Chapter 1.

Introduction

1.1 General Introduction

We live in a world that is rich in visual stimuli, and we are able to generate appropriate motor responses to these stimuli. For example, we direct an eye movement toward a blinking fire alarm and an arm reach toward a glass of water. The ease with which we interact with visual stimuli is a significant achievement when we consider the overwhelming amount of visual information that our brains receive. Most visual environments are complex and constantly evolving: many elements are static, but some appear, disappear, or move about. In addition to these changes in the visual environment, the image of the world constantly shifts on our retinas as we move our eyes to explore our surroundings. With so many things happening concurrently, it is a remarkable that our brains have no trouble accurately tracking the spatial locations of objects in the visual environment.

We make rapid eye movements, also known as saccades, in order to explore a visual scene. We use saccades to direct our fovea, the area of the retina with the densest collection of photoreceptors, toward specific parts of the visual scene in order to examine them in greater detail. While saccadic eye movements allow us to foveate different objects, they also pose a significant challenge to spatial accuracy. The eye moving in the orbit and objects moving in space both create motion on the retina. When the eye moves, the spatial location of all objects remains constant. In contrast, when objects move, their spatial locations change and subsequent motor response trajectories to those objects must

reflect this change. How then does the brain differentiate between these two types of movement and appropriately update the spatial representation of visual objects?

For centuries, scientists puzzled over how the human brain knows when changes in the image on the retina result from volitional eye movements. In 1629, Descartes, in his Treatise on Man, noted that there was a difference in the stability of the visual scene when he moved his eye by self will, as opposed to when he deflected his eye by pushing on it: motion on the retina was the same in both cases, yet visual perception differed. Descartes inferred that there must exist a fundamental physiological difference between voluntary and involuntary eye movements. His inference hinted at the neural mechanism that underlies spatial accuracy: the brain generates an internal signal during volitional eye movements that is absent when the eye is moved passively or when the images of objects move actively across the retina.

We now know that in order to solve the problem of spatial accuracy around the time of a saccade, merely processing the stimuli that appear on the retina is insufficient. To solve this problem, the oculomotor system also monitors two 'extraretinal' sources of information about the eye movement: corollary discharge and oculomotor proprioception. Corollary discharge, also known as efference copy, is an internal copy of the motor command to the eye that is sent to other regions of the brain to alert them of the impending movement. Predictive saccade-related information is available via corollary discharge before volitional eye movements occur. Oculomotor proprioception, on the other hand, provides an eye position signal generated by the stretching or contraction of the extraocular muscles, and is only available after the eye movement. In order to explain spatial accuracy, we must consider mechanisms that do not exist solely at level of the

retina, but which utilize these extraretinal signals to compensate for the disruptive effects of saccades.

There are currently two widely accepted models that have been used to solve the problem of spatial accuracy despite a constantly moving eye: shifting receptive fields (Duhamel et al., 1992) and gain field coordinate transformations (Andersen et al., 1985a; Zipser and Andersen, 1988; Andersen, 1997). While both mechanisms process retinal and extraretinal signals to encode the location of saccade targets in space, they solve this problem in different ways. The shifting receptive field model postulates that the brain preserves visual information in retinal coordinates. In this model, the brain monitors the eye movements that divide the acquisition of each static retinal image and uses this information to localize each snapshot in a 'retinotopic' map of space. The gain field model solves spatial accuracy in a different way: it suggests that the brain maintains an accurate representation of objects in space by transforming the locations of objects on the retina into their locations in absolute space. This 'spatiotopic' map of space would therefore be invariant to changes in eye position and the motion of objects on the retina.

Regardless of the underlying mechanism, our ability to compute the spatial location of visual objects accurately across eye movements confirms that the brain has access to an internal representation of visual space that consists of more than a single retinal image at a time. Oculomotor behavior, such as viewing an array of targets and making sequential saccades to them after they have disappeared, requires that sensory stimuli be encoded in a higher-order spatial map across saccades. Thus, creating and maintaining an accurate map of objects in the environment is the first step to generating appropriate motor responses and interacting with those objects.

The process by which sensory stimuli are converted into motor commands is known as a 'sensorimotor transformation'. In the transformation process, sensory information, such as a spot of light or a noise, is converted into a motor command signal to react to the stimulus. This process is essential to any biological organism that possesses the ability to react to the environment. We can direct our eyes toward a ball when it is thrown at us, we can reach for an apple that is hanging from a branch, and we can turn our heads to localize the origin of a loud bang. The ease with which we transform sensory stimuli into appropriate motor responses belies the complexity of accurately encoding the spatial location of an object of interest.

Coordinating eye movements toward objects in space is perhaps the most common type of sensorimotor transformation. We live in a world that offers an abundance of visual stimuli. Nevertheless, we easily make accurate eye movements to the visual targets of our choosing and we rarely lose track of where our eyes are relative to a point of interest in space. Coordinating eye movements to visual stimuli is less computationally challenging than coordinating most other types of movements: visual information arrives in the same eye-centered frame of reference in which saccades are performed. Therefore, understanding how the brain coordinates accurate eye movements to targets in space is a fundamental question in sensorimotor transformation theory. Additionally, any model that seeks to explain the sensorimotor transformation process should at least be able to predict oculomotor behavior to visual stimuli accurately.

In this chapter, I will begin by reviewing the signals that alert the brain about eye movements: corollary discharge, oculomotor proprioception and visual reafference. I will examine the pathway by which each of these signals reaches the cortex and summarize a

few experiments that highlight the role of each signal in visual perception and oculomotor control. I will then review the two models, shifting receptive fields and the gain field coordinate transformation, that have accumulated the most evidence supporting their role in maintaining spatial accuracy around the time of a saccade. Finally, I will end with a selective review of experiments conducted in the lateral intraparietal area (LIP). I will cover the anatomy of LIP and nearby structures in the intraparietal sulcus (IPS) and describe the role of LIP in oculomotor control, the allocation of attention, and higher-level cognitive processes.

1.2 Signals that contribute to spatial accuracy

Around the time that a saccade is executed, the brain receives three signals that reflect the eye movement: corollary discharge, oculomotor proprioception and visual reafference. These three signals all report that an eye movement has been made, but each signal utilizes its own pathway and conveys unique information regarding the saccade. I will discuss how the brain receives and processes each of these three eye position signals, and how each signal contributes to the visual perception of target locations and the coordination of subsequent eye movements.

1.2.1 Corollary discharge

Corollary discharge, also referred to as efference copy, is a copy of a movement command that instructs other brain areas to anticipate the impending movement. Early philosophers, such as Descartes, realized that there was a fundamental difference between moving the eye voluntarily, by self will, and moving the eye passively, by pushing on the

eyeball. The Dutch scientist Aquilonius concluded in 1613 that “an internal faculty of the soul perceives the movement of the eye”. In the 19th century, Helmholtz postulated that a copy of the eye motor command, which he called the ‘effort of will’, fed back to sensory systems to compensate for changes in the visual representation that arise as the result of eye movements (Helmholtz, 1962).

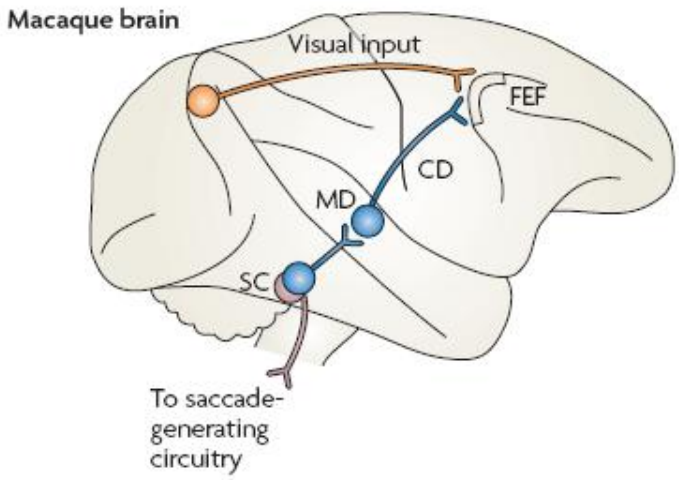
Scientists now refer to this effort of will as corollary discharge or efference copy. The term ‘corollary discharge’ was coined by the neurophysiologist Sperry in 1950 (Sperry, 1950). To demonstrate this concept, Sperry surgically rotated the eyes of fish by 180 degrees. He noticed that these fish swam in circles and concluded that the resultant behavior was caused by a dissonance between the retinal and kinetic signals associated with the perceived motion. When fish with rotated eyes swam forward, the retinal slip was in the same direction as the corollary discharge, leading to accentuated retinal motion and circling behavior. When fish with normal eyes swam forward, the retinal slip was cancelled out by a corollary discharge that anticipated the forward motion, leading to normal behavior

The term ‘efference copy’ was coined by von Holst and Mittelstaedt in the same year (von Holst and Mittelstaedt, 1950). They demonstrated paradoxical movement in flies during an optokinetic response task, behavior which they attributed to a mismatch between efferent and afferent signals. I will, for the sake of consistency, use the term corollary discharge in my discussions of the signal. Although the two terms are often used interchangeably, corollary discharge is more appropriate for the topics that I will address: efference copy implies a copy of the output closer to the muscles, while the neuronal mechanisms related to spatial accuracy are closer to the cortical level of the

nervous system. Regardless of the nomenclature, corollary discharge has been well studied and is thought to play a major role in visual perception and the coordination of saccades.

Across the animal kingdom, corollary discharge is a ubiquitous strategy for distinguishing between sensory input due to self-motion and sensory input due to changes in the environment (Crapse and Sommer, 2008). Corollary discharge pathways have been well studied in simple organisms, such as the nematode C. elegans. Corollary discharge helps these creatures differentiate between the approach of a predator in the water, which elicits a withdrawal reflex, and self-propelled forward motion, for which the withdrawal reflex is suppressed (Chalfie et al., 1985; Rankin, 1991). Similar experiments have been conducted in tadpoles, crickets, lobsters, birds and monkeys. Perhaps the best studied and understood corollary discharge pathway in the primate brain, both anatomically and functionally, is the circuit that carries corollary information about saccades.

When the brain computes the motor command for an eye movement to a retinal location, it also generates a corollary discharge signal (Figure 1.1). The retinal location of the saccade target passes through the lateral geniculate nucleus (LGN) of the thalamus and arrives in striate cortex (V1). From V1, saccade information is distributed to two extrastriate areas: the lateral intraparietal area (LIP) of the posterior parietal cortex and the frontal eye fields (FEF) of the dorsal frontal cortex (Wurtz, 2008). These two areas work in concert to select the spatial location of the subsequent eye movement. From these two brain regions, saccade information descends to the superior colliculus (SC) in the midbrain and splits. The motor command signal proceeds to the midbrain and pontine reticular formation, which project to the oculomotor nuclei that control the extraocular



Adapted from Crapse and Sommer, 2008

Figure 1.1. A corollary discharge pathway in the macaque brain. Corollary discharge splits from the motor signal in the superior colliculus (SC) and travels through the medial dorsal (MD) nucleus of the thalamus to the frontal eye fields (FEF).

muscles. The corollary of the motor command is redirected back toward the FEF through the medial dorsal (MD) nucleus of the thalamus (Lynch et al., 1994; Sommer and Wurtz, 2002). The evidence that this pathway carries corollary discharge and the effects of blocking conduction along this pathway will be discussed in the shifting receptive field section (section 1.3.1).

The role of corollary discharge in visual perception was made clear by a number of experiments. In a set of paralysis experiments, subjects were partially paralyzed using curare (Stevens et al., 1976). When asked to make an upward eye movement, all of the subjects reported seeing the world "jerk" or reappear above its original spatial locus and fading of the image over time. The illusory motion was presumably a result of the discrepancy between corollary discharge, which prepared the visual system for the impending eye movement, and the actual saccade, which fell short of the expected goal due to the paralysis. Another set of experiments helped to explain the perceived motion of the world when the eye is passively moved by pushing the eyeball. This effect was believed to result from displacement of the eye without the corresponding corollary

discharge. Bridgeman and Stark showed that pushing the eye actually resulted in minimal displacement of the eye and that the perceptual effect was in the direction opposite the force applied (Stark and Bridgeman, 1983; Bridgeman and Stark, 1991). They concluded that the perceived motion resulted from the corollary discharge that countered the force applied to the eye, rather than from passive rotation of the eye. The results from these experiments demonstrated that corollary discharge shifts the visual scene in preparation for an eye movement, and when there is a dissonance between the command signal, represented by the corollary discharge, and the actual eye movement, an illusory sense of motion is perceived.

It is well established that corollary discharge provides sufficient extraretinal eye position information for online computation for localization and action. The 'double-step task' (Hallett and Lightstone, 1976) has traditionally been used to show that the oculomotor system can calculate the endpoint of a saccade to a target that disappeared before an intervening saccade. In the double-step task, the subject first fixates a stable point of light. Then, two stimuli appear simultaneously, and the subject makes a sequence of saccades to the targets in the order designated by the stimuli (usually by color or shape). The first saccade moves the eye and creates a dissonance between the original retinal location of the second saccade target and the new vector of the saccade necessary to acquire it. This task requires an extraretinal signal to provide information about the first saccade, in order to update the trajectory required to acquire the second saccade target. When corollary discharge was blocked along saccade-generating pathways, the number of localization errors in the double-step task increased (Sommer and Wurtz, 2002, 2006). However, when afferent fibers from the extraocular muscles were cut,

monkeys did not show increased target localization errors in either the single or double-step saccade tasks (Guthrie et al., 1983). These experiments are often cited as evidence that corollary discharge provides sufficient information for accurate online visual processing for action.

1.2.2 Oculomotor Proprioception

The proprioceptive eye position signal is another extraretinal signal that can alert the brain of an eye movement. Unlike corollary discharge, which signals an impending eye movement, proprioception provides the other side of the coin: it signals a movement that has already begun or been completed. In the early 1900's, Sherrington hypothesized that "inflow", signals transduced by eye muscle proprioceptors, provides the oculomotor system with necessary information about eye position and movements (Sherrington, 1918). For many decades, researchers have debated the role of inflow in visual processing and computations for eye movements (Carpenter, 1988).

Despite extensive research on inflow theory, only putative proprioceptors in the eye muscles have been discovered. The primary candidates are muscle spindles and myotendinous cylinders (palisade endings). Muscle spindles, thin intrafusal fibers that lie in parallel with extrafusal fibers, are a primary carrier of proprioceptive information in human skeletal muscle. In extraocular muscles, however, there is a loss of normal spindle structure and density that jeopardizes their ability to monitor muscle activity (Ruskell, 1989). Palisade endings are a class of muscle receptor that is unique to the extraocular muscles. They are found in the distal myotendinous junction of human and monkey extraocular muscle, and consist of networks of fine neural filaments associated with

extrafusal fibers (Ruskell, 1978; Richmond et al., 1984; Buttner-Ennever et al., 2003; Eberhorn et al., 2005b; Eberhorn et al., 2005a). However, palisade endings are absent in infants from age 2 weeks to 4 years, which casts some doubt on their role as the extraocular muscles' primary proprioceptor (Bruenech and Ruskell, 2000). No one has yet succeeded in recording from either spindle or palisade fibers, and so the information they transduce is not certain. Golgi tendon organs, the other main sensory receptor in skeletal muscle, are not present in human extraocular muscle (Sodi et al., 1988).

Research on the afferent pathways has likewise yielded only speculative results. Experiments conducted using horseradish peroxidase (HRP) injections in monkey extraocular muscles found cell bodies labeled in the ipsilateral trigeminal ganglion (Porter et al., 1983) and suggest that afferent fibers travel from the oculomotor nerves to the ophthalmic branch of the trigeminal (V1). From the trigeminal ganglion, axons travel to the ipsilateral brainstem, and synapse in both the spinal trigeminal nucleus and cuneate nucleus (Porter, 1986). This work, however, has been contradicted by Wallerian degeneration studies, which question the ability of a relatively small population of myelinated fibers in V1 to carry sufficient proprioceptive information (Gentle and Ruskell, 1997). Stimulation of afferent fibers does, however, lead to a response in a large number of visual and oculomotor structures, including the cerebellum (Baker et al., 1972), the vestibular nuclei (Buisseret-Delmas et al., 1990), the abducens nucleus (Donaldson and Knox, 1991), and the superior colliculus (Donaldson and Long, 1980).

While the identities of the proprioceptors and the afferent pathways from the extraocular muscles remain uncertain, the existence of a proprioceptive representation of eye position in cortex is not. A proprioceptive eye position signal was discovered in area

3a of primate somatosensory cortex (Wang et al., 2007). This signal was modulated by the position of the eye in the orbit, and changes in neuronal activity persisted during eye deviation. Area 3a eye position cells encoded for all directions of eye position and were neither visually responsive nor related to direction of gaze in space. In a key experiment, one eye was transiently paralyzed using a retrobulbar block. Signal changes in the contralateral area 3a disappeared during paralysis and returned after the eye recovered, despite the persistence of corollary discharge throughout the experiment, thus proving the signal's proprioceptive nature.

The proprioceptive response in area 3a to a saccade task has two components, a phasic and a tonic response, which resemble the dynamic and static γ-motor firing patterns, respectively, of a fusimotor response (Taylor et al., 2006). While the tonic component appears to reflect eye position after some amount of time, it is not clear when this information becomes reliable. The area 3a eye position signal modulates other brain regions, such as primary motor cortex (Huerta and Pons, 1990) and the frontal eye fields (Stanton et al., 2005), and may subserve cortical function. Without knowing the time course of accurate eye position information, however, it remains difficult to speculate on the role of the area 3a proprioceptive eye position signal in visual and oculomotor processes.

The finding by Keller and Robinson that extraocular muscles lack a stretch reflex was at the time widely regarded as strong evidence that eye proprioceptors did not provide the brain with useful eye position information (Keller and Robinson, 1971). In the experiment, monkeys were trained to make several visually guided eye movements – saccades, smooth pursuit, and fixation. There were no significant changes, either

excitatory or inhibitory, in the firing rates of neurons in the ipsilateral abducens nucleus while the monkeys performed these tasks.

More recently, some researchers have begun to mount evidence that eye proprioception may play a role in visual perception, particularly in the localization of objects in space. Passive deviation of one eye using a scleral contact caused localization errors when subjects performed an open-loop pointing task using the unimpeded eye (Gauthier et al., 1990). Experiments in which the eye muscles were vibrated (Velay et al., 1994), an accepted way of stimulating muscle spindles (Goodwin et al., 1972), have shown similar mislocalization effects. In an interesting case, Lewis and Zee studied a patient with congenital trigeminal-oculomotor synkinesis, in which the left medial rectus muscle was innervated by the trigeminal nerve (Lewis and Zee, 1993). The patient was able to adduct his left eye by contracting the left lateral pterygoid muscle, thereby stimulating proprioceptive outputs independent of the normal efferent command. The experimenters found significant errors in open-loop pointing, further supporting the argument that oculomotor proprioception contributes to central processing for spatial localization.

Other experiments, however, have contradicted these findings. In a critical experiment, researchers artificially changed the position of a monkey's eye by stimulating the motor areas of the brainstem while the monkey prepared to make a saccade to a visual target. The monkeys were unable to compensate for the intervening saccade and made an inaccurate saccade to the visual target (Schiller and Sandell, 1983; Sparks and Mays, 1983; Sparks et al., 1987). When the experimenters stimulated the superior colliculus during the same task, monkeys were able to perform the task

correctly, presumably due to a corollary discharge signal. In a different set of experiments, when fibers carrying proprioceptive information were cut, monkeys had no trouble making open-loop arm movements to visual targets (Lewis et al., 1998). Similarly, when the extraocular muscles were paralyzed using botulinum toxin, human patients had no trouble performing open-loop pointing several hours after the injection (Dengis et al., 1998). Finally, in an experiment based on images fixed on the retina (afterimages), afterimages remained stable when subjects' eyes were moved passively in the dark, even though proprioceptive feedback should have reflected the change in orbital position (Bridgeman, 2007). All of these studies suggested that within minutes or even hours, there are no effects of altered proprioceptive eye position feedback on spatial targeting.

Early experimenters also speculated that proprioception was involved in online oculomotor control. In a classic experiment, experimenters passively rotated one of the subject's eyes in the dark using a scleral contact (Skavenski, 1972). Not only were subjects able to report the direction of the passive rotation, they were also able to counter the force and maintain fixation in the dark. Researchers found that in cats, sectioning the ophthalmic branch of the trigeminal nerve affects fixation stability in the dark (Fiorentini and Maffei, 1977), and retrobulbar injections of a paralytic drug reduced movements in both the ipsilateral treated eye and the contralateral untreated eye (O'Keefe and Berkley, 1991). Experimenters have also hypothesized that proprioception works in conjunction with corollary discharge to maintain the accuracy of saccades (Li and Matin, 1992).

More recent work argues that eye proprioception is involved in the long-term, parametric calibration of the efference copy signal, rather than the online control of

fixation, alignment and saccades (Lewis et al., 2001). In monkeys with vertical muscle palsies (super oblique, inferior rectus), ocular alignment and saccade conjugacy gradually worsened over several weeks after deafferentiation, but not when afferents remained intact (Lewis et al., 1994). The experimenters proposed that oculomotor proprioception is used to generate an error signal when perturbations to extraocular muscles produce a discrepancy between the efferent command and motion of the eye in the orbit. This error signal is probably negligible in normal animals, in which the efference copy and afferent feedback closely coincide with one another.

1.2.3 Visual reafference

The expression "reafference" (von Holst and Mittelstaedt, 1950) is used to describe shifts of the visual scene during eye movements. This is in contrast to "exafference", which is a result of displacement of the visual field of view. Distinguishing between reafference and exafference is a computational challenge for the visual system. Theoretically, when retinal motion occurs, the brain can couple visual signals with an extraretinal signal, such as corollary discharge or proprioceptive feedback, to classify whether the visual shift was the result of endogenous or exogenous motion. In the real world, however, full-field motion is commonly a result of eye movements and rarely a result of the entire world shifting. Thus, the visual system has developed a preference for visual information over extraretinal eye position signals, regardless of its accuracy.

A set of paralysis experiments clearly demonstrated the importance of visual reafference to visual perception (Matin et al., 1982). The extraocular muscles of subjects in the study were reversibly weakened through systemic injections of *d*-tubocurarine.

Subjects were tilted in a reclining chair until they reported the target, a point of light, appeared to be at eye level. In darkness, the visual system relied on inaccurate eye position information provided by corollary discharge and subjects subsequently mislocalized the visual target. In the presence of normal illumination, however, the corollary discharge was not corroborated by a visual reafferent. Thus, subjects identified that the visual target was stable in space and correctly localized the targets in the tilt task. In the lit environment, perception was controlled by vision, rather than an extraretinal signal. This result provided a clear perspective on the hierarchy of eye position signals: when both visual and extraretinal information are available, vision prevails.

This is not to say that visual input always provides accurate information regarding eye movements and the spatial locations of visual stimuli. Exogenous visual motion can provide powerful illusory evidence to the oculomotor system that self-motion has occurred, even in the absence of corroborating extraretinal cues. The Duncker Illusion separates veridical from perceived motion and is a classic example of the influences of visual motion on spatial perception. Subjects were presented a saccade target somewhere in the visual field and then asked to pursue a horizontally moving target against a uniformly moving background. After the pursuit, when subjects were instructed to make an eye movement to the location of the saccade target, they mislocalized the target in the direction opposite the background motion. When asked about the motion of the pursuit target, subjects reported that they followed the diagonal motion of the pursuit target, even though measurements of their eye movements revealed that their eyes accurately followed the horizontally-moving pursuit target. This effect has been observed in humans (Duncker, 1929) and Rhesus monkeys (Zivotofsky et al., 2005). Other experiments have

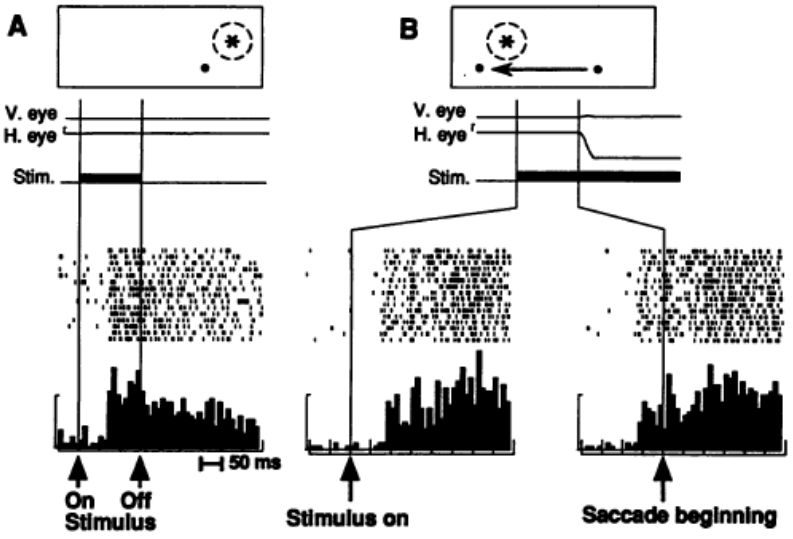
shown that visual perception can also be influenced by motion that is more subtle than the full-field motion presented in the Duncker Illusion (Whitney and Cavanagh, 2000). It is likely that the visual system as a whole continuously evaluates and integrates motion information present on the retina with the locations of visual objects in space; sometimes this evaluation is accurate, but not always.

1.3 Two models of spatial accuracy

Although spatial accuracy despite a constantly moving eye is a complex and challenging process to understand, behavioral, experimental and theoretical neurobiologists have made substantial progress in resolving the issue. While there have been many speculations and hypotheses regarding the mechanism underlying spatial accuracy, I will discuss the two most widely accepted and best understood models: shifting receptive fields and the gain field coordinate transformation. The shifting receptive field model, also referred to as receptive field remapping or spatial updating, postulates that visual information is processed primarily in a retinotopic manner: a series of retinotopic images are interwoven across saccades. The gain field model, on the other hand, suggests that visual information is transformed out of retinotopic coordinates into a spatiotopic coordinate frame that is invariant to changes in eye position. While there are some similarities between the two mechanisms, the fundamental principles by which each solves the issue of spatial accuracy are different.

1.3.1 Shifting receptive fields

The shifting of receptive fields around the time of a saccade is one mechanism that could solve the problem of spatial accuracy. Right before a saccade, the receptive fields of some visual neurons shift, or remap, to the spatial location that the receptive field will occupy after the eye movement (Figure 1.2). These neurons can be driven by stimuli in their current receptive fields, defined by the presaccadic eye position, or their future receptive fields, defined by the postsaccadic eye position. Shifting receptive fields were first discovered in LIP (Duhamel et al., 1992; Colby et al., 1996), but have since been demonstrated in FEF (Umeno and Goldberg, 1997, 2001; Sommer and Wurtz, 2006), SC (Walker et al., 1995), MIP (Batista et al., 1999a), and early extrastriate visual areas (Tolias et al., 2001; Nakamura and Colby, 2002).



Adapted from Duhamel et al., 1992

Figure 1.2. **Predictive remapping of a visual response in LIP. (A)** The response of an LIP neuron to a visual stimulus presented in its current, retinotopic receptive field. **(B)** The response of an LIP neuron to a visual stimulus presented in its future receptive field, prior to the onset of the saccade. The neuron fires robustly even though the stimulus is not yet in the retinotopic location of its receptive field (right).

In the macaque monkey, when a visual stimulus flashed in the future receptive field of an LIP neuron up to 150 ms before a saccade, cells responded as though the eye movement had already occurred. The predictive remapping of receptive fields to the postsaccadic eye position is dependent on both the presence of a visual stimulus in the future receptive field and the execution of a saccade. When a saccade was made in the absence of a visual stimulus in the future receptive field, or when a visual stimulus flashed in the future receptive field without the need for the monkey to execute a saccade, no predictive activity was seen (Duhamel et al., 1992).

The early response in the future receptive field of neurons demonstrates that the oculomotor system is aware of impending eye movements before they occur. Logically, the shifting receptive field mechanism must be driven by corollary discharge, since it is the only predictive source of saccade information; both proprioceptive feedback and visual reafference are available only after the eye movement. This was proven experimentally in a series of experiments by Sommer and Wurtz (Sommer and Wurtz, 2002, 2006; Crapse and Sommer, 2008). These experiments showed that as a monkey prepares a saccade, neurons in the medial dorsal (MD) nucleus of the thalamus send a copy of the saccade vector to FEF, and that the receptive field shift is synchronized with the MD discharge. As described previously (section 1.2.1), the SC-MD-FEF pathway conveys a corollary discharge signal. It is logical that if this pathway provides FEF neurons with saccade information for receptive field remapping, blocking it should reduce, if not completely eliminate, predictive activity in the future receptive field of FEF neurons. When Sommer and Wurtz injected muscimol into MD thalamus, they noticed that predictive activity in the future receptive field of FEF neurons was greatly reduced

(about 50%), while the response in the current receptive field was unchanged. This result proves that corollary discharge is responsible for the predictive remapping of receptive fields in FEF.

The shifting receptive field model provides a framework for disambiguating visual stimulation around the time of a saccade. When a receptive field shifts, an object in the future receptive field is represented by some level of activity. After the saccade, when the saccade restores the receptive field to its original retinal location and as reafferent visual information becomes available, the object is again represented by some level of activity. If the two levels of activity are congruent, then the eye must have moved correctly from one fixation point to the other. If the two levels of activity are different, then it could mean several things: an object may have appeared suddenly in the environment, the object that should have been brought into the current receptive field by the saccade moved during the saccade, or there is a calibration error in the oculomotor system.

How then does the shifting receptive field model solve the problem of spatial accuracy? When a saccade target is presented, the visual system records its retinal position. As the oculomotor system prepares to move the eye, a corollary discharge of the saccade vector is generated. The corollary discharge signal shifts a set of receptive fields to their postsaccadic retinal locations before the saccade is executed. The location of the saccade target is calculated in the new retinal coordinates via a simple vector subtraction and is accurate by the time the eye achieves its new orbital position. This remapping process repeats itself after each eye movement. When it finally comes time to make a

saccade to the initial target, the target's spatial location has been accurately preserved and an updated saccade vector is calculated in retinotopic coordinates.

1.3.2 The gain field coordinate transformation

Another way the brain could maintain an accurate representation of objects in space is by encoding the world using a spatiotopic coordinate system that is independent of eye position. This spatiotopic map supersedes the retinotopic map, and as the visual scene changes, the brain updates the spatiotopic locations of objects in this higher-order map. This idea is very appealing because fits with our perception of space: we experience a seamless representation of the world around us, rather than a series of snapshots. Thus, the idea of a higher-order map that allows the brain to operate independently of images moving on the retina seems to be an intuitive theory. Unfortunately, the vast majority of visually response neurons in the brain encode visual targets in a retinotopic, or eye-centered, coordinate frame (Andersen and Buneo, 2003; Gardner et al., 2008; Wurtz, 2008). How, then, does the motor system as a whole operate in spatiotopic coordinates, independent of eye movements?

Gain fields provide the solution to the spatiotopic map problem. Gain fields are neuronal responses modulated by some form of positional input, such as eye position or arm position. Neuronal responses modulated by orbital eye position were first observed in area 7a of the posterior parietal cortex during a simple memory-guided saccade task (Andersen and Mountcastle, 1983). The area 7a neurons were retinotopic in that they had classic receptive fields. However, their activity went either up or down depending on the position of the eye in the orbit. Gain modulated responses have proven to be ubiquitous

throughout the brain. They appear in early visual areas, such as the lateral geniculate nucleus of the thalamus (Lal and Friedlander, 1990) and V1 (Trotter and Celebrini, 1999) and continue along both the dorsal and ventral pathways (Galletti and Fattori, 2002). Modulation also occurs in cortical areas such as V3A (Galletti and Battaglini, 1989), FEF (Cassanello and Ferrera, 2007), supplementary eye field (Schlag et al., 1992) and dorsolateral prefrontal cortex (Funahashi and Takeda, 2002).

The majority of eye position modulated neurons in posterior parietal cortex exhibit predictable, planar patterns of modulation (Andersen et al., 1985a; Andersen et al., 1990). The orientation of these visual gain fields led theorists to model a network of neurons that formed a distributed spatiotopic map (Zipser and Andersen, 1988). Zipser and Andersen modeled a three layer network using retinal and eye position signals as inputs and head-centered target locations as outputs. The hidden layer between the input and output layers exhibited strong similarities to the planar gain fields. A number of other theoretical models have used gain fields to solve the problem of spatial accuracy (Salinas and Abbott, 1996; Pouget and Sejnowski, 1997; Pouget and Snyder, 2000) by transforming visual target positions from retinotopic coordinates into stable, head-centered coordinates (Andersen, 1997). While such models do not prove the existence of a spatiotopic map, it is nevertheless tempting to presume that the brain utilizes the resources available to it for neural computation.

It seems intuitive that neurons in the posterior parietal cortex, an association area that combines information from different modalities, including visual, proprioceptive, auditory and motor, could encode a spatiotopic map. One shortcoming of the gain field model, however, is that neurons with spatiotopic receptive fields are limited, and the

primary spatiotopic map in the monkey brain remains distributed (Wurtz, 2008). Researchers have identified 'real position' neurons in area V6a (Galletti and Battaglini, 1989) and VIP (Duhamel et al., 1997). The neurons in these brain regions have spatially invariant receptive fields and respond to stimuli in one region of visual space, rather than one point on the retina. While neurons that have these characteristics may represent elements of a spatiotopic map, maps of visual space on the individual cell level are almost entirely coded in retinotopic and not spatiotopic coordinates (Gardner et al., 2008).

Neurons in LIP show saccadic activity that precedes the actual eye movement (Andersen et al., 1990). This pre-saccadic response, which seems to predict a motor outcome, has prompted researchers to speculate that LIP gain fields underlie the sensorimotor transformation process that allows eye movements to be directed accurately toward targets in space (Andersen, 1997). In order for the gain fields to maintain spatial accuracy during the transformation process, they must be accurate around the time of a saccade. While researchers have speculated that corollary discharge provides an accurate eye position input to the gain fields (Andersen and Mountcastle, 1983; Chang et al., 2009), neither the time course nor the identity of the input has been experimentally tested. Nevertheless, gain field theorists believe the model can solve the double-step saccade task, a fundamental oculomotor task that requires a supraretinal mechanism (Hallett and Lightstone, 1976). According to gain field theory, as soon as the saccade targets for the double-step task are presented, LIP gain fields transform the target locations from retinal coordinates into supraretinal, head-centered coordinates. Thus, when the monkey

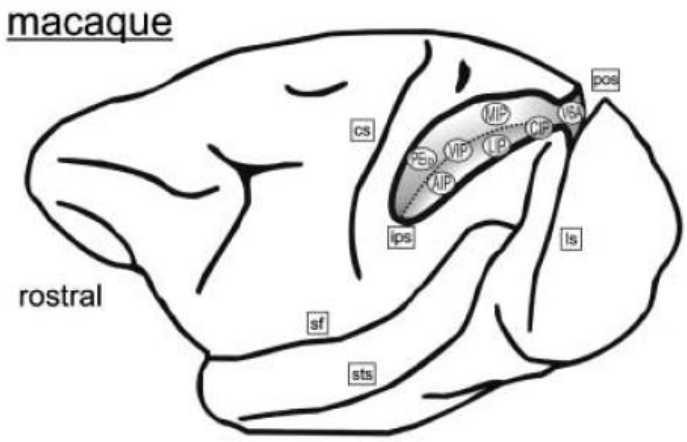
executes the second saccade, LIP directs the eyes to the correct spatial location despite the dissonance between the original retinal location of the target and the saccade goal.

Gain field theory has not been limited to sensorimotor transformations that involve eye movements. The parietal reach region (PRR) is thought to play a role in coordinating visually guided arm movements (Andersen, 1997; Snyder et al., 1997). PRR is located in the lateral bank of the intraparietal sulcus, between the medial intraparietal area (MIP) and V6A (Chang et al., 2008). The neurons in PRR have been shown to encode reach targets in eye-centered coordinates (Batista et al., 1999a), which means the spatial tuning of individual PRR neurons depends on the position of the eye in the orbit, rather than the position of the hand in space. The visual responses of PRR neurons are, however, modulated by eye and hand position, which are equal in magnitude, but opposite in direction. This gain field relationship ensures that the responses of PRR neurons to a reach target are the same so long as the position of the hand relative to the eye remains constant. Chang and colleagues demonstrated that a network of PRR neurons can calculate hand-to-object distance, and its output could be used to drive hand movements to objects in space (Chang et al., 2009).

1.4 The Lateral Intraparietal Area

1.4.1 Anatomy

The lateral intraparietal area (LIP) is just one of several distinct functional areas in the posterior parietal cortex located along the intraparietal sulcus (IPS) (Figure 1.3). The IPS in the Rhesus Macaque monkey is located between the somatosensory and visual cortex.



Adapted from Grefkes and Fink, 2005

Figure 1.3. **The organization of structures in the intraparietal sulcus.** LIP is located on the lateral bank of the sulcus and has strong connections visual, motivational, motor and cognitive brain areas.

Anterior portions of the IPS are more concerned with sensorimotor processing, while the posterior portions are more concerned with visual processing (Grefkes and Fink, 2005). Each area of the IPS processes information from more than one sensory modality. The brain regions that line the IPS have been systematically tested and are defined by their preferred types of stimuli and behavior. These regions are LIP, the anterior intraparietal area (AIP), the ventral intraparietal area (VIP), the medial intra-parietal area (MIP), and the caudal intraparietal area (CIP).

Area LIP is located on the lateral bank of the monkey IPS. LIP is an association cortex that receives anatomical inputs from visual, motor, motivational and cognitive information areas. It has extensive connections with oculomotor structures, the frontal eye field (FEF) in the frontal lobe and the superior colliculus in the brainstem (Lynch et al., 1985; Blatt et al., 1990). LIP is also linked to neighboring parietal areas that are related to skeletal movements (Lewis and Van Essen, 2000a). In addition, LIP is reciprocally connected to extrastriate visual areas in the dorsal stream, including the areas V3, V3A, V4, middle temporal area (MT) and middle superior temporal area (MST), and shape and color selective areas in the ventral stream (Blatt et al., 1990). LIP also has bi-

directional connections with the perirhinal and parahippocampal cortex, which are associated with learning and memory, and the posterior cingulate cortex, which is part of the limbic system (Blatt et al., 1990; Lewis and Van Essen, 2000b). Finally, LIP receives a disynaptic input from the brainstem horizontal eye position integrator network (nucleus prepositis hypogloosi) via the central lateral and ventral lateral thalamic nuclei (Prevosto et al., 2009), but not from the vertical and torsional integrators in the midbrain.

Area AIP is located on the lateral bank of the anterior IPS. The neurons in this area are responsive during the manipulation of objects, primarily visually-guided, and are selective for the size, shape and orientation of objects (Sakata et al., 1995). AIP is connected to the ventral premotor cortex (Matelli et al., 1986) and likely works with motor area F5 to coordinate visually guided grasping movements (Rizzolatti et al., 1998).

The neurons of area CIP, located on the lateral bank of the caudal IPS, are primarily responsive to the visual analysis of 3D object features and orientations (Sakata, 2003). CIP receives projections from nearby visual areas V3, V3A and V4 (Cavada and Goldman-Rakic, 1989; Tsutsui et al., 2003).

Area VIP is located in the fundus of the IPS. VIP is a polymodal association area that responds to visual, tactile, vestibular and auditory stimuli (Colby et al., 1993; Duhamel et al., 1998; Bremmer et al., 1999; Klam and Graf, 2003) and receives projections from visual (MT, MST), motor, somatosensory, auditory and vestibular areas (Maunsell and van Essen, 1983; Lewis and Van Essen, 2000a). VIP is unique because some of its neurons encode in a head-centered coordinate frame: the receptive fields of these cells represent the spatial location of visual targets irrespective of eye position (Duhamel et al., 1997). These spatially invariant cells responded equally to visual

stimulation and somatic sensation, such as when the brow of the animal was touched (Duhamel et al., 1998). Interestingly, when neurons in macaque VIP were stimulated, monkeys exhibited avoidance behavior, such as eye closure, contraction of facial muscles, and arm movements (Cooke et al., 2003). This evidence suggests that VIP may play a role in encoding for interactions in near extrapersonal space.

Area MIP is located on the medial bank of the IPS and, along with area V6A and parts of area PE, is part of the parietal reach region (PRR). PRR neurons respond to either saccade or reach targets (Cohen and Andersen, 2002), although they are more responsive to reach than eye movements (Snyder et al., 1997; Eskandar and Assad, 2002). These and similar results have led experimenters to conclude that MIP neurons perform sensorimotor transformations of target location from retinal coordinates into motor coordinates (Cohen and Andersen, 2002). While the visual responses of MIP neurons are eye-centered (Batista et al., 1999a), they are modulated both by eye- and hand-position, such that a network of MIP neurons could calculate the distance between gaze and hand location (Chang et al., 2009) and control goal-directed reaches.

1.4.2 Response of an LIP neuron to a salient stimulus

Consistent with its rich and diverse visual inputs, most LIP neurons have visual responses and spatial receptive fields. These receptive fields are typically contralateral to the recording hemisphere and are confined to a single quadrant (Ben Hamed et al., 2001). The receptive fields in LIP are retinotopic: they always occupy the same place on the retina and move with the eye. The responses of many LIP neurons are, however, also

modulated by an extraretinal eye position signal (Andersen et al., 1990) and a head-on-body position signal (Brotchie et al., 1995; Snyder et al., 1998).

The canonical LIP response (Figure 1.4) can be seen when recording in monkeys performing a memory-guided saccade task (Hikosaka and Wurtz, 1983). In this task, the subject fixates a stationary point of light on a dark screen. A visual stimulus, usually another point of light, flashes briefly somewhere on the screen. The subject waits until the fixation point goes out and then makes a saccade to the remembered location of the flashed stimulus. When the visual stimulus appears in the receptive field of an LIP neuron, the cell will initially respond with a vigorous visual response. The visual onset responses of LIP neurons occur with latencies as short as 40 ms and are remarkably precise and reliable (Bisley et al., 2004). When the visual stimulus disappears, many LIP neurons continue to fire as the subject waits to make a saccade to the target. The rate of the memory or delay period response is usually reduced compared to the visual response. When the fixation point goes out and the monkey prepares to make a saccade to the target, LIP neurons often exhibit a ramping up of activity before the saccade, called the

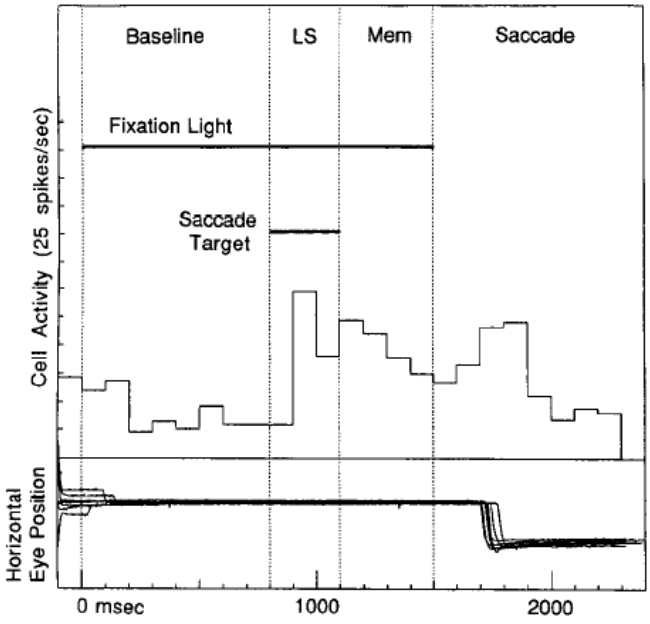


Figure 1.4. **The canonical LIP response.** The response of an LIP neuron during the memory-guided saccade task. The short-latency light sensitive (LS) burst is followed by memory- and saccade-related activity. The saccadic rise in activity precedes the eye movement.

Adapted from Andersen et al., 1990

pre-saccadic response (Gnadt and Andersen, 1988). After the pre-saccadic response and completion of the eye movement, the response of the LIP neuron immediately returns to its baseline.

1.4.3 Intention and attention in the parietal posterior cortex

The goal of a saccade and the locus of attention are closely linked: our attention is drawn to the goal of an eye movement, and we commonly direct our eyes toward objects of attention. In fact, around the time of a saccade, there is selective coupling of the saccade program and visual attention to one common location, such that attention is obligatory at the saccade target (Deubel and Schneider, 1996). The coupling of visual attention to saccades is at the heart of the debate over whether neurons in the posterior parietal cortex encode motor intention or visual attention. Although it is clear that posterior parietal neurons respond to visual stimuli, it is not immediately clear whether this response is dedicated to processing saccadic eye movements or if it has a more general, attentional function that is independent of specific movement generation.

The argument for motor intention was raised more than 30 years ago, when Mountcastle and his colleagues described neurons in the posterior parietal cortex that discharged in association with eye movements and visually guided hand movements (Mountcastle et al., 1975). The observation that passive viewing of visual stimuli did not elicit a response from posterior parietal cortex neurons prompted them to conclude that the posterior parietal cortex reflected 'motor intention' and acted as a command apparatus for operation of the limbs, hands, and eyes within immediate extrapersonal space.

A few years later, Robinson and his colleagues reached a different set of conclusions regarding the function of the posterior parietal cortex (Robinson et al., 1978). They found cells that fired in association with movement could also be driven by passive sensory stimuli delivered in the absence of movement. They also found that parietal neurons responded to sensory stimulation in the absence of movement, but not to movement in the absence of a visual stimulus. They argued that posterior parietal cortex should be viewed as a sensory association area and that while in some contexts its activity was related to movement, its activity was always related to 'visual attention'. This proposed function of the posterior parietal cortex later became consistent with the 'where' function (i.e., the localization of visual stimuli) ascribed to the occipitoparietal pathway of cortical visual areas (Ungerleider and Mishkin, 1982).

1.4.4 Motor intention

The discovery that LIP neurons had unique connections to oculomotor areas (Andersen et al., 1985b) led some researchers to argue that LIP was involved in the planning and execution of saccades (Gnadt and Andersen, 1988). Neurons in LIP discharge throughout the delay period of a memory-guided saccade task and exhibit a saccadic response that precedes the eye movement. This pattern of activity led a number of investigators to conclude that during the delay period, LIP was preparing a motor plan or providing an intention signal for the saccade (Mazzoni et al., 1996; Andersen, 1997).

Researchers have speculated on the mechanism that allows LIP neurons to compute motor plans for action. The activity of LIP neurons is modulated by eye position (Andersen et al., 1990), and researchers have speculated that these LIP 'gain fields' are

involved in sensorimotor transformations for the programming of saccadic eye movements (Andersen, 1997). While LIP gain fields could compute saccade target location in supraretinal coordinates (Zipser and Andersen, 1988), a unified spatiotopic map has not been identified in the monkey brain (Wurtz, 2008). Although the idea that gain fields form a distributed spatiotopic map is supported by modeling studies (Salinas and Abbott, 1996; Pouget and Sejnowski, 1997), there is no direct evidence that the gain fields in LIP are used for coordinating eye movements.

The motor intention theory of LIP states that once a saccade target is encoded in spatiotopic coordinates, LIP sends the command signal to the oculomotor system to shift the eyes to that location in space. Experiments in which monkeys simultaneously planned a saccade and a reach to different spatial targets seemed to support this hypothesis. Delay period activity in LIP was greater when a monkey was planning a saccade to the target than when a monkey was planning a reach to it (Snyder et al., 1997). In contrast, activity in PRR was greater for reaches than for saccades. The authors argued that the effector preference seen in these two parietal regions supported the motor intention hypothesis, since both the motor response location and effector were specified by the posterior parietal cortex signals.

If LIP is involved in the sensorimotor transformations that coordinate eye movements, inactivating LIP should cause noticeable saccadic deficits, such as inaccuracies or increased latencies. In one set of experiments, transient inactivation of LIP using musciomol injected into multiple sites did not produce deficits in the latency or accuracy of saccades to single targets in either a visually or memory-guided saccade task (Wardak et al., 2002). A second set of LIP inactivation studies reported that monkeys

showed deficits making memory guided saccades, while visually guided saccades remained relatively unaffected (Li et al., 1999; Li and Andersen, 2001). The effects of inactivation in these studies on both types of saccades were, however, quite subtle. In a separate experiment, researchers reported that monkeys showed a increase in saccadic latency during LIP inactivation, although the effects were again quite modest (~10 ms) and were not accompanied by a change in saccadic accuracy, precision, duration or error rate (Liu et al., 2010). In contrast to these data, inactivation of FEF (Dias and Segraves, 1999) and superior colliculus (Aizawa and Wurtz, 1998) lead to significant decreases in accuracy and increases in latency. In sum, these studies seem to suggest that inactivation of LIP has a minimal effect on oculomotor planning and performance.

Conversely, stimulating LIP neurons should produce saccades if LIP is involved in coordinating eye movements. Stimulation of LIP neurons produced saccades, but only at high microstimulation currents (Thier and Andersen, 1998; Constantin et al., 2007; Constantin et al., 2009). In contrast, stimulating oculomotor areas such as FEF (Robinson and Fuchs, 1969; Bruce et al., 1985) and the superior colliculus (Robinson, 1972) produced saccades at much lower stimulation currents.

The antisaccade task is one way a visual stimulus can be separated from the goal of the saccade, and it has been used to study the role of LIP in coordinating eye movements. In the antisaccade task, the subject fixates a central point that is either red or green. A visual cue is presented, and depending on the color of the fixation point, the subject executes a saccade to the location of the cue or a location diametrically opposite the cue (the antisaccade). There is no visual stimulus at the location of the saccade goal, so an LIP neuron during the antisaccade task presumably only encodes the saccade goal,

according to the motor intention theory, or the visual cue, according to the visual attention theory. Gottlieb and Goldberg discovered that when monkeys performed the antisaccade task, the large majority of neurons in LIP preferred the location of the visual cue and not the location of the antisaccade (Gottlieb and Goldberg, 1999). They concluded that LIP encoded the locus of visual attention since most LIP neurons had only weak, if any, saccade-related activity independent of visual stimulation. Zhang and Barash arrived at a different set of conclusions using a memory-antisaccade task in which a delay period was introduced between the cue and the "GO" signal (Zhang and Barash, 2000; Zhang and Barash, 2004). They observed that neuronal activity in LIP reflected a shift from visual activity at the location of the cue to saccadic activity at the location of the saccade. They argued that this represented a sensorimotor transformation that produced a motor plan indicating the direction of the saccade. While this explanation is plausible, the results of Gottlieb and Goldberg clearly showed that LIP activity at the saccade goal was not necessary for the monkey to perform the antisaccade task.

1.4.5. Attentional mechanisms

While motor intention is a relatively tangible concept, attention is a more abstract term. We intuitively understand that attention is the mental resource that allows us to filter through the sights, sounds, smells and touches that constantly bombard our sensory apparatus. Attention chooses the most relevant objects for further processing and suppresses our awareness of less important objects. How then does the brain, and more specifically LIP, represent where in space attention should be directed?

Much of modern thinking about attention stems from William James' famous description:

> "Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others" (James, 1890).

James was describing one kind of attention, which we now call 'top-down' attention. Top-down influences arise when the brain willfully directs attention toward a specific object or area of visual space. For example, top-down attention allows us to focus on the road when we drive or on catching a ball when it is thrown at us.

The relationship between the activity of LIP neurons and top-down attention was demonstrated in an experiment by Gottlieb and colleagues (Gottlieb et al., 1998). The experimenters used a visual search task in which monkeys made saccades that brought one of eight stable objects in an array into the receptive field of a neuron. The visual response to the object was usually weak, but when the monkey was cued to find the object that was brought into the receptive field, the response was markedly enhanced. The top-down enhancement of neuronal responses for visual search targets has been demonstrated in several subsequent experiments (Ipata et al., 2006; Buschman and Miller, 2007; Thomas and Pare, 2007). In each of these experiments, neurons showed increased firing when the target of the search task, rather than a distractor, appeared in the receptive field. Inactivation studies also support the role of LIP in top-down attention (Wardak et al., 2002, 2004; Liu et al., 2010). When monkeys with muscimol injections in LIP were asked to perform a search task, search times for targets in the contralateral visual hemifield increased significantly, especially as the number of items increased. In

sum, these results suggest that LIP neurons reflect the top-down selection of targets for saccades in the context of competing visual stimuli.

William James also intuited that there are fundamental things that draw a different kind of attention: “In passive immediate sensorial attention the stimulus is a sense-impression, either very intense, voluminous, or sudden … strange things, moving things, wild animals, bright things, pretty thing … blood” (James, 1890). These are things that attract what we now refer to as ‘bottom-up’ attention. Our sensory system automatically allocates attentional resources to objects that draw bottom-up attention, even without effort of will. For example, a flashing fire-alarm is distracting even when we know there is no fire, and an object that quickly darts across the periphery of our visual field will likely draw a quick glance.

Activity in the parietal cortex is associated with vision as well as attention, so a logical question to ask is whether the “visual response” of an LIP neuron is induced by stimulation of the retina or by bottom-up attention. Stimuli can enter receptive fields in two ways: they can appear suddenly or they can be brought into receptive fields by eye movements. In both cases, the pattern of stimulation in the receptive field is similar (an object suddenly appears), but flashed stimuli should elicit a different response according to the bottom-up theory of attention. Gottlieb and Goldberg demonstrated that when a stable visual stimulus was brought into the receptive field of an LIP neuron by a saccade, the neuron responded less vigorously than when a stimulus abruptly appeared in the receptive field (Gottlieb et al., 1998). Additionally, when an object flashed before the saccade that brought the location into the receptive field, the neuron also fired robustly. While we now know that this observation was due to the shifting of receptive fields

around the time of a saccade, the result can be applied more broadly: objects that draw bottom-up attention are specially tracked by the parietal cortex neurons, even when they are irrelevant for task performance.

1.4.6. The priority map

The concept of a saliency map was introduced by Koch, Itti, and colleagues (Koch and Ullman, 1985; Itti and Koch, 2000). A saliency map acts as a bottom-up filter on the visual scene, discriminating for preattentive features, such as color and brightness. Attention is allocated to the highest peak in the saliency map, in a winner-takes-all fashion. LIP is influenced by bottom-up attention, but it is also influenced by top-down attention. Thus, the term priority map has been used to imply that both bottom-up and top-down attention play a role in LIP to determine the locus of attention (Fecteau and Munoz, 2006; Serences and Yantis, 2006; Ipata et al., 2009)

Under most circumstances, saccades and attention are linked. Attention directed via a saccade is called "overt attention' (Posner, 1980) and has been described in both humans (Kowler et al., 1995; Yantis and Egeth, 1999) and monkeys (Bisley and Goldberg, 2003, 2006). 'Covert attention', in contrast, describes the allocation of attention without making a corresponding eye movement. If LIP acts as a priority map, then its activity must describe not only the allocation of overt attention, but covert attention as well, since humans and primates are able to attend to locations in space without moving their eyes.

There are two traditional methods to measure attention: reaction time (Posner, 1978) and perceptual threshold (Bashinski and Bacharach, 1980). To link the activity in

LIP and covert attention, Bisley and Goldberg trained monkeys on a GO-NOGO task in which they identified the locus of attention by measuring contrast sensitivities (Bisley and Goldberg, 2003). Monkeys were trained to plan memory-guided eye movements to locations in space. An array of four rings, one of which was either a forward or backward C, flashed briefly. Depending on the location of the gap, the monkey either executed (GO) or canceled (NOGO) the impending saccade. By varying the contrast of the four rings, the experimenters tested the attentional advantage at each location. On some trials, a task-irrelevant distractor flashed at a location opposite the saccade goal in order to briefly redirect or capture the monkeys' attention. Behaviorally, attention started at the saccade goal and shifted to the distractor 200 ms after it was flashed. Attention remained at the location of the distractor for approximately 300 ms before returning to the saccade goal. Neuronally, the activity of LIP neurons reflected the same time course. Neurons responded with a visual burst to the target for the memory-guided saccade and maintained elevated, persistent activity. For trials in which a distractor flashed, the activity at the location of the distractor exceeded the activity at the location of the saccade for approximately 300 ms. Thus, the activity of LIP neurons predicted the locus of greatest attentional advantage during the discrimination task. This result suggests that the activity in LIP reflects the allocation of covert as well as overt attention, and that visual attention as a whole is allocated to the peak of the priority map in LIP.

1.4.7. Beyond saccades and attention

In addition to encoding the locus of attention, the activity of LIP neurons also reflects the dynamics of a decision-making process. When experimenters modulated the reward value

associated with a monkey's saccade choice, the visual responses of LIP neurons reflected the expected reward outcome (Platt and Glimcher, 1999). In a separate experiment, monkeys were trained to choose between two possible saccade targets based on the direction of motion in a random-dot pattern. Activity in LIP increased in neurons that represented the eventual saccade goal and decreased in neurons that represented the rejected goal, and the rate of change in activity was proportional to the strength of the motion (Gold and Shadlen, 2000). These experiments provide evidence supporting the idea that LIP does not just allocate attentional resources, but actively weighs abstract decision variables as part of the sensory-decision-motor process.

The response of LIP neurons is not always associated with a spatial decision. In one study, researchers trained monkeys to report the orientation of a peripheral visual cue by releasing a bar grasped with the right or left hand (Oristaglio et al., 2006). Surprisingly, this non-targeting behavior modulated the visual response when the cue, but not the distractor, was in the receptive field. In a separate categorization task, monkeys were shown one of twelve different motion stimuli that had been arbitrarily assigned to two different categories (Freedman and Assad, 2006). The monkeys had to categorize the detected motion and indicated their categorization choice by releasing a bar. LIP neurons gave differential responses depending on the category of the stimulus, even though the visual stimulus was arbitrarily assigned and the motor response was constant. From these results, it appears neurons in LIP are also modulated by an abstract concept of behavior or object categorization in the absence of any differences in sensory input or motor output.

1.5 Thesis Outline

The review above summarized the role of extraretinal signals in visual and oculomotor processes. It also described two models that could be used to maintain an accurate representation of visual space and track the location of saccade targets across eye movements. The work of this thesis investigates the time course of eye position modulation of neuronal activity in the parietal lobe, specifically area 3a in anterior parietal cortex and area LIP in posterior parietal cortex. Experimenters have shown that the area 3a eye position signal is proprioceptive in nature (Wang et al., 2007), but the time course of accurate eye position information in area 3a is unknown. Similarly, researchers have speculated on the function of eye position modulation in LIP, the gain fields (Andersen, 1997), but the time course of this modulation has also not been studied. My aim is to test if eye position modulated activity in either brain area is accurate in time to contribute to the cortical functions they are thought to subserve.

Experiment #1

In my first set of experiments, I study the time course of the proprioceptive eye position signal in area 3a of somatosensory cortex. The normal area 3a eye position response has two components: phasic and tonic. The tonic component reflects the position of the eye in the orbit, but its onset is masked by the phasic component during a saccade task. To study the time course of the tonic eye position signal, I use two oculomotor tasks, smooth pursuit and the vestubuloocular reflex, that evoke slow eye movements and suppress the phasic response. My hypothesis is that the proprioceptive eye position signal in area 3a is too slow to contribute to oculomotor and visual processes that occur at the time of a

saccade. It is likely, however, that the onset of the response is reliable enough to subserve cortical function, such as calibrating the corollary discharge signal for accurate eye movements.

Experiment #2

In my second set of experiments, I study the time course of gain fields in LIP. I record visual responses to stimuli presented immediately after a saccade, to test when gain field modulation accurately reflects eye position. Gain field theorists presume that the gain fields derive their eye position input from corollary discharge and are therefore always accurate. This point, however, has not been experimentally tested. My hypothesis is that visual gain fields in LIP are slow and derive their eye position input from oculomotor proprioception, just as proprioception drives head-on-body gain fields in LIP (Snyder et al., 1997). If this is true, then gain field modulation of LIP visual responses should not be spatially accurate until after the area 3a neurons accurately reflect eye position. I also investigate whether or not the accuracy of the gain fields immediately after a saccade is reflected in the accuracy of saccades directed to visual targets presented during this time.

This thesis is organized into 5 chapters. The first chapter is a literature review. Chapter 2 is a general methods section that applies to all of the experiments described. Chapter 3 examines the time course of the proprioceptive eye position signal in area 3a. Chapter 4 investigates the time course of gain field modulation of visual responses in LIP, and the role of the gain fields in computing the spatial location of saccade targets. Finally,

Chapter 5 summarizes the results of the experiments described in the previous chapters and provides some general conclusions.

Chapter 2.

General Methods

This chapter describes the general methods that were common to both sets of experiments. Experimental procedures unique to each experiment will be described in further detail in the relevant chapters.

All of the protocols were approved by the Animal Care and Use Committees at Columbia University and the New York State Psychiatric Institute as complying with the guidelines established in the *United States Public Health Service Guide for the Care and Use of Laboratory Animals*.

2.1 Surgery and Recording

We implanted the monkeys with head restraint devices, scleral eye coils (Judge et al., 1980) and recording chambers during aseptic surgery under ketamine and isoflurane anesthesia. The head restraint device interfaced with the primate chair in order to prevent monkeys' head movements during the experimental sessions. The recording chambers were positioned using magnetic resonance images taken from the animals while anesthetized. Animals were given time to fully recover before behavioral training and experimental testing commenced.

We controlled all experiments using the REX system (Hays et al., 1982). We recorded single-unit activity with 1-2 MΩ glass-insulated tungsten electrodes (Alpha-Omega) introduced through a guide tube positioned in a grid (Crist et al., 1988). We controlled the depth of the electrode with a hydraulic Narishige microdrive. Electrode

penetrations were spaced with approximately a 1 mm resolution on both x- and y-axes. We used commercially available amplification (FHC or Alpha-Omega) and filtering (Krohn-Heit) equipment. Data from the recording electrodes were sorted and digitized during each recording session using the MEX system (available by download from lsr-web.net). We measured eye position signals sampled at 1 kHz from the scleral search coils using a two channel Riverbend Phase Detector. We monitored the monkey using a closed circuit camera during each training or experimental session.

We used a Hitachi CPX275 LCD projector running the VEX open GL-based graphics system (available by download from lsrweb.net) to rear-project behavioral stimuli onto a screen. We used a photoprobe, which emitted a TTL pulse following light stimulation, to verify the timing of visual stimuli. All experiments were conducted in complete darkness, aside from the light emitted by the projector, in a light and sound-attenuated Faraday booth. Visual stimuli were 440 cd/m^2 on a screen background of 1.5 cd/m^2 and decayed to background luminance within 1 ms of stimulus offset.

2.2 Behavior

We first trained the monkeys to sit in a primate chair and drink either water or juice droplets through a molded acrylic spout. During experimental sessions, monkeys worked for their daily fluid intake and were supplemented with dried and fresh fruits. We carefully monitored the monkeys' weights on a daily basis. Experimental sessions typically lasted between 1.5 to 3 hours, depending on the monkey's willingness to work and the number of cells that we were able to isolate. The monkeys sat head-fixed at a distance of approximately 72 cm from the projection screen during all of the experimental sessions.

2.3 Data analysis

We formatted and analyzed collected data using MATLAB (MathWorks, Natick, MA).

To examine the pattern of activity, we calculated spike-density functions by convolving the spike train, sampled at 1 kHz, with a Gaussian of 10 ms (Richmond et al., 1987).

Chapter 3.

The time course of the tonic oculomotor proprioceptive signal in somatosensory cortex

3.1 Introduction

In the early 1900's, Sherrington hypothesized that "inflow", signals transduced by extraocular muscle proprioceptors, provides the oculomotor system with necessary information about eye position and movements (Sherrington, 1918). This went against the widely accepted theory of Helmholtz, who in the 19th century postulated that a copy of the motor command, which he called the 'sense of effort', fed back to the sensory system to compensate for changes in the visual representation that arise as the result of eye movements (Helmholtz, 1962). For many decades, researchers debated whether the eyes had any proprioceptive sense and if inflow played a role in visual processing at all (Carpenter, 1988).

Although there are putative fusimotor receptors in the eye that could signal muscle length and hence eye position (Donaldson, 2000; Weir, 2000), their function is unclear. The monkey extraocular muscles lack a stretch reflex (Keller and Robinson, 1971). Monkeys with lesions of the trigeminal nerve do not show increased target mislocalization in single- and double-step saccades, nor do their saccades show any changes in velocity or amplitude (Guthrie et al., 1983). They also do not show a deficit in open-loop pointing (Lewis et al., 1998). However, their vergence performance gradually decays over time, and they cannot compensate for surgical weakening of eye muscles,

suggesting the proprioceptive signals may have a calibratory function (Lewis et al., 1994).

There is a proprioceptive representation of eye position in area 3a of somatosensory cortex (Wang et al., 2007). This signal arises from the contralateral eye and monotonically increases with increasing ocular eccentricity from the center of gaze. Cells in area 3a encode all directions of eye displacement and represent the orbital position of the contralateral eye, rather than a space-related gaze position signal. Area 3a projects to areas that could use the eye position signal for motor feedback and spatial processing, such as primary motor cortex (Huerta and Pons, 1990) and the frontal eye fields (Stanton et al., 2005).

The proprioceptive signal carried by area 3a neurons has two components: a short-latency phasic component and a persistent tonic component. These components resemble the dynamic and static γ-motor firing patterns, respectively, of a fusimotor response (Taylor et al., 2006). The onset of the tonic signal, which reflects the position of the eye in the orbit, is masked by the phasic component during a saccade task, making it difficult to determine when area 3a has access to stable eye position information. In order to discuss the utility of this eye position signal, it is important to determine when downstream neurons have access to tonic eye position information and if the delay is reliable. We used both a smooth pursuit and a VOR task to evoke slow eye movements in the absence of saccades and phasic eye position responses. We report a consistent proprioceptive delay of approximately 60 ms in two monkeys using these two oculomotor tasks.

3.2 Methods

Two rhesus monkeys (*Macaca mulatta*), both male (Monkey C and Monkey W), were used in these experiments. Monkey C weighed 14kg and Monkey W weighed 11kg.

3.2.1 Surgery and Recording

We positioned 2 cm recording chambers at anterior 20 mm, lateral 27 mm using magnetic resonance images taken from the animals while anesthetized. We identified area 3a by typical neuronal activities during a fixation task (Wang et al., 2007).

The rotating platform consisted of a rectangular metal plate mounted on the vertical axis of a custom-built servo-controlled voltage-driven one-dimensional rotator. We calculated output voltages using the REX system (Hays et al., 1982). The rotator featured a feedback circuit that returned an analog voltage signal proportional to its angle of rotation. We recorded this analog signal to monitor the rotator's position during experimental sessions.

3.2.2 Behavioral tasks

We first trained the monkeys to perform a fixation task, which we later used to map the directional tuning of area 3a eye position neurons. In this task, the monkeys fixated a stable spot of light, measuring 2° by 2°, within a ±5° window. The fixation point appeared in one of nine possible locations: either in the center of the screen or in one of eight evenly spaced locations (0, 45, 90, 135, 180, 225, 270, or 315°), 15° radially from the center. The fixation point persisted for 2 to 5 s.

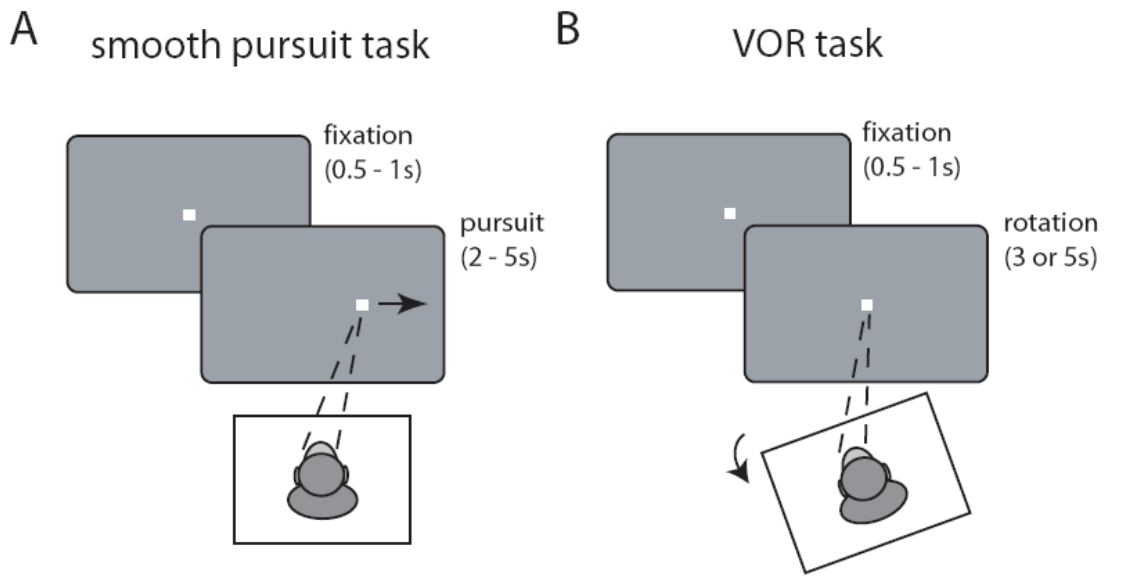
After the monkeys had reached an asymptotic performance level (95% correct), we trained both monkeys to perform two additional tasks that were meant to elicit changes in the tonic component of the proprioceptive eye position response and suppress the phasic component. The two tasks were also designed to test the effects of direction of gaze, retinal motion and vestibular inputs on the proprioceptive response and delay.

In the smooth pursuit task (Figure 3.1A), the monkeys fixated a stable point of light, measuring 2° by 2°, in the center of the screen. After a delay of 500 to 1000 ms, the fixation point began to move sinusoidally in one of eight evenly spaced directions (0, 45, 90, 135, 180, 225, 270 or 315°) to an amplitude of 10° or 15°. During the pursuit period, lasting 2, 3, 4 or 5 s (0.5, 0.33, 0.25 or 0.2 Hz), the monkeys were required to maintain pursuit within a ±5° window.

In the VOR task (Figure 3.1B), the monkeys fixated a stable point of light, measuring 2° by 2° for 500 to 1000 ms, after which the monkey's chair was rotated on a vertical axis. During the rotation period, lasting 3 or 5 s (0.33 or 0.2 Hz), the monkeys were required to maintain fixation within a ±5° window. The platform rotated at a sinusoidal velocity in either a clockwise or counter-clockwise direction to an amplitude of 15° before returning to the origin (Figure 1B). The monkey's head was fixed to the primate chair, and its head and body rotated en bloc with the platform.

We constrained duration and amplitude in both tasks to maximize the monkeys' performance. At the end of each task, an additional 0.5s fixation was imposed within a ±3° window, after which the trial terminated and the monkey was provided with a drop of liquid reward.

Figure 3.1. **The smooth pursuit and VOR tasks. (A)** The smooth pursuit task. After a stationary fixation period (0.5 to 1 s), the fixation point moved at a sinusoidal velocity to an amplitude of 10° or 15°. Pursuit duration ranged from 2 to 5 s. (**B)** The VOR task. After a stationary fixation period (0.5 to 1 s), the platform on which the monkeys sat rotated 15° in either a clockwise or counterclockwise direction at a sinusoidal velocity. The fixation point remained stationary in the center of the screen. Rotation lasted 3 or 5s.



3.2.3 Data analyses

We mapped directional tuning of area 3a cells using the fixation task described above. We characterized a neuron as spatially tuned when there was a significant difference (paired *t*-test, $p > 0.05$) between the fixation responses for the preferred and anti-preferred directions after the first 150 ms. We chose the direction with maximal activity for the smooth pursuit and VOR tasks. Only horizontally tuned cells were tested using the VOR task.

The raw eye position signal consisted of the horizontal and vertical coordinates of the fovea, sampled at 1 kHz. To reduce these data onto one dimension, we projected the

horizontal and vertical eye position onto the line passing through the center of gaze in the preferred direction of pursuit for each neuron and calculated its displacement from center (in degrees). This was accomplished by multiplying the projection matrix:

$$\begin{matrix} \cos(\alpha)^2 & \cos(\alpha)\sin(\alpha) \\ \cos(\alpha)\sin(\alpha) & \sin(\alpha)^2 \end{matrix}$$

by the vector [eye_h, eye_v], where α is the preferred angle of pursuit. Finally, we multiplied the displacement values such they were positive when the eye was in the preferred direction and negative when in the anti-preferred direction.

We normalized the eye and neuronal signals for each cell by subtracting the starting value and dividing by the maximum value of each signal. We decomposed both signals into their fundamental frequencies using the fft (fast Fourier transform) function in Matlab. We computed the frequency of maximum power and its percent deviation from the task frequency for both signals.

We used cross covariance analysis to compute the time lag between the eye position and neuronal waveform for each cell using the xcov function in Matlab. All trials were aligned on the end of the eye movement. We analyzed a window of eye position and neuronal activity, from 500 ms after the onset of the eye movement until 500 ms before the end of eye movement, in order to eliminate the effects of catch-up saccades and abruptly stationary targets, respectively. The analysis produced normalized power values that could range from 1 (perfect correlation) to -1 (perfect anticorrelation). The time-shift increments used in the analysis matched the temporal resolution of our system sampling rate (1 kHz). We generated a neuronal autocovariance to confirm the maximum expected power of the neuronal response data (power = 1). We also compared eye position with a randomly shuffled neuronal response to quantify the minimum expected power (power ~

0). We computed individual delay times from the time shifts associated with the peaks of the covariance plots. We calculated the 95% confidence intervals for each delay time by first generating an ideal sine wave with phase equal to the calculated delay. We then used the Matlab fit function to fit our normalized neuronal activity to the ideal sine wave, using the 'sin1' fittype: f(x) = a1*sin(b1*x+c1). We used the 95% confidence intervals for a1 and c1 as indicators of signal noise and phase reliability, respectively.

We produced line fits using the polyfit function, and performed linear regressions using the regress function in Matlab.

3.3 Results

3.3.1. Behavior

We trained two monkeys in both a smooth pursuit (Figure 3.1A) and a VOR task (Figure 3.1B) to elicit slow eye movements and minimize the number of saccades. Both monkeys performed the task correctly on 90–95% of the trials when the selected eye movement duration was between 2 to 5s and amplitude was either 10° or 15°.

3.3.2. Proprioceptive eye position delay in area 3a delay

We collected a total of 49 neurons from two monkeys (28 from monkey C, 21 from monkey W). We used the nine-point fixation task to confirm that each neuron was significantly tuned ($p > 0.05$, *t*-test comparing preferred with the directly opposite, anti-preferred direction) for one of eight evenly spaced locations 15° radially from the center (Figure 3.2). We then studied the response of the neuron to pursuit along a trajectory

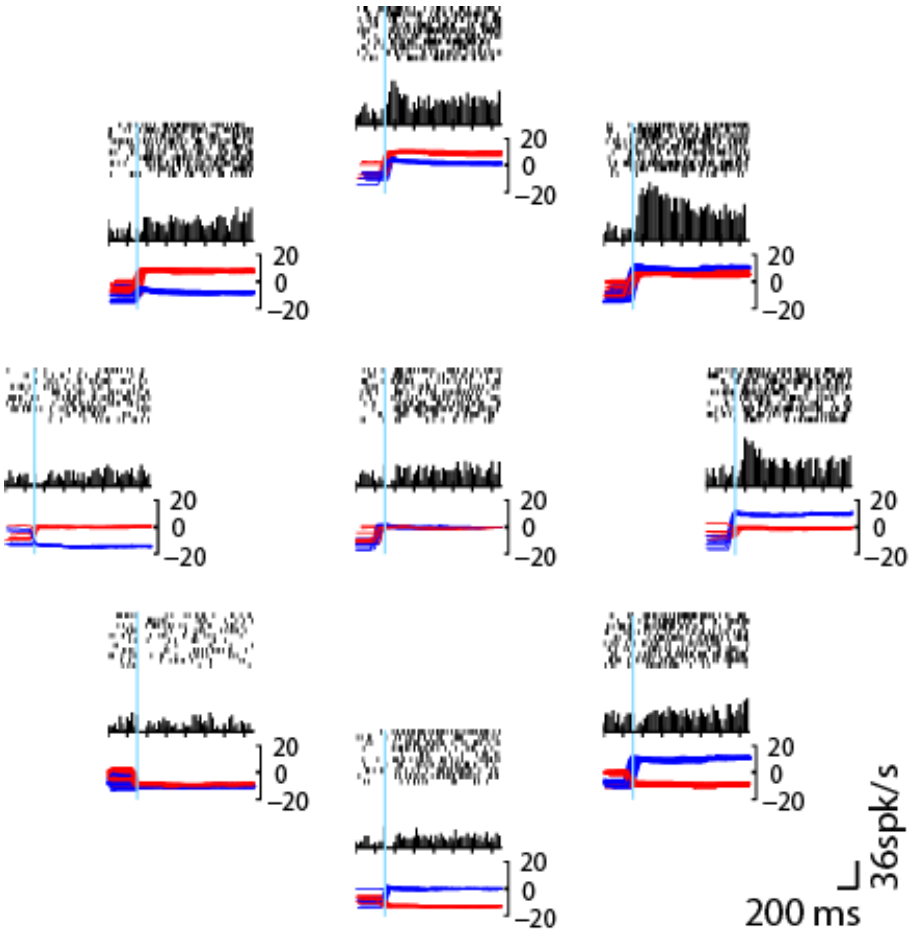
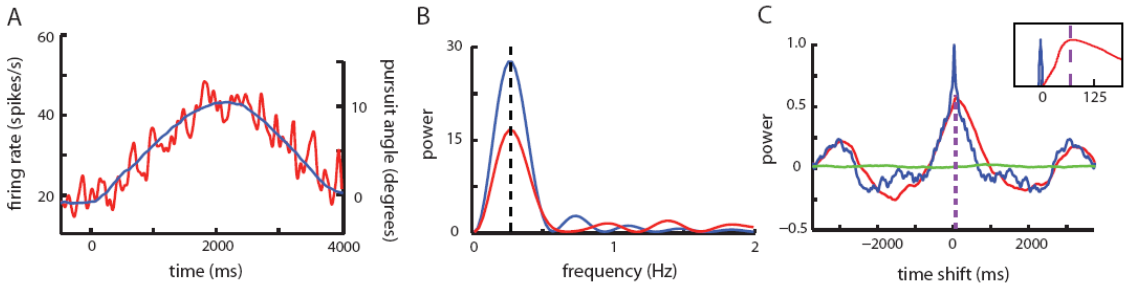


Figure 3.2. **Activity during the fixation task.** Single neuron example of eye position response in area 3a. Nine possible fixation point locations, one at the center of the orbit and eight others positioned radially 15° from the center. The position of the raster diagram is related to the position of the eye in the orbit. Each tick is an action potential, and each line is a trial. Plots are synchronized on the end of the foveating saccade (light blue line). Eye position before the saccade was uncontrolled. Histograms with a bin width of 25 ms are shown below the corresponding rasters without smoothing. Eye positions for each trial are superimposed beneath each histogram (horizontal, blue line; vertical, red line). This example cell is tuned for right, upwards eye position.

Figure 3.3. **Single neuron response during the smooth pursuit task.** (**A)** Single neuron example of activity during smooth pursuit eye movements from monkey C. Average eye position (blue line) and the activity of a single neuron (red line) are plotted as a function of time during smooth pursuit eye movements. Eye position was calculated as the displacement (in degrees) of the fovea (pursuit angle = 0, right axis) from the center of gaze in the preferred direction of pursuit (*see methods*). Neural spike trains were aligned to the onset of pursuit, convolved with a 10 ms Gaussian filter, and averaged across trials. (**B)** Single neuron example of the frequency power spectra of the eye position trace (blue line) and normalized activity (red line) from Fig. 3A. The frequency of maximum power for both spectra matches the frequency of pursuit (0.25 Hz, dotted line) (*see methods*). (**C)** Single neuron example of the cross covariance analysis (*see methods*). The power of covariance is plotted against time shift comparing the eye position and neuronal response from Fig. 3A (red line). Covariance between eye position and a shuffled neuronal response (green line) along with the neuronal autocovariance (blue line) are plotted to demonstrate minimum and maximum experimental power, respectively. The peak of the covariance plot corresponds to a 74 ms neuronal delay in response to the pursuit task, while the peak of the autocovariance plot indicates no delay (inset).



from the center of gaze to the eye position with the optimal response (Figure 3.3A). For cells whose optimal eye position was in a horizontal direction from the center of gaze, we studied the activity of the cell during the horizontal VOR (Figure 3.4A). Every cell that

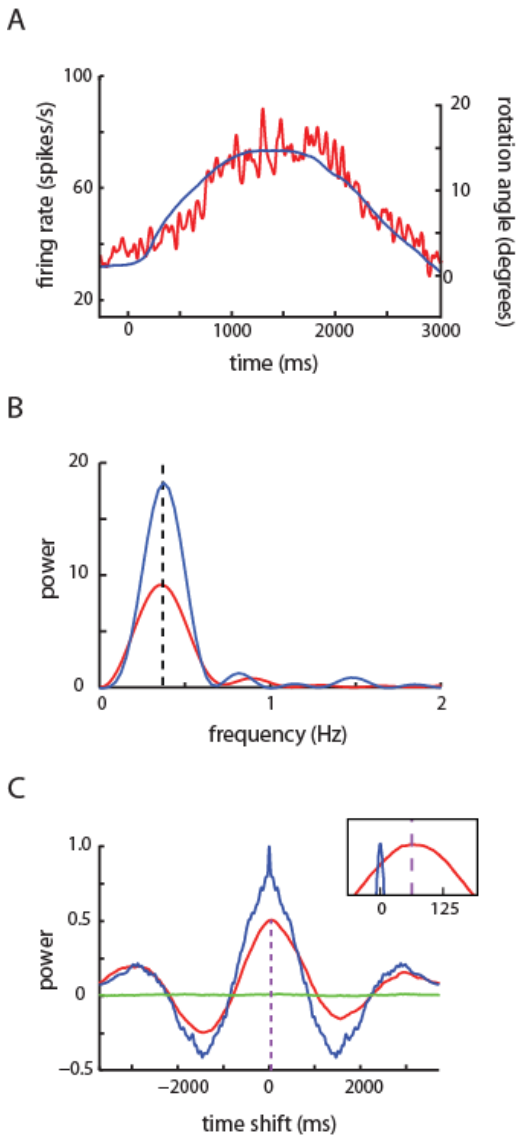


Figure 3.4. **Single neuron response during the VOR task** **(A)** Single neuron example of activity during VOR eye movements from monkey W. **(B)** Frequency power spectra of the data from Fig. 3D. The frequency of rotation was 0.33 Hz. **(C)** The covariance plot of neuronal response from Fig. 3D, indicates a 65 ms neuronal delay in response to the VOR task, while the autocovariance plot indicates no delay (inset).

had a significant modulation of activity by eye position in the nine-point fixation task was also modulated significantly during pursuit or VOR ($p > 0.05$, paired *t*-test comparing peak with baseline activity). In order to compare the activity of individual neurons with the analog eye traces, we first convolved the spike trains with a Gaussian kernel. The peak modulation of the low frequency power spectra of the neuronal response in these cells matched (deviated less than 5%) the pursuit (Figure 3.3B) or rotational frequency (Figure 3.4B), depending on the task. We used cross covariance analysis to determine

delay times for individual cells (Figure 3.3C for smooth pursuit; Figure 3.4C for VOR). The power of the delay peak was greater than 0.5 for all reported cells.

We observed similar distributions of delay times in both monkeys during the smooth pursuit task ($p > 0.05$, KS-test) and pooled these neurons (n = 35; 20 from monkey C, 15 from monkey W) for the purpose of calculating the delay of the tonic component (Figure 3.5). The mean delay time for the two monkeys was 61.4 ± 5.4 ms

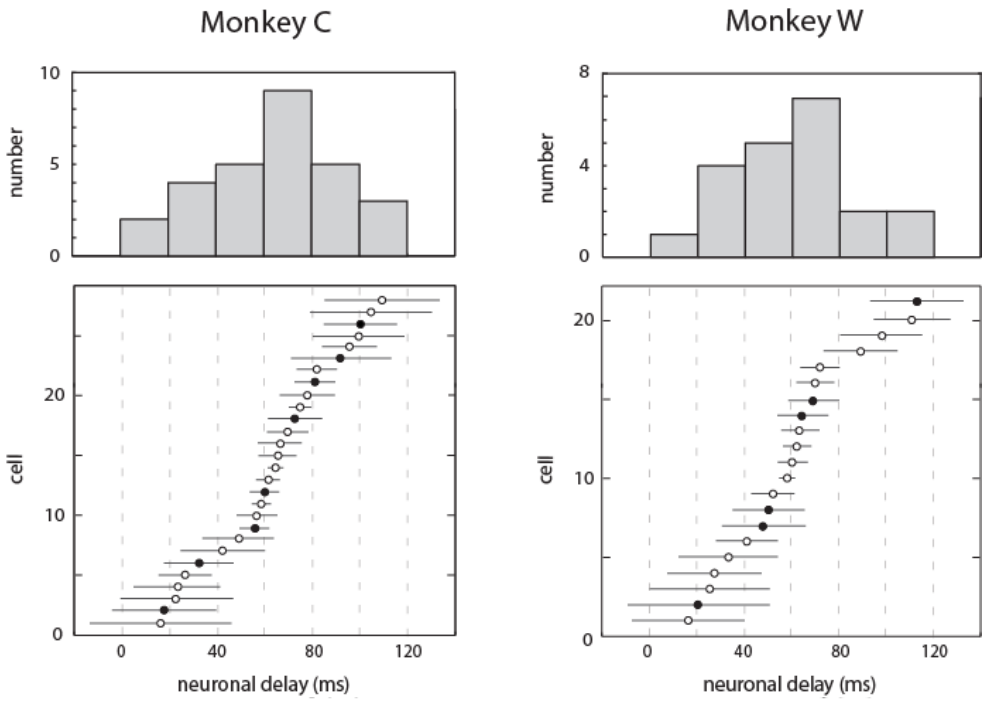


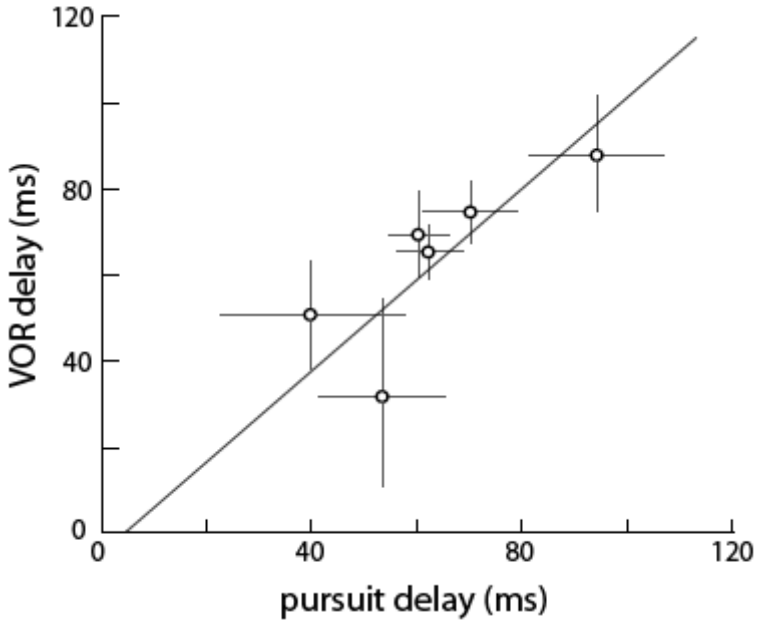
Figure 3.5. **Population proprioceptive delay times.** Rank order distributions of population delay times of individual cells in the pursuit and VOR tasks for monkey C (left; n = 28) and monkey W (right; n = 21). Error bars indicate 95% confidence interval for each cell. Delay times for neurons during pursuit (empty circles) and VOR (filled circles) were similar ($p > 0.05$, KS-test) and normally distributed ($p < 0.05$ by Lilliefors test) for both monkeys. The mean delay was 64.6 ± 28.6ms (SD) for monkey C and 59.3 ± 29.8ms (SD) for monkey W. Corresponding histograms are plotted in 20 ms bins (top).

(SEM). Delay times fell along a normal distribution (Lilliefors test, $p > 0.05$). We plotted 95% c onfidence intervals for each cell's delay time. Outlying delay times tended to arise from sessions with fewer successful trials or a noisier averaged response, and were accompanied by larger confidence intervals. These results demonstrated that area 3a eye position neurons reliably reflect changes in eye position approximately 60 ms after an eye movement in the smooth pursuit task.

We studied the activity of eye position neurons using the vestibuloocular reflex to see if the tonic component of the eye position signal was related to gaze direction, retinal motion or vestibular inputs. In the VOR task, the head moves with the body, producing vestibular modulation, and the eye moves in the orbit, maintaining the direction of gaze. The fixation point is stationary, so retinal stimulation is constant throughout the trial. If the proprioceptive signal is modulated by any of these factors, then there should be a difference in delay times between the two tasks. We recorded 14 horizontally tuned neurons (8 from monkey C, 6 from monkey W) during the VOR task. The delay times (Figure 3.5) were consistent between the two monkeys (mean delay = 62.7 ± 5.8 ms (SEM); $p > 0.05$, KS-test). The delay times between the two tasks were also consistent (61.7 ± 6.2 ms (SEM); $p > 0.05$, KS-test). We also recorded 6 cells, 3 from each monkey, during both the smooth pursuit and the VOR tasks, under identical eye movement conditions. Delay times were identical in both tasks ($p > 0.05$, KS-test). The mean delay time was 57.7 ± 11 ms (SEM) during the VOR task, and 61.2 ± 9.9 ms (SEM) for the same cells during smooth pursuit (Figure 3.6). We calculated the regression line (slope = 1.04, $R^2 = 0.93$, $p < 0.05$) for the population. These results showed that the proprioceptive

eye position signal in area 3a is unaffected by direction of gaze, retinal motion and vestibular inputs.

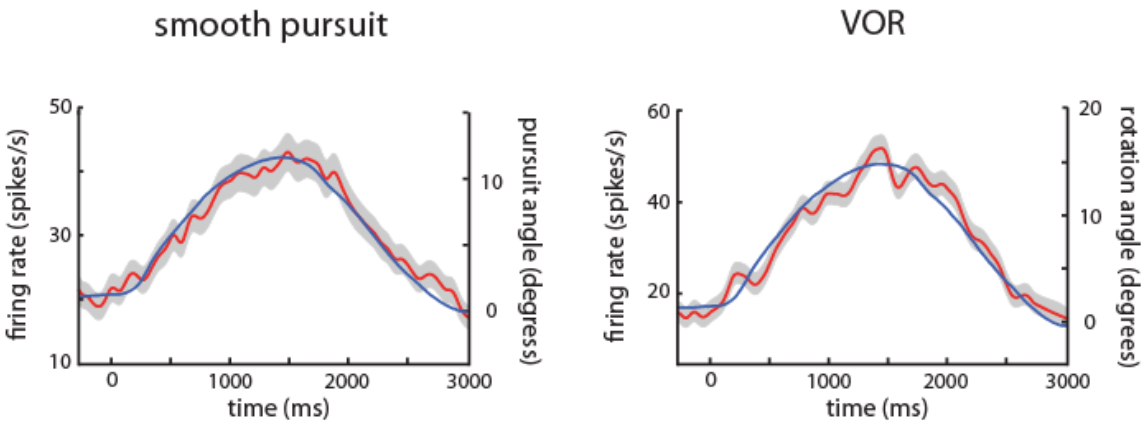
Figure 3.6. **Smooth pursuit versus VOR delay times.** Single neuron delay times for both the pursuit and VOR tasks. Delays in the VOR task plotted against the smooth pursuit task for 6 horizontally tuned cells (3 from each monkey) with the corresponding linear regression (slope = 1.04, R^2 = 0.93, $p < 0.05$). The mean delay time was 57.7 $\pm$ 11 ms during VOR and 61.2 $\pm$ 9.9 ms during smooth pursuit. Error bars indicate 95% confidence intervals for each cell.



We validated the cross-covariance analysis using Fourier analysis. We calculated the mean eye and neuronal signals for all 3-second duration smooth pursuit and VOR trials from both monkeys (Figure 3.7). We then computed the Fourier transformation for each signal and calculated the phase difference between the peaks of the first harmonics for the eye and neuronal signals from each task. The neuron's response lagged the eye by 56.2 ms in the smooth pursuit task (n = 15) and by 65.5 ms in the VOR task (n = 10).

These delays closely approximate the mean delays we found when we analyzed individual cells using cross-covariance.

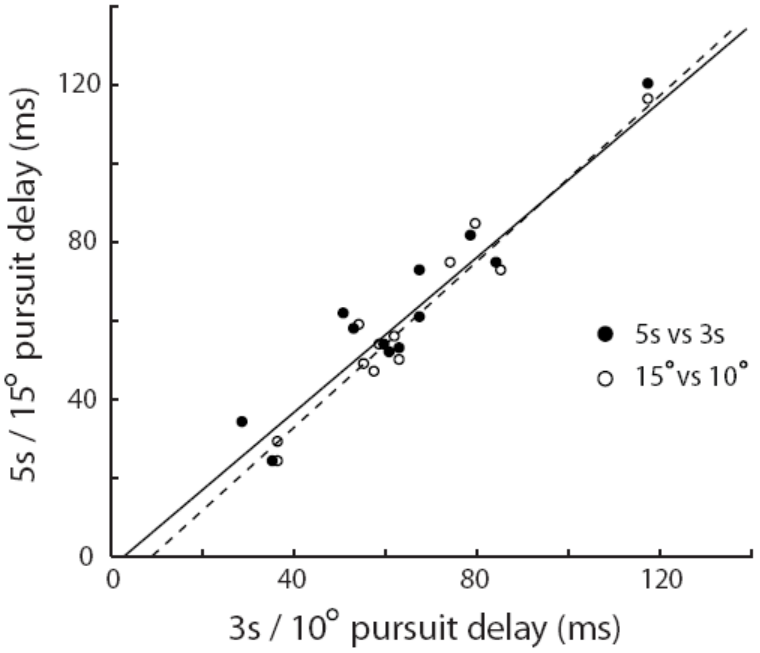
Figure 3.7. **Subpopulation proprioceptive delay times.** Mean eye (blue) and neuronal (red) signals for all 3-second duration smooth pursuit (left) and VOR (right) trials from both monkeys. Shading indicates standard error. The phase difference from Fourier analysis showed the neuronal response lagged eye position by 56.2 ms in the smooth pursuit task (n = 15) and by 65.5 ms in the VOR task (n = 10).



3.3.3. The effect of varying pursuit parameters on the delay

We analyzed the effects of varying task parameters on the eye position signal delay of in dividual cells to see if delay times were affected by any specific attributes of an eye movement. For 13 smooth pursuit cells (7 for monkey C, 5 for monkey W), we modulated two different sets of task parameters: pursuit duration (3 s or 5 s) and amplitude (10° or 15°). Although delays varied between individual cells, there was no significant difference in the delay across the population of cells for either parameter ($p > 0.05$ by KS-test) (Figure 3.8). We calculated regression lines for both the duration (slope = 1.08, $R^2 = 0.90$ for amplitude, $p < 0.05$) and amplitude (slope = 1.11, $R^2 = 0.94$ for amplitude, $p < 0.05$) parameter comparisons.

Figure 3.8. **Single neuron delay times sorted by pursuit condition.** Delay times for the 5s vs. 3s duration comparison (filled circles) and the 15° vs. 10° amplitude comparison (empty circles) with corresponding regression lines (duration is solid line, slope = 1.08, $R^2 = 0.90$, $p < 0.05$; amplitude is dotted line, slope = 1.15, $R^2 = 0.94$, $p < 0.05$) are plotted for both monkeys. There was no difference in delay times in either comparison ($p > 0.05$ by KS-test).



We also analyzed the effects of varying task parameters on eye position signal delays across the population of smooth pursuit cells. In addition to the two previous criteria, duration and amplitude, we also grouped cells according to optimal tuned direction (horizontal or non-horizontal) and maximum pursuit velocity (greater or less than 7°/s). In order to avoid re-sampling cells that had been exposed to multiple task parameters and homogenizing our population results, we randomly distributed these cells and used them only once for each parameter analysis. Again, the results showed no significant delay differences between the monkeys ($p > 0.05$ by KS-test for all cases) for

pursuit duration (Table 3.1), amplitude (Table 3.2), direction (Table 3.3), or velocity (Table 3.4). These results indicated that the tonic proprioceptive signal delay of area 3a neurons is invariant to changes in pursuit parameters, including duration, amplitude, direction and velocity.

Table 3.1. – Table 3.4. **Population delay times grouped by task condition.** Population delay times grouped according to 4 different task conditions: duration (Table 3.1.), amplitude (Table 3.2.), direction (Table 3.3.) and velocity (Table 3.4.). The row headings list the conditions by which delay times are grouped. The delay time for each individual condition is listed for both monkey C and W (column headings), along with the SEM and the number of cells analyzed (in parentheses). There were no significant delay differences within any of the condition comparisons for either monkey ($p > 0.05$ by KS-test).

Table 3.1 - **Effect of pursuit duration on latency**

Pursuit duration	Monkey C	Monkey W
2 or 3s	63.5 ± 9.1 (12)	53.5 ± 15.5 (7)
4 or 5s	66.0 ± 8.4 (8)	62.6 ± 11.0 (8)

Table 3.2 - **Effect of pursuit trajectory amplitude on latency**

Pursuit amplitude	Monkey C	Monkey W
10°	66.1 ± 8.2 (8)	58.5 ± 10.5 (8)
15°	60.7 ± 16.5 (12)	57.6 ± 12.6 (7)

Table 3.3 - **Effect of pursuit trajectory direction on latency**

Pursuit direction	Monkey C	Monkey W
Horizontal	72.1 ± 20.4 (5)	55.6 ± 11.1 (6)
Non-horizontal	62.2 ± 7.5 (15)	60.4 ± 11.2 (9)

Table 3.4 - **Effect of pursuit velocity on latency**

Pursuit speed	Monkey C	Monkey W
< 7° /s	59.8 ± 9.8 (11)	60.6 ± 9.9 (9)
> 7° /s	64.5 ± 11.3 (9)	54.6 ± 14.2 (6)

3.4 Discussion

In this experiment, we have shown that neurons in area 3a of somatosensory cortex convey a signal that reflects the position of the eye in the orbit during both a smooth pursuit and VOR task. The onset delay of this signal is consistent and invariant to changes in the task and eye movement parameters. We will discuss these findings in the context of a reliable proprioceptive eye position signal that could be used for visual and oculomotor processing.

3.4.1. The accuracy and reliability of the area 3a eye position signal

The proprioceptive eye position signal in area 3a has two components: a short-latency phasic component and a persistent tonic component. When Wang et al. used a retrobulbar block to transiently paralyze movement in one eye, both the phasic and tonic responses in contralateral area 3a disappeared and returned when the eye recovered (Wang et al., 2007). This demonstrated that both of these components comprise the proprioceptive eye position signal in area 3a. The phasic proprioceptive response is excitatory for saccades in the on-direction and inhibitory for saccades in the off-direction. From the work of Wang et al., we estimate that the duration of the short-latency inhibitory transient, which masks the onset of the tonic response after saccades in the off-direction, is approximately 100 ms. After 100 ms, the off-direction response settles and the stable eye position signal becomes apparent. It is more difficult to approximate the tonic response delay after saccades in the on-direction, since the excitatory transient is more sustained. Therefore, it

is not possible to dissociate the tonic from the phasic component and accurately determine the onset delay of the tonic response during a saccade task.

We used a smooth pursuit and VOR task to show that the tonic component is accurate about 60 ms after a change in eye position. The reliability of delay times around 60 ms was high in both tasks, as indicated by generally small confidence intervals. Additionally, the Fourier and cross covariance analyses show that area 3a neurons robustly preserve tracking frequency across different eye movements. Our results also show that the length of the proprioceptive delay, whether for individual cells or across the population, is unaffected by eye movement parameters such as amplitude, duration, and direction. This result is expected of a signal that reflects orbital eye position, but would not hold true for a velocity or pursuit signal. These results demonstrate that proprioception can provide cortical pathways with accurate and reliable eye position information under a variety of eye movement conditions.

In the VOR task, the monkey's eye and body positions change, while the angle of gaze in space remains constant. Even though the monkey fixates a stationary target, area 3a neurons reflect a change in position. This finding supports the static head-on-body rotation experiment by Wang et al., which concluded that responses of area 3a eye position neurons represent the position of the monkey's eye in the orbit, rather than the monkey's direction of gaze in space (Wang et al., 2007). Additionally, the retinal image is stable during VOR and moves during smooth pursuit, yet the eye position signals and delays are identical. This demonstrates that the eye position signal in area 3a has little or no visual component. Finally, the closely matched eye position signals and delay times in the pursuit and VOR tasks also suggest that this signal does not receive a vestibular input,

nor does it contribute to mechanistic differences between the two types of eye movements.

3.4.2 The length of the proprioceptive delay

Previous experiments have investigated the timing of eye position neurons in primate central thalamus (Tanaka, 2007). If these thalamic cells lie along the pathways that transmit proprioceptive signals to somatosensory cortex, their long post-saccadic response delay (119.7 ± 87.9 ms) would cast doubt on the validity of our reported area 3a delay times. There are, however, several reasons to believe that this is not the case. Proprioceptive fibers are thought to pass through the spinal trigeminal nucleus (Porter, 1986) to the ventral posterior medial (VPM) nucleus (Martin, 2003). Also, central thalamic nuclei receive eye position inputs via a projection from the brainstem horizontal eye position integrator network (Prevosto et al., 2009) and many of the eye position neurons in central thalamus discharge before the eye movement (Tanaka, 2007). Finally, these thalamic cells show a directional preference along the horizontal axis, whereas area 3a neurons do not (Wang et al., 2007). All of these results suggest that central thalamus does not transmit proprioceptive eye position information to area 3a.

The length of the reported delay exceeds the duration expected from a proprioceptive signal carried by the cranial nerves. We speculate that the extended proprioceptive delay likely stems from the signal's integrative nature: eye position signals in area 3a reflect all directions of visual space, not just ones represented by individual extraocular muscles (Wang et al., 2007). A network of neurons must integrate signals from each extraocular muscle in order to encode all possible eye positions. We

find that horizontal and non-horizontal eye movements yield identical delay times in area 3a neurons, so this integration likely occurs upstream of area 3a. The extended response delay in area 3a may reflect the processing demands of computing the eye position signal.

3.4.3. The function of oculomotor proprioception

The length of the reported delay suggests the proprioceptive eye position signal is too slow to contribute significantly to processes that occur around the time of an eye movement, such as computing the locations of saccade targets or maintaining perceptual stability. Humans can perceive passive changes in eye position, and the proprioceptive eye position signal could clearly provide the information for this (Skavenski, 1972), However, the visual and oculomotor systems as a whole are more likely to rely on the process of corollary discharge for neural calculations that precede the physical movement (Duhamel et al., 1992; Walker et al., 1995; Umeno and Goldberg, 1997; Crapse and Sommer, 2008). There is also significant evidence that efference alone provides sufficient information for visual stability (Sommer and Wurtz, 2002, 2006) and processing for action (Guthrie et al., 1983; Lewis et al., 1998).

While the proprioceptive eye position signal is unlikely to be used for online visual processing for action, it may play a role in the long-term correction of errors in the oculomotor system. We agree that a slow proprioceptive response is well suited for the calibration of a corollary discharge signal (Lewis et al., 2001). While it has been presumed that LIP gain fields derive their eye position input from corollary discharge (Andersen and Mountcastle, 1983; Chang et al., 2009), this has never been experimentally proven. Neck proprioception likely drives head-on-body gain fields in

LIP (Snyder et al., 1998), so it is possible that eye proprioception drives eye position gain fields in LIP. Also, LIP must receive the corollary discharge of eye movement commands, as neurons in LIP show predictive receptive field remapping before a saccade (Duhamel et al., 1992). LIP could compute an error signal for calibration by comparing efferent and afferent signals on a trial by trial basis. While a cortical eye position error signal has never been discovered, evidence suggests that such a signal would only be apparent when perturbations to extraocular muscles produce a persistent discrepancy between efferent command and motion of the eye in the orbit (Lewis et al., 1994; Dengis et al., 1998).

The oculomotor and visual systems have access to an accurate proprioceptive representation of eye position approximately 60 ms after an eye movement. The existence of a slow but reliable delay is a strong argument that this signal is useful for some visual or oculomotor processes. The present findings indicate that area 3a neuronal activity is not likely to be utilized for visual stability or motor command, although it may be of some use for regulating later phases of movement execution. More likely, this signal is used in the long-term calibration of the oculomotor system for accurate eye movements.

Chapter 4.

The oculomotor system does not use visual gain fields to calculate saccade target positions

4.1 Introduction

The gain field coordinate transformation model is a neurobiological theory that has been proposed to solve the problem of spatial accuracy despite a constantly moving eye (Zipser and Andersen, 1988). The visual response of parietal neurons often varies monotonically with increasingly eccentric orbital position, the 'gain field' (Andersen and Mountcastle, 1983; Andersen et al., 1985a), and a number of computational theories have used gain fields to solve the problem of spatial accuracy by encoding a distributed spatiotopic map (Zipser and Andersen, 1988; Salinas and Abbott, 1996; Andersen, 1997; Pouget and Sejnowski, 1997; Pouget and Snyder, 2000; Cassanello and Ferrera, 2007). In this way, gain fields have become a generally accepted mechanism by which the brain calculates object locations in space.

The gain field model relies on an extraretinal signal in order to maintain spatial accuracy around the time of the saccade. There are two extraretinal signals that provide information about a saccade: corollary discharge, a copy of the motor command to the eye, and oculomotor proprioception, a feedback signal generated by stretching or contracting the extraocular muscles. Of the two signals, corollary discharge is the only one that is available before an eye movement, and has been shown to be sufficient for the localization of saccade targets (Guthrie et al., 1983). Proprioceptive feedback, on the

other hand, is only available after an eye movement (Wang et al., 2007) and is thought to play a role in the calibration of the oculomotor system (Lewis et al., 2001).

The gain fields must accurately reflect eye position in order to be useful for computing object locations in supraretinal coordinates. While the gain fields are thought to derive their eye position input from corollary discharge (Andersen and Mountcastle, 1983; Chang et al., 2009) and be accurate around the time of a saccade, this has never been experimentally tested. We used a two- and three-saccade task to study the time course of the eye position modulation of LIP visual responses and determine the accuracy of the gain fields immediately after a conditioning saccade. We report that after a monkey makes a saccade, visual gain fields in the lateral intraparietal area (LIP) are inaccurate for more than 150 ms and do not reliably reflect the postsaccadic eye position. Nonetheless, when monkeys are asked to make saccades to stimuli that appear immediately after a conditioning saccade, all saccades were accurate despite the inaccuracy of the gain fields.

4.2 Methods

Two rhesus monkeys (*Macaca mulatta*), both male (Monkey G and Monkey W), were used in these experiments. Monkey G weighed 7kg and Monkey W weighed 11kg.

4.2.1 Surgery and Recording

We positioned 2 cm recording chambers at posterior 5 mm, lateral 12 mm using magnetic resonance images taken from the anesthetized animals. We identified area LIP by typical neuronal activities during a simple memory-guided saccade task (Hikosaka and Wurtz, 1983).

4.2.2 Behavioral tasks

We first trained the monkeys to perform a simple memory-guided saccade task. We used this task to map the receptive fields of the neurons which we isolated. In this task, the monkeys fixated a stable spot of light, measuring 2° by 2°, within a ±5° window. A small white square flashed for 50 ms at a location in the visual field while the monkeys continued to maintain fixation. The fixation point was extinguished following a variable delay between 500 to 1000 ms, and the monkeys made a saccade to the location where the square flashed.

We then trained the monkeys to perform a 9-point variation of the memory-guided saccade task, which we used to map the directional tuning of visual gain fields in LIP neurons (Andersen and Mountcastle, 1983). In this task, the fixation point for the memory-guided saccade task appeared randomly in one of nine possible locations, either in the center of the screen or in one of eight evenly spaced locations (10° between fixation stimuli) arranged in a square around the center (Figure 4.1).

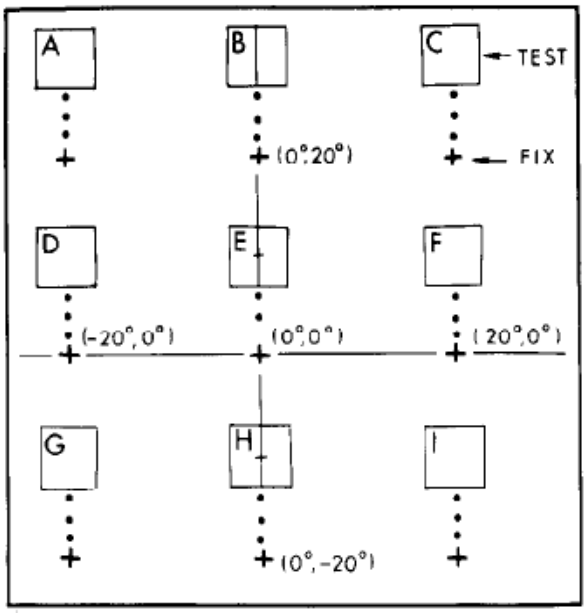


Figure 4.1. **The gain field mapping task.** Diagram of the 9-point memory-guided saccade task used to map the orientation of the gain field for an individual neuron. Crosses represent potential locations of fixation point. Squares represent receptive field locations, which were constant for all fixation points, but varied from cell to cell.

In order to test the time course of visual gain field modulation of LIP neurons following a saccade, we trained the monkeys to perform the two-saccade task (Figure 4.2A) after they had reached an asymptotic performance level in the 9-point memory-guided saccade task (98% correct). In this task, the monkeys were required to perform two sequential saccades. The first saccade had an amplitude of 20° along the direction of the gain field of the neuron under study, either from an eye position with a strong visual response to one with a weak visual response (high-to-low gain field direction), or vice versa (low-to-high gain field direction). We then flashed a 50 ms visual probe in the neuron's receptive field after a variable delay (50, 100, 150, 250, 350, 450, 650 ± 15ms) at the end of the first saccade. Then, after another delay (400 to 1000 ms), the second

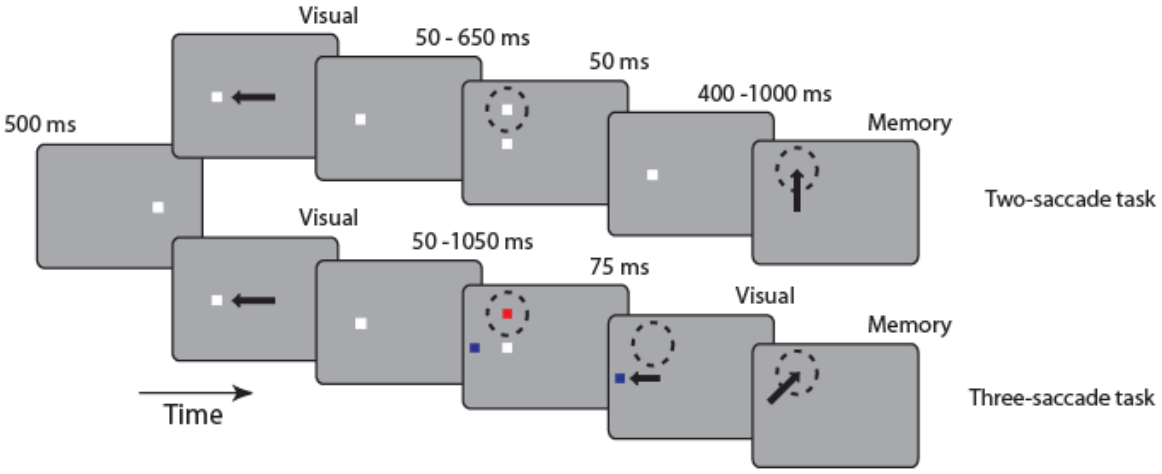


Figure 4.2. **The two- and three-sacade tasks.** Diagram of timing of visual stimuli in the two- (top) and three-saccade (bottom) tasks. Dashed circle represents RF of neuron under study and arrows, directions of saccades. In the three-saccade task, the blue stimulus flashed outside of the RF and is the target for the second, visually guided saccade. The red probe flashed inside the RF and is the target for the third, memory-guided saccade, which immediately followed the second saccade.

fixation point disappeared and the monkey made a memory-guided saccade to the location of the visual probe. In each two-saccade task block, normal probe trials were randomly interleaved with trials in which probes appeared well outside the RF (> 20° degrees) or not at all to ensure the monkey attended to the probe's location.

We also trained both monkeys to perform the three-saccade task (Figure 4.2B), which consisted of a 20° conditioning saccade followed by the two targets of the traditional double-step saccade task (Hallett and Lightstone, 1976). This three-saccade task requires a supraretinal mechanism in order to make the third saccade accurately because there is a dissonance between the retinal vector of the stimulus and the vector of the saccade necessary to acquire it. In the three-saccade task, the monkeys first made a saccade along the direction of the gain field of the neuron under study in either the high-to-low or low-to-high gain field direction. Then, two targets, one blue and one red (the probe), appeared simultaneously, 50, 550 or 1050 ± 25 ms after the end of the first saccade. The blue target was placed outside the cell's receptive field (> 20° degrees) and remained on until the monkey made a visually guided saccade to its location. The red probe, which flashed for 75 ms in the receptive field of the neuron and had disappeared by the time of the second saccade, indicated the target location for a third, memory-guided saccade. In each three-saccade task block, normal probe trials were randomly interleaved with trials in which the red probe randomly appeared outside of the RF, but always far away (> 20° degrees) from the blue target, to ensure the monkey attended to the red probe's location.

We imposed fixation requirements in each of our three tasks (9-point memory-guided, two-saccade and three-saccade) to ensure that the monkeys performed the tasks

correctly. Each trial started when a fixation point appeared, and if the animal maintained fixation within a ±3° window for 500 to 1000 ms, the task began. After this, the monkeys were required to make saccades to subsequent targets within a ±5° window. After the final saccade and an additional 200 ms fixation, the trial terminated and a drop of liquid reward was provided. There was no constraint on the monkeys' eye position before or after each trial.

4.2.3 Data analyses

We classified a cell as a visual gain field neuron if its response from 0 to 160 ms after the late probe presentation differed significantly for saccades in opposing directions (two-sample t-test, $p > 0.05$) and the peak activity difference which was at least 15% of the mean response. We determined static postsaccadic gain field responses based on the late probes flashed at 650 and 1050 ms in the two-and three-saccade tasks, respectively. We calculated static gain field differences by subtracting responses to late probe flashes for saccades in the low gain field direction from responses to late probe flashes for saccades in the high gain field direction.

We calculated gain field update times by fitting a sigmoid curve to the peak visual responses of all probe delays for saccades in one gain field direction. We defined the gain field update time as the probe delay subsequent to the inflection point of the sigmoid fit.

We calculated the gain field index to quantify the relationship between the early probe response mislocalization and the static gain field difference. The gain field gain field index for a saccade in one direction was calculated as: (early probe response – late probe response) / (high gain field response – low gain field response). Early probes

flashed at 50ms in both tasks, and the late probes flashed at 650 and 1050 ms in the two- and three-saccade tasks, respectively.

We reoriented all the behavioral eye position data, which was collected in absolute coordinates, so that we could observe the effects of the first and second saccades on the monkeys' behavior. The distribution of first and second saccade directions was random and was determined by the orientation of the gain field and receptive field of the neuron, respectively. Behavioral data were reoriented so that the first or the second saccade vector pointed in the horizontal, rightward direction:

$$x' = x*\cos((360-\theta)*\pi/180)-y*\sin((360-\theta)*\pi/180)$$

$$y' = x*\sin((360-\theta)*\pi/180)+y*\cos((360-\theta)*\pi/180)$$

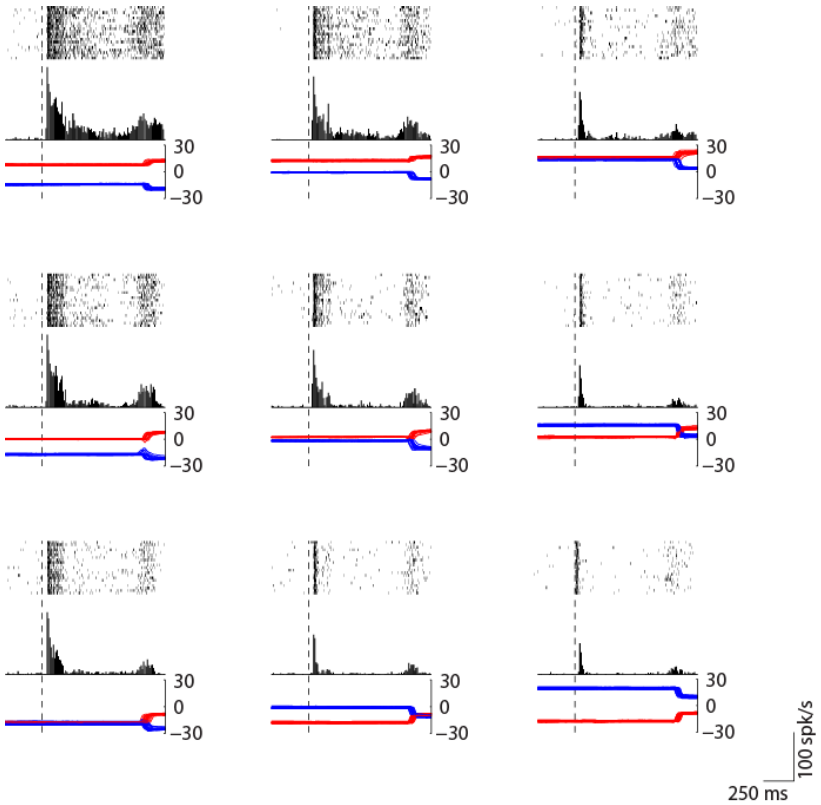
x and y represent the original saccade vector in real space, θ the angle of rotation, and x' and y' the reoriented saccade vector. Consequently, corresponding saccade mislocalization vectors for each trial block, defined as: mean endpoint of saccades to early probe – mean endpoint of saccades to late probe were also reoriented. We used a KS-test to evaluate the effect of either the first or second saccade direction on the distribution of mislocalization vectors.

4.3 Results

4.3.1 Behavior

We trained both monkeys in the memory-guided saccade task, which they performed correctly on 95–99% of the trials when the fixation point was within 10° of the center. We also trained both monkeys in the two-saccade and three-saccade tasks. Monkey G and Monkey W performed both tasks at 90–95% and 75-80 % accuracy, respectively.

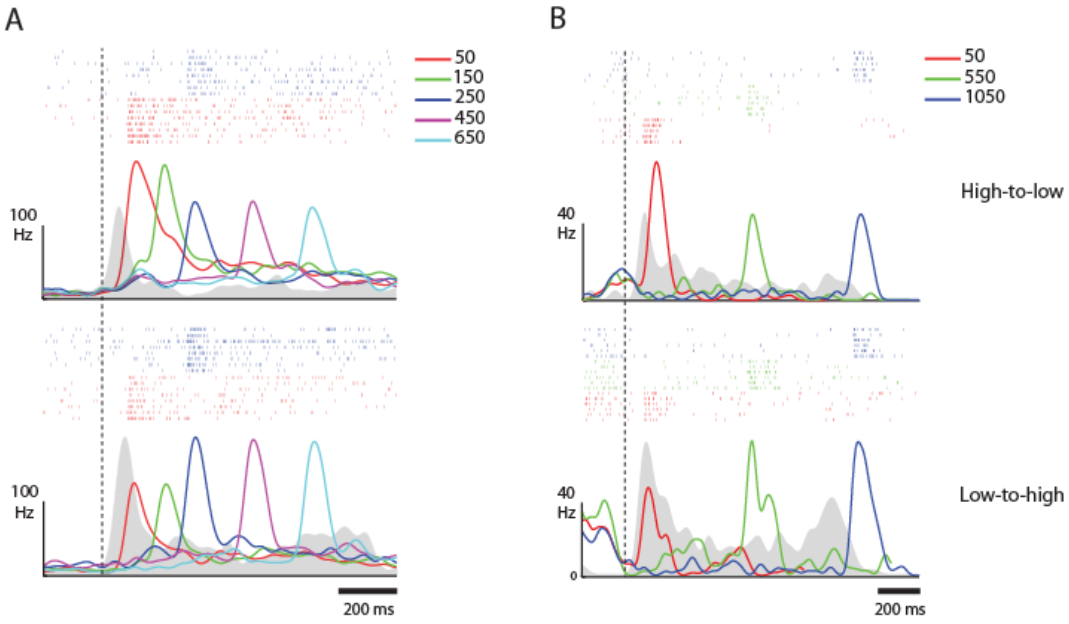
Figure 4.3. **Static gain field response of LIP neuron.** Single LIP neuron example of response in the memory-guided saccade task at nine different fixation points, spaced 10° either horizontally and/or vertically. Activity is aligned on saccade target presentation (dotted line). The histogram beneath each raster average, without smoothing, the activity of the raster above, with a bin width of 20 ms. Eye positions for each trial are superimposed beneath each raster (horizontal, blue; vertical, red).



4.3.2 The time course of visual gain fields in LIP

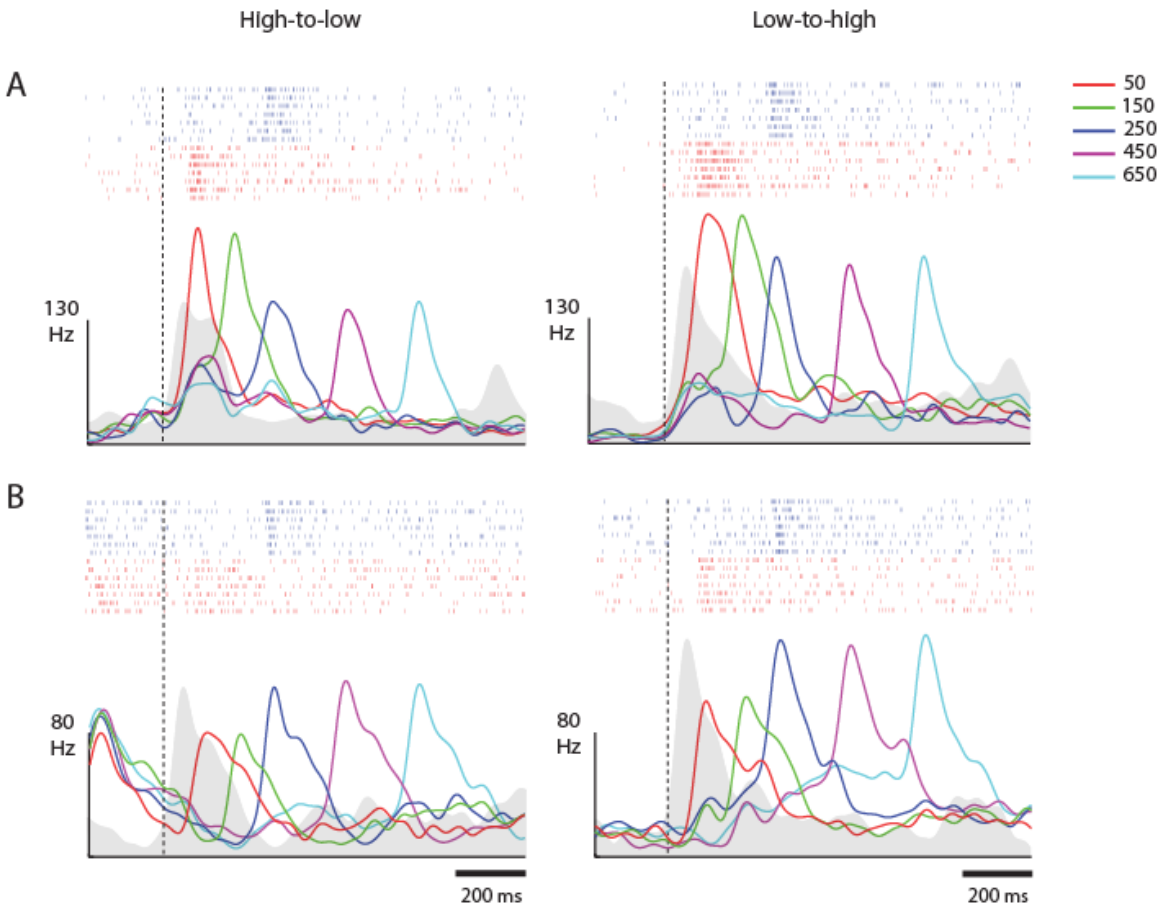
We recorded a total of 89 LIP neurons that exhibited static visual gain fields in two monkeys (Figure 4.3), 47 in the two-saccade task and 42 in the three-saccade task. We observed similar types of neural responses to stimuli flashed 50 ms after the first saccade in both tasks and for both monkeys. We pooled these results for the purposes of analyzing responses to stimuli flashed immediately after the first saccade. 61 of the 89 neurons with

Figure 4.4. **Consistent visual responses of LIP neuron. (A)** Single LIP neuron example of gain field modulated visual response in the two-saccade task for identical saccades, but in opposite gain field directions (top, high-to-low; bottom, low-to-high). Activity is aligned on probe onset, averaged across trials, convolved with a 20 ms Gaussian filter, and plotted according to probe delay from end of first saccade (dotted line). Colors indicate different timings of the probe (100 and 350 ms not shown). Rasters show spikes in the 50 (bottom) and 250 (top) ms probe delay conditions. The solid curve (grey) shows the static gain field response at the postsaccadic orbital position during the memory-guided saccade task. **(B)** Single LIP neuron example of gain field modulated visual response in the three-saccade task for saccades in the high-to-low (top) and low-to-high (bottom) directions with corresponding rasters (50 ms, bottom; 550 ms, middle; 1050 ms, top).



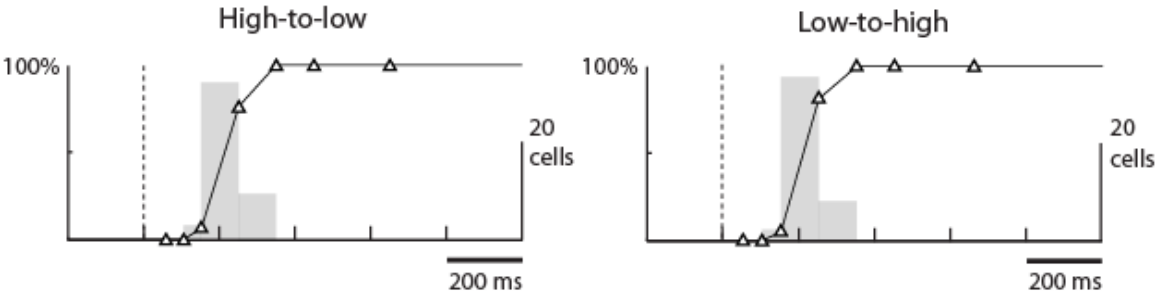
static gain fields (69%) responded to a stimulus flashed 50 ms after the end of the saccade with the intensity expected from the presaccadic eye position, as if the eyes had not moved (Figure 4.4A for the two-saccade task; Figure 4.4B for the three-saccade task). This modulation consistently reflected the presaccadic orbital position for saccades in both high-to-low and low-to-high gain field directions. The remaining 28 cells (31%)

Figure 4.5. **Inconsistent visual responses of LIP neurons. (A)** Single LIP neuron example of inconsistent visual gain field response in the two-saccade task that shows high-to-low modulation for saccades in both the high-to-low (left) and low-to-high (right) gain field directions with corresponding 50 (bottom) and 250 (top) ms rasters. **(B)** Single LIP neuron example of inconsistent visual gain field response in the two-saccade task that shows low-to-high modulation for saccades in both the high-to-low (left) and low-to-high (right) gain field directions with corresponding 50 (bottom) and 250 (top) ms rasters.



gave responses that inconsistently reflected the presaccadic orbital position. For some of these cells, the immediate postsaccadic response was higher than the expected postsaccadic gain field value for both high-to-low and low-to-high gain field saccades (Figure 4.5A); for others, the immediate postsaccadic response was lower (Figure 4.5B).

Figure 4.6. **Update delays of LIP cells during the two-saccade task**. Update delays for all neurons during the two-saccade task (n = 47) in the high-to-low (left) and low-to-high (right) directions. Dotted line represents end of first saccade..Triangles represent probe presentation times. Solid line represents total percentage of cells updated (left y-axis) and grey bars represent number of cells updated in each probe interval (right y-axis).



We did not find any cells that exhibited the expected postsaccadic visual responses 50 ms after saccades in both directions.

When the visual probe flashed later, both the consistent and inconsistent neurons gave the eye-position-modulated response predicted by the postsaccadic gain field (Figure 4.4A for a consistent cell in the two-saccade task, Figure 4.4B for a consistent cell in the three-saccade task, Figure 4.5 for inconsistent cells in the two-saccade task). The time course of the orbital position modulation was apparent in the visual responses for the two-saccade task (Figure 4.6). Only two cells exhibited visual responses that reflected the postsaccadic orbital position by 150 ms after the first saccade. The majority of cells (n = 40, 85%) were accurate by 250 ms, and the remainder were accurate by 350 ms (n = 7). 43 of the 47 cells (91%) became accurate in the same stimulus interval for saccades in either direction. All of the cells in the three-saccade task (n = 42) were accurate in the 550 ms probe condition.

4.3.3 Saccadic accuracy during the three-saccade task

In the three-saccade task the monkey had to perform the classic double-step saccade after a conditioning saccade. Despite the inaccuracy of the gain fields immediately after the first saccade in the three-saccade task, third saccades were largely accurate regardless of when the probe flashed (Figure 4.7). There were only small mislocalizations of third-saccade endpoints in the early compared to the late probe condition (50 and 1050 ms delay, respectively) for both monkeys (2.89° maximum, 0.90 ± 0.52° mean). When we reoriented the mislocalization vectors (*see methods*) according to the direction of the gain field (first) saccade, there was no net mislocalization effect (mean x = 0.05 ± 0.68°, $p > 0.05$ by KS-test; mean y = -0.05 ± 0.79°, $p > 0.05$ by KS-test) (Figure 4.8A). When we reoriented the mislocalization vectors according to the direction of the second saccade, however, a consistent and significant effect emerged (x =

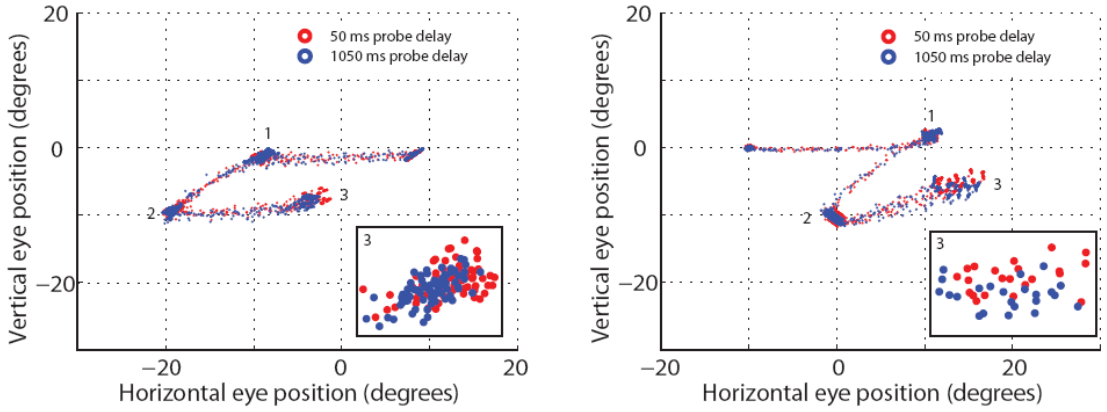
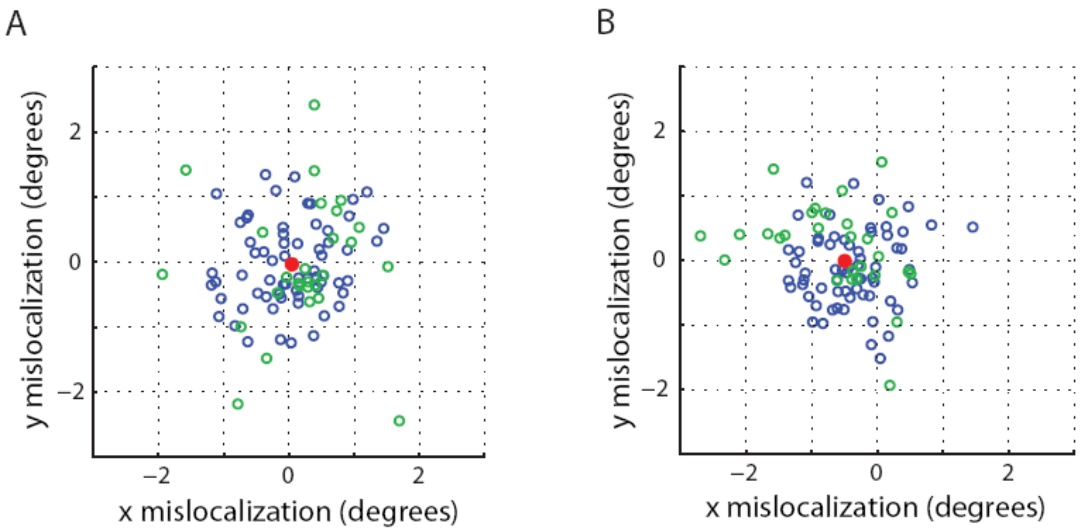


Figure 4.7. **Saccadic accuracy in the three-saccade task.** Eye traces from all trials in one experimental block are shown for first saccades in both directions (monkey G). Comparison of behavior when the probe is presented early (50 ms, red) and late (1050 ms, blue). Numbers (1, 2, 3) indicate order of saccades. Third saccade endpoint distributions for both delay conditions are shown (inset).

-0.47 ± 0.69°, $p < 0.05$ by KS-test; y = -0.01 ± 0.64°, $p > 0.05$ by KS-test) (Figure 4.8B). Therefore, the small mislocalization of the third saccade in the early probe condition was unrelated to the inaccuracy of the gain fields, and was instead determined by the direction of the preceding (second) saccade.

Figure 4.8 **Probe mislocalization in the three-saccade task (A)** Plot of third saccade mislocalization vectors in monkey G (blue) and W (green) normalized to first saccade vectors aligned in the horizontal, rightward direction (mean x = 0.05 ± 0.68°, mean y = -0.05 ± 0.79°; KS-test, $p > 0.05$). Mean mislocalization shows no net effect (red dot). **(B)** Plot of third saccade mislocalization vectors when reoriented according to second saccade vectors normalized to the horizontal, rightward direction. (mean x = -0.47 ± 0.69°, Lilliefors test, $p > 0.05$; mean y = -0.01 ± 0.64°, KS-test, $p > 0.05$). Mean mislocalization corresponds to the direction opposite that of the second saccade (red dot).



4.3.4 Quantifying the inaccuracy of the gain field response

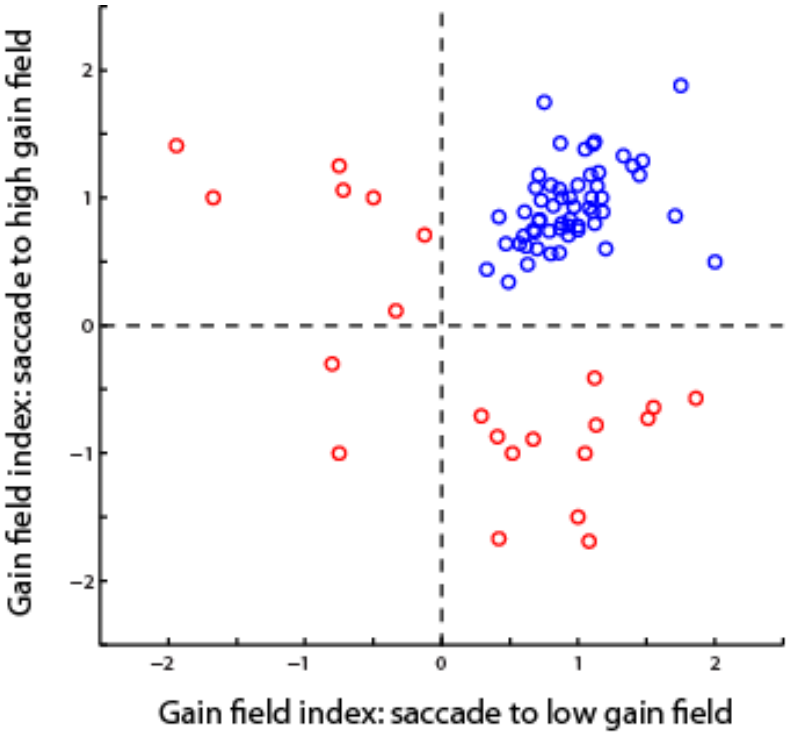
We quantified the relationship between the early, 50 ms delay probe response and the expected postsaccadic gain field response for all recorded neurons by calculating a gain field index. The gain field index for a saccade in one direction was calculated as:

(early probe response – postsaccadic gain field response) / (presaccadic gain field response – postsaccadic gain field response). Saccades that showed high-to-low activity modulation produced positive gain field index values and saccades that showed low-to-high activity modulation produced negative gain field index values. An index of 1 meant the early postsaccadic response reflected the presaccadic eye position. An index of zero meant that the early probe response reflected the postsaccadic eye position. None of the cells we recorded displayed visual activity immediately (< 100 ms) after a saccade that significantly matched the gain field modulation predicted by the late probe response (gain field index < 0.05).

The consistent cells, whose immediate postsaccadic response resembled the presaccadic visual response, had a mean gain field index of 0.98 ± 0.42 for high-to-low gain field saccades and 1.02 ± 0.44 for low-to-high gain field saccades (Figure 4.9). The inconsistent cells, whose immediate postsaccadic responses were modulated little, if at all, by orbital position showed positive gain field indices for saccades in one direction (mean = 2.12 ± 2.07; one-sample t-test, $p < 0.05$) and negative gain field indices for saccades in the other (-1.73 ± 2.03 ; one-sample t-test, $p < 0.05$).

The early probe responses in the inconsistent cells, while spatially inaccurate, were higher or lower than the expected postsaccadic gain field responses for saccades in both gain field directions. These cells might encode the spatial location of the target, either by a static or scalar rate modulation mechanism. We did not, however, find consistent evidence for a static rate difference between early and late probe responses (mean difference = 22.56 ± 29.97 spk/s; one-sample t-test, $p < 0.05$; Lilliefors test, $p < 0.05$) or scalar modulation of the late probe response (mean quotient = 1.37 ± 0.43; one-

Figure 4.9. **Population gain field indices.** Gain field indices of visual gain field modulation in the 50 ms probe delay condition for all neurons recorded in the two- and three-saccade tasks. Gain field indices for saccades in the low-to-high direction are plotted against gain field indices for saccades in the high-to-low direction. Gain field indices for individual consistent cells (blue circles) were strongly predictive of the presaccadic eye position (mean x = 1.02 ± 0.44, mean y = 0.98 ± 0.42). Gain field indices for individual inconsistent cells (red circles) showed no predictive value for the pre- or postsaccadic eye positions (mean positive = 2.12 ± 2.07, mean negative = -1.73 ± 2.03).

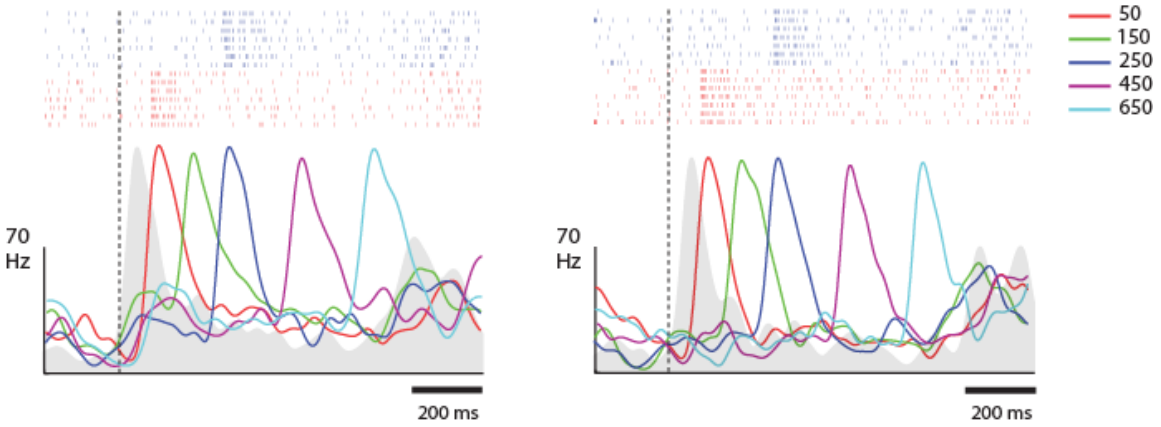


sample t-test, $p < 0.05$; Lilliefors test, $p < 0.05$). Therefore, it is unlikely that accurate spatial information could be computed from these inconsistent visual responses immediately after a saccade.

4.3.5 Visual responses in cells that lack gain field modulation

We recorded 13 cells that lacked eye position modulation of visual responses, 5 cells during the two-saccade task and 8 cells during the three-saccade task, to test if the spatial inaccuracy of immediate postsaccadic visual responses were simply the result of flashing stimuli around the time of a saccade. For these cells, responses to visual probes were not different regardless of probe delay length and the direction of the first saccade (ANOVA, $p > 0.05$) (Figure 4.10).

Figure 4.10. **Visual responses of LIP neuron without gain fields.** Single LIP neuron example of visual responses in the two-saccade task that did not show postsaccadic modulation for saccades in two opposing directions. Corresponding 50 (bottom) and 250 (top) ms rasters are shown.



4.4 Discussion

In this experiment, we have shown that the visual responses of LIP neurons modulated by gain fields are spatially inaccurate for approximately 150 ms after a saccade. We have also shown that saccades to targets flashed during this period are generally accurate, even if an intervening saccade creates a dissonance between the saccade goal and the retinal location of the saccade target. We will discuss these findings in the context of the gain field coordinate transformation model, which is widely thought to be the mechanism used

by the brain to maintain a spatially accurate representation of objects across eye movements.

4.4.1. The gain fields and spatial accuracy

Although LIP neurons are modulated by eye position, our results in the two-saccade task show that gain field modulated visual responses are not spatially accurate immediately after a saccade. For more than 150 ms, the visual responses of the majority of LIP neurons reflect the presaccadic orbital position. If the brain performs a gain field transformation using visual responses immediately after a saccade as a basis function or the hidden layer of a network, a saccade target should be calculated relative to the presaccadic eye position and saccades to it should be grossly inaccurate (Zipser and Andersen, 1988; Pouget and Snyder, 2000). Nevertheless, monkeys make accurate saccades to stimuli flashed immediately after a conditioning saccade, even when there is a dissonance between the retinal location of a stimulus and the saccade necessary to acquire it.

These results call into question the gain field model that calculates saccade target positions online (Andersen, 1997). The gain field model, according to our results, cannot accurately solve the double-step task. A mechanism that has the temporal properties to enable monkeys to make such accurate saccades is the dynamic shifting of receptive fields at the time of a saccade, which can easily solve the double-step saccade problem. This mechanism has been shown to be driven by corollary discharge and occurs before the saccade (Sommer and Wurtz, 2006). In the shifting receptive field model, the spatial

location of the second saccade target is updated via a vector subtraction and is accurate by the time the first saccade is complete.

4.4.2. Modulation of LIP visual responses around time of a saccade

A previous study by Bremmer and colleagues reported that the visual responses of LIP neurons are not modulated around the time of a saccade (Bremmer et al., 2009). Their results agree with our finding in cells that lacked gain fields, in which activity was not significantly different immediately (50 ms) and well after (> 500 ms) the first saccade, but seem to contradict our primary finding, that visual responses to probes flashed immediately after saccades are spatially inaccurate. There are some key task differences that may help explain these discrepancies. In the study by Bremmer et al., the conditioning saccade was always in the same horizontal direction, from left 10° to right 10°. When we consider that about 50% of LIP neurons have robust planar gain fields (Andersen et al., 1990), and only a fraction of these are horizontally tuned, the lack of an overall modulatory gain field effect is unsurprising. Bremmer et al. also averaged visual responses across the entire population of LIP neurons (n = 154). It is likely that some cells demonstrated perisaccadic enhancement or suppression of visual responses. Averaging across the population, however, would nullify some, if not all, of the effects seen among individual cells. Finally, Bremmer et al. used large vertical bar stimuli that spanned the entire vertical field of view, rather than small visual targets that stimulated specific parts of the receptive field. Non-specific stimulation of the receptive field may have unpredictable modulatory effects on the visual response, since the stimulus covers multiple regions of the gain field. In summary, while it appears some LIP neurons

respond accurately to visual stimuli flashed around the time of a saccade, these responses are seen only among cells that are not modulated by gain fields.

4.4.3. The inconsistent response

LIP neurons do not respond to visual stimuli at the intensity predicted by the postsaccadic gain field immediately after a saccade. While the majority of these cells consistently exhibit visual responses that indicate the presaccadic eye position, we also found a minority population of cells that inconsistently reflected the presaccadic eye position immediately after the saccade. The visual responses in these cells were either higher or lower than the expected postsaccadic responses for saccades in both directions of the gain field. While these responses were also spatially inaccurate, their pattern is more difficult to explain. There are several possible explanations for the inconsistent responses: they indirectly encode the correct gain field value, they are a generalized result of flashing visual stimuli around the time of a saccade, or they reflect a component of the eye position input signal.

Although the visual responses of the inconsistent cells to early probes do not directly reflect the postsaccadic gain field, there are several ways in which they could still encode the expected gain field value. One possibility is that the early probe response is the expected postsaccadic response plus or minus an additional fraction of the gain field difference between the two eye positions. This modulation pattern seems unlikely based on the distribution of computed gain field indices for the inconsistent cells. Another possibility is that the early probe response may be the expected postsaccadic response multiplied by a scalar value or plus/minus a static firing rate. These modulation patterns

also seem unlikely: we could not predict the postsaccadic response by multiplying the early response by a scalar or by adding/subtracting a constant. Therefore, it seems unlikely that LIP could indirectly calculate the spatially accurate late gain field response from the inconsistent responses to probes flashed immediately after a saccade, even if LIP were aware that the gain fields were not directly accurate.

The inconsistent response could also reflect some form of generalized postsaccadic enhancement or suppression of visual activity. Postsaccadic enhancement is a relatively common occurrence in the brain, and is believed to underlie increased visual sensitivity following a saccade. Postsaccadic enhancement has been observed as low as the lateral geniculate nucleus (LGN) (Ramcharan et al., 2001; Reppas et al., 2002; Royal et al., 2006) and in parietal regions such as MT, MST and VIP (Ibbotson et al., 2008; Bremmer et al., 2009)**.** Presaccadic suppression of visual activity has also been observed in these brain regions, although postsaccadic suppression is uncommon. Two observations from our data, however, weaken the likelihood of this explanation: only a fraction of LIP neurons are transiently excited or inhibited immediately after a saccade, and this type of modulation is entirely absent in LIP neurons that lack gain fields.

More likely, the inconsistent response reflects a component of the eye position input that modulates LIP gain fields. As our results show, LIP neurons that are not modulated by eye position do not show any visual response modulation immediately after a saccade. Therefore, it seems reasonable to attribute the inconsistent response to the input that provides LIP neurons with eye position information. Phasic enhancement and suppression are seen immediately after a change in eye position and precede the onset of the tonic eye position signal in area 3a of somatosensory cortex. While the inconsistent

cells also show phasic enhancement and suppression of the visual response, their response pattern is different. In area 3a, suppression occurs for saccades in the off-direction and enhancement occurs for saccades in on-direction (Wang et al., 2007), whereas in LIP, suppression and enhancement are cell specific, but saccade direction independent. These findings suggest that the enhancement and suppression seen in LIP are not a direct reflection of phasic activity from area 3a, although they could certainly reflect a portion of the area 3a response to a change in eye position.

4.4.4. Mislocalizations of the third saccade

Despite the inaccuracy of the gain fields in the immediate postsaccadic epoch, our results show that monkeys have no trouble solving the three-saccade task and make generally accurate saccades to the probe (the third saccade target). Monkeys did, however, slightly mislocalize the probe in the early compared to the late probe condition. The mislocalization of objects flashed around the time of a saccade is a well-known phenomenon in both humans (Honda, 1991; Dassonville et al., 1992; Schlag and Schlag-Rey, 1992, 1995; Ross et al., 2001) and monkeys (Jeffries et al., 2007). In humans, the mislocalization is bimodal: stimuli that appear before the saccade are mislocalized in the direction of the saccade and stimuli that appear after the saccade are mislocalized in the direction opposite the saccade. In monkeys, perisaccadic mislocalization is consistently in the opposite direction (the 'anti-direction') of the saccade preceding the stimulus presentation (Jeffries et al., 2007).

In light of these previous experiments, we were surprised to find that the first saccade in the three-saccade task did not contribute to the direction of the probe

mislocalization vector. In the three-saccade task, stimuli for the double-step task flashed 50 ms after the end of the first saccade, which is during the epoch when Jeffries et al. reported perisaccadic mislocalization of visual stimuli. A small mislocalization of the probe in the presaccadic direction of the first saccade would have correlated with the neuronal responses and made sense in the context of previous behavioral findings. The absence of a net mislocalization, however, suggests that errors in the oculomotor system are only determined by the direction of the most recent (in the three-saccade task, the second) saccade. It is possible that potential mislocalizations due to the first saccade were eliminated by the visually persistent second saccade stimulus. Nonetheless, it seems that the inaccuracy of the gain fields around the time of a saccade do not predict the specific mislocalizations seen in the three-saccade task and cannot explain the general phenomenon of perisaccadic mislocalization.

When we oriented the mislocalization vectors so that the direction of the second saccade was in the rightward, horizontal direction, a net mislocalization vector in the anti-direction of the second saccade emerged. According to the work of Jeffries et al., when the targets of a double-step task flashed simultaneously, monkeys mislocalized the second saccade target. Therefore, we think it is likely that the monkey mislocalized the third saccade target (the probe) even in the late probe condition, since it flashed at the same time as the second saccade target. Unfortunately, we could not confirm this mislocalization since we did not have monkeys make visually guided saccades to the veridical probe location. Nevertheless, when we compared the behavioral results of the early and late probe conditions, we noticed a net probe mislocalization in the anti-direction of the second saccade. Given that the only difference between the two probe

conditions was when the double-step stimuli were presented after first saccade, it appears that a conditioning saccade that precedes the stimuli for the double-step task does not contribute a mislocalization vector to the final saccade, but merely enhances the error predicted by the anti-direction of the saccade that precedes it.

4.4.5. The function of the gain fields

In order discuss the function of the gain fields, it is important necessary to speculate on the origin of the eye position modulation seen in the LIP gain fields. The eye position modulation of the gain fields could arise from a corollary discharge, but the slow time course is more consistent with that of the proprioceptive eye position signal in area 3a of somatosensory cortex(see Chapter 3). Oculomotor proprioception could provide visual gain fields in LIP with eye position information, just as neck proprioception likely provides LIP head gain fields with head-on-body information (Snyder et al., 1998). While no specific projections from area 3a to LIP have been discovered in the macaque, there are extensive connections between area 3a and the posterior parietal cortex in the marmoset monkey (Huffman and Krubitzer, 2001).

If LIP gain fields derive their input from oculomotor proprioception, their utility in visual and oculomotor processes would be limited. The visual system can accurately localize targets in the absence of proprioceptive feedback (Guthrie et al., 1983). Similarly, the oculomotor system can maintain fixation and alignment and execute saccade even when the afferent pathways carrying proprioceptive eye position information are blocked. Researchers have speculated that oculomotor proprioception

provides slow eye position feedback and is more likely involved in oculomotor system calibration than online target selection (Lewis et al., 2001).

Gain field modulation of LIP neurons is inaccurate for at least 150 ms after the end of a saccade. The slow time course of the gain fields argues against a role in updating the spatial location of saccade targets across eye movements. Although our results are limited to the oculomotor system, it is unlikely that the skeletal motor system has access to visual information that uses an entirely different, accurate and rapid gain field system. We believe that gain fields may instead provide feedback to recalibrate the efference copy signal after an eye movement.

Chapter 5.

Discussion

5.1 Summary

A major problem in psychology has been how the brain can compute an accurate visual map for action despite a constantly moving eye. Previous experimental data have demonstrated that neurons in the posterior parietal cortex are modulated by eye position (Andersen and Mountcastle, 1983; Andersen et al., 1990). The gain fields, including those in LIP, have become a widely accepted theory of how the brain computes object locations in supraretinal coordinates, thus solving the problem of spatial accuracy for eye movements (Zipser and Andersen, 1988). Gain field theory now extends far outside the realm computing saccade trajectories and includes models for reach movement coordination (Chang et al., 2009), attention (Salinas and Abbott, 1997) and spatial neglect (Pouget and Sejnowski, 1997).

In contrast, previous experiments studying the proprioceptive eye position signal have marginalized its role in oculomotor and visual processes that occur around the time of a saccade (Guthrie et al., 1983; Sparks and Mays, 1983; Lewis et al., 1994). The most important role of proprioception appears to be calibrating and maintaining the spatial accuracy of the oculomotor system in the occurrence of a disparity between the motor command and actual eye movement (Lewis et al., 2001). A proprioceptive representation of eye position exists in area 3a of somatosensory cortex (Wang et al., 2007), although its accuracy and reliability around the time of an eye movement has not been studied.

5.1.1 The time course of the tonic proprioceptive eye position signal in area 3a

In chapter 3, I investigated the timing of the tonic proprioceptive eye position signal in area 3a of somatosensory cortex. Previous experiments proved the proprioceptive nature of this eye position signal using a saccade task. The saccade task evoked a phasic proprioceptive response that masked the onset of the tonic proprioceptive response. This made it difficult to quantify how long it takes for area 3a to receive accurate eye position information and whether the onset of the tonic proprioceptive response is reliable or not. We tested the time course of the tonic eye position signal in area 3a with the hypothesis that the delay of the tonic proprioceptive signal would be long and the signal would be too slow to be used in oculomotor and visual processes that occur around the time of a saccade.

We first used a smooth pursuit task to study the time course of the tonic proprioceptive eye position signal. The task successfully removed the phasic component of the proprioceptive response. The tonic response closely tracked the orbital position of the eye in the pursuit task, and we obtained a consistent proprioceptive delay of 60 ms.

We then used a vestibuloocular reflex (VOR) task to confirm the results we obtained using smooth pursuit. We did not notice a difference in the length of the delay or the response of the neuron in the VOR task compared to the smooth pursuit task. The neuronal responses in the VOR task, which tracked the eye movements, confirmed that the signal in area 3a reflects orbital eye position and is not related to the direction of gaze, which was constant. Furthermore, visual and vestibular inputs differed between the two oculomotor tasks, but the neuronal responses were similar, which suggests that neither of these inputs contributes to the area 3a eye position signal.

These data show that the proprioceptive delay in area 3a is approximately 60 ms. The proprioceptive delay is relatively long for a signal carried by the cranial nerves and supports the studies that found no significant contribution of proprioception to the localization of spatial targets and online coordination of eye movements. The area 3a proprioceptive eye position signal is, however, accurate and reliable 60 ms after a change in eye position, which suggests it could be used to calibrate a corollary discharge signal or provide slow eye position modulation in other cortical areas.

5.1.2 The role of the gain fields in calculating saccade target positions

In chapter 4, I investigated the time course of eye position gain fields in LIP. Previous models have assumed that the gain fields receive eye position information from corollary discharge and are accurate around the time of a saccade (Andersen and Mountcastle, 1983). However, this assumption has never been tested experimentally. If this assumption holds true and the gain fields are responsible for spatial accuracy, then the visual responses of LIP neurons should be modulated by the postsaccadic eye position immediately after a saccade. To test this hypothesis, we designed a two-saccade task in which visual stimuli flashed immediately after the monkey made a saccade. We discovered two populations of neurons: the visual response of the majority population reflected the presaccadic eye position, and the visual response of the minority population was entirely unrelated to eye position. Visual responses modulated by the correct postsaccadic orbital position appeared only after 150 ms.

We designed a three-saccade task to test whether inaccuracies in the gain field immediately after a saccade would be reflected in the accuracy of saccades directed to

spatial targets presented during this time. A benefit of the three-saccade task is that it dissociates the saccade goal from the retinal location of the target. This type of saccade necessitates a supraretinal mechanism, such as an accurate gain field coordinate transformation or receptive field remapping. We confirmed that the visual response to a probe flashed during the first 150 ms after the first saccade was inaccurate in the three-saccade task, similar to the result obtained in the two-saccade task. We then analyzed the monkeys' behavioral accuracy in the three-saccade task by comparing mean saccadic endpoints in the trials when the probe flashed immediately after the saccade to trials when the probe flashed later on. We observed only small mislocalizations when comparing the two conditions, on the order of a few degrees, which was much smaller than the mislocalization predicted by the gain field response. There was a systematic error when we aligned the mislocalization vectors according to the direction of the second saccade, which was unrelated to the orientation of the gain field. There was, however, no consistent error when we aligned the mislocalization vectors according to the direction of the first saccade.

These data demonstrate that LIP gain fields are inaccurate immediately after a saccade, yet eye movements to saccade targets flashed during this time are generally accurate. This supports the hypothesis that gain fields are not directly involved in maintaining an accurate representation of target positions across eye movements. If LIP gain fields are not accurate immediately after a saccade, then they likely do not derive their eye position input from corollary discharge. We speculate that the proprioceptive eye position signal in area 3a of somatosensory cortex provides the gain fields with eye

position information and that spatial accuracy is maintained by the shifting of receptive fields around the time of a saccade.

5.2 Oculomotor proprioception and the gain fields

5.2.1 Proving the proprioceptive nature of LIP gain fields

While I have speculated on the origin of the eye position input that modulates the gain fields in LIP, merely demonstrating that proprioception can reliably provide accurate eye position information before the gain fields update does not prove causality. If eye position modulation in LIP is truly proprioceptive in nature, when we block the proprioceptive eye position signal along its conducting pathway, we should see gain field modulation in LIP diminish, if not disappear altogether. There are several locations along the proprioceptive pathway that could be targeted. One way to abolish the proprioceptive signal is to paralyze the extraocular muscles by injecting an anesthetic such as muscimol or lidocaine directly into the orbit. This technique was used by Wang et al. to prove that the area 3a eye position signal is proprioceptive in nature (Wang et al., 2007). Alternatively, the proprioceptive signal could be blocked after it reaches area 3a. Injection of muscimol or lidocaine directly into neural tissue is a technique commonly used to inhibit neuronal firing and cortical function (Martin and Ghez, 1999). Until LIP gain fields are abolished using one of these methods, or a similar method, claims that the eye position modulation of the gain fields is proprioceptive in origin are merely speculative.

5.2.2 A revised model of spatial accuracy

In chapters 3 and 4, I explored the time course of eye position modulation in parietal cortex. The results demonstrate that the eye position modulation of LIP gain fields after an eye movement is slow, similar to the modulation of the proprioceptive eye position response in area 3a. These results suggest that gain fields are not used to maintain an accurate internal representation of target locations. The question remains: how does the brain maintain an accurate representation of visual space despite a constantly moving eye?

These results bolster the likelihood that the brain uses the shifting receptive field mechanism to maintain spatial accuracy around the time of an eye movement. The predictive remapping of receptive fields to their future, postsaccadic locations preserves perceptual continuity and a subtraction of the saccade vector from preexisting retinal targets maintains their spatial accuracy. In this way, visual information is faithfully preserved until the eye reaches its postsaccadic location.

Although it appears that the slow eye position modulation of LIP visual responses cannot solve the problem of spatial accuracy alone, it may still play a complementary role in the shifting receptive field model. While it is clear that corollary discharge modulates the visual responses of LIP neurons and causes receptive fields to shift to their future locations before a saccade, it is not clear what signal alerts LIP that receptive fields at the presaccadic eye position, which become obsolete after the eye movement, are no longer relevant. Neurons in LIP remain responsive to stimuli presented in their receptive fields up to 200 ms after the eye has moved, which is consistent with the time course of LIP gain fields (did I make this up? I don't remember the reference). Rather than relying on

an arbitrary and independent timing mechanism to retract attentional resources from the presaccadic eye position, LIP may rely on proprioceptive feedback in the form of the gain fields. If shifting receptive fields are responsible for spatial accuracy before the saccade, the gain fields may be responsible for providing feedback that the framework for the shift is no longer necessary at the presaccadic orbital position.

5.2.3 A slow spatiotopic map

While target positions computed using LIP visual responses immediately after a saccade are spatially inaccurate, the gain fields may still be useful for coordinate transformation purposes once they are updated. This is not a well-developed idea in traditional gain field theory, which postulates visual and eye position information are combined immediately to encode an object in spatiotopic coordinates. The visual response is the most accurate and consistent component of the canonical LIP response and provides the gain field model with a visual input in retinotopic coordinates. The delay period response, on the other hand, has complicated, cognitive functions that transcend simple visual analysis (Andersen and Buneo, 2003). The delay period response is thought to carry information about expected reward (Platt and Glimcher, 1999; Sugrue et al., 2004) and reflect elements of a decision making process (Roitman and Shadlen, 2002; Mazurek et al., 2003; Churchland et al., 2008), and the time course of its relationship to the initial visual burst has not been well studied. The gain fields may form a late but accurate spatiotopic map using the delay period response, but it has yet to be shown that the delay period response provides accurate information regarding the retinotopic location of a visual stimulus.

If we assume that delay period activity is spatially accurate after 250 ms, the brain could rely on the gain field mechanism at this point to compute target positions in spatiotopic coordinates. In our three-saccade task, however, the probe flashed 50 ms after the end of the conditioning saccade, and the typical saccadic latency of the monkeys was approximately 150 ms. Within 200 ms, the monkeys eyes had already shifted to the next (second) saccade target. Also, the probe disappeared during the time that monkeys planned the second saccade, so the gain fields could not subsequently use additional visual information to update the probe's spatial location. Even if gain field modulated delay period activity accurately reflected the spatial location of the probe after 250 ms, saccades in the three-saccade task occurred too quickly to allow delay period activity to become accurate. Therefore, the brain must rely on some other mechanism, such as shifting receptive fields, in order to solve the three-saccade task. It would be surprising if the brain utilized an effective system for the generation of online action around the time of a saccade and then switched to the gain field mechanism later on.

5.2.4 Calibrating the oculomotor system

Previous experimental data have shown that activity in LIP serves as a priority map that can be used by the visual system to guide attention and by the oculomotor system to guide eye movements (Goldberg et al., 2002; Goldberg et al., 2006; Ipata et al., 2006; Gottlieb, 2007; Gottlieb et al., 2009b; Gottlieb et al., 2009a; Ipata et al., 2009). The priority map in LIP receives a myriad of signals regarding the behavioral relevance of locations in the environment. In order to maintain spatial accuracy, the priority map in LIP must incorporate eye position information to update salient locations and maintain an accurate retinotopic representation of those locations after a saccade (Duhamel et al., 1992; Gottlieb et al., 1998).

LIP connects to oculomotor regions, such as FEF and SC. When the priority map in LIP is updated, the oculomotor system as a whole is also likely updated. Oculomotor calibration may occur in LIP, where visual activity is modulated both before and after changes in eye position: rapid, presaccadic receptive field shifts in LIP are followed by slow, postsaccadic gain field modulation. While researchers have speculated on the calibratory role of the proprioceptive eye position signal, a cortical eye position error signal has not been reported. An error signal could be calculated by subtracting the actual eye position from the intended eye position. In a normal, calibrated oculomotor system, however, this error is zero, which may explain be why researchers have yet to discover such an error signal.

The oculomotor system could compute an error signal in several ways. The corollary discharge of the SC motor command encodes a saccade vector, which is difficult to compare directly to the proprioceptive eye position signal. LIP also, however, receives a corollary discharge from the neural integrator in the nucleus prepositus hypoglossi, which is part of the horizontal gaze holding system and could convey eye position information (Prevosto et al., 2009). Alternatively, an error signal could be calculated at the individual neuron level. While the LIP gain field response is modulated by eye position some time after a saccade, it has never been tested if the remapped visual response of an LIP neuron is modulated by the intended eye position prior to a saccade. If so, the remapped response could be directly compared to the late gain field response, since both would be modulated by eye position.

5.3 Broader implications

In this body of work, I studied the time course of eye position modulation in area 3a and LIP. I showed that the gain field modulation of visual responses in LIP is inaccurate immediately after a saccade, which weakens the theory that LIP gain fields are used to calculate saccade target positions online. I also showed that the proprioceptive eye position signal in area 3a is slow, but available in time to provide the gain fields in LIP with accurate and reliable eye position information. These findings extend beyond area 3a and LIP and have broader implications on gain field theory as a whole.

5.3.1 The function of the gain fields

Previous experiments demonstrated that passive head-on-body rotation modulates LIP neurons, and concluded that LIP neck gain fields are likely driven by neck proprioceptors (Snyder et al., 1998). Our current findings support the hypothesis that LIP eye gain fields are driven by extraocular muscle proprioceptors. While other gain fields must be tested to determine the origin of their positional modulation, it is not unreasonable to speculate that gain fields, as a whole, are driven by proprioceptive inputs, rather than corollary discharge.

While it appears unlikely that gain fields are involved coordinating eye movements, gain fields are also thought to maintain spatial accuracy for reach movements (Chang et al., 2009). Neurons in PRR are modulated by eye position as well as hand position (Batista et al., 1999b). Although our results are limited to the oculomotor system, it is unlikely that the skeletal motor system has access to a class of visual information that uses an entirely different, rapid and accurate gain field system. Reach movements, however, take longer to initiate than eye movements. The short

latency reaches take 250 ms to initiate, by which time the majority of visual gain fields in LIP are accurate (Rogal et al., 1985). Whether eye and hand position modulation are accurate in time for compound gain fields in PRR to update the trajectory of reach movements online is a matter that needs to be tested experimentally.

If proprioceptive eye and hand position drive the gain fields in PRR, this may provide evidence for an expanded role of proprioception in skeletal motor processing. However, previous experiments have demonstrated that corollary discharge is sufficient for coordinating accurate saccades and arm reaches to visual targets (Lewis et al., 1998). Even if proprioceptive signals are accurate in time to adjust a reach command signal, it would be strange to find that the oculomotor system uses corollary discharge to update the spatial location of saccade targets while the skeletal motor system uses proprioception to update the spatial location of reach targets. Therefore, if the gain fields in PRR are modulated by arm proprioception, it is logical to presume that they are involved in calibrating the reach system, rather than actively planning reach movements.

5.3.2 Perceptual stability

How the brain maintains perceptual stability around the time of a saccade is a problem that is related to the issue of spatial accuracy. Both problems arise from rapid saccadic eye movements, and the solutions to both problems require the contribution of supraretinal signals. Perceptual stability is actually two problems: displacement of the retinal image with each saccade and blurring of the image during the saccade. The same two mechanisms used to solve the issue of spatial accuracy, shifting receptive fields and

gain field coordinate transformations, are also regarded as solutions to the first problem of perceptual stability, displacement (Wurtz, 2008).

In order to perceive the world as a continuous and seamless entity, the visual system requires that space be encoded in supraretinal coordinates before or at the time of a saccade. Otherwise, visual perception would lag the eye, and we would perceive the world as a series of images on the retina. The shifting receptive field model easily solves the problem of perceptual stability. At the time of a saccade, some receptive fields are remapped to the postsaccadic eye position. In this way, the brain computes two concurrent representations of the visual scene and switches to the appropriate image when the eye moves. The gain field model solves the issue of perceptual stability in the same way it solves the issue of spatial accuracy: images on the retina are transformed out of retinotopic coordinates and into spatiotopic coordinates. During the time of an eye movement, our internal representation of visual space is already encoded in the spatiotopic map, so visual perception is uninterrupted.

Our results show that LIP gain fields are inaccurate immediately after a saccade. If the visual system relied on the gain field mechanism to solve the problem of displacement of the retinal image at the time of a saccade, the retinal image would not be spatially accurate for at least 150 ms. Therefore, the gain field model cannot be used to explain perceptual stability, which is a predictive process, just as it cannot explain the spatial accuracy of visual targets presented around the time of a saccade.

5.4 Conclusion

Activity in area LIP serves as a priority map which can be used to guide visual attention and oculomotor behavior. This visual activity is modulated by eye position and a population of

LIP neurons could encode a distributed representation of visual space in spatiotopic coordinates. The orbital modulation of LIP gain fields is slow, however, when compared to the demands of visual stability for accurate eye movements. Monkeys are able to make accurate eye movements to visual targets presented during a period of time after a saccade when the gain fields do not accurately predict the monkey's eye position. This slow orbital modulation is not consistent with a corollary discharge input providing the gain fields with eye position information. It is more likely that the gain fields receive a proprioceptive eye position input from area 3a of somatosensory cortex, which is accurate and reliable before the gain fields update. The slow temporal dynamics of the gain fields suggests that they would be better suited to calibrate the priority map in LIP. The task of maintaining an accurate spatial representation of visual targets for eye movements is best left to the remapping of receptive fields, which has been shown to be accurate around the time of a saccade.

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