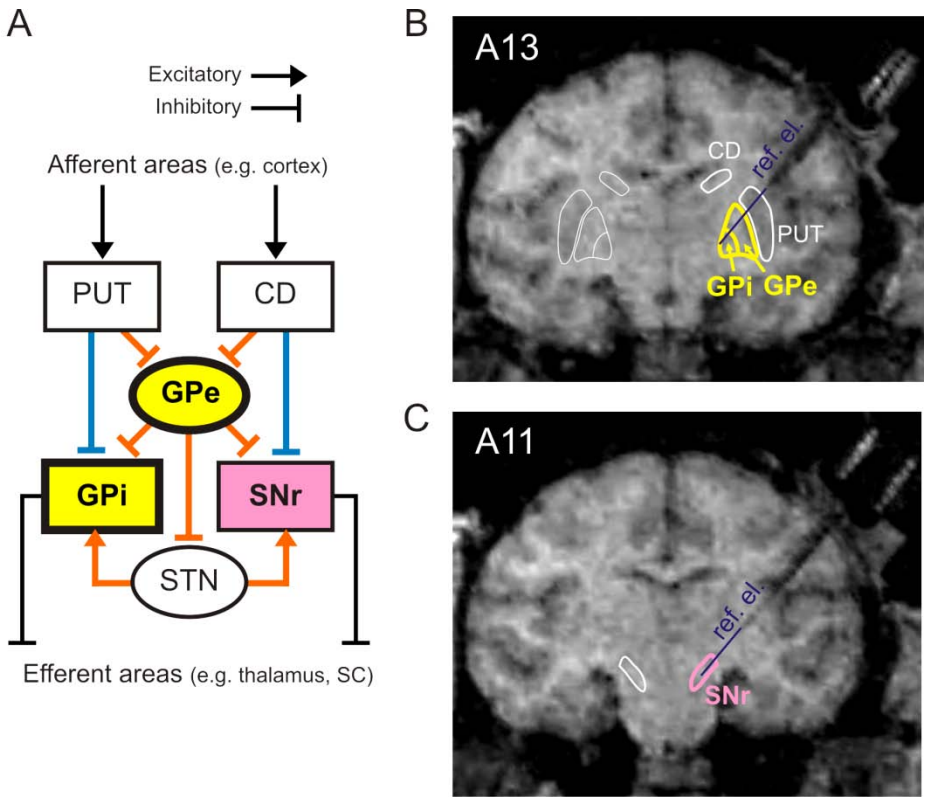

Figure 3: The basal ganglia

A) Diagram of basic circuits: blue lines, direct pathways; orange lines, indirect pathways. PUT, putamen; CD, caudate nucleus; STN, subthalamic nucleus; other abbreviations as in text. B) Coronal MRI from one monkey shows our electrode approach in relation to the basal ganglia.The reference electrode (ref. el.) was implanted above the location of task-related pallidal neurons, but we kept it out of the putamen to preclude any risk to the basal ganglia during imaging. The track that the electrode would have taken in a recording experiment is shown with the blue line. C) Similarly, our electrode approach in relation to the SNr, showing a second, simultaneously implanted ref. el. Note that the ref. el. location in panel B was selected to be near the medial edge of the pallidal recording range, so that its image could be distinguished clearly from the other ref. el. pointing at SNr only 2 mm posterior to it (A13 and A11 indicate the stereotaxic planes of the MRI slices). Exact boundaries of basal ganglia nuclei could not always be seen in the MRI sections, but were determined by comparing the images with stereotaxic atlases.

Our main goal was to determine whether the firing rates of GPe and GPi neurons are modulated in saccadic tasks, and if they are, to quantitatively characterize the modulation. We predicted that the activity of some neurons in GPi is related to oculomotor behavior because deep brain stimulation and pallidotomy in human GPi are known to affect eye movements (Blekher et al. 2000; Fawcett et al. 2005; O'Sullivan et al. 2003; Straube et al. 1998). In addition to these clinical reports, recent laboratory studies implicate pallidal neurons in oculomotor behavior. Kato and Hikosaka (1995) described saccade-related activity in GPe during a combined hand-eye task. Pharmacological manipulation of indirect pathways influence saccadic tasks (Nakamura and Hikosaka, 2006). Hong and Hikosaka (2008) found that GPi is a source of reward- related signals to the lHB during a reward-biased oculomotor task. A recent study reported that some pallidal neurons have activity around the time of a saccade that is enhanced when monkeys look away from a visual target as opposed to toward a target (Yoshida and Tanaka 2009a).

The previous reports of GPe and GPi neurons analyzed specific types of signals, but there has been no general assessment of the signal content carried by pallidal neurons in oculomotor tasks. Nor has there been any direct comparison of pallidal neurons with SNr neurons. We hypothesized that the activity of neurons in GPe and GPi exhibit multiple types of activity during oculomotor behavior. As found previously in the SNr, this activity could represent a spectrum of events such as detection of a visual stimulus, memory of it during a delay period, saccade generation toward it (Hikosaka and Wurtz, 1983a, 1983c; Handel and Glimcher, 2000), and delivery of reward. We recorded from GPe and GPi neurons, mapped their response fields, and analyzed their patterns of activity while monkeys made memory-guided saccades to the response field centers. In contrast to previous methods that used fixed target eccentricities (e.g., Hong and Hikosaka 2008; Kato and Hikosaka 1995; Yoshida and Tanaka 2009a), the approach that we

adopted – tailoring the target location to each neuron's response field center – is more time consuming but should optimize the analysis of neuronal signals. We recorded from SNr neurons in the same monkeys using the same tasks. The results provide the first quantitative assessment of the diversity and spatial representations of visual, delay, saccade, and reward-related signals in GPe and GPi, in the context of direct comparisons with SNr.

2.2 METHODS

2.2.1 Surgical Procedure

Three rhesus monkeys (*Macaca mulatta*) were surgically prepared in aseptic conditions under isofluorothane anesthesia. We implanted scleral search coils for eye position monitoring (Judge et al. 1980), a chamber for neuronal recordings, and a post for immobilizing the head during experiments (see Sommer and Wurtz 2000 for details). Dental acrylic held together the chamber, head post, and eye coil plugs, and the entire implant was attached to the skull via bone screws. The chamber was centered at 11 AP, 28 ML, and angled 40° from vertical in the coronal plane to access the GPe, GPi, and SNr in the right hemisphere. We assessed chamber placement using magnetic resonance imaging (MRI) with reference electrodes (Fig.3B,C). MRI images were compared with stereotaxic atlases to confirm the location of the basal ganglia structures (Martin et al., 1996; Paxinos et al., 2000; http://www.brainmaps.org). All procedures were approved by the Institute for Animal Care and Use Committee in accordance with the National Institutes of Health Guide for the care and Use of Animals.

2.2.2 Behavioral Paradigm

First, we determined the preferred direction of a neuron by having the monkey make memory-guided saccades as described below to targets in eight different directions (the cardinal axes and diagonals). For this assessment we used an amplitude estimated to be optimal for the neuron. From inspection of on-line spike rasters and spike density functions, we determined the direction that elicited the highest firing rate of the neuron. If two neighboring directions yielded similar maximal firing rates, the best direction was considered to be the angle that bisected those two directions; hence our resolution was 22.5° in circular angle. Along this best direction, we honed in on the optimal amplitude by having the monkey make visually-guided saccades to targets at multiple eccentricities (typically eight: 2, 5, 10, 30, 40, 50, and 60°; if pressed for time we used 5, 10, and 30°). If the best amplitude determined by this procedure differed from the initially estimated best amplitude, we re-ran the directional tuning assessment using the newly determined amplitude. See Sommer and Wurtz (2004) for more details of this iterative procedure. By alternating between these direction and amplitude tests and fine-tuning the target locations accordingly, we were able to find the "hot spot" of the neuron's response field in a time-efficient manner.

After determining a neuron's best direction and amplitude, we ran the monkey on a memory-guided saccade task with two targets, one at the response field center and one at the diametrically opposite location. We typically collected 10-20 trials at each location, but sometimes up to 40 trials if a neuron's isolation was exceptionally stable. Trials in the diametrically opposite location were run to maintain spatial symmetry, thus discouraging the monkey from making anticipatory saccades and precluding the possibility of causing inadvertent biases to the natural response field lateralities. We focused on the memory-guided saccade task

because it permits temporal separation of visual-, delay-, and saccade-related activity (Hikosaka and Wurtz 1983c; Mays and Sparks 1980) and it was used in many previous studies of the SNr (e.g., Basso and Liu 2007; Handel and Glimcher 2000; Hikosaka and Wurtz 1983c). A monkey fixated a spot for a random duration of 500-800 ms, a target appeared in the center of the response field for 50 ms, a delay period of 500-1000 ms ensued, and then the fixation spot disappeared, which was the cue to move. After making the saccade to the location of the (absent) target, the monkey had to fixate the target location for 200 ms. Then the target reappeared and 300 ms later, reward was delivered. The electronic window for verifying fixations on-line was 3 deg. square. The window around the target location for verifying a correct saccade on-line was adjusted by the investigator as a function of eccentricity (larger windows for larger eccentricities). For 15 deg. eccentricities, as an example, the window was typically 4 deg. horizontal x 6 deg. vertical. It was larger in the vertical dimension because of normal upshifts in making memory-guided saccades (White et al. 1994). Regardless of these on-line windows, we always inspected every trial off-line and omitted trials from analysis if a fixation or saccade endpoint fell outside the main cluster of eye positions.

2.2.3 Recording Procedure

GPe and GPi neurons were identified by their anatomical location relative to landmarks such as the putamen, internal capsule, lateral geniculate nucleus, and third cranial (oculomotor) nerve. Physiological properties of the neurons such as action potential shapes and streaks of intermittent pauses that are common in GPe provided further confirmation (DeLong 1971). We sometimes encountered both GPe and GPi neurons on single penetrations (Fig. 3B). Other days, we encountered a few millimeters of the GPe but could not enter GPi, because we were near the

caudal boundary of GPe (and GPe is broader than GPi). The top of GPe was easily identifiable due to the sudden increase in spontaneous firing rate at the putamen/GPe border (DeLong 1971). The GPe/GPi border was not always obvious because neurons in both structures have high firing rates and there is only a thin laminar border between them. Therefore, after recording all of the neurons but before quantitatively analyzing their signals, we applied a stringent depth criterion: for a neuron to be classified as GPi it had to be located more than 2.5-3mm below the top of GPe. According to atlases (Martin et al. 1996; Paxinos et al. 2000) and previous studies (Anderson and Turner 1991; Elias et al. 2007), only GPi neurons are found that deep. The criterion varied from 2.5 to 3 mm due to gradual changes in the GPe/GPi border with anteroposterior location. Task-modulated neurons were clustered within a volume of a few mm^3, accessible by 3-4 adjacent grid holes each separated by 1 mm (Crist Instruments, Hagerstown, MD, USA), and were found at the posterior and mediodorsal portion of GPe and GPi based on the landmarks noted above and magnetic resonance imaging. The distribution of recording depths of GPe and GPi neurons is shown in Figure 4A. As a post-hoc test of the GPe/GPi categorization, after analyzing all of the neuronal signals we examined how they varied with depth through the pallidum (Fig. 4B, using the Reward-Visual Index (RVI) analysis described below). We found a sudden change in signal content at the estimated GPe/GPi boundary, implying that few, if any, of the GPe or GPi neurons were misclassified.

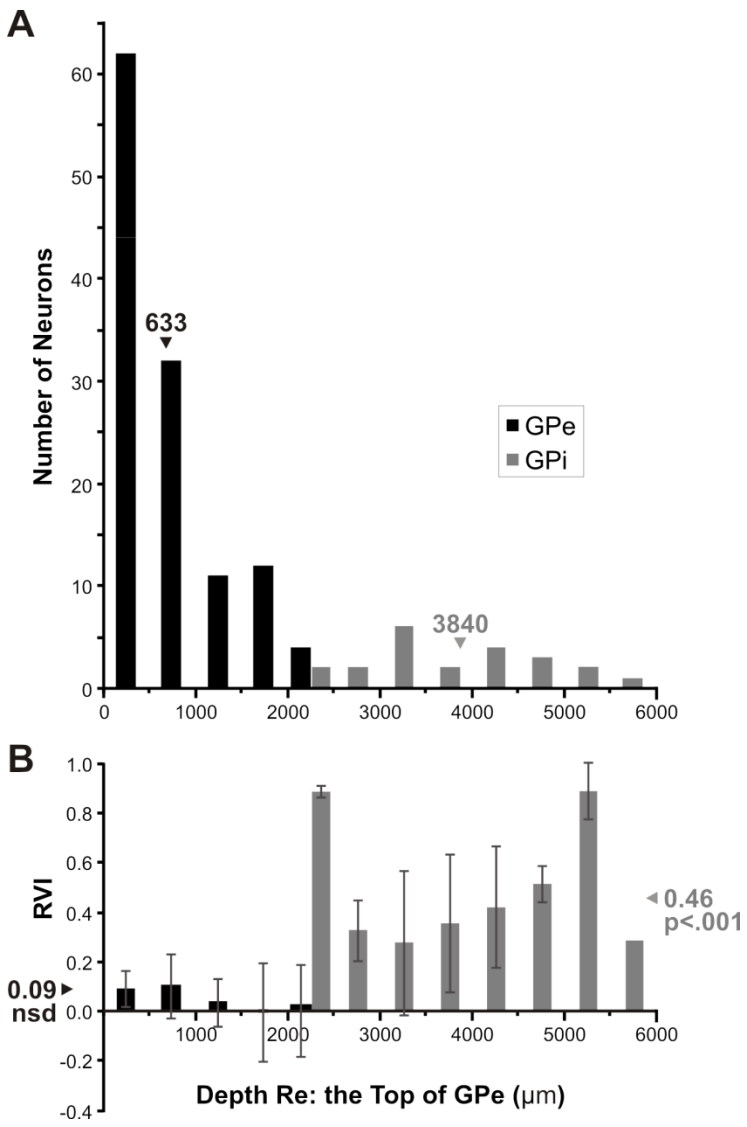

Figure 4: Recording depth of GP sample and RVI

A) Recording depth of GPe and GPi task-modulated neurons. Black and grey represent neurons judged to be in GPe and GPi, respectively. The numbers above the arrowheads indicate the means of the distributions of GPe and GPi recording depths. Recording depth was measured relative to the top of GPe. B) Average (mean +/- SE) of the Reward-Visual Index (RVI) for the same neurons. The numbers by the arrowheads indicate the overall mean RVI for GPe (black), which was not different from 0 ($P>0.05$), and for GPi (grey), which was significantly greater than 0 ($P<0.001$, both by 1-sample t-test). The data indicate that signal content changed abruptly at the border, implying that GPe and GPi neurons at the border were classified correctly as to their structural membership. No SE is shown for the rightmost bin because it contained only one neuron.

We recorded from the SNr from the same chamber in all three monkeys (Fig. 3C). Finding the SNr allowed us to be certain that we were not accidentally including SNr neurons in our pallidal samples, and recording from its neurons provided a firm basis of comparison with pallidal neurons (rather than just comparing our pallidal neurons with prior descriptions of SNr neurons in the literature). SNr neurons were identified by their high baseline firing rate (50-90sp/s) (Hikosaka and Wurtz 1983a) and their proximity to nearby landmarks including the internal capsule, subthalamic nucleus, zona incerta, oculomotor nucleus and rostral interstitial nucleus of the medial longitudinal fasciculus. Relative to the GPi, the SNr was 4-5mm more posterior, ~4 mm deeper, and on the other side of (medial to) the easily identifiable internal capsule.

In all structures, the activity of single neurons was recorded extracellularly with parylene-insulated tungsten electrodes (FHC Corp.). Action potentials were amplified and isolated using time and amplitude criteria on a digital oscilloscope. Time-stamps of action potentials were stored in data files. Visual stimuli were back-projected using an LCD projector onto a tangent screen 58 cm in front of the monkey. Eye position data were collected at 1 ms resolution. Data collection and the behavioral paradigm were under the control of the REX real-time system (Hays et al. 1982).

2.2.4 Data Analysis

To determine the signals carried by the neurons, we measured average firing rates in five epochs of the memory-guided saccade task: a baseline epoch 0 to 100 ms before target onset, a visual epoch 50 to 150 ms after target onset, a delay epoch 0 to 100 ms before the cue to move, a saccade epoch 50 ms before to 50 ms after saccade initiation, and a reward epoch 0 to 100 ms

before reward onset. We ran an ANOVA on the firing rates across the five epochs, and if this was significant at $P < 0.01$, the neuron was considered to be task-modulated. We used a parametric ANOVA if the firing rate distributions passed a test of normality and equal variance, or a nonparametric one otherwise (Kruskal-Wallis One Way Analysis of Variance on Ranks). For neurons with significant ANOVA results, we performed an all–pairwise multiple comparison test (Student-Newman Keuls or Dunn's at $P < 0.05$) to compare average firing rates between the various epochs. A neuron had a *visual-related* signal if its firing rate in the visual epoch differed from that in the baseline epoch, a *delay-related* signal if its firing rate in the delay epoch differed from that in the baseline epoch, a *saccade-related* signal if its firing rate in the saccade epoch differed from that in both the delay and baseline epochs, and a *reward-related* signal if the firing rate in the reward epoch differed from that in both the baseline and saccadic epochs. The test for saccade-related signals involved a double comparison (versus both the delay and baseline epochs) to make sure that apparent saccadic activity was neither an extension of delay activity nor a simple return to baseline activity. The analyses typically involved 10 trials, but ranged from a minimum of 7 trials to a maximum of 40.

On a closed-circuit infrared camera system we watched the monkeys carefully for other types of body movements that might modulate neuronal activity, such as orofacial and limb movements. The animals made occasional postural adjustments, limb movements, and facial movements such as blinking and licking. If we determined that a neuron was modulated by such movements we excluded it from further analyses. We routinely gave the animals free drops of liquid reward to see if this evoked licking, somatosensory, or other non-task-related modulations in activity, and excluded such neurons, but we were not set up to quantitatively assess such fine

details. Hence although we could detect reward-related signals, and we think that most were not due to trivial reasons such as licking, we remain cautious in interpreting them.

We analyzed how signals varied as a function of depth through the pallidum using an index that quantified the relative amounts of visual- and reward-related activity in single neurons. The ratio of these activity types, as described in Results, was the main difference in signal content between GPe and GPi. The Reward-Visual Index (RVI) was the contrast ratio of the visual and reward activity, with each activity level measured relative to baseline and absolute-valued to treat increases and decreases identically:

RVI = (|reward-baseline| - |visual-baseline|) / (|reward-baseline| + |visual-baseline|).

If RVI = 0, a neuron had equivalent reward and visual modulations, if RVI was between 0 and 1, a neuron had stronger reward than visual modulations, and if RVI was between 0 and -1, a neuron had stronger visual than reward modulations.

We determined the spatial tuning curves of neurons for which we obtained memory-guided task data in all eight directions at the optimal amplitude. We routinely collected 10 trials of data at each target direction. Since the major signals of neurons were visual-, saccade-, and reward-related (delay-related activity was relatively rare), we focused on those three signals. They were measured as average firing rates in the epochs described above. First, to determine if the signals varied as a function of direction, for each signal type we ran an ANOVA on firing rates in the eight directions ($P < 0.05$ significance level). An insignificant ANOVA suggested that the neuron was omni-directionally tuned. To characterize the tuning at a finer scale that considered modulations at each direction individually, we also compared the firing rates with baseline activity on a direction-by-direction basis. The baseline epoch preceded target onset and therefore was not influenced by target direction; hence when analyzing spatial tuning plots we

used a single baseline firing rate derived by averaging baseline data from all eight directions. We constructed separate polar plots of spatial tuning for each type of signal conveyed by a neuron. Relative to baseline, a neuron could have a significant change in activity in one or more (sometimes all) directions (t-tests, $P < 0.05$, Bonferroni corrected for multiple comparisons against the baseline activity). Small numbers of significant directions indicated sharp tuning, large numbers broad tuning.

In addition to analyzing spatial characteristics of the signals we also analyzed their timing, specifically the point at which they started during a trial. We determined onset latencies of each signal type in the following manner (see Sommer and Wurtz 2004 for details). First, we generated spike density functions (σ = 10 ms) aligned to events of interest such as visual stimulus onset. The mean and standard deviation of the baseline activity provided the threshold for determining the time at which event-related modulations became significant (threshold was twice the standard deviation of baseline). This crossing time was the onset latency. If the neuronal signal was an increase in activity, the firing rate had to exceed threshold (two standard deviations above baseline); if the signal was a pause in activity, the firing rate had to drop below threshold (two standard deviations below baseline).

2.3 RESULTS

We recorded from 320 GPe neurons in three monkeys and 101 GPi neurons in two monkeys. Overall, 34% of the neurons (n=143) were modulated significantly in the memory-guided saccade task (38% of GPe neurons, n=121; 22% of GPi neurons, n=22).

2.3.1 Task-related signals carried by pallidal neurons

Examples of single neuron activity in GPe and GPi during the memory-guided saccade task are shown Figure 5. We found a wide variety of activity patterns. The neurons typically had high spontaneous activity (means and SEs: 78.9 +/- 28.6 sp/s for GPe; 76.3 +/- 23.2 sp/s for GPi). Relative to these baseline firing rates, GPe and GPi neurons could show increases or decreases in activity in association with events such as visual stimulation (Figs. 5A, 5B, and 5D), delay (Figs. 5C and 5G), saccade generation (Figs. 5B, 5E, and 5G), and reward (Fig. 5C and 5F). As can be seen in Figures 2 and 3, single neurons could carry one signal or any combination of signals (quantified below). Aside from these signals of interest, there were rare, miscellaneous signals that we did not quantify such as phasic visual responses to target reappearance (Fig. 5D) and apparent auditory responses to reward solenoid clicks (Fig. 5B).

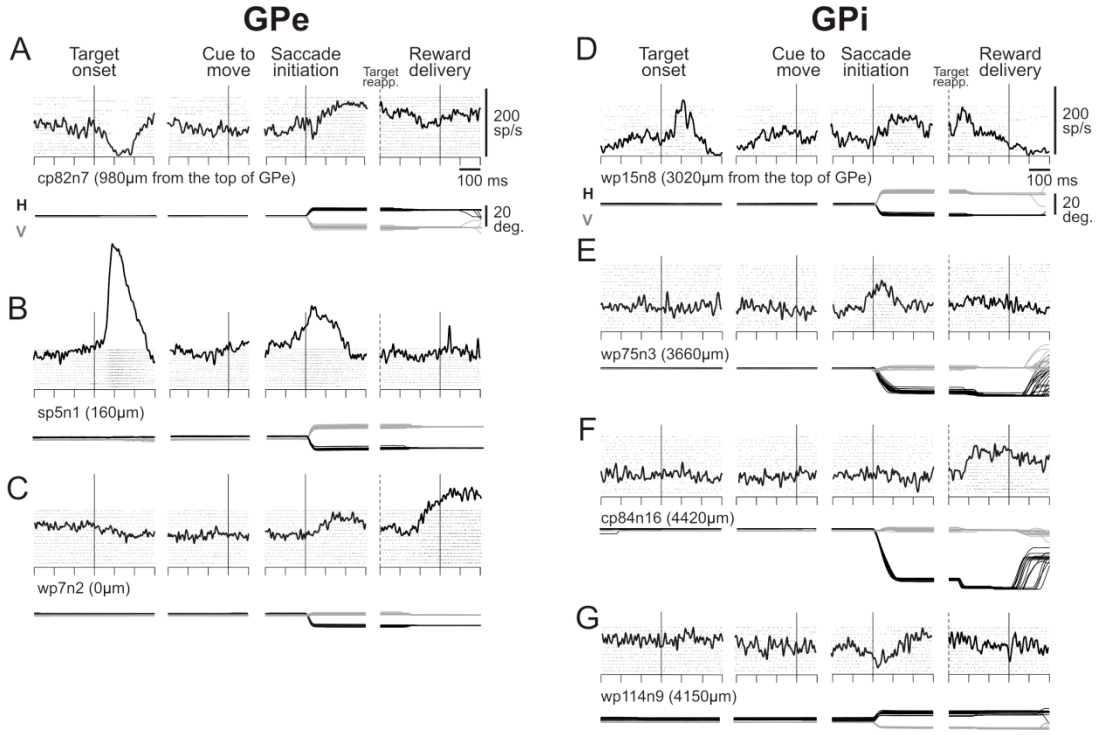

Figure 5: Activity of example GPe and GPi neurons

Spike rasters and spike density functions are aligned to events of the memory-guided saccade task. Below the spike data are shown eye movement traces from the recording sessions (H, black: horizontal component; V, gray: vertical component). The labels below spike rasters show each neuron's identification number, and the adjacent values in parentheses show the depth of the neuron below the first GPe neuron encountered (i.e., below the detected top of the GPe). Target reapp., target reappearance after saccade to the remembered location. The neuron in B) exhibits two transients in activity after reward delivery that seemed to be auditory responses to the solenoid clicks (the transients occurred for targets in the opposite direction as well). D) shows the only visual-related neuron we found in GPi. In that same panel, a transient visual response to target reapp. can be seen; such responses were rare and brief. They ended (as did modulations seemingly linked to saccade termination) prior to the reward analysis epoch 100-0 ms before reward delivery.

Due to the wide variety of signals, pooling the data to show population firing rates tended to obscure the modulations (Fig. 6). It was evident, however, that for both GPe and GPi and for each type of signal, the average increasing and decreasing modulations were similar (Fig. 6B,C). We analyzed the timings of the task-related modulations quantitatively (see Methods) and found that GPe neurons had remarkably quick visual latencies regardless of whether the responses were of the increasing or decreasing type (means 50 and 51 ms, respectively; Table 1, Fig. 7). The one visual-related GPi neuron that we found was comparable (see Fig. 5D).

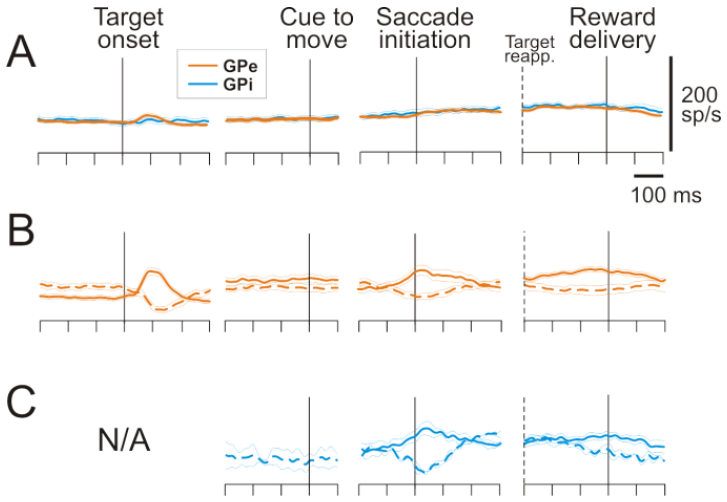

Figure 6: Summaries of population firing rates

A) Average spike density functions of GPe (orange) and GPi (blue) neurons. Little modulation is seen because the increasing and decreasing types of modulations cancel each other out. B) Average spike density functions of GPe neurons separated into the two valence categories: modulations that either increased (solid lines) or decreased (dashed line) relative to baseline. There were no striking differences between the average increasing and decreasing modulations. C) Same as panel *B*, but for GPi neurons. For GPi, we found only one neuron with visual activity, so the visual category is blank (N/A, not applicable), and only one neuron with increasing delay activity, so there is no solid line in the delay category.

Table 1: Average and standard error of signal latencies

	Visual		**Saccade**		**Reward**	
	+	-	+	-	+	-
GPe	50 ±22	51 ±27	-94 ±60	-89 ±56	-198 ±76	-216 ±73
GPi	N/A	N/A	-75 ±34	N/A	-200 ±76	-152 ±65

This table summarizes the times (ms, mean +/- SD) when modulation became significant relative to visual target onset (Visual data), saccade initiation (Saccade data), and reward delivery (Reward data), for increasing types of neurons (+) and decreasing types (-). Negative values are times before an event, positive values times after an event.

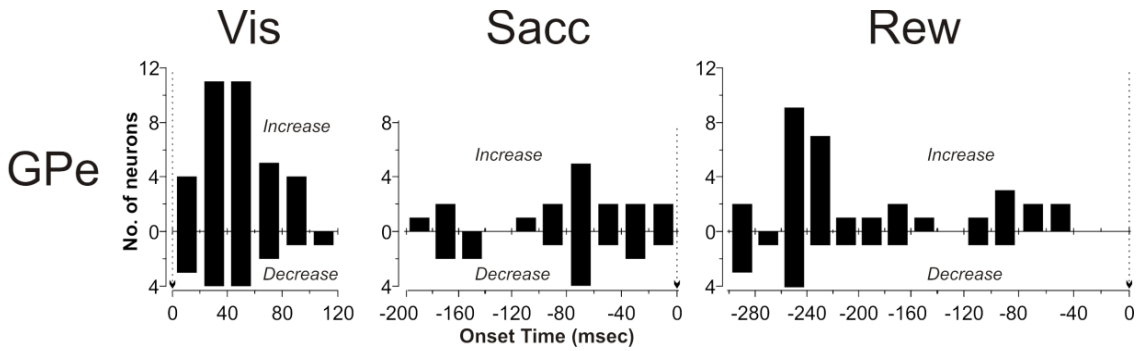

Figure 7: Distribution of signal latencies for GPe neurons

Histograms represent the distributions of latencies for visual, saccade, and reward signals, from left to right. Upper and lower parts represent the latencies of increasing and decreasing types of neurons, respectively. Vertical dotted lines represent the onsets of events (i.e., visual stimulation, saccade initiation, reward delivery)

In general across all of the samples, saccade-related activity started to modulate around 70-100 ms before saccade onset and reward-related activity around 200 ms before reward delivery. We found no significant differences in latency (t-tests, $P > 0.05$) as a function of area (e.g., GPe saccade vs. GPi saccade) or valence of activity (e.g., GPe saccade increase vs. GPe saccade decrease).

Our quantitative analysis of the full diversity of pallidal signals is summarized in Figure 8. The overall distributions of signal types were significantly different between the GPe and GPi samples (Fig. 8A; 4x2 Exact Contingency Table test, $P < 0.001$). Visual responses were far more common in GPe (44%, or 53/121 task-related neurons) than in GPi (5%, 1/22 task-related neurons). In contrast, reward-related signals were more common in GPi than in GPe (73% vs.

53% of task-related neurons). Saccade-related signals were found in about a quarter of task-related neurons in both structures (26%, GPe; 27%, GPi). Delay-related signals were relatively infrequent (21%, GPe; 18%, GPi).

Individual neurons could carry one signal or multiple signals (Fig. 8B). As classified by the combination of signals they carried, the distributions of neuron types were significantly different in GPe vs. GPi (4x2 Exact Contingency Table test, $P < 0.001$). GPe neurons were much more likely than GPi neurons to have visual activity as their only signal. Conversely, while reward-related activity was prominent in both structures, GPi neurons were much more likely than GPe neurons to have reward activity as their only signal. The GPi had slightly more saccade-only neurons than GPe, and in both structures, neurons with only delay signals were rare. The percent of neurons carrying multiple signals was comparable in the two structures.

The various signals carried by the neurons, including the myriad combinations that could be found in single neurons, are illustrated in detail using Venn diagrams in Figure 8C. Although the Venn diagrams are intricate for the sake of reporting all of the signal combinations, the take-home message is simple. There were three prominent types of neurons: Visual-only GPe neurons and reward-only GPe and GPi neurons. Beyond that, the co-occurrence of signals was fairly homogeneously distributed in GPe (the data were too sparse to draw a similar conclusion for GPi).

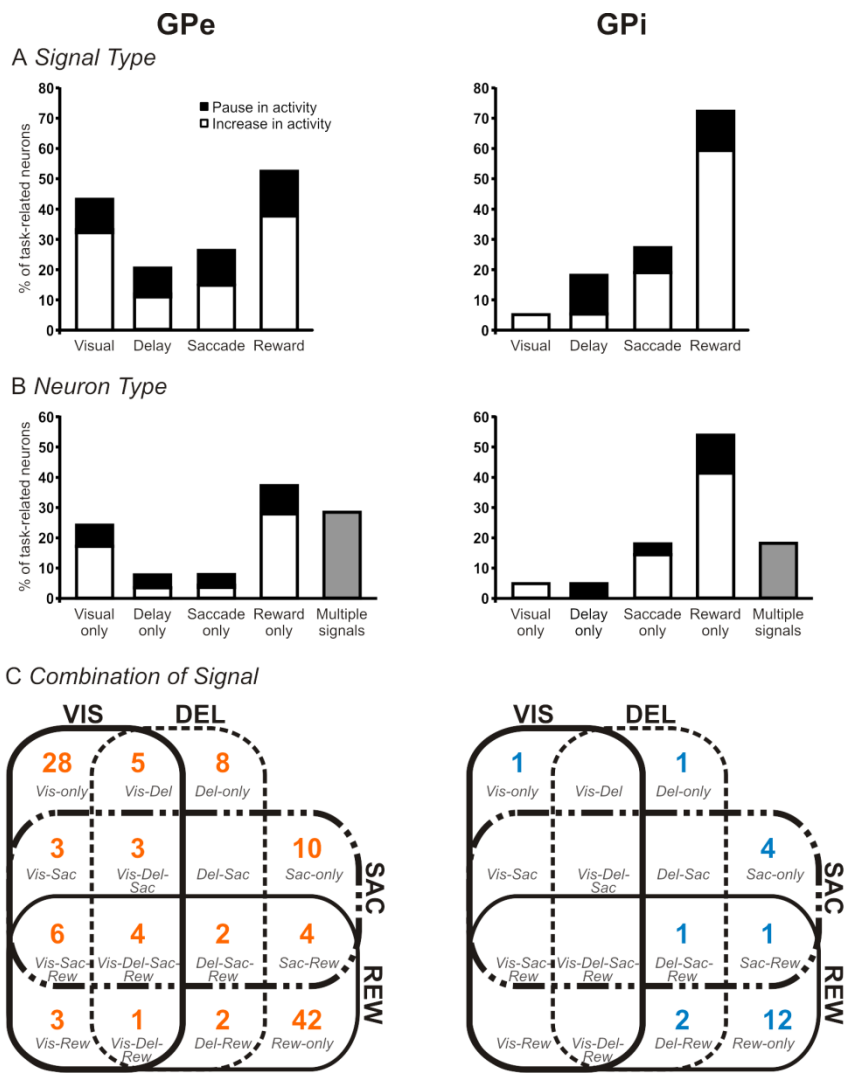

Figure 8: Population data for GPe and GPi

A) Distributions of signals carried by task-modulated neurons. Signals were conveyed as increases (white) or decreases (black) relative to the baseline firing rate. B) Distributions of neurons categorized by whether they carried one type of signal or multiple types (gray). C) Venn diagrams showing the numbers of neurons that had various combinations of signal types. The four categories of signals (VIS, visual; DEL, delay; SAC, saccade; REW, reward) are represented with rounded rectangles using four different types of line to help with clarity. Regions overlapped by more than one rectangle represent neurons with the depicted combination of more than one signal. Regions are mutually exclusive (i.e., sum of numbers in all regions is the total number of modulated neurons). Each possible combination of signal is written in italic in the respective regions. (GPe, orange; GPi, blue).

2.3.2 Comparison with SNr neurons

We recorded from SNr neurons in all three monkeys to confirm that we were not accidentally including SNr neurons in our pallidal samples and to compare task-related properties between pallidal and SNr neurons. In each monkey, we found that the SNr was located 5-6 mm ventroposterior to, and across the distinctive internal capsule from, the GPe and GPi recording sites. Hence we are certain that no SNr neurons were in the GPe or GPi samples. The SNr neurons had high baseline firing rates, nearly always more than 50 sp/s, which demonstrated that we were not in the nearby subthalamic nucleus with its baseline firing rates of ~25-30 sp/s (Hikosaka and Wurtz 1983a; Soares et al. 2004).

As expected from prior work (e.g., Hikosaka and Wurtz 1983c), we found that many SNr neurons (45%, 42/93) were modulated in the memory-guided saccade task. Similar to GPe and GPi neurons, the SNr neurons could exhibit either task-related bursts or pauses (Fig. 9). At the population level (Fig. 10), the SNr neurons were more similar to GPe neurons than GPi neurons, in that the majority of modulated SNr neurons carried visual-related and reward-related signals. Still, the distributions of signal types were different between the two structures (4x2 Exact Contingency Table test, $P = 0.002$). This difference seemed due to the SNr having more visual activity (69% vs. 44%) and less reward activity (29% vs. 53%) than the GPe. Differences in signal content were even greater between SNr and GPi (4x2 Exact Contingency Table test, $P < 0.001$), because the GPi had such a paucity of visual responses and abundance of reward-related activity, as was discussed above.

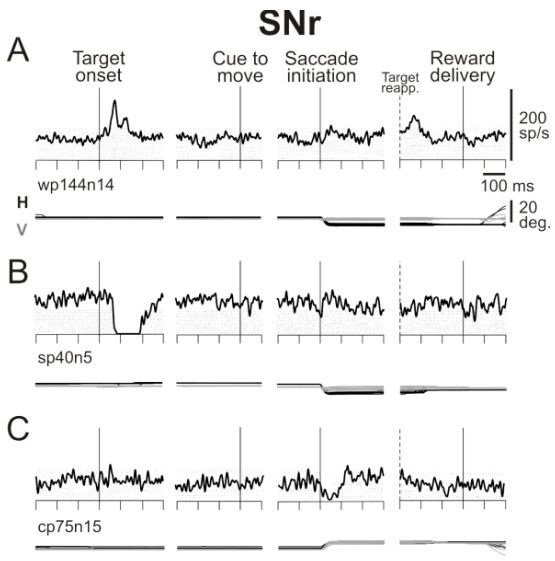

Figure 9: Activity of example SNr neurons

Neurons with A) a visual increase, B) a visual decrease, or C) a saccadic decrease are shown. Other conventions are the same as in Fig. 5.

Our finding that SNr neurons are more similar to GPe than GPi neurons is consistent with anatomy, in that the SNr receives projections from GPe but is relatively isolated from GPi (recall Fig. 5C). The inhibitory nature of the GPe-SNr projection leads to a hypothesis that there may be a sign reversal in signals from GPe to SNr. To test this, we compared the total numbers of increasing vs. decreasing signal types in GPe (Fig. 8A, left) and SNr (Fig. 10A). We found that increasing modulations were more common in GPe (68% of its signals) than in SNr (33% of its signals). In turn this meant that decreasing modulations were more common in SNr than in GPe (67% vs. 32% of signals, respectively). These differences were significantly different (Chi-square test, $P < 0.0001$), supporting the hypothesis that excitatory signals in GPe may contribute, via the known inhibitory projection, to pauses in the SNr.

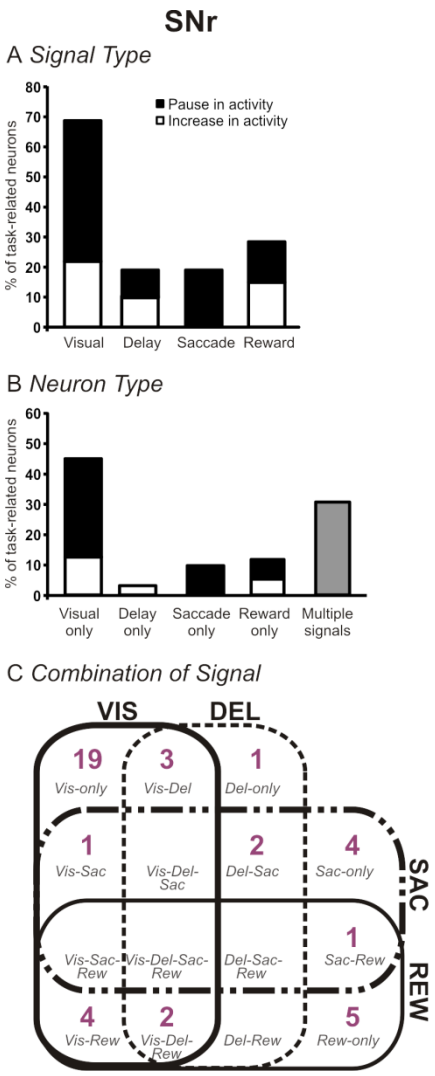

Figure 10: Population data for signal types in SNr

Conventions are the same as in Figure 8.

2.3.3 Tuning of response fields

Next we analyzed the ranges of target directions and amplitudes that could evoke task-related modulations, i.e., the response fields of the neurons. As described in Methods, our iterative mapping procedure determined the “hot spot” – optimal direction and amplitude – for each

neuron individually. Overall (GPe and GPi neurons pooled), we found that the amplitudes of the response field centers ranged from 2° to 64° with an average of 18° and SD of 12°. These amplitudes were comparable in GPe (range 5-64 deg., mean 18 deg., SD 11 deg.) and GPi (range 2-60 deg., mean 20 deg., SD 13 deg.). Using the optimal amplitude for each neuron, we evaluated the directional tuning using a set of eight directions (cardinal axes and diagonals). We found that the response field shapes were biased toward one hemifield – i.e., lateralized – in the majority of neurons (77% of task-modulated GPe neurons, 95/123; 52% of task-modulated GPi neurons, 11/21). For those neurons, contralateral response fields were the most common (75% of lateralized fields for GPi; 64% for GPi). For 15% of task- modulated GPe and 43% of task-modulated GPi neurons, the response field was not lateralized but extended into both the contralateral and ipsilateral fields (i.e., bilateral). The remaining neurons had response fields aligned vertically (8% of GPe and 5% GPi neurons).

For the GPe and GPi task-modulated neurons that were fully tested on memory-guided saccades in eight directions (at each neuron's optimal amplitude), we analyzed the details of receptive field directional tuning. Figure 11 shows example tuning curves (means +/- SEs) of neurons in GPe and GPi, and for comparison, SNr. The rows show data from each anatomical structure and the columns show examples of the tuning for each signal type (the data in each panel were selected to show typical response fields and were not necessarily from the same neuron). In all tuning plots, baseline activity of the neuron is shown with grey curves. As reported above, signal modulations could be above or below baseline. Sharpness of tuning varied from neuron to neuron. Some neurons showed fairly sharp tuning with significant modulations for only one to three directions (e.g., the GPe Visual plot). Others had broad or even omni-directional tuning spanning all eight directions (e.g., the GPe Reward plot). The significantly

modulated directions were generally contiguous; in our entire experiment, we found only two neurons with distinctly separated lobes pointing in different directions.

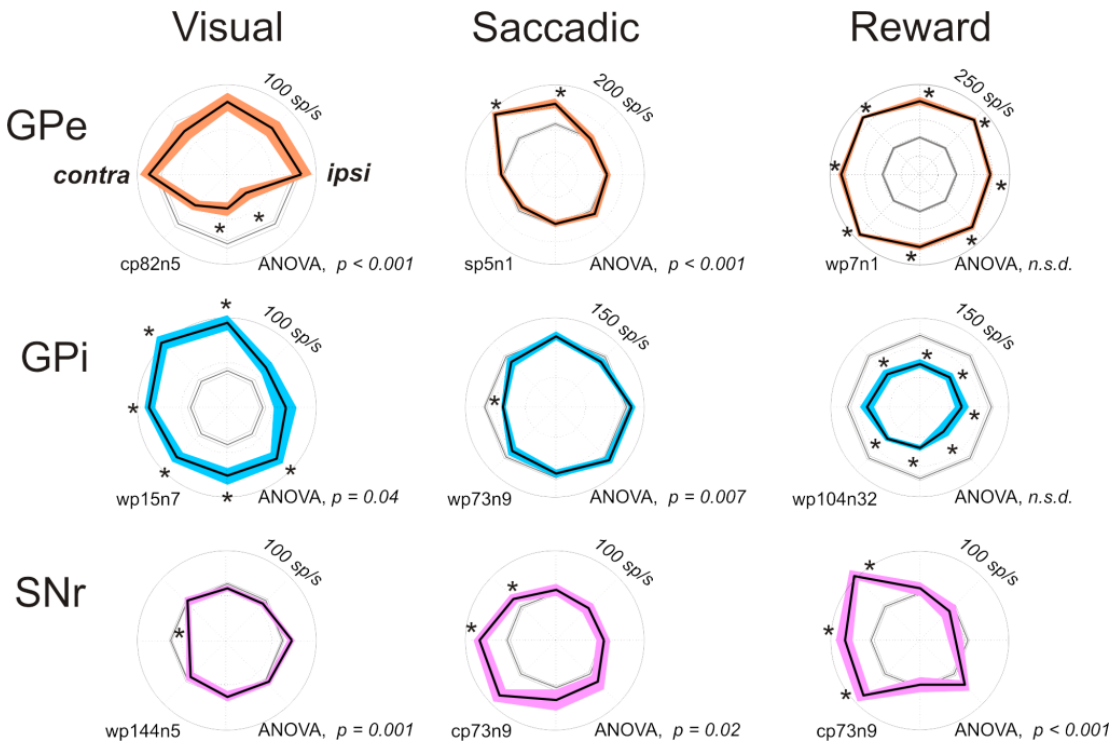

Figure 11: Response field tuning curves from example neurons

Rows show data from neurons recorded in GPe (top, orange), GPi (middle, blue), and SNr (bottom, purple). *Columns* show tuning curves of the neurons' visual (left), saccade (middle), and reward (right) related signals. Firing rates during the respective signal epochs were plotted for the eight target directions and connected by lines (means) and shaded areas (+/- SEs). Grey lines show the baseline firing rates (mean +/- SE) for the neurons. The concentric circles depict 50 sp/s increments, with peak of the scale shown near top right of each graph. Relative to the recorded neurons, contralateral (contra) is to left, ipsilateral (ipsi) to right. ANOVA results are shown near bottom right of each graph, and individually significant directions by t-test ($P < 0.05$, Bonferroni corrected) are labeled with asterisks. Individual neurons' identification numbers are shown at bottom left of each graph.

The GPe neurons provided the largest data set with regard to tuning curves (n = 89), and they carried all possible signal types, so we concentrated on them for analyzing population tuning data (Fig. 12). The upper row (Fig. 12A-C) and lower row (Fig. 12D-F) show averaged tuning curves for GPe neurons with increasing and decreasing types of signals, respectively. Before we constructed the average plots, we normalized the firing rates for each neuron relative to its baseline (hence the average baseline curves, grey, are equal to one). We did not perform any other normalizations; specifically, the directions are veridical (as in Fig. 11, contralateral is to left and ipsilateral to right). Visual, saccadic, and reward response fields are separated by columns. We found that the increasing visual responses of GPe neurons were significantly biased contralaterally on average (ANOVA, $P < 0.001$, Fig. 12A). This was also true for most of the individual neurons (30/33, 91%). Most neurons with decreasing visual responses also showed a contralateralized bias (8/9, 89%). In the average tuning curve of those neurons (Fig. 12D) this bias was not significant by ANOVA ($P > 0.05$), but it was significant in two contralateral directions by t-test (asterisks).

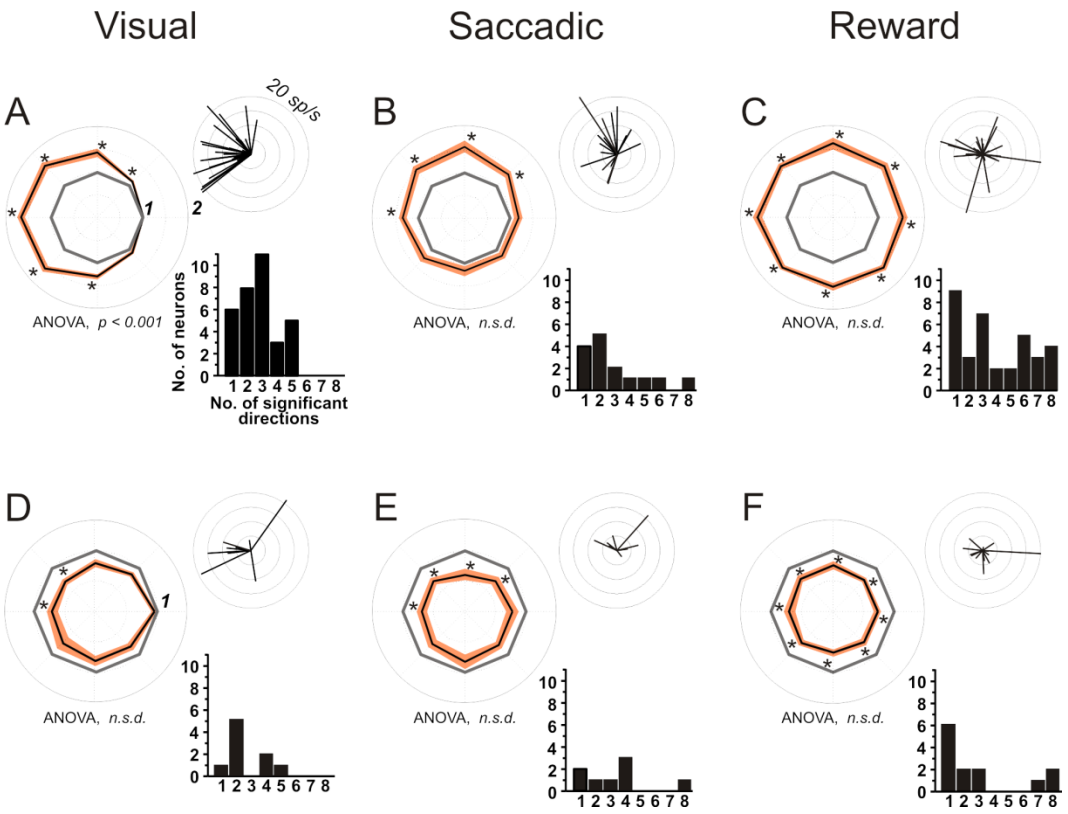

Figure 12: Average response field tuning curves for the population of GPe neurons

Rows show data from neurons with increasing (top) or decreasing (bottom) signals relative to baseline. *Columns* show data from the visual (left), saccade (middle), and reward (right) related epochs. (A-F). In each panel, the average tuning curve (mean +/- SE) of the sample of GPe neurons having the specific category of signal is shown at *left*. These average tuning curves were from normalized data in which each individual neurons' curve was scaled relative to its baseline firing rate (hence all baseline mean data = 1 in these graphs). Smaller polar plots in *upper right insets* represent the tuning curve average vectors (straight black lines) for each neuron that contributed to the average tuning curve (black lines). Histograms in *lower right insets* show the number of significantly modulated directions found by t-tests, which represents the sharpness of tuning (small numbers = relatively narrow tuning, large numbers = relatively broad tuning). Other conventions as in Fig. 11. For more details, see text.

In each panel of Figure 8, the upper right insets illustrate the individual tuning vectors for each neuron that contributed to the average plot. The lower right insets show the number of

significant directions for the individual neurons. Most of the GPe visual neurons (increasing and decreasing types, Fig. 12A,D) had relatively sharp tuning, with≤ 3 directions that were different from baseline, and none had omni-directional tuning (i.e., 8 modulated directions).

Compared with those visual signals, the average tuning of saccadic signals for both increasing and decreasing types (Fig. 12B,E) showed no significance by ANOVA and weaker contralateral biases according to the direction-by-direction t-tests (Fig. 12B,E, asterisks). At the individual neuron level, significant lateralizations were found in 10/15 neurons (67%) with increasing signals and in 3/8 neurons (38%) with decreasing signals. There was more of a tendency for broad tuning in saccadic signals than was seen for visual signals (lower insets); a couple of neurons even had omni-directional saccadic tuning.

Reward-related signals (Fig. 12C,F) were even more uniformly tuned across space. The average tuning plots were not significantly biased (by ANOVA), but activity in all eight directions was significantly greater than (Fig. 12C) or less than (Fig. 12F) baseline activity (by t-tests). The population omni-directionality was due in part to tunings that could point in any direction for individual neurons (upper right insets), but even those individual neurons had broad tunings with many occurrences of omni-directionality (lower right insets). Only a few individual neurons showed a significant directional bias (increasing type: 10/35, 29%; decreasing type: 1/13, 8%). Summarizing all of the data in Figure 12, the general conclusion is that the spatial tuning of GPe neurons became less contralateralized and broader as the events in a trial proceed from visual to saccade to reward.

GPi task-modulated neurons were also analyzed, but we were unable to collect full data on the tuning curves for most of those neurons, so the data are sparse (n = 17). We show only the

histograms of number of modulated directions (Fig. 13). A tendency for broader tuning as trials progressed seemed to be present in our GPi sample.

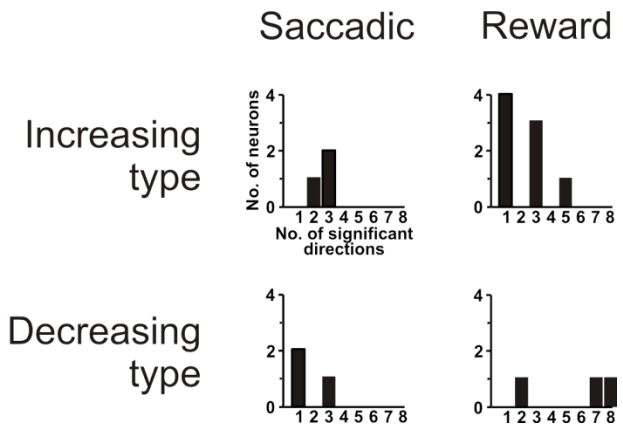

Figure 13: Population results for GPi showing the number of significantly modulated directions

Conventions as for the lower right insets of Fig. 12. Visual category is absent because we found only one GPi neuron with a visual signal.

For comparison, SNr neurons were analyzed in the same way (n = 36). On average, visual responses of SNr neurons were lateralized (ANOVAs: $P = 0.01$ for increasing signals and $P = 0.002$ for decreasing signals; Fig. 13A,C). These biases in the population were strongly contralateral (asterisks in Fig. 14A,C) due to underlying strong contralateral biases of individual neurons (upper right insets). In those individual neurons, significant lateralized biases were found in 80% (8/10) of the increasing type and 75% (15/20) of the decreasing type. Saccade and reward-related signals in our SNr neurons, however, did not show biased laterality (ANOVA, $P > 0.05$).

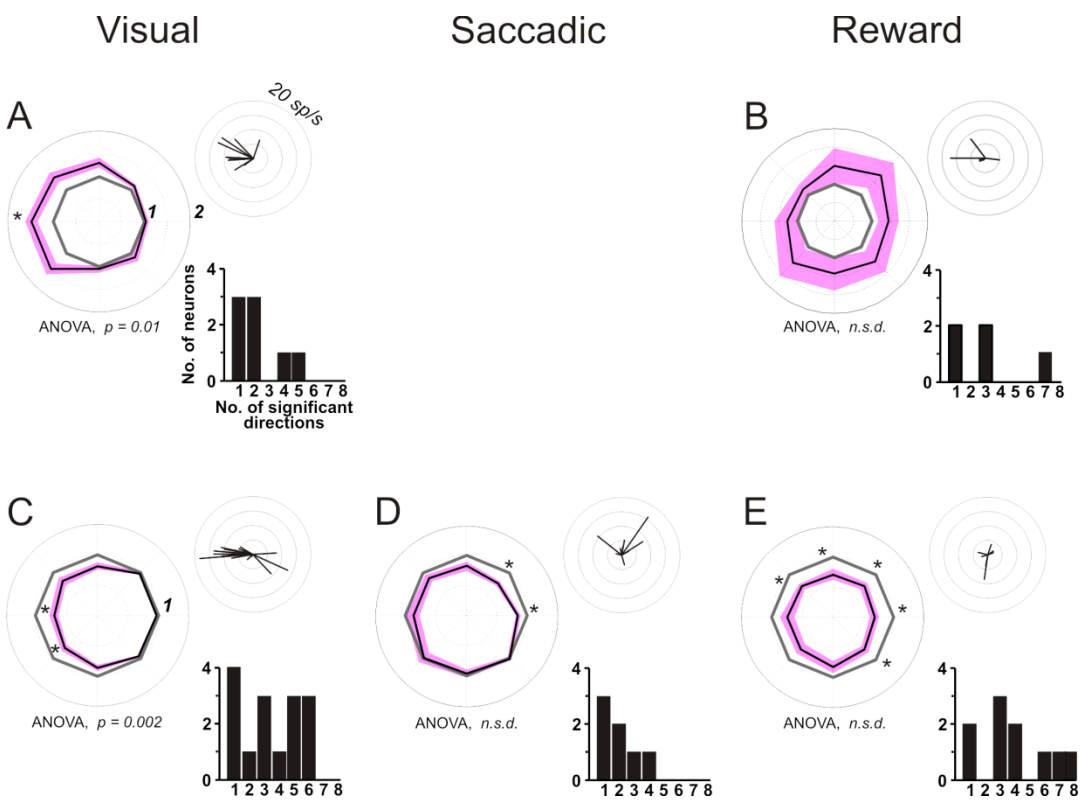

Figure 14: Population tuning curves for SNr neurons

Conventions are the same as in Fig. 12. Our SNr sample had no increasing type of saccade-related neurons, so that category is absent.

As noted above, there seemed to be a broadening of response fields during a trial. To further analyze this, we quantitatively analyzed the shapes of the response fields for the GPe population. First we considered the neurons with increasing types of signals (Fig. 14). The method was described in detail elsewhere (Crapse and Sommer 2009). We normalized each individual response field to its maximal firing rate (Fig. 15A), which was set to one, and rotated the normalized curves so that direction of maximal firing rate was pointing to the left (Fig. 15B). With all of the tuning curves superimposed in this way, the firing rates and tuning directions were removed as factors, thus revealing their shapes. We computed average shapes from these

the individual curves (Fig. 15C, mean +/- SE). Qualitatively, the shapes changed as we suspected from the previous analyses, becoming broader (enclosing more area) from visual (left) to saccadic (middle) to reward activity (right). This effect was quantified by calculating the areas within the tuning curves. The area calculations were performed on the normalized tuning plots for each signal (from Fig. 15A or B). Using this absolute area value, the relative area was calculated as a percentage of the absolute area to the maximum possible area (i.e., the area of an equilateral octagon of radius one). This transformed the area data into a range for which 0% = narrowest possible tuning and 100% = broadest possible tuning. The distributions of relative areas are plotted in histograms in Figure 15D. While the relative areas of the saccadic tuning plots (mean 51%) tended to be broader than the relative areas of the visual tuning plots (mean 46%), the two were not significantly different from each other. However, both were significantly less than the relative areas of the reward tuning plots (mean 63%, t-tests).

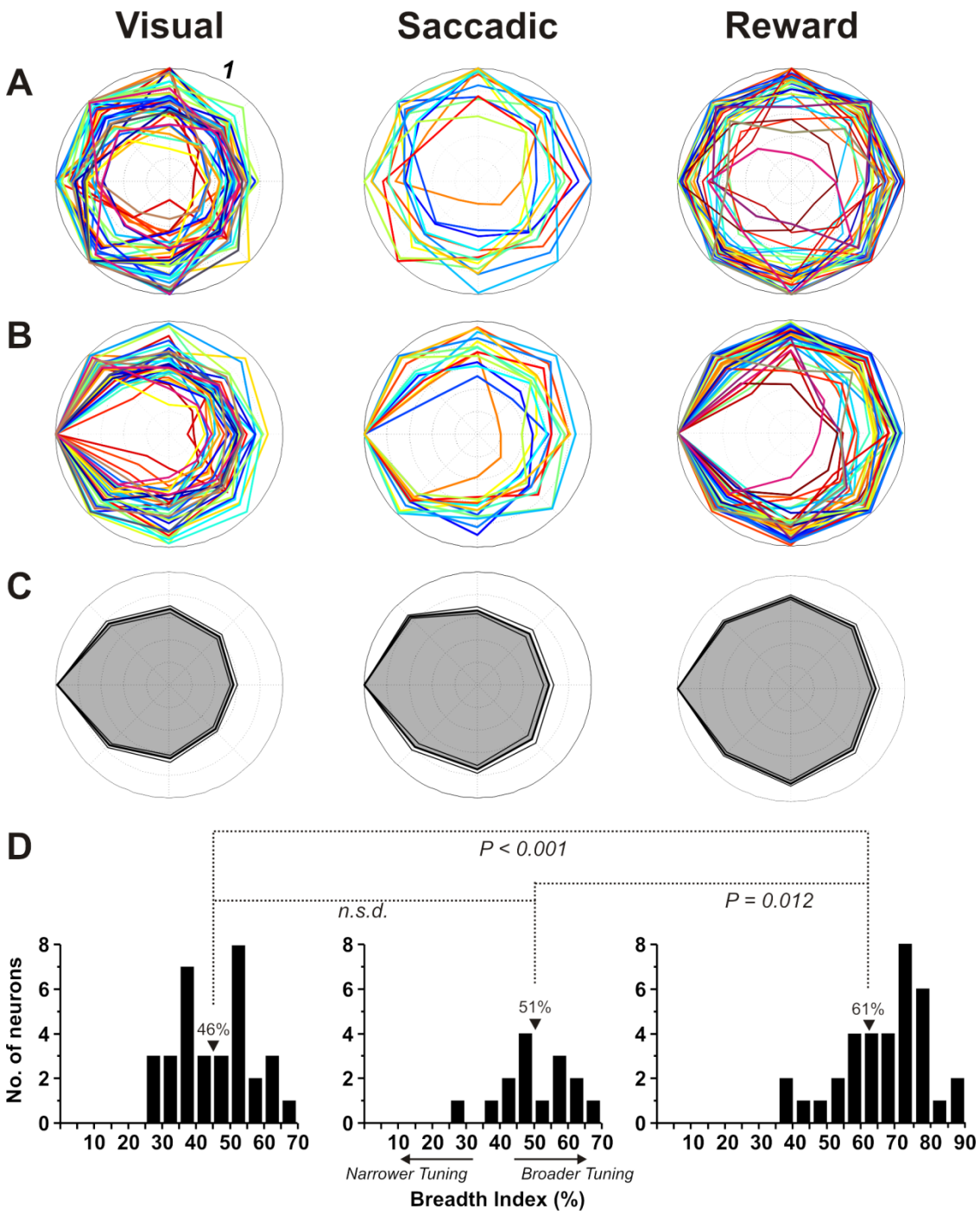

Figure 15: Breadths of tuning curves for the increasing type of GPe neurons

For details of constructing the graphs, see text. *Columns* show data from the visual (left), saccade (middle), and reward (right) related epochs. A) Tuning curves from individual GPe neurons with data normalized to peak firing rate (which is set to 1). Baseline data are irrelevant for these analyses and are not shown. B) Same tuning curves as

in *A*, but rotated so that the peak firing rate for each neuron is to the left. C) Means and SEs of the normalized, rotated tuning curves from panel *B*. As suggested by the data in Fig. 8A-C, the tuning curves did become more broadly tuned as trials progressed from visual to saccadic to reward events. D) Histograms showing the distribution of relative tuning curve areas for each signal. Tuning curve absolute areas were calculated as in panel *C* for each neuron individually and then converted to relative areas by expressing them as a percentage of the maximal possible area (i.e., the area that would be enclosed by an equilateral octagon having all points = 1). Arrowheads and labels show the mean of each distribution, and the results of multiple t-tests are shown.

Similar analyses were performed on decreasing types of signals (Fig. 16), except that the individual neuron firing rates were normalized to the trough of the tuning curve, which was set to 0.2 (innermost of the concentric circles). Relative areas of each tuning plots were calculated by dividing the absolute area values by the minimum area (i.e., equilateral octagon with radius 0.2). This value was always > 1. To achieve a comparable breadth index as used in Fig. 15, we took the reciprocal of the relative area (always < 1) and multiplied it by 100%. Hence, analogous to the result in Figure 15, indices near 0% represent extremely narrow tuning (a notch at the preferred direction and high firing rates elsewhere) and indices near 100% extremely broad tuning (similar decreases for all directions). The distributions of breadth indices are shown in Figure 16D. We found no significant differences in the tuning curve breadths as a function of signal type for these decreasing modulations ($P > 0.05$ for all comparisons).

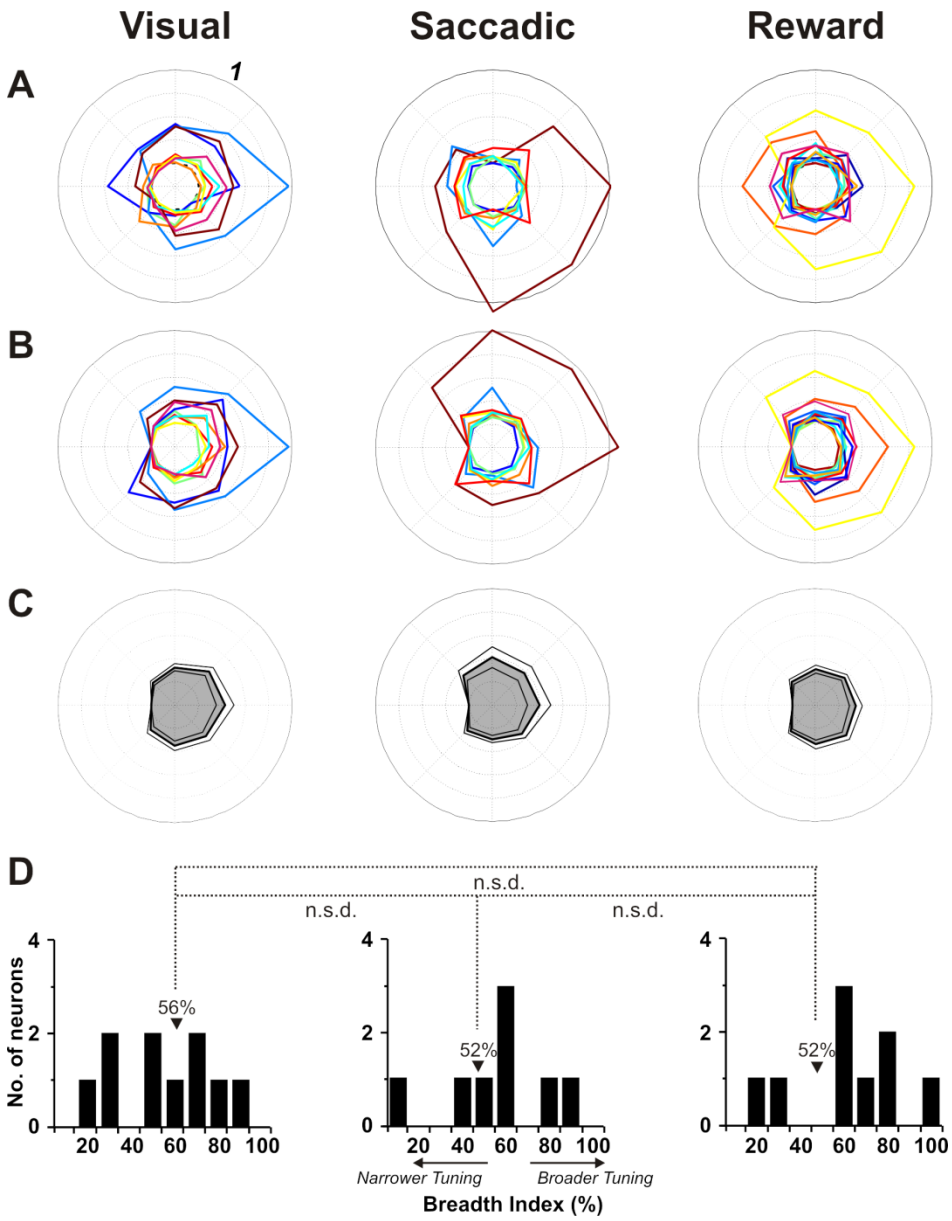

Figure 16: Breadths of tuning curves for the decreasing type of GPe neurons

Conventions are the same as in Fig. 15 except that each tuning curve is normalized to its minimum firing rate (set to 0.2, innermost concentric ring), and thus the calculation of breadth index was different. For details of constructing the graphs and calculation of the index, see text.

The same analyses were performed on our SNr sample (Figs. 17 and 18), but they did not reveal any significant differences in the breadths of tuning ($P > 0.05$ for all comparisons). When

the distributions of breadth indices for each group of SNr neurons was compared with the respective data from GPe (e.g., increasing visual GPe vs. increasing visual SNr), none of the comparisons were significantly different (t-tests, $P > 0.05$).

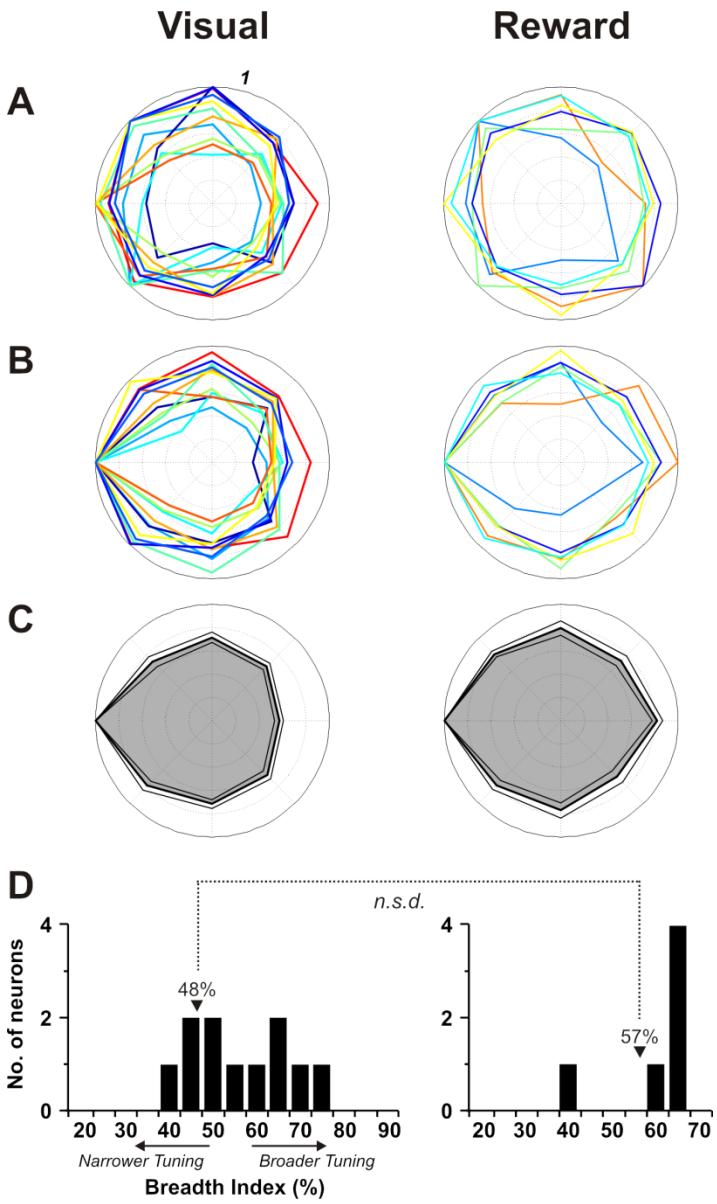

Figure 17: Breadths of tuning curves for the increasing type of SNr neurons

Our SNr sample had no increasing saccade-related neurons, so that column is absent. Other conventions are the same as in Fig. 15.

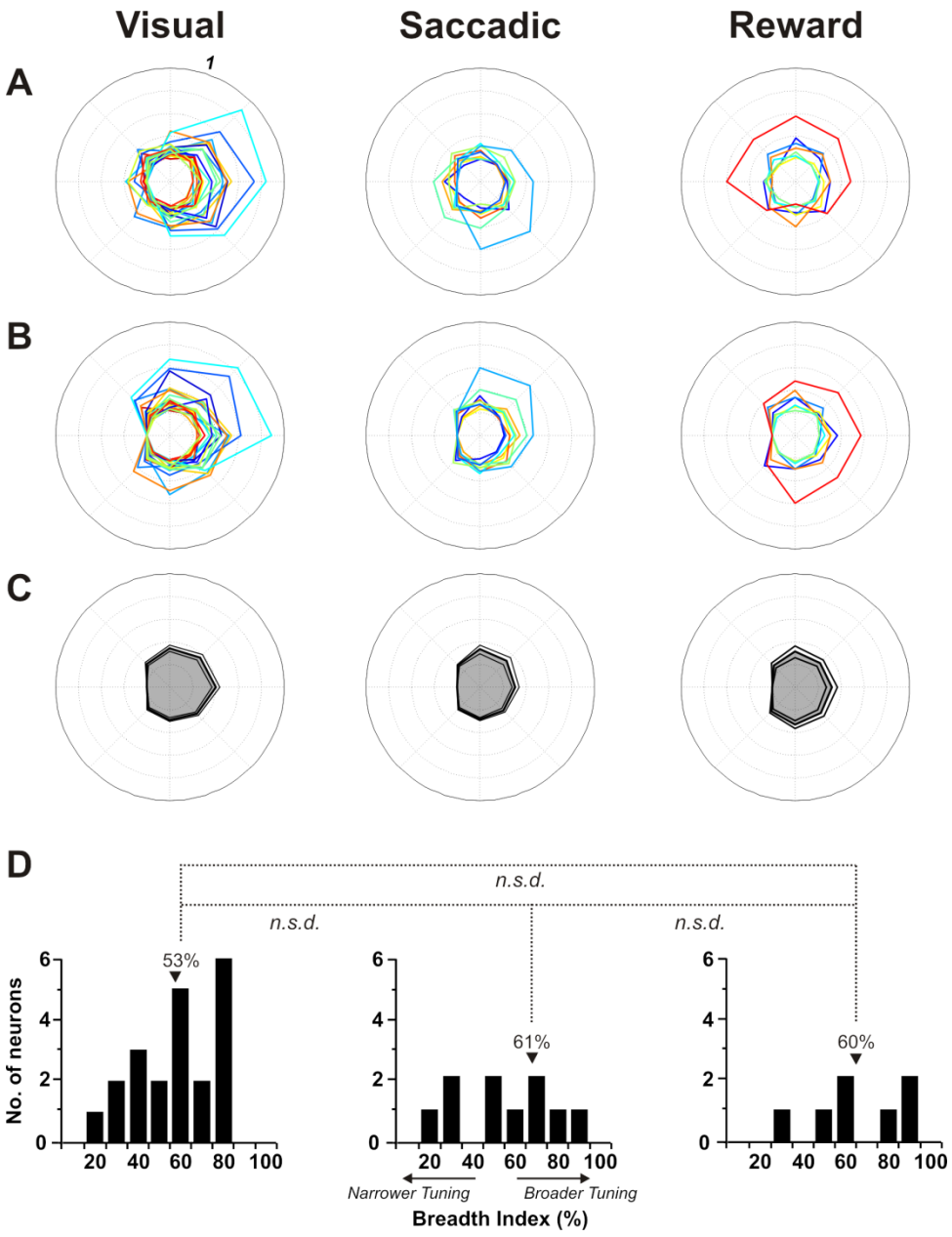

Figure 18: Summaries of population firing rates

Breadths of tuning curves for the decreasing type of SNr neurons. Conventions are the same as in Fig. 16

2.4 DISCUSSION

Our findings support the hypothesis that GPe and GPi neurons are active in diverse ways during oculomotor behavior. The neurons have high firing rates that increase or decrease during visual, saccade, or reward events of a memory-guided task. Comparing between the structures, GPe neurons were strongly visual-related, while GPi neurons almost lacked visual activity. Reward activity was common in both structures but was found in a higher proportion in GPi than in GPe. There was considerable saccade-related activity in both structures but infrequent delay activity. As expected from the GPe-to-SNr inhibitory projection, the signal content of GPe neurons closely resembled that of SNr neurons except for a general sign reversal. The signal contents of GPi and SNr had little in common. In both GPe and GPi, spatial response fields could be centered at nearly any amplitude and were relatively sharply tuned and contralaterally directed for visual signals, less distinctly tuned for saccadic signals, and largely omni-directional for reward signals.

It is well established that control of eye movements involves the caudate nucleus and SNr (Basso and Liu 2007; Basso and Wurtz 2002; Handel and Glimcher 2000; 1999; Hikosaka et al. 2000; Hikosaka and Wurtz 1983e; 1985b; 1983d; Jiang et al. 2003; Liu and Basso 2008; Sato and Hikosaka 2002). But just because the caudate-SNr pathway is an important oculomotor circuit does not mean that it is the *only* such circuit in the basal ganglia. When we began our study, the direct pathway through GPi, and the indirect pathways through GPe, had not been ruled out as oculomotor circuits; to our knowledge they simply had not been studied (with one exception: Kato and Hikosaka 1995). Traditionally, the GPi had been implicated in skeletomotor, not oculomotor, behavior. The GPe was known to be part of an indirect pathway that could influence the SNr, but no quantified summaries of its signal content during oculomotor behavior

had been reported. Very recently, accounts of pallidal signals during anti- and prosaccades (Yoshida and Tanaka 2009a) and smooth pursuit (Yoshida and Tanaka 2009b) have been published. Our data extend these new findings to provide a quantified assessment of the wide range of information carried by GPe and GPi neurons during saccadic behavior.

Our data reinforce the emerging view that the GPe and GPi may play an oculomotor role. Neurons in both structures (as in SNr) have visual-, saccade-, and reward-related modulations. Similar signals are found in well-known oculomotor structures outside of the basal ganglia such as the superior colliculus (Goldberg and Wurtz 1972a; 1972b; Schiller and Koerner 1971; Wurtz and Goldberg 1972a; 1972b) and the frontal eye field (Bruce and Goldberg 1985; Schall 1991; Tehovnik et al. 2000). The signals are represented differently between the structures – as bursts and pauses relative to a high firing rate in GPe, GPi, and SNr, but primarily as bursts relative to a low firing rate in superior colliculus, frontal eye field, and most other areas including the caudate nucleus – but the information carried by the signals in all of these structures is comparable. This is not to say that the signals from the various structures are equivalent in their behavioral impact. The GPi, in particular, seems to convey far fewer oculomotor signals than undisputed saccade-related structures such as the superior colliculus. Our point is that GPe and GPi neurons represent multiple events during oculomotor behavior using bursts and pauses as seen elsewhere in the visuosaccadic system, thus making them feasible candidate for participation in eye movements.

Three previous studies provided important data on the signals carried by GPe and GPi neurons during oculomotor behavior. The pioneering study of GPe by Kato and Hikosaka (1995) showed evidence for saccade-related activity in a task that also required lever presses. They used targets at multiple directions and eccentricities but did not quantify population response field characteristics. Hong and Hikosaka (2008) found that neurons in GPi carry visual signals

representing negative rewards in a biased-reward saccade task. They used targets at 15° eccentricity, left and right of fixation. Yoshida and Tanaka (2009a) reported saccade-related activity in GP using targets at 16° eccentricity, in multiple directions. The eccentricities in the two recent studies (Hong and Hikosaka 2008; Yoshida and Tanaka 2009a) were close to the average eccentricity of response field centers found by us (18°), but our mapping revealed that the range of optimal eccentricities was expansive (2-64°). Only 35% of our GP neurons had response field centers between 10 and 25° eccentricity. It seems unlikely that the other 65% of neurons in our sample would have been adequately characterized in the prior work. Our systematic response field mapping may also explain why most fields in the present study were found to be spatially tuned, as compared with an apparent prevalence of omni-directional fields in the previous work.

A somewhat surprising difference between previous work (Hikosaka et al. 2008; Hong and Hikosaka 2008; Kato and Hikosaka 1995; Yoshida and Tanaka 2009a) and our study pertains to saccade-related activity in GP, which was more prevalent in their data than in ours. This could be due to the subpopulation of GP neurons recorded. Neurons in the previous studies had relatively low baseline firing rates (~33-45 sp/s) characteristic of GP "border neurons" (DeLong 1971), while our neurons had higher firing rates (~80 sp/s) and seemed to be located throughout GPe and GPi (Fig. 4A). In terms of anterior-posterior location, we estimated from MRI, atlases, and physiological landmarks that our pallidal neurons were clustered 4-7 mm posterior to the anterior commissure, but Yoshida and Tanaka (2009a) localized their sample to within 2 mm of the anterior commissure. Also, there were methodological differences between the studies. Yoshida and Tanaka (2009a) used memory-guided saccades, antisaccades, and prosaccades, and found highest saccade-related modulations for antisaccades. We did not test

antisaccades, so we may have missed some potential saccade-related modulations. Yoshida and Tanaka (2009a) used a relatively broad epoch for defining saccade-related activity (100 ms before to 200 ms after saccade initiation) and only required it to differ from delay activity. We analyzed a more restricted epoch, 50 ms before to 50 ms after saccade initiation, and required it to differ from both baseline and delay activity, to minimize false positives.

Neuronal recording results are correlational and do not demonstrate functional impact. More experiments in the future should attempt causal perturbations of GPe and GPi to see if stimulation or inactivation affects oculomotor behavior. The latter manipulation was done in GPe by Yoshida and Tanaka (2009a), who found impairment in antisaccades. Some clinical and neurosurgical evidence suggests a causal oculomotor function for GPi. Deep brain stimulation of posteroventral GPi in human Parkinson's and Huntington's patients, and posteroventral pallidotomy in Parkinson's patients, have been shown to influence eye movements (Blekher et al. 2000; Fawcett et al. 2005; O'Sullivan et al. 2003; Straube et al. 1998).

Although we found neuronal signals related to vision, saccades, and rewards, some of the activity modulations may have been correlated with events that we did not monitor directly. One example could be the subtle contraction of neck muscles. This is difficult to rule out even when recording from the most well-understood oculomotor structures. Recently it was shown that the activity of saccade-related neurons in the superior colliculus and the frontal eye field is correlated with neck muscle activation (Elsley et al. 2007; Rezvani and Corneil 2008). The activity of some GPi and GPe neurons may be similarly complex, but this possibility does not weaken our fundamental finding that signals exist in both structures to implicate them in oculomotor behavior. Some of our neurons had small-eccentricity response field centers; for example 39% had centers at 10° or smaller eccentricity, and 72% had centers at $\leq$ 20°

eccentricity. In head unrestrained monkeys, saccades of 20° amplitude are accompanied by only negligible head movement (reviewed by Freedman 2008). These data provide evidence, albeit indirect, that most of the movement-related activity modulation of our neurons was due to the saccades that were made rather than head movements that may have been attempted.

We found that GPe and GPi neurons had different distributions of signals. GPe neurons had more visual activity, and GPi neurons had more reward-related activity. The high proportion of reward-related activity in GPi concurs with its connectivity. The GPi has reciprocal connections with substantia nigra pars compacta (Charara and Parent 1994; Smith et al. 1989) and sends efferents to the lHB (Hazrati and Parent 1991; Lecourtier and Kelly 2007; Parent et al. 2001). Matsumoto and Hikosaka (2007) reported that the lHB predicts negative reward value and provides inputs to compacta neurons that predict positive reward value. A follow-up study using antidromic stimulation to identify GPi projection neurons provided direct evidence that they contribute to the negative value signals in lHB (Hikosaka et al. 2008; Hong and Hikosaka 2008).

We found that in GPe neurons, too, reward-related signals were present. GPe neurons have no known direct connection with the lHB; instead, they interconnect mostly with other structures in the basal ganglia (Parent and Hazrati 1995). Many such structures, including SNr, GPi, and caudate nucleus, are implicated in reward processing, so the reward-related neurons in GPe might contribute to oculomotor behavior through them.

A prominent feature of GPe neurons was their strong visual responsivity. This characteristic hints at where the neurons may project. Two major targets of GPe are the subthalamic nucleus and SNr (Sato et al. 2000), structures that have many neurons with visual responses (Hikosaka et al. 2000; Hikosaka and Wurtz 1983a; 1983b; 1983c; 1983d; Matsumura et al. 1992). Another major target of GPe neurons is GPi (Sato et al. 2000), but as we showed,

GPi neurons have little visual responsivity. The simplest explanation is that the GPe neurons that we studied preferentially project to subthalamic nucleus and SNr, rather than to GPi. GPe neurons are inhibitory, and supporting the idea that our GPe neurons may influence the SNr, we found that the valences of signals in our GPe and SNr samples were generally opposite; increasing signals predominated in the GPe former and decreasing signals in the SNr.

In our analysis of the response fields, we identified a surprising trend: the fields became less lateralized, and more omnidirectional, as events proceeded from visual stimulation to saccade generation to reward delivery. The most striking difference (and the only change that was statistically significant) was the sudden broadening of fields at the final, reward delivery, stage of the task. Fundamentally, GPe and GPi neurons fired in advance of rewards regardless of the spatial details of a particular trial. The nonspatial nature of the activity reinforces the idea that it was related to predicting reward (a nonspatial entity) and was not a late response yoked to particular vectors of visual stimulation or saccadic movement.

Somewhat neglected in our report has been the potential role of the subthalamic nucleus, a glutamatergic basal ganglia structure (see Fig. 3A). We do not mean to minimize its potential importance. The connections between GPe and the subthalamic nucleus are reciprocal, and much of the increasing type of modulation we see in the GPe could be due to excitatory inputs from the subthalamic nucleus. Future studies that use antidromic and orthodromic stimulation to identify more of the inputs and outputs of the GPe are needed to test hypotheses like these.

A provocative implication of our study is that *both* output nodes of the basal ganglia, the GPi and the SNr, may contribute to oculomotor behavior. We suggest that the functions of these two output nodes may complement each other. A major difference between the GPi and SNr is their anatomical realm of influence. The most prominent trans-thalamic targets of GPi are motor

and premotor cortex (Alexander et al. 1986; Kayahara and Nakano 1996; Strick et al. 1995), while the SNr strongly targets the frontal eye field (Lynch et al. 1994). Hence, the GPi may relay oculomotor information to parts of the cerebral cortex that the SNr does not reach. Subcortically, the GPi influences many brainstem structures but apparently not the superior colliculus, which is a well known target of the SNr. It may be, then, that the GPi does not contribute to saccade generation per se. A more likely hypothesis is that it helps to integrate eye movements and skeletal movements. Taking into account its strong reward-related activity, the GPi may help to coordinate various modalities of action according to reward context.

3.0 CONTEXTUAL MODULATION OF OCULOMOTOR ACTIVITY IN NEURONS OF THE PRIMATE GLOBUS PALLIDUS AND SUBSTANTIA NIGRA PARS RETICULATA

3.1 INTRODUCTION

The general hypothesis that the basal ganglia are selectively involved in the control of voluntary movements has long been controversial. Supporting the hypothesis, patients with basal ganglia disorders experience a loss of voluntary control over movements with relatively spared sensory-guided movements. Hikosaka and Wurtz (1983a,b,c, 1985a,b) reported that saccade-related activity of SNr neurons depended on task context. They concluded that SNr neurons were preferentially involved in the control of memory-guided saccadic eye movements, which are made in the absence of sensory cues (Hikoska and Wurtz 1985a). Paradoxically, however, they also found movement-related activity to be extremely weak in a condition that should depend entirely on volition: spontaneous saccades in the dark.

Follow-up studies provided mixed support for the original conclusions of Hikosaka and Wurtz. Electrical stimulation in SNr affects only memory-guided saccades (Basso and Liu 2007). But recent recording experiments reported that activity in the SNr is modulated in similar ways for sensory- and memory-guided conditions, and further suggested that reward contingency may

contribute to differential saccadic modulations when task context is varied (Bayer et al. 2004; Handel and Glimcher 2000).

The focus on SNr in these previous studies was based on the original work showing its neurons carry eye movement related signals and influence the superior colliculus (Hikosaka and Wurtz 1985). Recently, we found that, in addition to SNr, a subset of neurons in both segments of globus pallidus are also modulated by eye movements (Shin and Sommer 2010). Another recent study has also reported preferential modulation in globus pallidus during antisaccades (Yoshida and Tanaka 2009a).

In studies that examine task contingency, *voluntary movement* is operationally defined in one of two ways: by what it is not, a movement that does not require sensory input, or by what it is, an internally guided act. These two views of voluntary movements are complementary but not redundant. Studies that compare memory-guided and visually-guided saccades for example, focus on the first definition of voluntary movement, that it should not be sensory-driven (e.g., Hikosaka and Wurtz 1985b, Basso and Liu 2007). In both tasks, however, subjects are instructed when and where to move by visual cues, thus violating the second definition of voluntary movement. Tasks involving generation of eye movements away from visual spot (i.e., anti-saccade task) similarly define voluntary as "not sensory driven" but implicitly provide instructions about when and where to move (e.g., Yoshida and Tanaka, 2009a).

Studies that adhere to the second definition of voluntary behavior, that it should be internally guided, generally examine spontaneous movements (e.g., Hikosaka and Wurtz 1983a,b,c; Handel and Glimcher 2000). In previous studies of spontaneously generated saccades, however, making eye movements was not beneficial to the monkey (i.e., not contingent to reward). The actions were entirely willful but also aimless, and the lack of reward may have been

a confounding factor, contributing to the low activity that was uniformly found in those studies. In contrast, most standard laboratory tasks, which serve as benchmarks for evaluating the activity in spontaneous tasks, are rewarded trial-by-trial and therefore keep the animals motivated.

In this study, we took into account both aspects of voluntary movements: their independence from sensory input and their spontaneous generation. The four tasks that we used were designed to dissociate the contribution of sensory and instructional contexts to neuronal activity during eye movements of the same vectors (Fig. 19A). Moreover, we supplied reward during the spontaneous conditions to provide a fairer comparison with standard tasks. Our aim was to investigate whether pallidal eye movement-related neurons, and for comparison SNr neurons, are modulated by context, and to identify the critical contextual components that contribute to such modulation.

Two predictions are illustrated schematically in Figure 19B and C. If the first factor related to voluntariness, the presence vs. absence of sensory cues, is the primary contextual component for peri-saccadic modulation, then differential modulations should be large between tasks with different level of sensory-dependence, regardless of whether instructions were provided or not (Fig. 19B). If the second factor, spontaneity of movement, is more important, neurons should show differential modulation between tasks with different level of instruction regardless of sensory inputs (Fig. 19C). It could also be that both factors play equal roles.

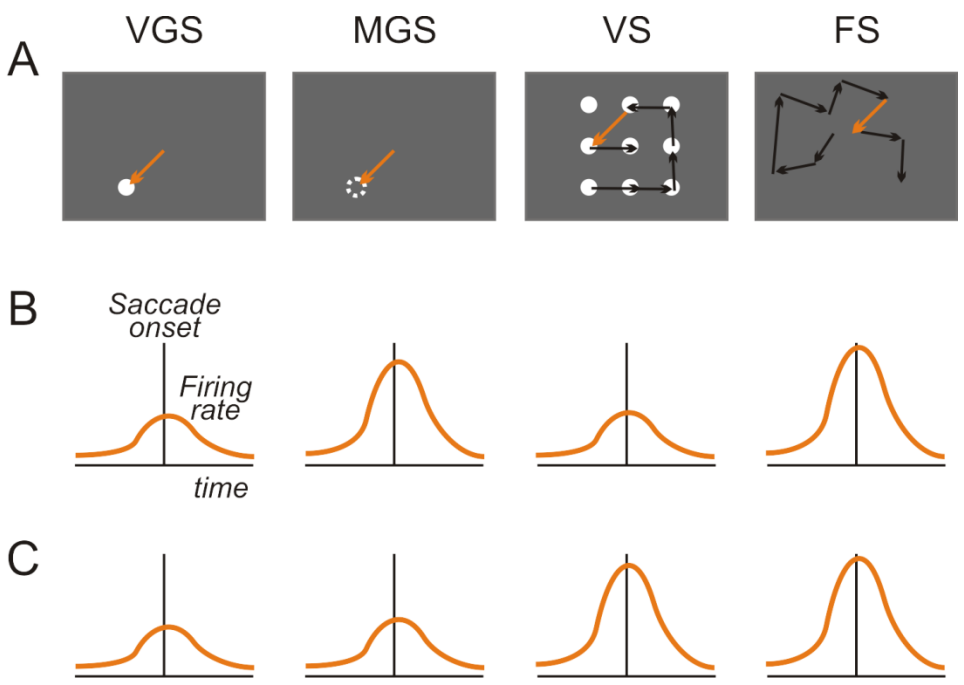

Figure 19: Predictions for the contextual modulation in basal ganglia

A) Schematic of the four tasks: from left to right, visually-guided saccades (VGS), memory-guided saccades (MGS), visual scan (VS), and free scan (FS). We compared neuronal activity during comparable vectors of saccades (e.g., orange arrows) made in the four task contexts. B) Hypothetical peri-saccadic neuronal modulation for the four tasks if the neurons are preferential for voluntary movement in the sense of being non-sensory driven. C) Hypothetical neuronal modulation for the four tasks if the neurons are preferential for voluntary movement in the sense of being non-instructed. Note that the hypothetical neuronal modulation in this figure is to show the degree of modulation, not the direction of modulation. The direction of modulation can be either increasing or decreasing.

We quantitatively analyzed activity associated with identical saccade vectors produced during the four different tasks. The main findings were that eye movement-related pallidal activity is modulated between the tasks, and that instructional context is more important than sensory context; the relative patterns of activity were as in Fig. 19C. However, the relative pattern was inverted overall: both non-instructed scanning tasks had significantly *lower* activity than both instructed tasks. Our data argue against the general hypothesis that the basal ganglia

play a special role in generating voluntary movement. This conclusion has specific implications for interpreting the deficits of voluntary movement seen in Parkinson's disease.

3.2 METHODS

3.2.1 Surgical Procedure

The surgical procedure used in this study was described in *Section 2.0*. Briefly, three rhesus monkeys (*Macaca mulatta*) were surgically prepared in aseptic conditions under isofluorothane anesthesia. We implanted scleral search coils to monitor eye position (Judge et al. 1980), a recording chamber to access and record neuronal activity in the basal ganglia, and a headpost and eye coil plugs. The entire implant was mounted to the skull via bone screws. The center of the recording chamber was located at 11 anteroposterior (AP), 28 mediolateral (ML) with a 40° angle from vertical in the coronal plane to access GPe, GPi, and SNr in the right hemisphere in the three monkeys.

3.2.2 Behavioral Tasks

When we isolated a neuron, we first determined its preferred direction and amplitude. A detailed description of the mapping procedure to decide a neuron's movement field is described in 2.*3.3 Tuning of response fields*. Briefly, the best direction was determined by having the monkey make memory-guided saccade to targets in eight different directions (the cardinals and diagonals) at presumed optimal amplitude. Memory-guided saccades were used because *a priori* we did not know what task would activate globus pallidus neurons the best, but memory-guided saccades had been shown by Hikosaka and Wurtz (1983c) to activate SNr well. After estimating the best direction for evoking modulation, we ran an amplitude series (up to eight: 2, 5, 10, 30, 40, 50, 60°) at that direction to determine the best amplitude. If necessary, alternations between different

directional series and amplitude series were repeated, until we were confident that we had found the center of the response field.

After determining a neuron's best direction and amplitude, we ran four tasks involving varying degrees of voluntariness (Fig. 20). The tasks were designed to dissociate the relative contributions of sensory and instructional contexts to neuronal activity during eye movements. The tasks can be parsed in two ways. First, in terms of sensory context, the visually-guided saccade task (VGS; Fig. 20A) and visual scan task (VS; Fig. 20C) provided visual targets for saccades. In the VGS task, the target was a required place to look; in the VS task the targets were potential places to look. In the memory-guided saccade task (MGS; Fig. 20B) and free scan task (FS; Fig. 20D), in contrast, saccades were made to blank space on the screen. Second, in terms of instructional context, the VGS and MGS tasks were instructed. In both tasks, visual stimuli provided cues as to where and when to move its eyes, and the monkey had to abide by those instructions. The VS and FS tasks, in contrast, were non-instructed. Monkeys could make saccades whenever they wanted, wherever they wanted, for a period of several seconds. Only at the end of the trial did monkeys have to reach a specified stimulus on the screen to receive reward.

Each of the four tasks was run in a separate block of trials. Because of the length of time needed to run all these tasks, for some neurons we could obtain data using only a subset of the tasks. All of the data that we could collect were included in the population analyses. Regarding the two scan tasks, we nearly always ran monkeys on the FS task before VS task to reduce the possibility that they would make saccades to remembered target locations in the FS task (for only three neurons did we run VS first). Each block of scanning saccades lasted about a half an hour and evoked a couple of thousand spontaneous saccades, sufficient to map a movement field.

Details of each task are as follows. All ranges of times represent pseudo-randomization. All visual targets were 0.3˚ diameter squares. In the VGS task (Fig. 20A), the monkey foveated a central stimulus, and then after 500-800 ms a visual target appeared in the periphery and remained lit until the trial ended. After a delay period of 500-1000 ms, the fixation spot disappeared, signaling the monkey to make a saccade to the location of the target. In the MGS task (Fig. 20B), everything was the same as in the VGS task except that the visual target appeared only briefly (100ms). After the delay period (500-1000ms), a saccade to the remembered location of the target resulted in reward. For the VGS and MGS tasks, an electronic window for verifying fixation on-line was set to 3˚ × 3˚ square by default. The window around the target location for verifying a correct saccade on-line was adjusted by the investigator as a function of eccentricity (larger windows for larger eccentricities).

In the VS task (Fig. 20C), an array of nine white targets appeared on the screen (separated by 20˚, except in three sessions in which alternate separations were used that covered the movement field better). The monkey was permitted to make saccades at will, although its scanning pattern usually matched the array targets. After a scanning period (2-10 sec.) one of the array targets was selected, pseudo-randomized and unknown to the monkey, to be the baited target. The task ended when the monkey made a saccade to the baited target. Scanning tasks similar to the VS task have been used previously (Richards et al. 1994; Sommer 1994; 1997). In the FS task (Fig. 20D), no stimuli appeared initially. Monkeys made scanning saccades for 2-10 sec. over the blank screen and then at a pseudo-randomized location (one of the nine locations used in the VS task), a dim target appeared. The luminance of this target was near the monkey's detection threshold (determined qualitatively); typically it was 20% of the luminance of the targets used in the other tasks. The monkey was required to foveate the target within 600 ms to

receive the liquid reward. Because the animal was rewarded for making a saccade to the dim target at the end of each trial, it remained motivated. Because of the target's dimness, its random location, and the brief window of opportunity for foveating it after it appeared, the monkey made rapid scanning saccades of many directions and amplitudes across the blank screen. Finally, because the trials were blocked, as soon as a monkey detected the dim target once, it seemed to know that it had begun this particular task as evidenced by the commencement of avid scanning.

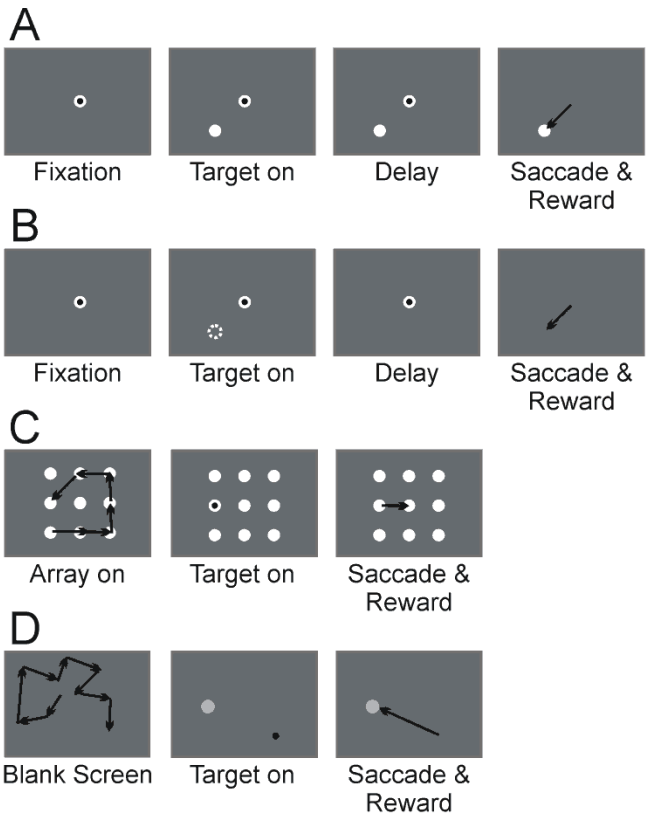

Figure 20: The tasks.

A) Sequence of events during the VGS task. A visual target appeared and stayed until the animal made a saccade to it after the cue to move (fixation point disappearance). B) Sequence of events during the MGS task. A visual target flashed briefly (for 100ms), cueing where to move. The monkey had to remember the location until the cue to move (fixation spot disappearance), and then make a saccade to the blank region that had occupied the target. . C) Sequence of events during the VS task. An array of stimuli appeared and the monkey was allowed to make saccades

at will. Almost all the saccades went to stimuli of the array, but order and timing of the saccades was left up to the monkey. After a randomized duration, one of the stimuli was covertly "baited"; when the monkey looked at it, reward was delivered. D) Sequence of events during the FS task. The monkey was presented with a blank (gray) screen. The animal could do whatever it wanted, but typically it made spontaneous saccades all over the screen. After a randomized duration, a dim target appeared, and if the animal made a saccade to it, it received reward. In all panels, small black dots represent fixations and arrows represent saccades.

3.2.3 Data Analysis

The main goal of the analysis was to compare neuronal activity across four different task contexts for comparable ranges of saccade vectors. A secondary goal was to make the same across-tasks comparison, but based on activity in the individual movement field centers or "hotspots" found during each task (unexpectedly, we found that for some neurons the hotspots differed between tasks). The peri-saccadic activity associated with all saccadic movements was calculated (details provided below) based on the analyses of peri-saccadic activity latency done in *Section 2.0*. Neurons showing significant peri-saccadic activity in any task were analyzed further. Comparison of firing rates between tasks was performed on the peri-saccadic activity *modulation* (activity relative to baseline).

To compare peri-saccadic modulation between tasks, we plotted it as a function of saccade vector in each task. For the VGS and MGS task this was straightforward, as initial fixations were all at the center and the raw data showed the vectors. For the VS and FS tasks, we had to extract the vectors from the raw data of diverse scanning saccades. Data from an example neuron tested on the FS task are shown in Figure 21. First, we plotted the raw eye movement traces (Fig. 21A), and then we found initial and final points of each saccade using velocity thresholds. Using these points we extracted the individual saccade vectors and plotted them in

polar coordinates where the saccade starting points were all at the center and the saccade ending points (representing the saccade vectors) were marked with dots (Fig. 21B). To summarize the movement fields, we generated pixelated thermal plots by averaging all the observed peri-saccadic modulations associated with saccade vectors within 4˚× 4˚ regions (Fig. 21C). For this procedure and all other analyses of neuronal activity in the FS task, the final three saccades of every trial were omitted from analyses, to rule out the chance of accidentally including primary or catchup saccades made to the appearance of the dim target.

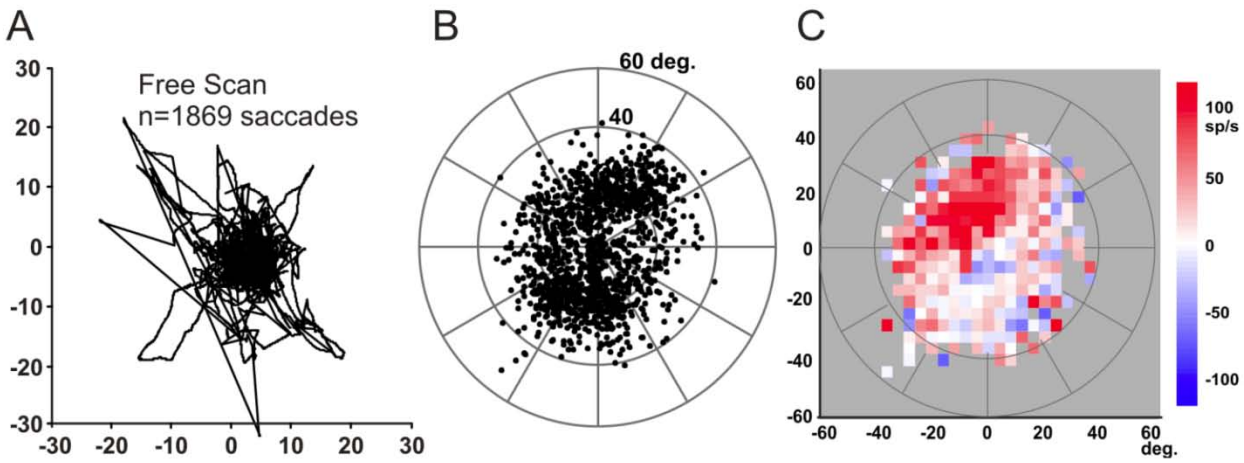

Figure 21: Analyses for scan tasks.

A) Scanning pattern of eye movements during an entire session of the FS task. B) Saccadic vectors from *A* are plotted in a polar plot. Hence each dot on the plot represents the direction and amplitude of a single scanning saccade. C) Thermal plot representing peri-saccadic modulation (i.e., firing rate during saccade – baseline) using epoch Ep. 2. Data were averaged within 4º × 4º pixels. This procedure was used for both analysis epochs and both scanning tasks (VS and FS).

Significance of peri-saccadic activity. We first determined whether each neuron carried significant peri-saccadic activity in any of the four tasks. In *Section 2.3.1. Task-related signals carried by pallidal neurons* we found that GPe and GPi neurons exhibited a range of timing in their peri-saccadic activity, so for thoroughness we measured average firing rates using two

epochs related to saccade onset: epoch 1 (Ep. 1) ranged from 50 ms before to 50 ms after saccade initiation, and epoch 2 (Ep. 2) ranged from 0 ms to 100 ms after saccade initiation. The results from these two epochs were evaluated separately. In all four tasks, peri-saccadic activity from both epochs was compared with baseline activity. In the VGS and MGS tasks, the baseline epoch was the range 100 ms before onset of visual stimulus. In the FS and VS tasks, the baseline epoch was from 150 ms to 100 ms before saccade onset. A significant difference between activity in a peri-saccadic epoch and baseline by t-test ($P<0.05$) was considered evidence of significant saccade activity. For neurons with such significant activity, we subtracted baseline levels from the peri-saccadic activity to assess the peri-saccadic modulation. For our comparison of neuronal modulation between tasks, neurons were included only if they had significant peri-saccadic modulation in at least one of four tasks on which they were tested.

Determination of the center of movement field in the scan tasks. For the first pass of the analysis, data from same-vector saccades were compared across tasks. An ellipse was constructed that delimited the range of saccades made into the movement field hotspot in the VGS and MGS tasks, and the same ellipse applied to movement fields found using the VS and FS tasks. Details are provided in the Results. In a few cases, however, the movement field shifted markedly in the VS and FS tasks, compared with the initially mapped hotspot that was used for target location in the VGS and MGS task. Hence our same-vector analysis could miss the saccadic vectors that happened to be optimal for evoking activity in the scan tasks, which might be viewed as providing an unfair comparison between all the tasks.

In a separate analysis, therefore, the movement fields in scan tasks were characterized independent of the movement fields found in MGS and VGS. We found the hotspot of the response field from the FS task (FS task was used because from it more number of and more

diverse saccade vectors were evoked than from VS) in the following way. From the two-dimensional pixilated thermal plot described above, a response field ellipse was fitted around the pixel with maximal modulation (either an increase or decrease) and was extended to include nearby pixels where 90% of the maximal responses occurred. Whether activity in this newly mapped hotspot ellipse was significant, or just represented noise in a homogeneous movement field, was tested using bootstrapping (Efron and Tibshirani 1993).

For both both the vector-matched and hotspot-matched data sets, a one way ANOVA (Kruskal-Wallis One Way Analysis of Variance on Ranks) was used to determine if peri-saccadic modulations differed at all across the four tasks. If a neuron showed overall significant modulation at $P<0.025$ (Bonferonni corrected from $P<0.05$ because the same VGS and MGS data were used in both the vector-matched and hotspot-matched comparisons), the ANOVA was followed by a multiple comparisons test between the four tasks (Student-Newman-Keuls Method for parametric data; Dunn's Method for non-parametric data; Bonferroni corrected to $P<0.025$).

Influence of reward contingency. In general we found lowered peri-saccadic modulations in the scanning tasks than in the VGS and MGS tasks. To determine if this effect was related to another major difference between the tasks -- reward contingency -- we performed a set of correlation analyses (Spearman's tests). The goal was to determine if neuronal modulation during the scan tasks (VS and FS) was sensitive to a growing expectation of reward delivery as a trial progressed. Since we could not measure reward expectation directly, as a proxy for it we used two observables that the monkey could use (in principle) to estimate the approximate time of reward delivery: elapsed time during a trial, and number of saccades made during a trial.

Influence of initial eye position. We examined whether initial eye position influenced the saccade-related modulation in VS and FS tasks. To do this we generated the same thermal plots

of neuronal modulation but with reference to absolute initial eye position, not saccade vector. The same method described above for finding hotspots in the movement field data was used to determine if there was a significant clusters of activity modulation related to initial eye position.

Patterning of saccades during the FS task. We examined whether the animals biased their scanning saccades in the FS task to the nine possible dim target locations. There were no visible references to those locations in the FS task, but since they were the same locations as used in the VS task, it was conceivable that after overtraining the animal may have begun to remember the nine locations and loiter at them). We plotted all initial eye positions made during the FS task in absolute space and averaged these fixation positions within $4^o \times 4^o$ pixels. The thermal plot depicted the numbers of fixations made at each quantized location on the screen, and thus would reveal if the fixations were clustered at specific locations such as the nine possible target locations.

3.3 RESULTS

In the previous section we described neuronal activity related to saccade generation in both the external and internal segments of the globus pallidus (GPe and GPi) as well as in the substantia nigra pars reticulata (SNr). In that work, we focused on saccades made in a single context: the MGS task. Here, we examined whether the activity varies if comparable saccades are made in different behavioral contexts.

3.3.1 Dataset

We studied a set of neurons recorded from GPe (total n=335), GPi (n=116), and SNr (n=93). The pallidal sample included neurons with relatively high baseline spike firing (>50sp/s). Different behavioral contexts were accomplished using four tasks (number of neurons recorded for the specific task is in the parentheses following): the VGS task (80 GPe, 39 GPi, 34 SNr), the MGS task (83 GPe, 40 GPi, 79 SNr), the VS task (47 GPe, 14 GPi, 12 SNr), and the FS task (56 GPe, 22 GPi, 16 SNr). The tasks involved various combinations of sensory input and instruction. The two extreme conditions were the VGS task (as non-voluntary as possible), which involved a visual target plus instructions on when and where to move (fixation spot disappearance and visual target location, respectively), and the FS task (as voluntary as possible), which involved a blank visual field and no instructions at all. Two intermediate conditions were the MGS task, which involved no visual target but instructions on when and where to move (fixation spot disappearance and previously flashed target location), and the VS task, which involved distinct visual stimuli but no instructions.

3.3.2 Pallidal Neurons were Modulated by Saccade Onset in Different Task Contexts

First, we examined whether each neuron has peri-saccadic activity in each task. For this summary we will group GPe and GPi neurons as pallidal neurons. We found that, in the VGS and MGS tasks, 29% (34/119) and 38% (47/123) of pallidal neurons were modulated, respectively. In the VS and FS tasks, 21% (13/61) and 12% (9/78) of pallidal neurons were modulated, respectively. In both GPe and GPi, the type of modulation could be either an increase or a decrease relative to baseline activity (as reported in *Section 2.0*; Shin and Sommer 2010).

The direction of modulation, up or down, was nearly always (except for five neurons) maintained across the four tasks (e.g., if a neuron showed an increase in one task, it showed an increase in the other task(s)).

For comparison, SNr neurons exhibited peri-saccadic modulations in the VGS and MGS tasks (34% (14/34) and 20% (16/79) of the neurons tested, respectively), and these modulations could be up or down relative to baseline. None of the SNr neurons, however, exhibited peri-saccadic modulations in either of the scan tasks (VS, 12 neurons tested; FS, 26 neurons tested).

3.3.3 Pallidal Peri-saccadic Activity was Differentially Modulated Depending on Task Context

Our primary analysis of between-task differences compared subsets of the data restricted to saccades of comparable vectors (saccade-vector matched analysis). As described in Methods (see *Section 3.2* for detail), before starting formal data collection we mapped a neuron's response field using the MGS task using targets at many different amplitudes and directions. During formal data collection of VGS and MGS trials, a target randomly appeared at either the center of the mapped field or (to prevent anticipatory saccades) at a diametrically opposite location. Based on the saccade vectors produced in the VGS and MGS data sets, we mapped a "local movement field" around the target (ellipses in Fig. 22). The purpose of this local movement field was to provide a basis for comparison with the scan tasks. We overlaid the same ellipses on the data collected with the scan tasks. Hence firing rates associated with the same ranges of saccade vectors were evaluated in all four tasks. A GPe example neuron (Fig. 22A) showed significant peri-saccadic activity across the four tasks. In the VGS and MGS tasks (left two plots), the neuron had a significant increase of firing rate (red) for 10° saccades made up and to

the left (with no modulation from baseline for the diametrically opposite location). In the VS and FS tasks (right two plots of 22A), an extensive portion of the entire movement field was delimited due to the broad ranges of saccadic amplitudes and directions produced by the monkey. As would be expected, the neuron increased its firing rate for saccades up and to the left but showed less modulation elsewhere. The local movement field ellipses were overlaid identically onto all four data sets, and we calculated the average firing rate within the ellipses in each of the tasks. This neuron showed significantly different activity modulation across the different task contexts (Fig. 22A, far right; $P<0.001$, ANOVA). A GPi example neuron (Fig. 22B) was similar, showing differential activity across the tasks for saccades of amplitude ~40° directed up and to the left (Fig. 22B, far right; $P<0.001$, ANOVA). Finally, an SNr example neuron (Fig. 22C) that paused for saccades was also modulated differentially across the tasks (Fig. 22C, far right; $P=0.001$, ANOVA).

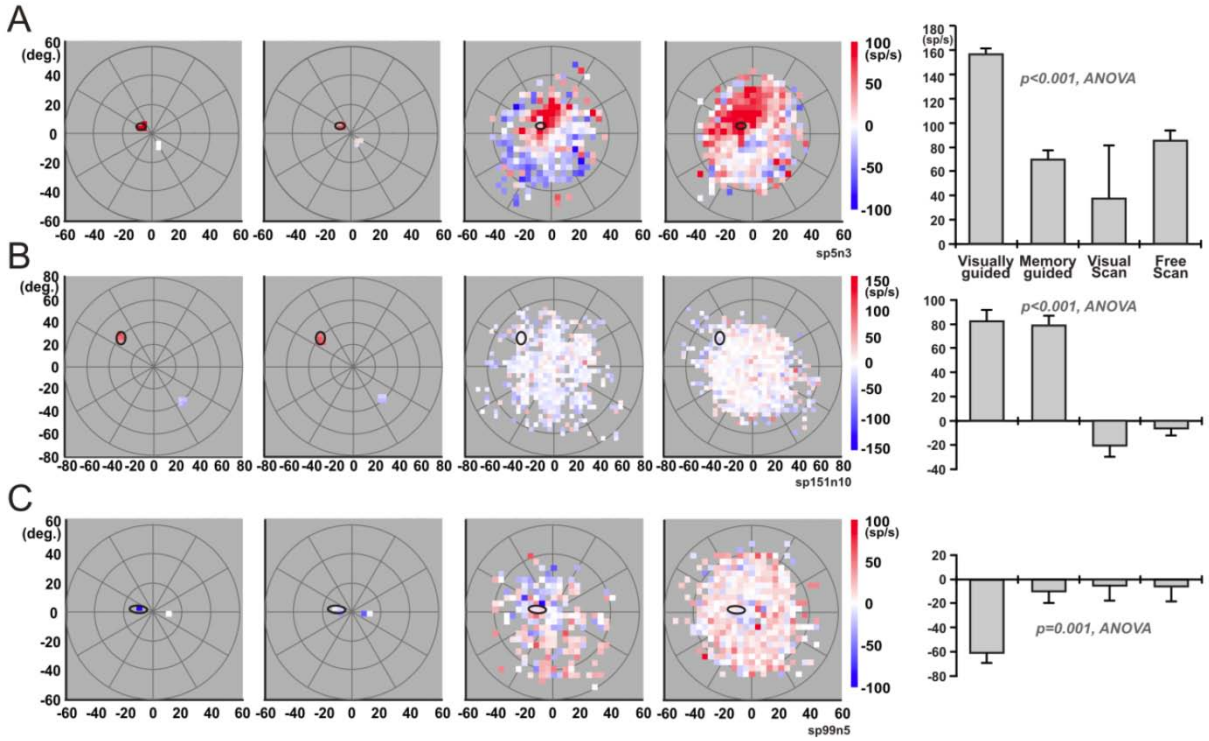

Figure 22: Comparison of single neurons from GPe, GPi, and SNr for the four tasks

A) GPe, B) GPi, and C) SNr neurons during VGS, MGS, VS, and FS tasks (left to right respectively). Ellipses in thermal plots represent the response fields. Bar graphs on far right show the average and SE of neuronal modulation (sp/s) for each example neuron.

We noticed that some neurons, surprisingly, showed a marked shift in the movement field for the scan tasks. For example, the GPe neuron of Figure 22A had a movement field hotspot that was positioned appreciably more upward in both scan tasks than initially mapped and used with the VGS and MGS tasks. Observations such as this one prompted us to perform a complementary analysis based on the hotspots of the individual fields. After determining the center of the movement field independently for the scan tasks (Fig. 23, left and center), we redid all of our ANOVAs (e.g., Fig. 23, right). As would be expected, the average activity modulation for the scanning saccades made into the newly hotspot-matched response field ellipse was stronger (dark grey bars) than found in the analysis of Figure 22 (copied here, light grey bars). For this neuron, however, the modulation across the tasks remained significantly different (P<0.001, ANOVA)

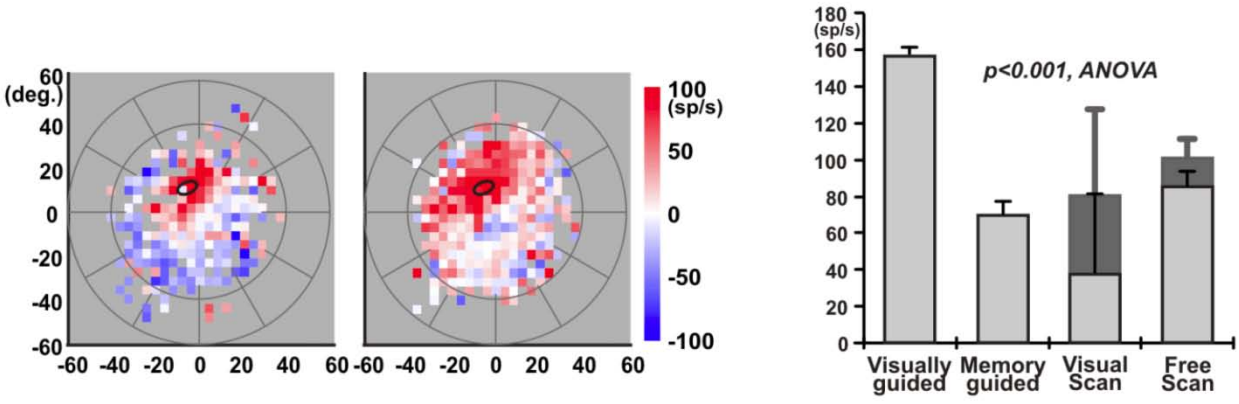

Figure 23: Response fields mapped from scan data (hotspot-matched response fields)

Same example GPe neuron in Figure 22A is shown. The darker bar graph represents the average and SE of neuronal modulation for the newly fitted response field and is overlaid.

At the population level, about half of the neurons in all three structures were modulated differently across the tasks according to the original (saccade-matched) analysis method of Figure 22: 49% of neurons in GPe (28/57), 47% in GPi (9/19), and 61% in SNr (14/23; ANOVAs). Using the alternate, hotspot-matched method of Figure 22, the numbers did not change much: 37% of GPe (21/57), 53% of GPi (10/19), and 61% of SNr (14/23) neurons were modulated differently across tasks. Because the same VGS and MGS data were used in both statistical comparisons, the criterion level was Bonferroni corrected to $P<0.025$ for these tests.

So far we have analyzed example neurons. Now we pool data across all neurons for globus pallidus (GPe and GPi combined, Fig. 24, 25) to understand the modulations at the population level (population data for GPe and GPi separately will be shown below). For our first comparison, we used the saccade-matched approach, for each saccade epoch (Ep. 1, Fig. 24A; Ep. 2, Fig. 24B; see inset for definitions of Eps. 1 and 2). The numbers (bottom of each graph) represent entire population averages; neurons with increasing modulations or decreasing modulations relative to baseline were pooled here to show simple net effects. The overall globus pallidus population showed significant activity modulation for Ep. 2 ($P=0.014$, ANOVA). Modulation during Ep.1 was not significant. Overall, activity modulation during instructed goal tasks (VGS and MGS) seemed stronger than that during scan tasks, although in this analysis none of the multiple comparisons of neuronal modulation between tasks was significant Also, the aggregate direction of the modulation was an increase relative to baseline.

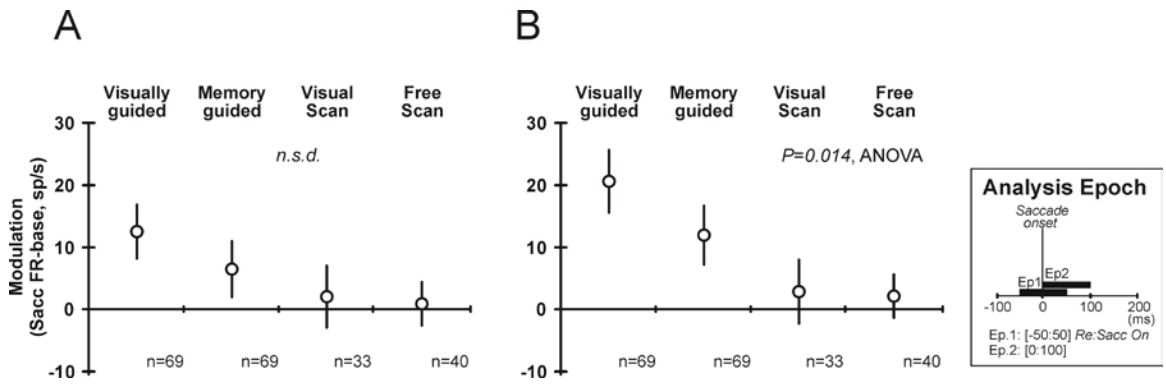

Figure 24: Context-dependent modulation in the globus pallidus population.

Neurons with significant activity in at least one task were included. For this analysis, GPe and GPi were combined. A) Neuronal modulation for Ep. 1 (see inset). From left to right, the average (circle) and SE (vertical line) of neuronal modulations for the VGS, MGS, VS, and FS tasks, respectively, are shown. B) Analogously, neuronal modulations using the alternative epoch Ep. 2 are shown. Significance by ANOVA and the neuron numbers that contribute to each data point accompany each graph.

Next, we divided the dataset by the direction of modulation relative to baseline, shown in Fig. 25 A-D (increases, red circles; decreases, blue circles). In our overall globus pallidus sample, context-dependent saccade-related modulation was observed in the increasing type of neurons for both analysis epochs ($P<0.001$, ANOVA; Fig. 25A,B upper part). In the decreasing type of neurons, significant differential modulation was observed in the data from Ep. 1 (Fig 25A lower part), but not in Ep.2 (Fig. 25B lower part). We followed significant ANOVAs with multiple comparison tests. There was significantly greater activity in the VGS task and in the MGS task than in each of the scan tasks as depicted with asterisks (Fig. 25A,B). All other pairings were not significant. This result provides quantified verification of the prediction of Fig. 18C, but in inverse (instructed tasks were associated with more activity, not less as predicted).

The results from our hotspot-matched analyses are shown in Figure 25C and D. To ensure the fairest comparison across tasks, we used data only from movement fields that had a significant hotspot (for significance test see *Section 3.2.3.*). General results were the same as in those from vector-matched analyses with one exception: overall modulation (i.e., significant ANOVA) shown for increasing type for Ep. 1 (Fig. 25A) disappeared in hotspot-matched analysis (Fig. 25C).

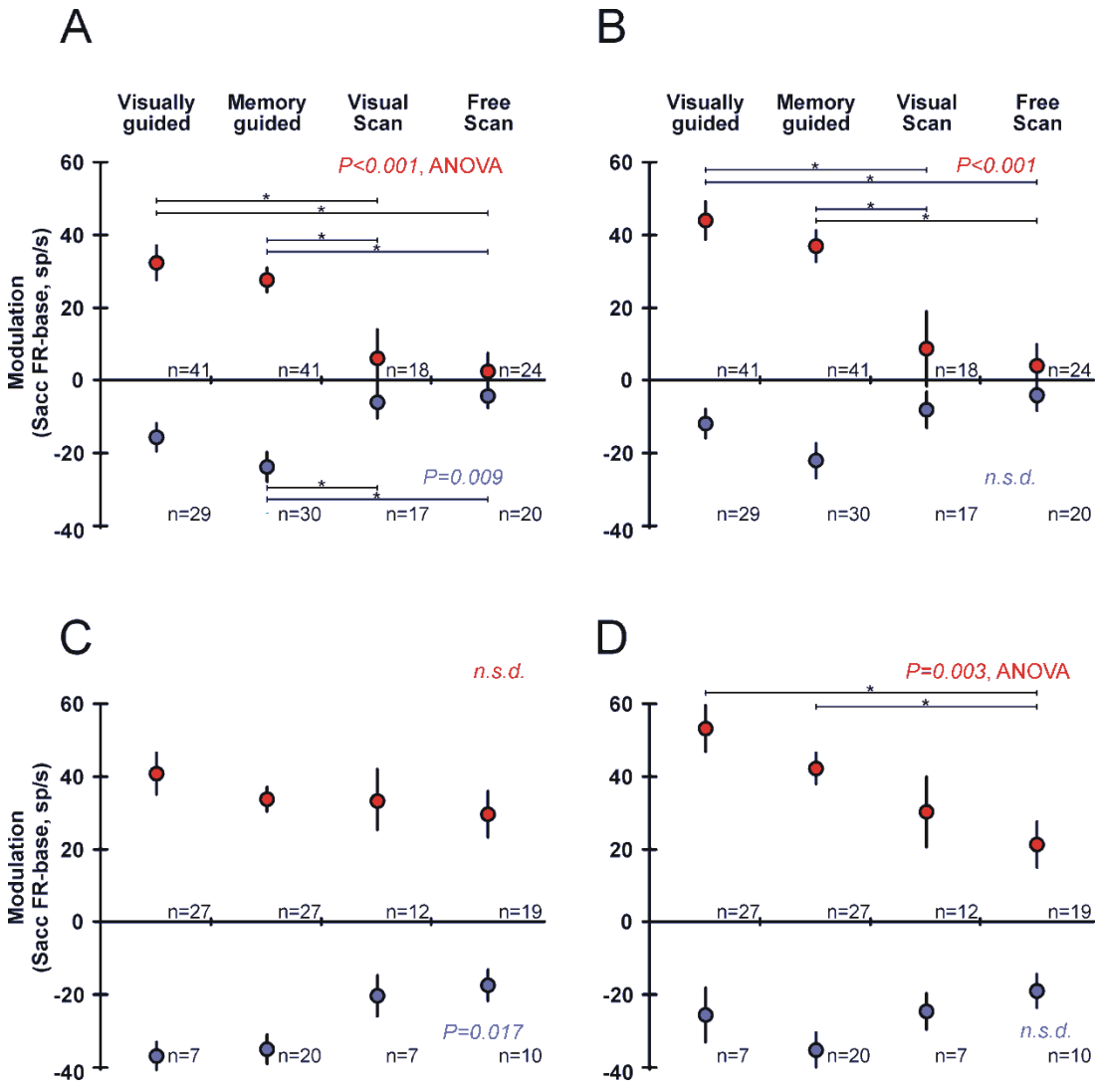

Figure 25: Context-dependent modulation in globus pallidus for different signs of modulation and different analysis methods.

In all panels, red symbols represent increasing types of modulation and blue symbols decreasing types of modulation. (A-B) Saccade-matched analyses using peri-saccadic epochs (A) Ep. 1 and (B) Ep. 2. (C-D) Hotspot-matched analyses using (C) Ep. 1 and (D) Ep. 2. Other conventions as in Figure 24.

In summary, the overall context-dependent modulation in globus pallidus was due to stronger modulation in instructed goal tasks (VGS and MGS) than in the more spontaneous scan tasks (VS and FS). This general conclusion was the same regardless of whether the neurons increased or decreased their activity relative to baseline, and regardless of whether the analysis was based on saccade-matched or hotspot-matched data.

When we separately considered GPe (Fig. 26) and GPi (Fig. 27) samples, the results were similar. While there was more variation, less individual-analysis significance by ANOVA, and no significant multiple comparison results, all due to smaller numbers, the overall pattern was to suggest greater modulations (above or below baseline) for the instructed, VGS and MGS tasks than for the non-instructed, VS and FS tasks.

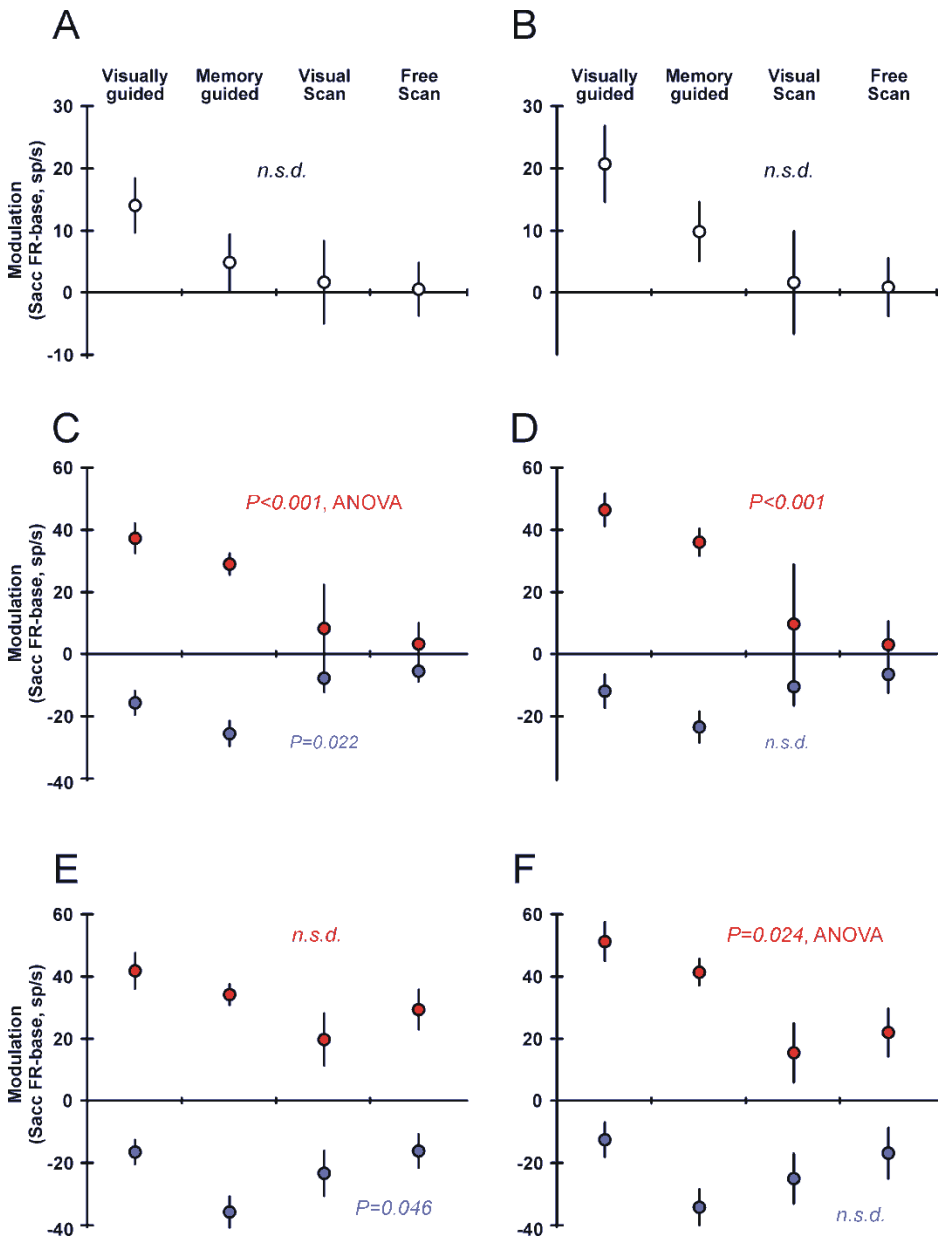

Figure 26: Context-dependent modulation in the GPe population

Left column (panels A,C,E) show analyses using Ep. 1. Right column (panels B,D,F) show analyses using Ep. 2. (A-B) Results for GPe using saccade-matched analysis (as in Fig. 24). (C-D) Same but with increasing and decreasing types of response separated (as in Fig. 25A,B). (E-F) Results for GPe using hotspot-matched analysis (as in Fig. 25C,D).

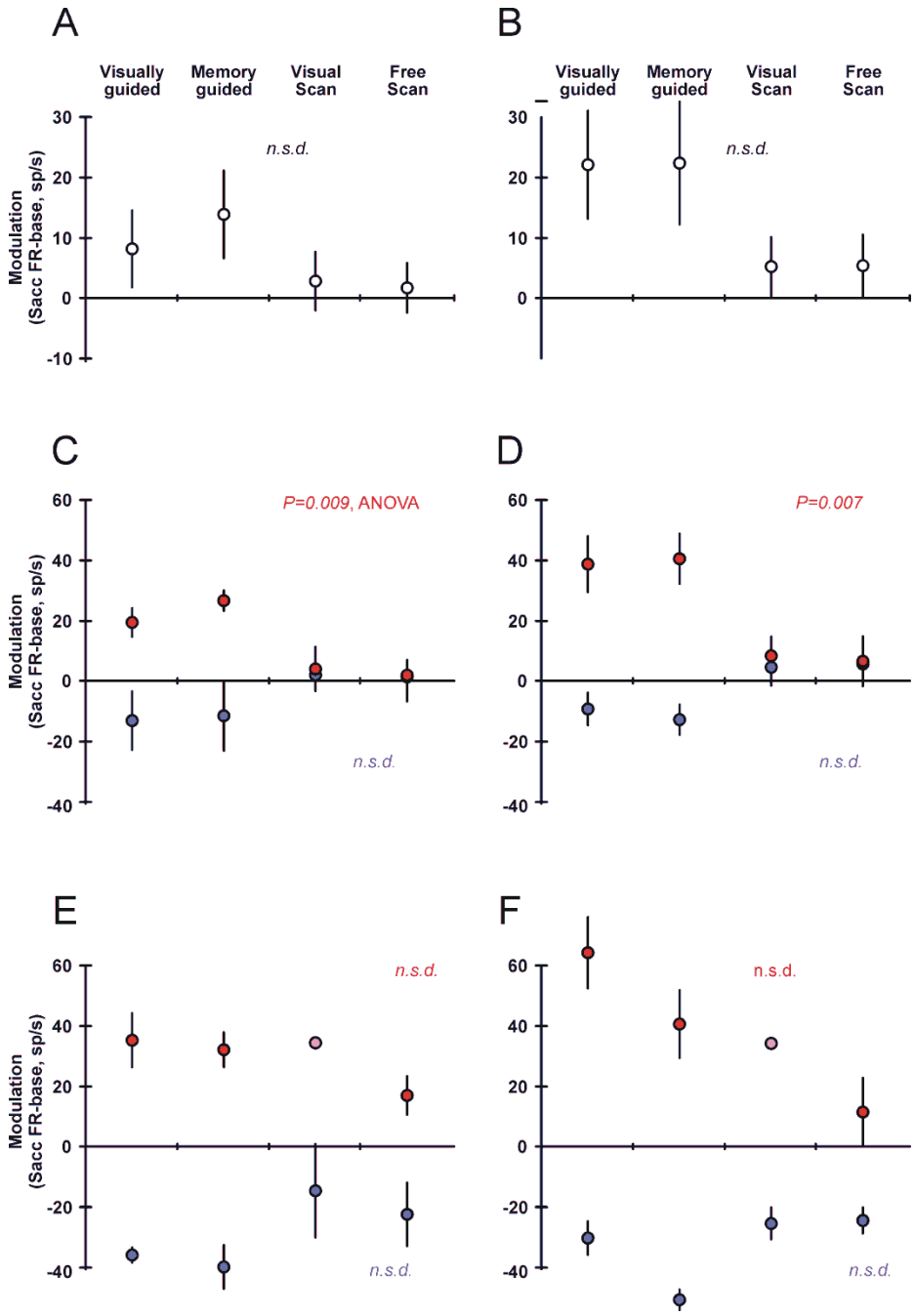

Figure 27: Context-dependent modulation in the GPi population.

Same as in Figure 26, but for GPi. Note, in panels E and F, the VS task data includes only 1 neuron; thus it is depicted in light pink without lines for SE.

For comparison, we recorded neurons from the SNr during all the tasks, but none were significantly modulated for saccades in the VS (n=12) and FS (n=16) tasks. We only wanted to include significantly modulated neurons in all of these analyses, and so for SNr neurons we could compare saccade related activity only during VGS and MGS tasks. Unlike pallidal neurons, in SNr only the decreasing type of neurons showed a significant difference in activity between tasks (Fig. 28). When saccades were made in the VGS task, neuronal activity paused more than when saccades were made in the MGS task. No difference was found between the tasks for the increasing type of neurons.

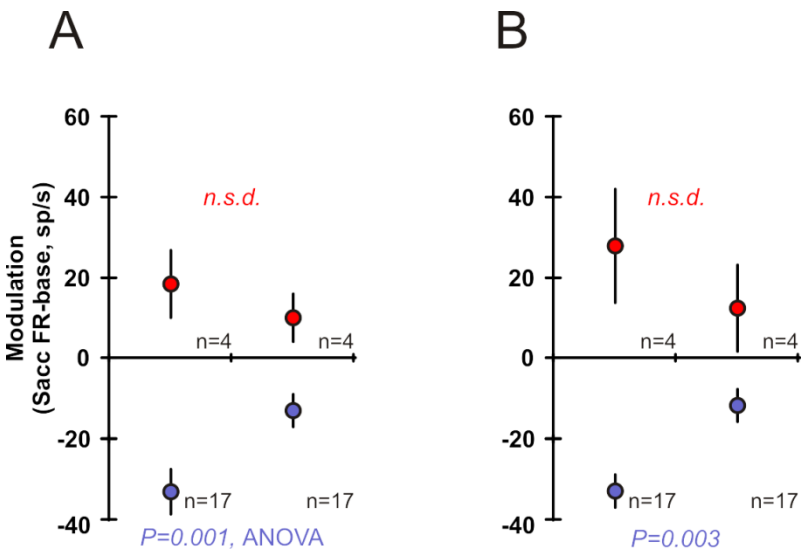

Figure 28: Context-dependent modulation in the SNr population.

A) Increasing (red circle) and decreasing (blue circle) types of responses for Ep. 1 are shown separately. B) Same but for Ep.2. Data from VS and FS tasks are not included due to absence of saccade-related modulation during those tasks.

3.3.4 Peri-saccadic modulation is not due to initial eye position

Many saccade-related brain areas show initial eye position-dependent modulation (e.g., LIP, Anderson et al. 1990; SC, Campos et al. 2006). We examined whether this was the case for our globus pallidus and SNr neurons. This analysis was done only for the scan tasks because initial eye position was invariant in the VGS and MGS tasks. Two-dimensional thermal plots representing neuronal modulation as a function of initial eye position were generated for each neuron separately for the VS and FS tasks. Figure 29 shows an example 2D eye position plot for the example neuron shown in Figures 22A and 23. To find any clustering of activity, the same statistical methods used for finding hotspots and testing their significance with bootstrapping methods were applied (See *Section 3.2 Methods*). For this example neuron and in most of our sample, there was no significant dependence on initial eye position (except for 1 GPe and 1 SNr neuron).

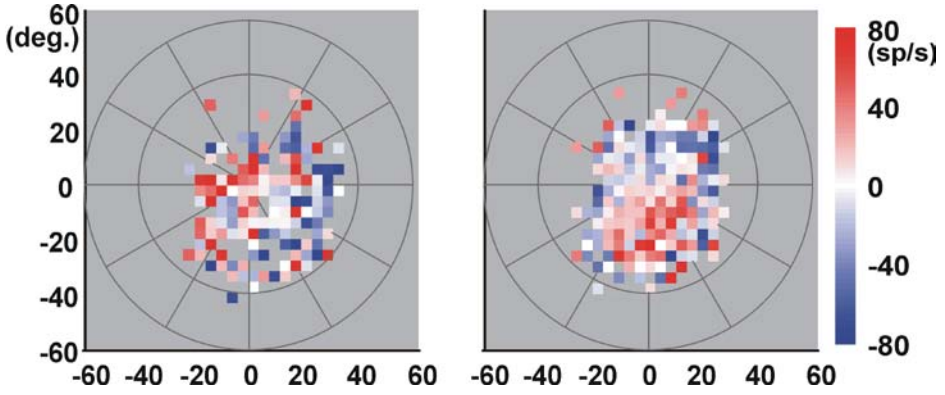

Figure 29: Example neuron showing peri-saccadic activity modulation as a function of initial eye position

Firing rates are shown as a function of initial eye position for the VS (left) and FS (task). This neuron did not have initial eye position dependent peri-saccadic activity modulation.

3.3.5 Effects of reward contingency activity modulations during scanning

Reward has been implicated as a contributor of contextual modulation in basal ganglia neurons (Handel and Glimcher 2000; Kawagoe et al. 1998). In our tasks, each successful saccade made in the VGS and MGS task was immediately rewarded, but nearly all the scanning saccades in the VS and FS tasks (except the final saccades of each trial) were not directly rewarded. If basal ganglia neurons are sensitive to reward expectation, this difference in reward scheduling could have contributed to the overall lower activity that we found in the scanning tasks. To test this hypothesis, we examined whether temporal proximity to reward affects the activity modulations of our basal ganglia neurons. The predication is that overall activity rates should rise toward the end of each trial. It was unclear whether the activity would rise as a function of *time*, or the cumulative *number* of saccades made, so we analyzed the data with respect to both.

We examined all neurons that were isolated for long enough to be tested on all four tasks (25 globus pallidus neurons). Only VS and FS task data are analyzed here, but VGS and MGS task data were needed to construct local movement field ellipses and conduct our standard vector-matched data segregation. Vector-matching was critical to ensure a fair analysis of neuronal modulation as a trial progressed; it was the only way to ensure that changes in neuronal modulation over the course of a trial would be related only to elapsed time or number of saccades made, and not to potential confounds such as a propensity to make different vectors of saccades as a trial progressed.

Figures 30A and B show data from an example neuron. Its saccade-related activity varied in the FS task as a function of both elapsed time from the onset of trial (Fig. 30A; R = 0.93, P=0.04) and sequential number of vector-matched saccades (Fig. 30B; R = 0.91, P=0.01). Activity modulation was correlated with neither factor, however, in the VS task (R = -0.04, n.s.d.

for time; R = -0.3, n.s.d. for sequential number; all correlation analyses in this section are Spearman's tests). This example neuron was atypical. Overall, only a small fraction of the neurons showed a significant correlation between neuronal modulation and time or saccade number (Table 2).

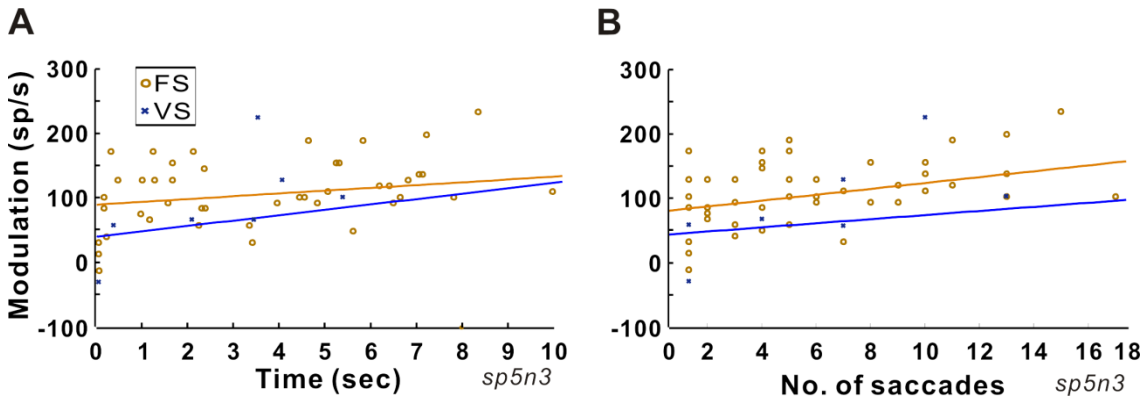

Figure 30: Example neuron showing the relationship between activity modulation and the proximity to the reward.

A) time or B) number of vector-matched saccades made, over the course of a trial. Both time and numbers of saccades made could be used by monkeys to predict when the reward stage of the task is nearing.

Table 2: Incidence of neurons with saccade-related modulation that varied over a trial

	Time		No. of Saccades	
	VS	**FS**	**VS**	**FS**
Ep. 1	4% (1/25)	12% (3/25)	12% (3/25)	4% (1/25)
Ep. 2	4% (1/25)	12% (3/25)	4% (1/25)	12% (3/25)

Numbers show percentages and, parenthetically, fractions of tested neurons having significant correlations between saccade-related modulation (measured in Ep. 1 or Ep. 2, rows) and time or number of saccades during a trial, for the VS and FS tasks (columns).

3.3.6 Other potential factors influencing task-dependent modulations

It is possible that other factors may have covaried with the four tasks and contributed to the pattern of task-dependent results that we found in previous sections. Saccadic peak velocity, for example, varies with behavioral context (Becker and Fuchs 1969; Bon and Lucchetti 1988). No previous studies to our knowledge have directly compared peak velocity across the four tasks that we used, but from a review of the literature it seems clear that the major task component that influences peak velocity is the presence or absence of a visual target. Velocities of saccades in VGS tasks are markedly higher than those in MGS tasks (Becker and Fuchs 1969; Smit et al. 1987), and similarly, velocities of scanning saccades made to lighted scenes are markedly higher than those made in dimness or darkness (Becker and Fuchs 1969; Bon and Lucchetti 1988). If our neuronal modulations had pointed toward a dependence on sensory context, we would have suspected peak velocity to be a confounding factor. But the modulations were more related to instructional context, which makes a relationship to peak velocity less likely, we think. We will conduct a thorough analysis of peak velocity as a covariate, but it is a nontrivial issue and, we think, unlikely to reveal positive results. A major methodological problem is the difficulty in correctly identify peak velocities of scanning saccades made in the absence of visual structure (as in our FS task); the velocity profiles of such saccades tend to be irregular (Becker and Fuchs 1969). We are currently evaluating whether to use the raw velocity traces in the FS task or replace them with Gaussian fits.

3.3.7 Patterning of scanning saccades

Patterning of scanning saccades during tasks similar to our VS task was observed previously (Desrochers et al., 2010; Richardson et al., 1994; Sommer 1994; Sommer 1997). Whether patterns of saccades occur in scanning tasks to featureless scenes (as in our FS task) has not been reported to our knowledge. We studied patterning by averaging the initial eye positions of scanning saccades within $4^{o} \times 4^{o}$ pixels (Fig. 31-32). In Figure 30, average initial eye positions measured in the VS (left) and FS (right) tasks, for all three monkeys that we tested, are displayed. In the VS task, eye positions tended to cluster around the nine spots, because the animals tended to make saccades from spot to spot. In the FS task, however, no such clustering was observed even though the eventual target would appear at one of the same nine positions. Hence the monkeys seemed to spend their time in the FS task making exploratory saccades that were not even influenced by memories or predictions of target locations. Individual monkeys may have different habits with respect to making sequential saccades, and therefore we looked at the data for each monkey individually as well (Fig. 32). Again, we found the expected nine clusters in the VS task, but no such clusters in the FS task for all three animals.

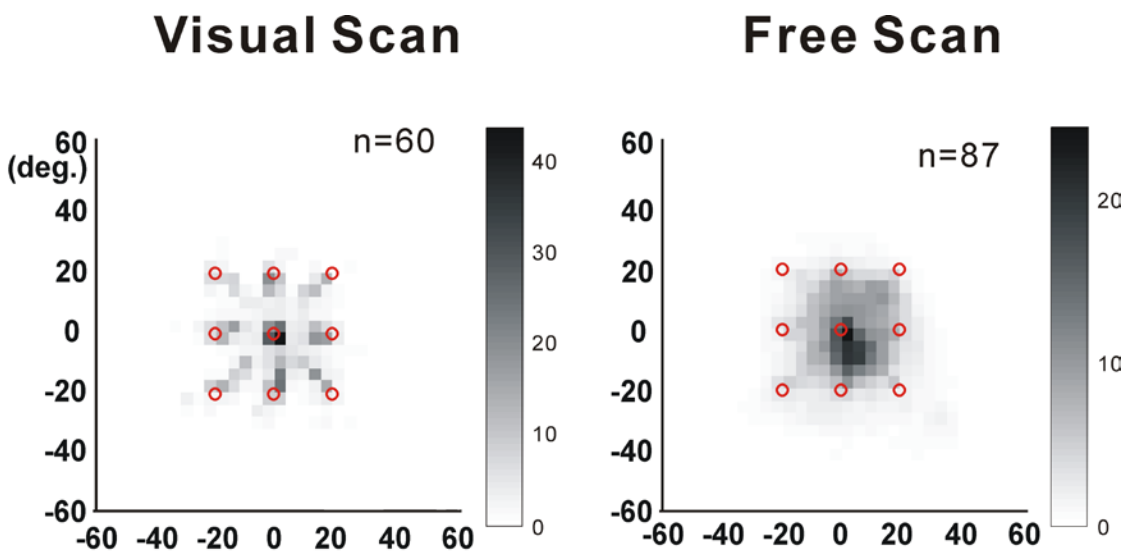

Figure 31: Average numbers of fixations over space for all three animals together

Red circles represent the (possible) location of actual visual spots on the screen. n is number of sessions pooled for the data shown. Thermal scale indicates number of initial eye positions found in each pixel of space.

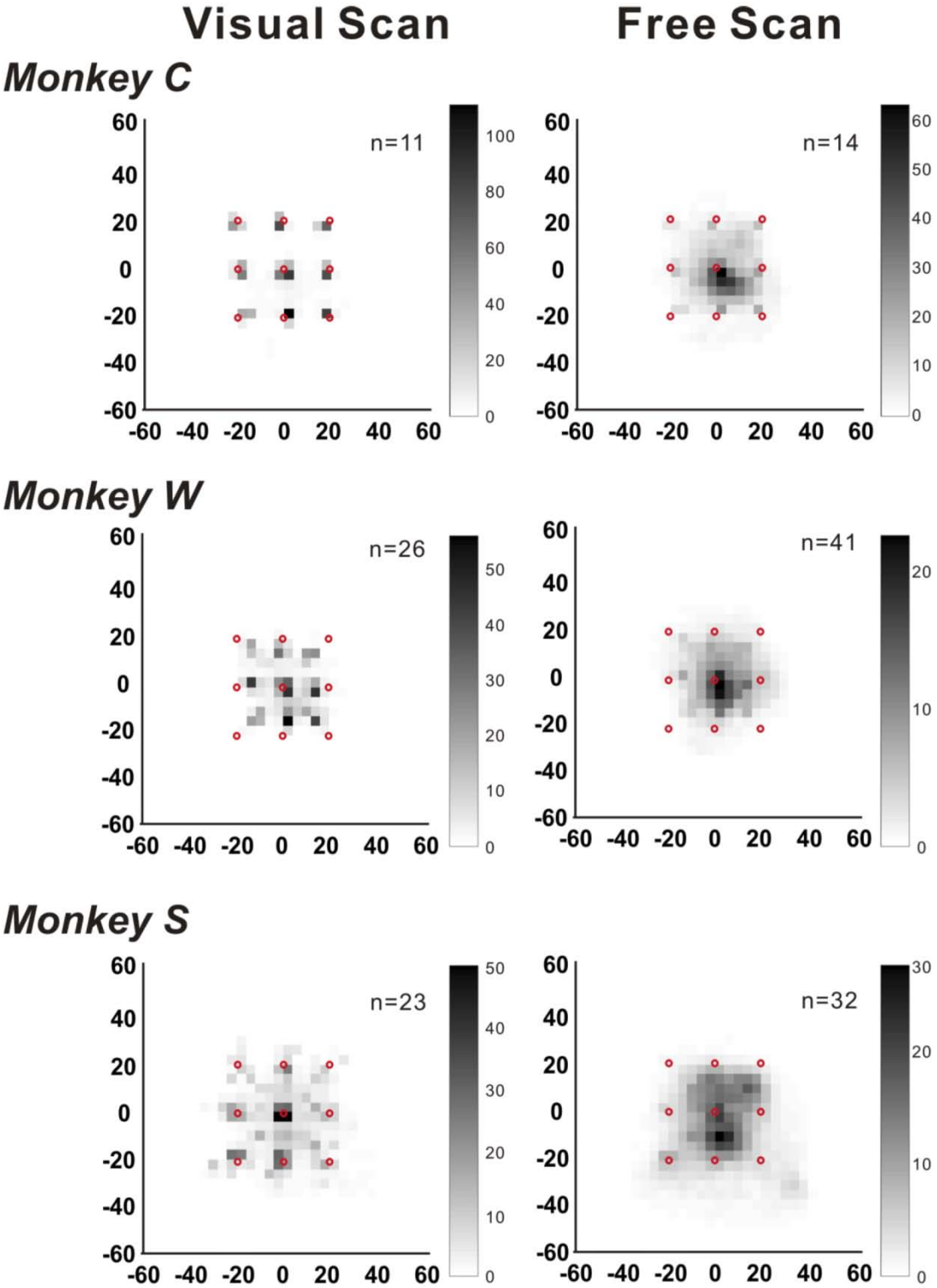

Figure 32: Average numbers of fixations over space for each of three animals

Same as in Figure 31.

3.4 DISCUSSION

3.4.1 Pallidal Neurons Are Modulated by Task Context

One of the main findings of this work is that for many pallidal neurons, activity modulations around saccade onset vary depending on the task context of the saccade. The baseline proportion of pallidal neurons modulated during saccades in any of four tasks was relatively small (21%, 96/451) compared with the proportion evaluated in a previous report of task-dependent modulation in basal ganglia (32% of SNr neurons tested with MGS and VGS tasks; Hikosaka and Wurtz 1983a,c). Nevertheless, for these pallidal neurons, peri-saccadic activity and its task dependency was prominent.

Perisaccadic activity modulation of pallidal neurons was assessed in four task contexts. More neurons were modulated during instructed tasks (VGS and MGS tasks) than in non-instructed, scanning tasks (VS and FS), and the strength of modulation was stronger in instructed tasks than in scan tasks. Between sensory driven vs. non-sensory driven conditions (VGS vs. MGS, VS vs. FS), in contrast, activity modulations were not significantly different. Hence the contextual factor that affects peri-saccadic modulation of pallidal neurons seems to be the presence or absence of instructions as to where and when to move, not the presence or absence of concurrent sensory input. Strikingly, the instructional dependence was exactly opposite to that expected if the basal ganglia are specialized for voluntary movements. As a rule, pallidal neurons were more active during instructed tasks than during tasks in which monkeys were free to make

saccades at will. Hence our results argue strongly against the general hypothesis that basal ganglia are preferentially involved in voluntary motor control.

An influence of instructional context on cerebral cortical function has been described previously. For example, M1 is regarded as the cortical command center of motor execution (Sherrington 1906). It is known to receive two categories of inputs (Passingham 1987): afferents that contribute to self-instructed voluntary action, from the basal ganglia and prefrontal cortex via pre supplemental motor area (preSMA; Picard and Strick 1996), and afferents that assist sensory-driven action, from early sensory areas via parietal cortex and lateral premotor area (Rizzolatti et al. 1998). In Passingham's work, at the population level more neurons encoded saccade-related signal in instructed conditions, as we found for globus pallidus. He also found, however, a minority of neurons that showed preferential or, at least significant, modulation during non-instructed scan tasks. In general it could be that the neurons we found in globus pallidas may ultimately subserve self-instructed eye movements at the level of cerebral cortex.

Our pallidal neurons related to saccades and task context were located in a small region of the dorsolateral part of caudal GPe and GPi. Anatomical connectivity of this region is not well understood, compared to the central parts of GPe and GPi that are known to be involved in skeletal motor behavior and the ventral portion known to be involved in limbic function. It would be helpful to know the efferent and afferent connectivity of the regions to better understand the possible functions of the neuronal modulations that we found.

Some neurons showed shifts in their movement field hotspots when we studied them in the scan tasks. The hotspot mismatches between tasks were unlikely to be artifacts of inaccurate initial mapping of movement fields at the very start of studying a neuron. We carefully mapped out the movement field centers before starting any formal data collecition, using alternating

series of target directions and amplitudes. The shift of hotspot between instructed and scan tasks was observed in only small number of neurons, and when it happened, the general area was greatly overlapped with only a modest change in the location of hotspot. Still, a systematic study of these task-depending movement field shifts would an intriguing topic for future work. They could be related to the shifts in movement fields seen by Stanford and Sparks (1994) between VGS and MGS tasks in the SC. In the FEF as well, the tuning of response fields can be altered by task context, specifically during sequences of saccades compared to single saccades (Desrochers TM, personal communication).

3.4.2 SNr Neurons are Modulated by both Instruction and Sensory Input

In SNr, the instructional influence on activity seems to be even more profound than in globus pallidus. None of the SNr neurons that we recorded were modulated during our two scan tasks at all. This is in agreement with the negative results of Handel and Glimcher (2000) and Hikosaka and Wurtz (1983a). Even our strategy of including an end-of-trial target and reward did not seem to matter for SNr neurons; they simply do not modulate with scanning saccades. Unlike in globus pallidus, a clear sensory dependence of SNr peri-saccadic modulation also was found. More SNr neurons were modulated in the VGS task than in the MGS task, and stronger modulations were observed in the VGS task than in the MGS task for the decreasing type of neurons which make up the majority of saccade related neurons in SNr. For the increasing type of SNr neurons, the same tendency (greater modulation for VGS than for MGS) was noticed, but it was not significant, possibly due to small number of data for the increasing type (n=4).

The pioneering report of Hikosaka and Wurtz (1985b) and follow-up study (Basso and Liu, 2007) did suggest a preference for the involvement of SNr in the MGS over the VGS task. Why the apparent discrepancy between their studies and the present one?

In the first study, the conclusion was based on the assumption that the SNr population with saccade related activity plays its major role in saccadic control through its projection to the SC. This was supported by experiments in which about half (45%, 29/65) of saccade related neurons found in the SNr were antidromically activated from the intermediate, saccade-related layer of the SC (Hikosaka and Wurtz 1983d). The conclusion was further supported by the observation that when SNr was inactivated by muscimol (and thus SC was disinhibited), behavioral deficits were more severe in the MGS task than in the VGS task. However, there are two points to keep in mind before we draw such a conclusion. First, even with more spotlight on data from the MGS task, the fractions of neurons that were modulated during saccades in the VGS task (32%, 50/155; Hikosaka and Wurtz 1983a) and in the MGS task (32%, 41/128, MGS; Hikosaka and Wurtz 1983c) were actually the same. Second, some 55% of visuo-saccadic neurons that they encounterd in the SNr could not be demonstrated as projecting to the SC. What about those neurons? Some of them undoubtedly project back to cortex via thalamus (especially to FEF, Lynch et al. 1994). Also, the nigrothalamic and nigrotectal populations are segregated, at least in rodents, but are basically the same morphological types (Grofova et al. 1982). Hence they would likely have similar neuronal properties in extracellular recording. Therefore it is possible that many of the remaining 55% of neurons were nigrothalamic projection neurons. In this study, we did not select neurons to record based on their projection but instead recorded all neurons that we encountered. My SNr population therefore may include both nigrotectal and nigrothalamic neurons. It is still a mystery whether the neurons that do not project to SC, and yet

are related to visuo-saccadic behavior, influence the FEF via thalamus. This would be one of the primary follow-ups to the work presented here.

In the later study done by Basso and Liu (2007), electrical stimulation during saccades in SNr neurons showed greater change in saccade vector direction and probability of saccade initiation for the MGS task than for the VGS task. One issue with a causal study like this one, or the above one that used muscimol injection, is that the manipulation may influence entire sets of neurons in the affected region. In SNr, there are increasing and decreasing neurons with a variety of profile of visuo-saccadic activities (i.e., various combinations of visual, saccade, delay activity with two valences of signals). Therefore, causal manipulation of the SNr seems hard to interpret.

3.4.3 Temporal Proximity between Peri-saccadic Modulation and Reward was Not Correlated

To rule out the possibility that varied neuronal modulation by context was due to differences in reward schedule between instructed and scan tasks, not due to instruction context itself, we analyzed the correlation between neuronal modulation and the proximity to reward. The analysis was done for the saccades with the same vectors. Proximity to reward was represented in two ways: elapsed time and saccade number. In both measures, there was no correlation observed in majority of neurons. Hence the influence of reward contingency was not major factor for overall modulation.

3.4.4 Eye Position Did Not Influence Neuronal Modulation

Many saccade-related brain areas show initial eye position-dependent modulation of visuo-saccadic activity (e.g., LIP, Andersen et al. 1990; SC, Campos et al. 2006). Since pallidum and SNr are connected to those areas directly or indirectly, it seemed possible that eye position might matter. Our analysis revealed that peri-saccadic modulation of neurons in globus pallidus and SNr were hardly modulated by eye position. In only 1 GPe and 1 SNr neurons, eye position dependent modulation was observed.

3.4.5 Patterning of Sequence of Saccades Did Not Occur During FS Task

It has been known that animals may settle into patterns in their sequences of saccades during VS tasks, with or without instructions (Descheros 2010). However, whether the patterning of saccades also occurs in free scanning of a featureless screen (i.e., FS task) was not known. Therefore, in separate analyses, we investigated the question by examining the clustering of initial eye positions. We found that in FS such patterning or habitual sequencing is not observed.

In most cases, we ran FS task first and then VS next. For the cases when the VS task occurred first (n=6) it is possible that the monkey could have held in memory the nine array locations, or relied on saccadic patterns in previously run VS trials and continued those same patterns during the FS task. Our data indicated that this was not the case. Therefore, unlike the patterning of saccades observed in the VS task (Descheros 2010), animals did not form saccadic patterns in our FS task regardless of whether it was run before or after VS. This was probably because it is difficult to establish reference points on the blank, featureless screen.

3.4.6 Limitations and Potential Confounds

The preferences that we found for instructed tasks may have been due to the way we characterized neurons: we first mapped out response field with the MGS task. Due to time constraints (it takes more than an hour to run all four tasks), sometimes we stopped recording a neuron and moved on to find a different one if the neuron showed no signs of activity modulation during eye movements (judged either by online examination of neuronal activity raster or by listening to the neuronal signal through a speaker while the animal made spontaneous saccades). But other times, we recorded neurons even when they did not show any peri-saccadic activity modulation in the MGS task (25 GPe; 13 GPi; 16 SNr). Among them 6 GPe and 3 GPi showed activity modulation exclusively either during VS or FS (but not in MGS or VGS). Therefore, I think these possible explanations of our results are unlikely.

Inspired by the previous negative results for spontaneous saccades made without reward (Handel and Glimcher 2000; Hikosaka and Wurtz 1983a), we designed our scan tasks with the opportunity for the monkey to earn reward on every trial. The reward was provided after the monkey scanned for a while and then made a saccade to a covertly baited target (VS task) or a suddenly appearing dim target (FS task). In this way the animal's motivation level was maintained and they usually made brisk eye movements. Nevertheless there were differences in reward contingency associated with scanning saccades as compared with the instructed saccades collected in our MGS or VGS tasks (which were rewarded much more frequently in terms of time and numbers of intervening saccades). This may be a factor in the low level of modulation in scan tasks compared to instructed tasks. Our tests of correlation between neuronal modulation and time or saccade number revealed little evidence that neurons were sensitive to reward expectancy during scanning, however, so we doubt that this confound was a major factor. To

better isolate trial-by-trial influences of reward contingency, it may be useful in future studies to implement biased reward tasks (e.g., Sato and Hikosaka 2002) or tasks with pseudorandom reward schedules (e.g., as in Pasquereau et al. 2007).

4.0 SUMMARY AND CONCLUSION

4.1 GLOBUS PADLLIDUS NEURONS ARE ACTIVE DURING VISUO-SACCADIC BEHAVIOR

The emphasis of nearly all previous research on the oculomotor role of basal ganglia has been on the caudate-SNr-SC pathway and its disinhibition mechanism. The SNr has been generally regarded as the main oculomotor center and output station of the basal ganglia. This view has been supported by a plethora of evidence from neuronal recording, pharmacological manipulation and clinical reports. Meanwhile, a few recording experiments done in GPe and GPi and clinical studies accomplished with deep brain stimulation in GPi in Parkinson's patients hinted at a new view: the oculomotor role of basal ganglia may involve more nuclei and pathways than previously thought.

The early evidence that GPe and GPi may have oculomotor functions was intriguing, but two fundamental questions remained. What exactly are the characteristics of visual-saccadic signals in GPe and GPi? And how do they compare with the signals in the more well-known SNr? These two questions were the jumping off point for this dissertation project. By recording from GPe and GPi and comparing the results from SNr in the same monkeys, we obtained a host of results that are summarized as follows and are discussed below: 1) neurons in both segments of globus pallidus are modulated in a standard oculomotor (MGS) task and the activity change,

an increase or decrease relative to the high firing rate baseline, is linked to visual stimulation, delay period, saccade generation, and/or reward; 2) GPe and GPi neurons have different distributions of signals (GPe more visual; GPi more reward-related), with GPe resembling a sign-inverted SNr; 3) Saccade-related signals are comparable in all three structures; 4) Response fields become less lateralized and more omnidirection as events proceeded from visual onset to saccade initiation to reward delivery, at least in GPe where we had enough data to test this thoroughly.

In Chapter 2 we reported that myriad visuosaccadic signals are present in both GPe and GPi. The distribution of signal types differed between the two nuclei in interesting ways, however. In studies of the basal ganglia during skeletal motor behavior, movement related signals in GPe and GPi have been described as similar to the extent that investigators routinely pool their GPe and GPi data (e.g., Turner and Anderson 2005; Mitchell et al. 1987). In agreement with that previous work, we found that activity linked to saccadic eye movement initiation was similar between GPe and GPi (leading us to often pool those data in Chapter 3), but we found marked differences in visual and reward signals. This distinction in signal content between GPe and GPi and the exclusive resemblance between GPe and SNr imply specific differences anatomical connectivity. A simple prediction is that neurons with visual and reward activity in GPe project to SNr, but not to GPi. The apparent sign reversal from GPe to SNr is consistent with the GABAergic nature of GPe neurons. GPe's high incidence of visual activity may come from visual activity in the caudate (Kato and Hikosaka 1995) or projections from the STN which receives visual inputs from cortical areas (Matsumura et al. 1992). The functional isolation from GPe and SNr, lack of visual activity, and abundance of reward activity suggests a unique oculomotor role for GPi. There is no trans-thalamic pathway from the dorsolateral and

caudal portion of GPi (where we found oculomotor related signals) directly to eye movement areas of cerebral cortex such as the FEF. We speculate that the GPi may not contribute to the direct control of saccade generation. Its signals and anatomical connections suggest, instead, that it may participate in the integration of oculomotor and skeletal motor signals (essentially, "eye-hand coordination"). Recently, a series of studies discovered that a subset of neurons in GPi send reward related signal to the lHB, a subcortical center that represents negative reward. Since we did not identify neuronal connectivity between our sample and the lHB, whether our sample included such projection neurons is uncertain. Still, the abundance of reward anticipatory activity that we found adds another piece of evidence supporting the role of GPi in reward mechanisms.

We observed that the response fields of our GPe neurons were tuned for early events of a trial (visual stimulation and saccade initiation), but gradually broadened in advance of reward delivery. This is different from findings in caudate and SNr where reward activity was combined with spatial information in performance of reward-biased directional task (Kawagoe et al. 1998; Sato and Hikosaka 2002). This difference between studies could be due to the different tasks, since reward had no spatial relevance in our experiment but was critically tied to spatial location the Hikosaka lab studies.

In summary, our Chapter 2 results provide evidence that GPe and GPi are not just bystanders in the realm of eye movement control. The caudate-SNr pathway clearly has an important oculomotor function, but from our work it is now clear that the other output station of the basal ganglia, the GPi, is likely to play some role as well. The presence of diverse eye-related signals in the GPe, a profusely connected nucleus and the mediator of the indirect pathways, suggests that oculomotor control may in fact be a widely distributed basal ganglia function.

4.2 PERI-SACCADIC ACTIVITY MODULATION OF GLOBUS PALLIDUS NEURONS IS INFLUENCED BY VOLUNTARY CONTEXT

Compelling evidence has supported the hypothesis that the basal ganglia are preferentially involved in the control of voluntary movements. Clinical observations of basal ganglia patients showed impaired generation of voluntary movements with relatively intact sensory-guided movements. There have been many attempts to study and explain this aspect of basal ganglia disease. Neuronal recording studies reported greater modulation in the SNr (Hikosaka and Wurtz 1983a), globus pallidus (Yoshida and Tanaka 2009), and caudate (Watanabe and Munoz 2010) for saccades considered to be more voluntary than those elicited in comparison conditions. Pharmacological and electrophysiological manipulations showed results in agreement with the hypothesis. On the other hand, neuronal recording and causal experiments in the globus pallidus during skeletal motor behavior showed mixed results, and some failed to find such contextual difference in modulation (Inase et al. 1996; Kimura et al. 1992; Mink and Thach 1991a; Turner and Anderson 2005; van Donkelaar et al. 1999; 2000).

Studying the concept of volition in animals is difficult. I can state whether I am moving my arm willfully, and if I wonder whether you are making voluntary movements I can simply ask you. We cannot communicate like this with animals and therefore must infer what they are doing. Voluntary behavior must be defined operationally, that is in terms of observables that we can document and measure. Two operational definitions of voluntary behavior were used in previous work on monkeys, whether or not the definitions were explicitly stated: voluntary actions that are not sensory driven (made in darkness or to blank space) and voluntary actions that are not instructed (made spontaneously). The definitions get at distinctly different aspects of voluntary behavior, and from a practical viewpoint, both have pros and cons in the laboratory.

The study of spontaneous movements, for example, is confounded by issues of how to reward and how to motivate, or post-hoc how to take into account the effects of absent reward or lowered arousal. Our goal was to design a set of tasks that included both aspects of voluntariness. We sought to determine the relative influence of both possible contextual aspects -- sensory stimulation and instruction -- on peri-saccadic activity in the basal ganglia. We used four different tasks with different combination of two factors. To help reduce reward and reduced motivation as confounds, we made sure that all the tasks included a specific end-goal and chance for reward. We found that 1) saccade-related activity in the globus pallidus was often modulated differentially in the four tasks; 2) this modulation was more a function of instructed vs. non-instructed context than sensory vs. non-sensory context; and 3) the modulation was opposite from expected, showing higher activity for "non-voluntary" (instructed) movements.

For a comparison, we examined perisaccadic activity modulation in SNr for the four tasks. We found a major similarity plus a major difference from globus pallidus. The similarity was that neurons in SNr were modulated much more by instructed tasks than non-instructed tasks. In fact, we found no examples at all of SNr neurons modulated significantly in the non-instructed (scanning) tasks. The main difference was that in SNr, there was also a distinct sensory influence: modulation was greater for an instructed task that included a visual target (VGS task) than an instructed task that involved making saccades to a blank spot (MGS task).

Our findings were surprising in two ways. First, the very fact that neurons in globus pallidus were modulated by spontaneous saccades (VS and FS tasks) was striking. Neither we nor any previous investigators found such a result for SNr neurons (Handel and Glimcher 2000; Hikosaka and Wurtz 1983a). This is most likely a real difference between the globus pallidus and SNr. We had suspected that the lack of modulation for spontaneous saccades in previous SNr

studies was related to lack or reward or motivation, but we seem to have ruled that out by testing globus pallidus and SNr neurons from the same monkeys performing exactly the same spontaneous-saccade tasks. Moreover, those tasks involved both a reward and an end-of-trial goal to keep the animal motivated. Still the SNr neurons remained unmodulated.

The second surprise was a fairly clear refutation of the hypothesis that the basal ganglia are preferentially modulated for memory-guided saccades than for visually-guided saccades. This hypothesis was emphatically not supported in both globus pallidus and SNr. In globus pallidus, presence or absence of sensory guidance had little effect on perisaccadic modulation. Presence or absence of instructions was the distinguishing factor (i.e., externally instructed or self-instructed). The same was true for SNr, with results that were even stronger. The neurons were modulated only in instructed tasks, and while sensory effects were also important in SNr, their effects were opposite from the hypothesis (preference for visually-guided over memory-guided saccades).

4.3 CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, we found that neurons in GPe and GPi are modulated during a variety of events during eye movement tasks just as SNr are. This study is the first to examine basic oculomotor signals in globus pallidus and compare them with neurons in SNr. Neurons in all three structures showed differences in signal content suggesting different roles for each structure in saccadic eye movements. We also discovered that perisaccadic signals in globus pallidus vary with voluntary context and that the critical contextual factor is the presence or absence of instruction. In SNr, the modulation varied with both instructional and sensory context.

Future work is necessary on several issues. First, using antidromic and/or orthodromic stimulation to determine the signals carried by identified neurons in the structures is essential. We now know a lot about the oculomotor signals within the globus pallidus, but we know nothing concrete about how the signals are distributed to connected structures. For example, we inferred a tight relationship between GPe signals and SNr signals in our data, but stimulating the SNr while recording from antidromically activated neurons in the GPe could directly determine the signals conveyed in this projection. And we now know that both of the basal ganglia output nuclei, the GPi and SNr, carry oculomotor signals. But where do those signals go exactly? It is well understood that some of the SNr signals go to the SC, but the SNr also projets to thalamus to influence cortex. Does it send the same signals to thalamus as it does to the SC? This could be tested by recording from SNr during antidromic activation of thalamus. And the influence of SNr on cortex could be tested, at least in part, by recording from an oculomotor area like the FEF while stimulating the SNr (we actually did a pilot study of this experiment, but the data were not included in this dissertation).

Second, with a growing body of evidence showing the role of the basal ganglia in reward, follow-ups to our work should explicitly manipulate reward delivery or expectation to determine if this influences the signals we reported here. The Hikosaka laboratory (Bromberg-Martin et al.2010; Hikosaka et al. 2008; Hong and Hikosaka 2008) discovered that GPi provide a reward-related source signal used by the lHB which in turn provide inputs to SNc. With advances in optogenetic techniques, one can manipulate dopaminergic signals in a spatially and temporally controlled manner in rodents (Kravitz et al. 2010; Kravitz and Kreitzer 2011) and this may be available soon in primates (Han et al. 2009). Given the critical relationship between dopamine and basal ganglia function in health and disease, I think that characterizing the relationship

between dopamine signals and affected single neurons during specific motor behaviors (including saccades), in various environmental contexts (including voluntary vs. non-voluntary), and in different animal models (including monkeys) will be crucial for further advances in establishing the role of basal ganglia in the control of movements.

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