Updating reach plans for smooth pursuit eye movements

by

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Dedication

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Abstract

Over the last several decades, significant progress has been made in understanding how primates use vision to guide reaches. Visually guided reaching is complicated by the fact that primates make continuous eye movements, causing visual information to shift multiple times a second. It is still poorly understood how the brain accounts for these visual shifts and maintains the spatial stability of visually guided reaching. Building upon the current science, this thesis presents new studies that advance our understanding of the neural mechanisms underlying visually guided reaching.

Visual information is perturbed by many types of motion, from the translation of the body through space, to head movements, to fast, saccadic eye movements. In particular, it is not well understood how the brain accounts for slower, tracking eye movements called smooth pursuits. We found that both smooth pursuit and the more common saccadic eye movements have equivalent effects on the neural substrates of visually guided reaching. This result suggests that the brain compensates for changes to visual information similarly even if the mechanism that moves the eyes is different.

Given that smooth pursuits can last many seconds, the time course of compensation for changes to visual information during the pursuit is unclear. We found that neural reach activity in the cortex changes continuously throughout the pursuit. This is the first finding that cortical reach neurons update continuously, and it implies that there are mechanisms to compensate for slow changes to vision that could potentially operate under other conditions like walking and head movements.

Finally, what signals does the brain use to account for eye movements? By manipulating the predictability of pursuits using visual feedback about their endpoint, we found that predictable eye movements were better compensated for than unpredictable eye movements. Many studies note the importance of feedforward signals related to the eye movement command. Our finding reinforces the view that the brain compensates for shifts to visual information by combining both feedback and feedforward signals.

Résumé

Au cours des dernières décennies, des progrès significatifs ont été faits dans la compréhension de l'utilisation de la vision chez les primates pour guider des tâches d'approche. Cependant, les mouvements continus des yeux des primates produisent de multiples décalages par seconde dans l'information visuelle, rendant les approches guidées par la vision complexes à évaluer. En effet, la façon dont le cerveau prend en compte ces décalages visuels tout en maintenant la stabilité spatiale des tâches d'approche est toujours mal comprise. En s'appuyant sur les avancées scientifiques actuelles, cette thèse présente de nouvelles études qui permettent une compréhension plus approfondie des mécanismes neuronaux fondamentaux aux approches guidées par la vision.

L'information visuelle est perturbée par plusieurs types de mouvement, allant du déplacement du corps dans l'espace, aux mouvements de la tête, jusqu'aux mouvements rapides et saccadés de l'oeil. Plus spécifiquement, il est encore mal compris comment le cerveau considère les mouvements de suivi plus lent de l'oeil, appelés poursuites douces. Nous avons, alors, trouvé que les poursuites douces et les mouvements saccadés de l'oeil, plus commun dans la littérature, ont des effets similaires sur le substrat neuronal relié aux approches guidées par la vision. Ce résultat suggère que le cerveau compense pour les changements dans l'information visuelle de façon similaire même si le mécanisme bougeant les yeux diffère.

Étant donné que les poursuites douces peuvent durer plusieurs secondes, l'évolution dans le temps pour l'adaptation aux changements visuels lors d'une tâche de poursuite n'est pas clair. Nous avons trouvé que l'activité neuronale dans le cortex, reliée à une tâche d'approche, change continuellement durant la poursuite. Ceci est le premier constat que les neurones corticaux reliés aux tâches d'approche s'adaptent de façon continue, et suggère la présence de mécanismes de compensation pour les changements lents en vision qui pourraient, potentiellement, fonctionner sous d'autres conditions comme la marche ou les mouvements de la tête.

Finalement, quels signaux le cerveau utilise-t-il afin de prendre en compte les mouvements de l'oeil? En manipulant la prévisibilité des poursuites à l'aide de

rétroactions visuelles de l'objectif final, nous avons trouvé que les mouvements de l’oeil prédictibles sont mieux compensés que ceux non-prédictibles. Bien que plusieurs études démontrent l'importance des signaux d'anticipation reliés au contrôle du mouvement de l'oeil, cette découverte renforce l'idée que le cerveau compense pour les décalages dans l'information visuelle en combinant les signaux de rétroaction et d'anticipation.

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Chapter 1

Introduction

1.1 Construction of spatial stability

Most organisms, from bacteria to humans, need to navigate and interact with their environment to survive. This can be as simple as a two neuron arc that allows an animal to sense the environment and move reflexively. However fundamental problems arise when sensory systems are used to orient the organism in space, such as a neutrophil cell using chemoreception to move along a chemical gradient, or a monkey reaching for a branch using photons incident on the retina. This requires a correct mapping between the pattern of sensory activation and the direction of movement, a computational task that is complicated by the fact that organisms and their sensory organs are often themselves in motion. In primates, this issue is particularly acute for the visual system, since eye movements are made 3-4 times every second. While much progress has been made into how the primate brain transforms continuously changing visual information into accurate, appropriate movements, the precise neural mechanisms underlying this behavior are still poorly understood.

The problem of spatial stability exists because information related to our own movements obscures sensory information related to the environment. In the example in Figure 1, the image of a coffee cup shifts from the centre of visual space, the fovea, to a position below it. The shifting image can signal real-world movement (the cup fell off the table, Fig. 1B) or our own movement (an upward eye movement, Fig. 1C). How does the brain tell them apart? Although the ambiguity can be resolved using visual feedback, for example by noticing that the table hasn't moved, this is unlikely to be the answer. In one of the classic physiological experiments, Descartes in his Treatise on Man noted that the visual scene shifted when he displaced his eye with his finger, but when he made an identical eye movement with the extraocular muscles the world appeared stable (Medendorp, 2011). The visual feedback is identical in both scenarios, but only in the latter is image motion

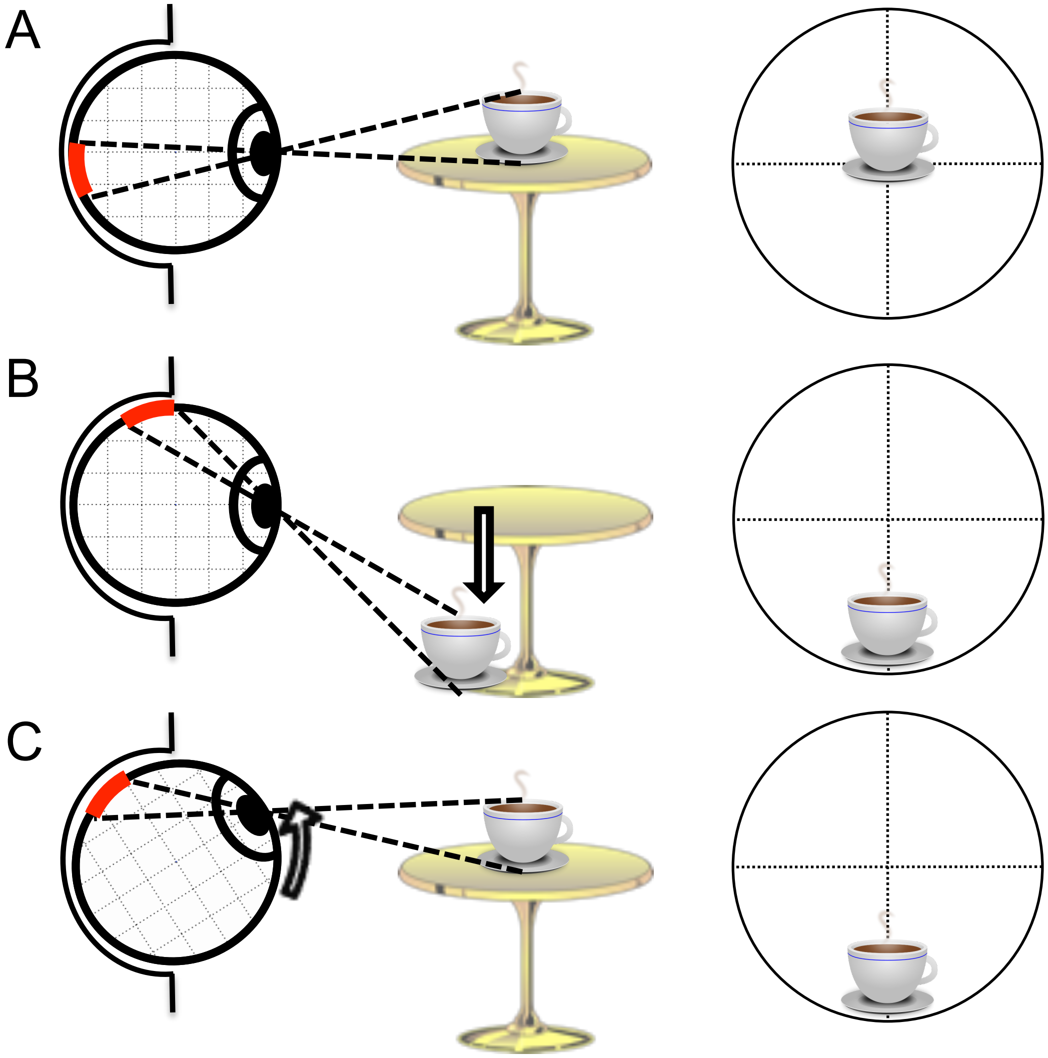

Figure 1. Visual ambiguity: external motion and self motion can have the same sensory consequences. A. Viewing a coffee cup (left) produces an image on the retina (right). B. External motion of the coffee cup causes the image to move to the bottom of visual space, i.e. below the fovea. C. The same shift of the image in visual space is achieved by an eye movement. Using only visual information about the cup (right) it is not possible to determine whether the image shift is due to external (B) or self-motion (C).

correctly interpreted. This simple example hints at the incredible feats of neural computation that underlie our ability to stitch narrow, often changing visual information into a stable representation of space.

Research into spatial stability has a long pedigree, being considered in one form or another by a line of eminent vision scientists, including Bell, Mach, and Purkinje (Wurtz, 2008). More recently, techniques like modern electrophysiology and magnetic resonance imaging (MRI) greatly increased our understanding of the underlying neural mechanisms. The ability to cancel visual signals caused by our own movements is called "spatial updating" or simply "updating" (Klier and Angelaki, 2008, Medendorp, 2011): the brain updates visual information in order to account for predictable, self-caused changes to visual information. At the most basic level spatial updating requires two basic components: 1) raw sensory information, and 2) knowledge of the motion of the sensing organ.

The problem of spatial stability equally applies to visual perception and motor systems that are guided by visual information. This thesis will focus on how primates generate accurate arm movements in space, a behavior intimately linked with vision. Two specific questions will be addressed. First, this thesis will address how slow, tracking eye movements (smooth pursuits) update reach plans. Chapter 2 uses electrophysiology to directly compare updating for smooth pursuit eye movements with the more common fast, saccadic eye movements. In Chapter 3, the temporal dynamics of updating for smooth pursuit eye movements is investigated. Second, this thesis will address the internal signals used to update neural representations of reaches across eye movements. Using neural recordings, Chapter 3 provides evidence that another signal, internal copies of the command to move the eye, are also used to update reach plans. Chapter 4 will discuss the multiple signals that the brain combines to update, along with presenting evidence for a novel updating signal. Taken together, this thesis provides insight into how the problem of spatial stability is solved for reaching behavior.

1.2 Visually guided reaching

Before discussing how the brain processes changing visual information to accurately reach, it is useful to understand how the brain computes visually guided reaches while the eyes are not moving. In general, preparatory planning is the first of two stages in visually guided reaching. These premotor computations estimate the location of the reach goal (reach “kinematics”) but are distinct from the muscle forces or joint angles required to move the arm to that location (reach “kinetics”). This divide can be framed in terms of “intention” versus “action” (Andersen and Buneo, 2002, Cui, 2014) where intention is a plan for a movement that will occur in the future rather than a current sensorimotor event (Andersen, 1995). Movement intention is referred to by a number of names, such as the “movement goal” or “movement plan”. In the brain, this movement plan is thought to be encoded as the spatial location of the goal of the movement (Kalaska et al., 1997, Musallam et al., 2004). Although there are exceptions, signals related to movement planning and execution are generally subserved by separate brain regions, such as the posterior parietal cortex which encodes movement goals but not kinetic variables of the movement (Kalaska and Crammond, 1995, Kalaska, 1996, Kalaska et al., 1997, Snyder et al., 2000). This thesis largely focuses on brain activity relating to the planning, kinematic signals specifying the spatial location of the reach.

1.2.1 The visuomotor transformation

Representing space with reference frames. Central to how the brain encodes reaches are the underlying neural representations of space – that is, the spatial reference frames. As in physics, a reference frame here is a coordinate system in which spatial information can be defined (Soechting and Flanders, 1992). These coordinate systems can be viewed as fixed axes overlaid on external three-dimensional space, allowing positions to be defined by a set of numbers or combination of basis vectors. Importantly, information set in a reference frame is relative to the motion of that reference frame. A classic explanatory example involves two reference frames, one fixed to a passenger on a moving train and the other fixed to a stationary observer on the ground. Within the passenger’s reference frame, a ball dropped on the train follows a straight line down; the same ball viewed in the external observer's reference frame traces a curved, parabolic line.

Because we use multiple sensing organs, sensory information arrives in the brain in multiple reference frames, and, similar to the train example, the same stimulus can be encoded in multiple reference frames. Sensory information is initially encoded in the reference frame of the sensing organ: a visual image is relative to the location of the eyes in space (eye-centered), vestibular information is relative to the head's motion through space (head-centered), and so on. What reference frames are used to encode more high level signals, such as movement goals? Studies of patients with brain lesions that lead to hemispatial neglect, or a tendency to ignore one half of space (Vallar, 1998, Kerkhoff, 2001), provide important clues. Exactly which region of space the lesion leads the patient to neglect – the left side of visual space, the left side of the body, or the left half of objects – sheds light on how a non-pathological brain processes spatial information. In general, patients demonstrate neglect in a variety of reference frames, both body- and world-centered (Bisiach and Vallar, 1988, Chatterjee, 1994, Marsh and Hillis, 2008, Humphreys et al., 2013). Interestingly, reference frames for reaching tend to be relative to visual space (Khan et al., 2005a, Khan et al., 2005b).

From visual to motor reference frames**.** In order to make a visually guided reach, visual information must be transformed from its native reference frame to a location relative to the arm or hand. For example, information from retinal cells stimulated by the image of a coffee cup must be transformed into the direction and distance the hand needs to travel to accurately reach the cup. This process is called a visuomotor transformation. Specifically for reaching, the visuomotor transformation recasts eye-centered signals about the movement goal into a hand-centered reference frame. (An additional transformation is required to turn the movement vector into the required joint-angle velocities and muscle forces needed to achieve the movement (Kakei et al., 1999, 2001, Sober and Sabes, 2005), although that is outside the scope of this thesis.) The problem of visuomotor transformation is therefore a fundamental process in visually guided reaching (Crawford et al., 2004).

While the movement itself requires a motor reference frame, in what reference frame is the movement plan represented? Given that a movement plan can be generated many seconds before the motor act, the answer to this question is not clear *a priori*: either the native sensory reference frame could persist into the planning, or the sensory information could be immediately transformed into a motor reference frame. The answer is important to neural mechanisms of spatial stability. If a movement plan, specifying a spatial location, is stored in the initial eye-centered reference frame, its representation will need to change, i.e. update, for each eye movement in order to maintain spatial accuracy with the external world. (Imagine that your coffee cup is at the center of visual space. If an eye movement is made down and to the left, the cup is now up and to the right of gaze location.) However, neurons that encode a stimulus in a hand-centered reference frame won't respond to the eye movement, since a location expressed relative to the hand position is independent of eye position. Thus if the visual-to-motor transformation occurs upstream of a reach planning brain area, its activity is represented in a reaching reference frame and independent of eye movements.

Specifying a reach requires localizing both the hand and reach target in space. Because there are two ways to sense hand position – visually or proprioceptively – there are two general mechanisms that could compute a visuomotor transformation (Fig. 2). These two methods are termed the "direct" and "indirect" visuomotor transformations (Andersen et al., 1993, Buneo et al., 2002). In the "direct" transformation, a hand-centered location is computed as the difference between the target and hand locations as viewed by the eyes (Fig. 2A). The word direct refers to the fact that no intermediate reference frames are needed, and the motor vector is computed directly from visual input of the target and the hand. The indirect transformation involves proprioceptive feedback of the initial hand, head and other body positions to represent the target in a sequence of reference frames. The head-centered location of the target can be computed by combining the eye-centered target location with the position of the eyes in their

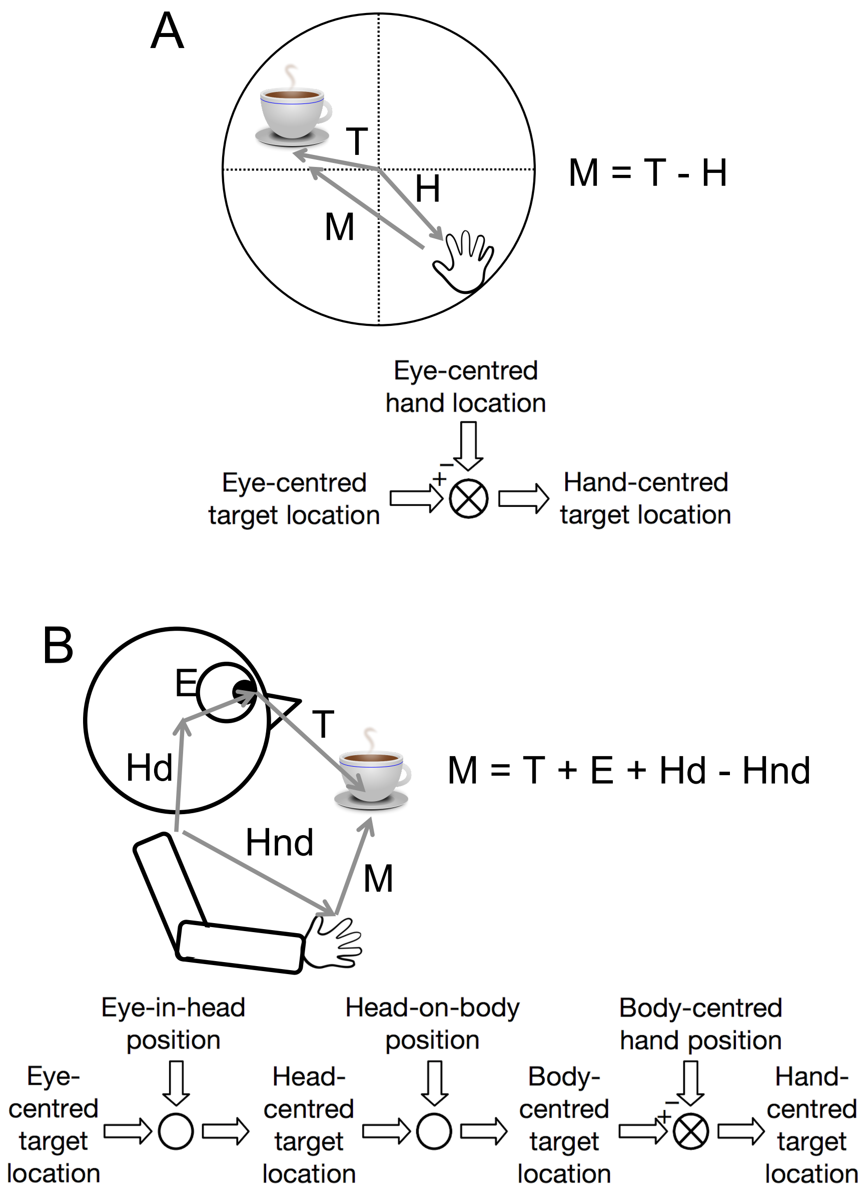

Figure 2. Visuomotor transformations for reaching. A. The direct visuomotor transformation. The fundamental problem of visuomotor transformations is how to compute a motor vector (*M*) from visual information of the target (*T*). M is the hand-centered target location, i.e. the reach vector. One solution is to compute M as the difference between the hand (*H*) and T in visual space: *M = T – H*. In this case M is computed entirely from eye-centered variables (*T* and *H*). B. The indirect visuomotor transformation involves computing M using proprioceptive information about the eye-in-head location (*E*), the head-on-body position (*Hd*), and the hand-on-body position (*Hnd*) together with visual information *T*. A sequential transformation would result in a range of egocentric reference frames (bottom). A and B, bottom, were reproduced from Buneo et al. (2002).

orbits, the body-centered can be compute by combining head-centered with head-on-body position, and so on (Fig. 2B).

Both mechanisms of visuomotor transformation make specific predictions about which reference frames exist in the brain as a result of the visuomotor transformation. The direction visuomotor transformation predicts that only eye-centered and hand-centered representations are present in the brain. In contrast, the indirect transformation predicts that, in addition to eye- and hand-centered representations, neurons could encode the target in head- and body-centered reference frames; furthermore, the indirect model predicts that postural signals about eye-in-head, head-on-body, and hand-on-body positions are required (Fig. 2B). As will be discussed in the next section, eye-centered schemes likely dominate the encoding of reach-related variables, arguing for direct transformations (Buneo and Andersen, 2006). The issue is complicated by heterogeneity between brain areas, with some regions encoding reach variables in a range of body-centered reference frames. Indeed, indirect schemes for visuomotor transformations probably do exist, since visual information of the target or hand can be unreliable (Engel et al., 2002), such as reaching in the dark. It's possible that both visuomotor transformation mechanisms exist in the brain, subserving different transformations (e.g. motor or perceptual) or on different time scales (Henriques et al., 1998, Pisella et al., 2000, Beurze et al., 2010, Xu et al., 2012, Tagliabue and McIntyre, 2014).

1.2.2 Reference frames for reaching

Eye-centered reference frames. Given that a reach requires a hand-centered vector, it's reasonable to guess that the brain encodes reach plans in a hand-centered reference frame. Indeed, an initial theory for motor control was that neurons tend to use reference frames specific to the behavioral response they controlled (Rizzolatti et al., 1994, Colby and Duhamel, 1996, Colby, 1998). Early experiments showed that neurons responsible for controlling head movements encoded information in head-centered space (Rizzolatti et al., 1987, Colby and Duhamel, 1991, Colby et al., 1993a, b), motor cortex neurons involved in limb control had limb-centered reference frames (Rizzolatti et al., 1988, Gentilucci et al., 1989, Graziano et al., 1994), and neurons in brain areas responsible for controlling eye movements had eye-centered reference frames (Goldberg and Bruce, 1990, Goldberg et al., 1990, Duhamel et al., 1992). Continuing this reasoning, it was predicted that neurons responsible for *planning* arm movements would do so with respect to arm position. Testing this hypothesis in a landmark study, Batista et al. (1999) discovered that counter to this theory, the medial intraparietal sulcus (MIP), a brain area that encodes reach plans, represented the reach plan in eye-centered coordinates. Thus visual reference frames, which persist throughout visual processing centers in the cortex (Hubel and Wiesel, 1959), appeared to persist into reach planning.

Subsequent work from behavior, electrophysiology, and brain imaging studies generally confirmed the primacy of eye-centered encoding for reach planning. Early behavioral work from Henriques et al. (1998) showed that, when reaching in complete darkness to remembered locations, people overreach relative to their gaze, even when gaze position is shifted by an eye movement. That is, reach behavior appeared tied to eye position. Numerous behavioral studies support this finding of gaze-dependent reaching errors under various conditions (McIntyre et al., 1997, Medendorp and Crawford, 2002, Pouget et al., 2002b, Poljac and Van Den Berg, 2003, Blangero et al., 2005, Beurze et al., 2006, Van Pelt and Medendorp, 2007, Sorrento and Henriques, 2008, Thompson and Henriques, 2008a, Fiehler et al., 2010, Jones and Henriques, 2010, Thompson et al., 2014), such as when reach targets are non-visual, for example proprioceptive or auditory targets (Pouget et al., 2002b), and even when the participants were blind (Reuschel et al., 2012). Lesions to the parietal cortex produce deficits in reaching to space, i.e. hemispatial neglect. These deficits are predominantly relative to the patient's gaze, as opposed to the head or the body, again reinforcing the idea that reaches are planned in eye-centered coordinates (Khan et al., 2005b, Dijkerman et al., 2006, Blangero et al., 2009, Jackson et al., 2009, Blangero et al., 2010, Khan et al., 2013).

This is confirmed by electrophysiology studies. Batista et al. (1999) showed that neurons in MIP responded consistently to reach goals at a specific direction from gaze location, and responses to the same reach target were modulated when eye position was varied. That is, eye-centered neurons were identified as those that responded consistently to a stimulus at a specific eye-centered location, but inconsistently to a world-fixed stimulus at different eye-centered locations. Eye-centered activity in macaque MIP neurons was reproduced by a number of other studies for visual (Buneo et al., 2002, Cisek and Kalaska, 2002, Cohen and Andersen, 2002, Buneo and Andersen, 2006, Buneo et al., 2008, Bhattacharyya et al., 2009, Chang et al., 2009) and auditory targets (Cohen and Andersen, 2000). Other brain areas involved in arm movement planning, such as the dorsal premotor cortex (PMd), were also found to encode reach plans relative to gaze location (Shen and Alexander, 1997, Boussaoud et al., 1998, Jouffrais and Boussaoud, 1999). Human brain imaging studies also found that areas in the human posterior parietal cortex analogous to MIP in monkeys encode reach targets in eye-centered coordinates (Sereno et al., 2001, Medendorp et al., 2003, Merriam et al., 2003, Medendorp et al., 2005, Bernier and Grafton, 2010, Beurze et al., 2010). Therefore, a wealth of information supports the idea that neurons responsible for encoding reach plans do so in an eye-centered reference frame.

However, the majority of studies finding eye-centered reaching used explicit, instructed eye positions. A study by Cisek and Kalaska (2002) using natural, free gaze conditions found that the effects of spontaneous saccades on PMd neurons during a reaching task were more modest than when the animals were trained to fixate. Therefore, more work is needed to uncover how neural modulations of reach neurons, which are often studied in laboratory settings with highly trained animals, generalize to conditions of free gaze.

Complex reference frames. A view that has emerged in the last two decades is that the brain contains many representations of the same spatial target for reaching. Although theoretical arguments have been made that a single reference frame across the brain could simplify reach planning (Soechting and Flanders, 1989, Cohen and Andersen, 2002, Engel et al., 2002, Buneo and Andersen, 2006), there is evidence that different reference frames are used in an adaptable, context-dependent manner (Heuer and Sangals, 1998, Carrozzo et al., 1999, Sober and Sabes, 2005). When reaching to remembered targets in complete darkness – without visual feedback of the hand – patterns of reaching errors are independent of eye position, suggesting that the remembered target had been transformed to a reference frame independent from visual space (Flanders et al., 1992). Imaging studies also showed that the human parietal cortex encodes space in reference frames fixed to the environment (Marchette et al., 2014) and switches between eye- and body-centered encoding depending on the sensory context (Bernier and Grafton, 2010).

Exceptions to eye-centered encoding broadly fall into two groups: i) hybrid reference frames relative to both the hand and the eye, or ii) reference frames independent from eye position, such as hand- or head-centered. In the first group, neurons sensitive to hand, eye, and target position are viewed as generally subserving the transformation from visual targets to motor output (Buneo et al., 2002, Mullette-Gillman et al., 2005, Mullette-Gillman et al., 2009, Chang and Snyder, 2010, McGuire and Sabes, 2011a, Chen et al., 2013). These reference frames can be considered "intermediate", that is neither in the sensory reference frame nor the motor reference frame, but partway between (Snyder, 2005). Indeed, a number of parietal movement planning areas have cells whose activity only partially shifts with eye movements (Stricanne et al., 1996b, Duhamel et al., 1997), supporting the idea that these areas employ intermediate reference frames (Pouget et al., 2002a).

The second broad group are those studies that found that reach related variables are encoded entirely independently from eye position, such as in a body-centered coordinates (Lacquaniti et al., 1995, Carrozzo et al., 1999, Batista et al., 2007). Indeed, a representation of the reach in terms of joint angles and muscle activations is a requirement for reaching (Flanders et al., 2003) and therefore to be expected. However, for most of the visuomotor pathway, eye-independent encoding of reach variables in the cortex is the exception, and an eye-centered reference frame, expressing spatial information relative to visual space, appears to be the predominant representation in the brain (Ambrosini et al., 2012), even when external visual cues like landmarks can be used for orientation (Schütz et al., 2013). Thus a central finding of research from the last two decades is that the native, eye-centered reference frame of visual information persists throughout much of the cortex. While the neural mechanisms of visuomotor transformations are not entirely clear, encoding schemes relative to eye position suggest that mechanisms must exist that update the location of reach targets for changes to gaze location and maintain spatial stability for world-fixed targets.

1.2.3 Cortical brain areas for reaching

Neurophysiology and neuroimaging studies show that a network of parietal, premotor and primary motor regions is involved in computing the visuomotor transformation (Kalaska et al., 1997, Kalaska, 2009, Beurze et al., 2010). The understood role of this network is to integrate sensory information about the spatial positions of the target and hand with different computations performed in different brain areas (Blangero et al., 2009, Cui and Andersen, 2011, Bremner and Andersen, 2012, Inouchi et al., 2013). Two major reach planning brain areas are the posterior parietal cortex (PPC) and the dorsal premotor cortex (PMd). Activity in these brain areas is one of the focuses of this thesis.

The PPC, located anatomically between the visual and motor cortices, is well situated to transform sensory information into action, and is thought to play a key role in both representing space and computing visuomotor transformations (Andersen et al., 2004, Buneo and Andersen, 2006). PPC is broadly subdivided into regions serving sensorimotor transformations for both hand and eye movements (Sereno and Huang, 2014), and is noted for containing a range of reference frames from eye-centered to hand-centered (McGuire and Sabes, 2011a). The lateral intraparietal sulcus (LIP), a subdivision of the PPC and the focus of many visuomotor studies, serves as a sensorimotor interface for the planning and control of eye movements. The medial intraparietal sulcus (MIP), which comprises the parietal reach region (PRR) along with area 6, is seen as serving analogous functions for reaching (Mountcastle et al., 1975, Kalaska and Crammond, 1992, Caminiti et al., 1996, Johnson et al., 1996). Area 5, located anatomically next to the PRR, also encodes reach-related variables, but is more heavily hand-centered than PRR (Bremner and Andersen, 2012) and likely controls different stages of reach planning than PRR (Cui and Andersen, 2011, Heed et al., 2011, Li and Cui, 2013). The anterior intraparietal sulci (AIP) is also involved in reaching, but encodes more context-specific variables for grasping movements (Baumann et al., 2009, Lehmann and Scherberger, 2013) and might be more involved in computing transformations of proprioceptive sensory signals (Grefkes et al., 2004). Neurons in the ventral intraparietal area (VIP) encode space in body- or face-centered reference frames (Colby and Duhamel, 1996) or a continuum of eye- to body-centered (Duhamel et al., 1997).

The visuomotor transformations that the PPC performs are often viewed as "intentions" to move (Snyder et al., 1997, 2000, Andersen and Buneo, 2002) – that is, computations in preparation of a volitional movement, which are separate from the movement itself. This is borne out by a stimulation study, where stimulation of the PPC in humans produced a "desire" or a "will" to move, without any overt movements being generated (Desmurget et al., 2009). Higher intensities led to sensations that a movement was just made.

Traditionally, the PPC was an "association area" where many variables were combined and integrated, including sensory, motor and cognitive signals. Indeed, high-level, abstract internal signals can modulate neural activity in the PPC, such as signals relating to the size of reward (Musallam et al., 2004) and past history of rewards associated with the movement (Rajalingham et al., 2014), as well as spatial attention (Bisley et al., 2011), although the latter is contentious (Quian Quiroga et al., 2006). For these reasons along with its role in sensory-motor integration, the PPC is sometimes viewed as serving the "cognitive functions related to action" (Andersen and Buneo, 2002). It is unclear what role reward plays in spatial processing in the PPC, although reward signals could be evidence that activity in the

PPC is involved in decision making, with reward signals representing a preferential weighting for a higher reward action (Platt and Glimcher, 1999). It's also possible that reward modulation is just a reflection of the tendency to move more quickly for a high reward, rather than a high-level upstream signal (Roesch and Olson, 2003).

The premotor cortex is also heavily involved in planning and guiding reaching movements. It is broadly subdivided into the dorsal premotor cortex (PMd), which underlies reaching (Beurze et al., 2007, Medendorp et al., 2008), and the ventral premotor cortex (PMv), which is more associated with grasping (Lehmann and Scherberger, 2013). Compared to the PPC, the PMd is more closely associated with the motor cortex anatomically and functionally closer to motor execution (Churchland et al., 2006). Indeed, whereas PPC stimulation led to the sensation of movement or a strong desire to move (Desmurget et al., 2009), stimulation of the dorsal premotor cortex led to actual arm movements in owl monkeys (Preuss et al., 1996) and humans (Desmurget et al., 2009) and did not produce any conscious sensation of movement. Importantly, MIP and PMd are densely connected anatomically (Johnson et al., 1996).

The primary motor cortex (M1) is traditionally the "last step" between the cortex and muscle activation, and approximately 30% of descending projections from the brain to the spinal cord originate in M1 (Hall, 2010). M1 is traditionally associated with movement execution, rather than planning. Indeed, many studies provide compelling evidence that activity in single M1 neurons covaries with the causal forces and muscle activity underlying limb movements. An early theory was that the level of activation of M1 neurons corresponded directly to force of muscle contraction (Evarts, 1968, Cheney and Fetz, 1980). This is supported by direct connections between projecting M1 neurons and spinal motoneurons (Porter and Lemon, 1993). More modern studies show that M1 neurons are involved with learning the forces needed to achieve an arm movement, notably when the arm is perturbed by forces during the movement (Richardson et al., 2012). Therefore in contrast to activity of neurons in reach planning areas like MIP and PMd, activity of cells in M1 is more directly connected to the movement execution.

1.3 Updating reach plans for eye movements

The previous section discussed how visual information from a single viewing angle is transformed into a motor plan. This section returns to the question of updating by discussing how reach plans are formed from changing visual information. Indeed, how does the brain solve the problem of combining disjointed visual scenes into a stable reach target? A trivial solution is for the brain to recalculate the movement vector for each "frame" of visual information. For example, if the hand and target remain visible, the brain can compute a movement vector for the hand via the direct visuomotor transformation ($M = T - H$) as discussed previously (Fig. 2A). The same process can be repeated after every subsequent eye movement, thereby computing a correct (stable) reach target across eye movements and largely solving the updating problem. In this case, the problem of dynamic visual information reduces to multiple instances of the static case.

This solution is not possible, however, when reaching to invisible, remembered targets. In such cases, internal representations of the target's location must be used to generate the reach, rather than inflowing sensory information about the target. These remembered locations are generally formed from past sensory information stored in short term memory and updated for intervening movements. For example, when typing at my desk I am capable of viewing the keyboard, closing my eyes, swiveling on my chair, and then reaching accurately towards the keyboard. As discussed, internal representations of the keyboard's location are predominantly encoded relative to visual space. Thus my initial retinal encoding of the keyboard was updated for the new relative positions of hand and keyboard following the swivel. How does the neural representation of such a reach plan update for self-caused, predictable changes to visual space?

1.3.1 The double-step saccade task

An early, intuitive theory for how the brain computes saccades posited that the visual (eye-centered) location of a saccade target is all that's needed to drive the saccade (Young and Stark, 1963, Schiller and Koerner, 1971). In this framework, the magnitude and direction of a saccade required to foveate a target is exactly equal to the "retinal error" of that target, i.e. its location in visual space relative to the fovea. Note that no updating occurs in this model, and saccades are simply driven by the location of visual signals. The now-classic "double-step saccade" experiment, conducted by Hallett and Lightstone (1976a), showed that this model is insufficient to explain movements to invisible targets. Instead, the brain likely stores sensory signals and update them.

The double-step saccade paradigm is similar in essence to our previous example of reaching to our keyboard, although rather than reaching, subjects made saccades to spatial targets. In this experiment, two saccade targets (*T1* and *T2*) were flashed in the subject's peripheral vision then extinguished (Fig. 3). The subjects were then required to saccade to both targets sequentially. Note that *T1* and *T2* are viewed before any eye movement is made. Therefore, for the first saccade, the eye-centered location of *T1* (R_{T1}) is a sufficient signal for driving the eyes toward *T1*. (R_{T1} is sometimes called the "retinal error" of *T1*, although this discussion will use "eye-centered location" for consistency.) However, because *T2* was observed when the eye was at its initial position, the eye-centered position of *T2* (R_{T2}) is not a sufficient signal for a gaze shift to *T2* (Fig. 3B). This is because the first saccade changes the movement required to foveate *T2*, rendering it unequal to R_{T2}. Since both humans (Hallett and Lightstone, 1976a) and monkeys (Goldberg and Bruce, 1990) are capable of making accurate saccades to *T2* in the double-step task, the internal representations of saccade targets must be updated for intervening eye movements.

What mechanisms underlie the ability to perform the double-step saccade task? At the level of vector arithmetic, there are two ways the brain can solve the double-step task (see Figure 3). In this scheme, accurately performing the double-step task requires calculating the eye movement vector *e2* (Fig. 3C). In the first solution, *e2* can be computed entirely from visual feedback: $e2 = R_{T2} - R_{T1}$. In this case, the difference in retinal locations of the targets yields the correct motor vector, which can be computed even prior to the first saccade. The second solution adjusts

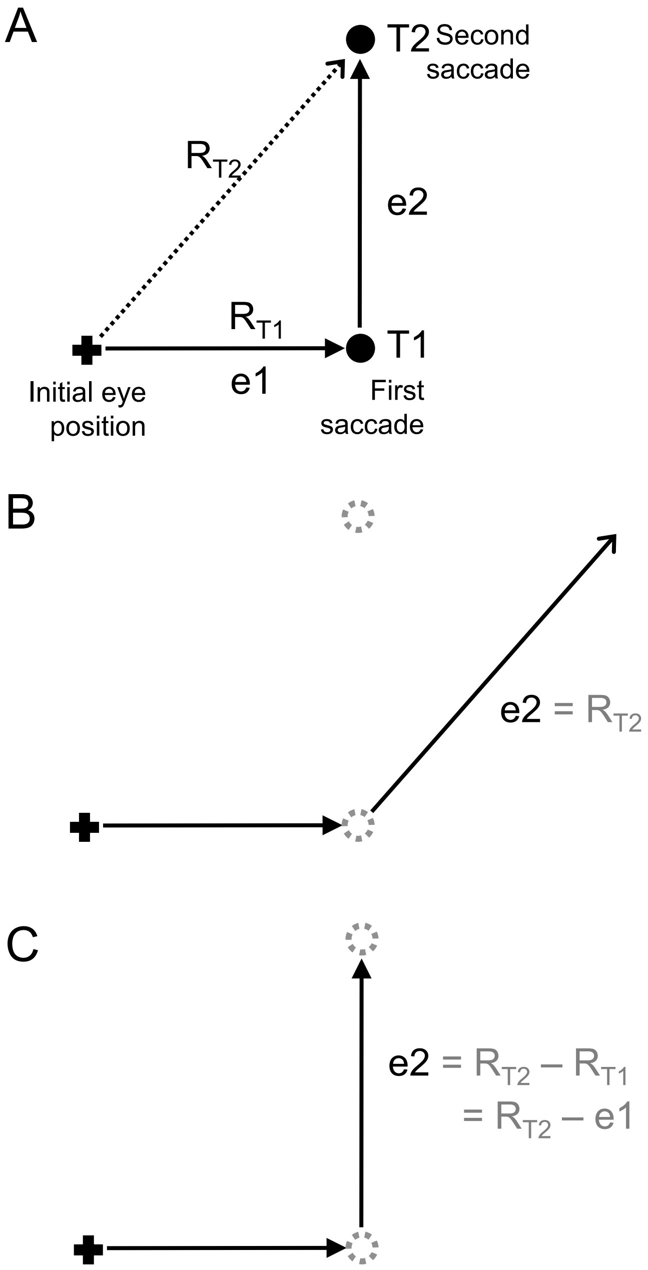

Figure 3. 2D vector arithmetic capable of solving the double-step saccade paradigm. A. The eye is initially fixated at the cross and two saccade targets (*T1* and *T2*) are flashed in the periphery and extinguished. R_{T1} and R_{T2} are the eye-centered locations of the two targets. *e1* and *e2* are the saccade vectors needed to sequentially foveate *T1* and *T2*. B. The initial eye centered locations of the targets are not sufficient to make an accurate second saccade *e2*. C. With spatial updating, the second saccade is adjusted for the first saccade. This can be accomplished with entirely visual information ($e2 = R_{T2} - R_{T1}$) or by combining visual information with knowledge of the first saccade ($e2 = R_{T2} - e1$).

R_{T2} for the direction and magnitude of the first intervening eye movement ($e1$): $e2 = R_{T2} - e1$. (Note that $e1$ can potentially be derived from both efferent feedforward signals as well as sensory feedback about the eye movement.) Because R_{T1} and $e1$ are identical vectors, these two solutions are mathematically equivalent. However, they differ in terms of the underlying neural computations and signals. In the first, no knowledge about the eye movement is necessary, and in fact no updating of saccade targets is required: the correct saccades are simply computed from the initial visual information and stored until needed. The second plan requires adjusting the visual location of the second target (R_{T2}) for each intervening eye movement.

In this context, how does the brain compute the accurate second saccade $e2$? The first answers to this question came in a series of elegant experiments beginning in the early 1980s. Mays and Sparks (1980) replicated the design of the double-step task, except that the first saccade was generated by electrical stimulation of the superior colliculus (SC), and therefore there was no retinal error R_{T1}. The fact that the monkeys made correct saccades to *T2* after stimulation demonstrated that feedback or feedforward information from the movement itself (i.e. $e1$) was being used to keep the saccade plan spatially accurate. However, this result does not exclude other signals from contributing to updating, nor does it reveal the actual computations performed by neurons. This idea of what signals drive updating will be returned to in the following sections.

1.3.2 Neural substrates of updating

After Hallett and Lightstone (1976a), subsequent electrophysiology studies revealed how updating was accomplished at the level of single neurons. Neural signatures of updating were first identified in the saccadic control system, specifically in area LIP. Gnadt and Andersen (1988) showed that cells in LIP respond when the goal of an upcoming eye movement is brought into their receptive field, even when the light signaling the location is extinguished before it is brought into the receptive field. Thus the activation of cells in LIP must come, at least in part, from a stored memory signal of the target. The lit cue initially stimulated one group of cells with a specific eye-centered receptive field; following the saccade, the representation of the target was transferred, or remapped, to the second group of cells encoding the target's remembered location. Thus even in the absence of visual information (the target is unlit) activity representing the spatial location of the target is remapped between groups of neurons with eye-centered receptive fields. A few years after Gnadt and Andersent, Duhamel et al. (1992) published a landmark paper showing that some LIP neurons remapped *before* the saccade. That is, LIP cells updated predictively. Predictive remapping has been reproduced in LIP (Kusunoki and Goldberg, 2003) and found in other saccade areas, like the cortical frontal eye fields (Umeno and Goldberg, 1997b, Sommer and Wurtz, 2006). Importantly, cells in reach area MIP also show the signatures of remapping (Batista et al., 1999).

In order to solve the problem of spatial stability, a movement plan must consistently point to the same object or location in external space. Receptive field remapping accomplishes this by transferring activity representing the movement plan between eye-centered neurons. For example, a saccade target initially at a specific location in visual space is represented by the activation of an LIP neuron with a receptive field covering that eye-centered location. When an eye movement is made, the movement plan activity is remapped to neurons whose receptive fields overlap with the new, post-eye movement location of the target. Thus the output of LIP cells consistently encodes the accurate location of the target. This requires the brain to predict the consequences of the saccade and correctly transfer activity to the appropriate group of post-saccade neurons.

Predictive remapping can also act as a spatial stability *detector* (MacKay, 1972, Wurtz, 2008). Because activity in an LIP neuron increases in anticipation of a stimulus being brought into its receptive field, as long as the target remains visible this prediction can be compared to actual visual feedback of the target. If they match, the object has remained stable in the world. If visual information is not accompanied by an LIP prediction, however, the lone visual response signals that a stimulus appeared in the real world. Similarly, if the stimulus predicted by LIP activity is absent, the brain knows that the object disappeared. Because LIP activity is a *prediction* about the consequences of eye movements, its output can be compared to real visual feedback in order to produce an error signal whose absence signals a stable visual scene.

1.3.3 Neural signals for updating

The internal signals that produce spatial stability must carry information about our body's motion through space. Classically, there are three candidates for these signals (Wurtz, 2008): visual feedback, resulting from retinal stimulation; muscle proprioception, such as from stretch receptors in the extraocular muscles; and internal copies of movement commands, called "efference copy" or "corollary discharge" (Sperry, 1950, von Holst and Mittelstaedt, 1950). As will be discussed this list is incomplete, and work over the last two decades has added to the internal signals capable of driving updating.

Indeed, in his Treatise on Man, Descartes noted that if we prod our eyes with a finger the world appears to move, but the world is still when we make an eye movement via the extraocular muscles, even though the actual shift of the retina may be identical. This observation led Hermann von Helmholtz to suggest that spatial stability is maintained by an active "force of will" (Helmholtz, 1867) as opposed to passive sensory feedback. Helmholtz noted two other pieces of evidence in favor of this active internal signal. First, visual displacement is perceived when an eye movement is attempted but the extraocular muscles are paralyzed, and thus no eye movement is actually made (Stevens et al., 1976). In this case the "force of will" is generated – an eye movement is attempted – but without an accompanying shift to visual information, and the discrepancy results in perceived change in the visual scene. Finally, fading visual images, or afterimages, have no perceived movement when the eye is moved by a finger in the dark, but they are perceived to move when an active eye movement is made (Bridgeman, 2007). Again, since the physical displacement of the retina can be identical in both cases, the source of the apparent motion is unlikely to come from visual or proprioceptive feedback. These lines of evidence argue against updating via either visual feedback or extraocular muscle proprioception. Therefore efference copy, the remaining signal of the three, is left as the most likely candidate for an updating signal. Multiple new lines of evidence support this view, although as will be discussed this leaves out other candidates that also likely contribute to updating.

Efference copy. The most likely candidate for an updating signal is efference copy. In addition to the previous examples, newer evidence from electrophysiology and stimulation studies provides two strong arguments for efference copy being the signal that drives updating. The first is a timing argument [see review in (Klier and Angelaki, 2008)]. As mentioned, LIP neurons alter their motor planning activity in response to eye movements, and this modulation is thought to be one of the neural signatures of updating. Importantly, this modulation occurs up to 200 ms in advance of the eye movement (Duhamel et al., 1992, Kusunoki and Goldberg, 2003). Similar signals are also found in the frontal eye fields (Umeno and Goldberg, 1997b, Sommer and Wurtz, 2006). Because feedback signals necessarily arrive *after* the eye movement, they are unsuitable candidates for the source of modulation.

Returning to the discussion of the double-step task, the second argument for efference copy builds on Mays and Sparks' (1980) landmark study. Their findings showed that monkeys could accurately perform the double-step task even if the first saccade was elicited by electrical stimulation. Subsequent studies showed that this ability, however, depended on the site of stimulation. Indeed, the second saccade was accurate, and therefore updating proceeded correctly, when the stimulation was applied to midbrain areas such as the SC (Mays and Sparks, 1980, Mays and Sparks, 1981). The second saccade was also accurate if the site of stimulation was in the cortex (Schiller and Sandell, 1983, Tehovnik and Sommer, 1996). However stimulation of the oculomotor nerve (Sparks and Mays, 1983) or abducens nucleus (Schiller and Sandell, 1983) resulted in inaccurate secondary saccades. Therefore, at least in the saccadic system, the brain is capable of accounting for saccades whose signals originate in the midbrain or cortex while saccades generated at the level of the muscles are not accounted for. Since proprioceptive and visual feedback of the stimulated saccade are identical regardless of the stimulation site, these studies argue against their contribution to updating. Combined with the classical arguments discussed, as well as timing arguments from LIP and FEF neurons, these results strongly suggest that updating relies on an internal, advance signal of the eye movement. This signal is likely sent from the superior colliculus via the thalamus to the cortex (Sommer and Wurtz, 2006, Sommer and Wurtz, 2008a).

Postural proprioception and vestibular feedback. While efference copy is a sufficient signal to drive updating, new evidence shows that the story is likely more complicated. Indeed, much of the evidence for efference copy comes from ruling out either eye muscle proprioception or visual feedback. Arguing for efference copy by elimination inadvertently neglects other sources that could potentially be used depending on their availability and the context. For example, recent studies using passive movements, such as a whole body rotation on a turntable where no efference copy was made, demonstrated that signals other than efference copy can drive updating (Klier et al., 2008b). Many studies have demonstrated that perceptual stability is maintained during passive rotations (Bloomberg et al., 1988, Blouin et al., 1995, Israël et al., 1995, Glasauer and Brandt, 2007) and translations (Israël et al., 1993, Berthoz et al., 1995, Israel et al., 1997, Siegler et al., 2000), as is the ability to make accurate saccadic eye movements to locations in the dark (Baker et al., 2003, Klier et al., 2005, Li and Angelaki, 2005a, Klier et al., 2007, Klier et al., 2008b). These studies show that, at least for updating of perception and saccade motor targets, spatial constancy for our internal models is maintained even when the only information about the movement is from sensory feedback.

In the particular case of whole body rotations, vestibular feedback, visual feedback, or a combination of the two is sufficient to update. A recent study has shown that gravitational cues like those from the vestibular otolith organ can contribute to updating (Klier et al., 2005). Confirming that vestibular signals contribute to updating, vestibular lesions significantly compromise monkeys' ability to update saccade targets (Li and Angelaki, 2005a, Wei et al., 2006). The reach system also likely uses vestibular feedback to update, as subjects were able to accurately reach to the locations of remembered targets in complete darkness even when they were first passively rotated by as much as 40° (Bresciani et al., 2002b). Similar to lesion studies, galvanic vestibular stimulation delivered so as to create apparent motion between the subject and a reaching target produced deviations in the arm movement (Bresciani et al., 2002a). However, updating using only vestibular information is not perfect, and compensating for passive rolls using sensory feedback alone can lead movements that are only partially accurate (Klier et al., 2007). Subjects updated differently depending on the axis of rotation, suggesting that vestibular gravitational cues may be used in addition to feedback about rotational acceleration (Klier et al., 2006). Similar results of imperfect updating for passive movements, this time translation, are observed in monkeys (Li et al., 2005a).

The brain is therefore capable of using multiple signals to update. However, is it combining these signals or is a single sensory or motor signal being used depending on the context? An early hypothesis was that the brain would use the most reliable signal, such as vision, and ignore the rest (Rock and Harris, 1967). A more current view is that when multiple signals are available, they are combined in a statistically optimal way, especially for complex whole body movements that involve simultaneous motion of the eyes, head and body (Ernst and Banks, 2002, Klier and Angelaki, 2008, Sabes, 2011). Indeed, participants updated saccade targets for rolls better when the movement was made with an active head movement (Medendorp et al., 2002) as compared to passive rotation (Klier et al., 2005). Updating was also better when visual and neck proprioception are available as opposed to just visual (Mergner et al., 1998). While the exact signals used and integration mechanisms aren't known (Sarlegna and Mutha, 2014), the emerging model is that the brain combines efference copy, vestibular signals relating to whole body movements, and postural signals like neck muscle proprioception, to calculate up-to-date spatial relationships between the hand, eyes and movement target.

1.3.4 Computational mechanisms for updating

Vector arithmetic for updating. In order to conceptualize the computations required to compute a spatially stable reach plan, vector arithmetic similar to that for the double-step saccade task (Fig. 3) can be used. Figure 4 shows how an accurate reach vector M, which defines the direction and amplitude the hand must move in order to acquire the target, can be calculated from the retinal locations of the reach target (R_T) and hand (H) as $M = R_T - H$. Occurring for a constant eye position, this transformation is the "direct" visuomotor transformation (Buneo et al., 2002) and is identical to the scheme in Figure 2A. However, if an eye movement is made at a later time (t_2), the reach target is no longer at an eye-centered location specified by R_T. In general there are three strategies for calculating a spatially accurate reach vector after the eye movement (M').

As discussed for the double-saccade, the first solution is the trivial case where the reach target remains visible. In this case R_T' and H', i.e. the retinal locations of the reach target and hand after the eye movement, can be obtained directly from visual information. Therefore, identically to calculating M at time t_1, M can be recomputed at time t_2 as $M' = R_T' - H'$. Since $M' = M$, the reach vector is the same before and after the eye movement, and the problem of spatial stability is solved.

The other two solutions apply when a reach is made to an invisible, *remembered* target. In this case, such as the example of reaching to your keyboard while closing your eyes, visual feedback about the target is not available after the eye movement. R_T is therefore the only available information about the location of the target, and R_T must be updated for changes to eye position in order to maintain a correct spatial registry between the reach plan and the real world at time t_2. Therefore, the second solution requires that the initial representations of the target (R_T) and hand (H) are updated for the intervening eye movement. In this case, the eye-centered target location after the eye movement can be computed as the initial location plus the dimensions of the eye movement, i.e. $R_T' = R_T + e$, where e is the vector defined by the eye movement. Hand location after the eye movement can be

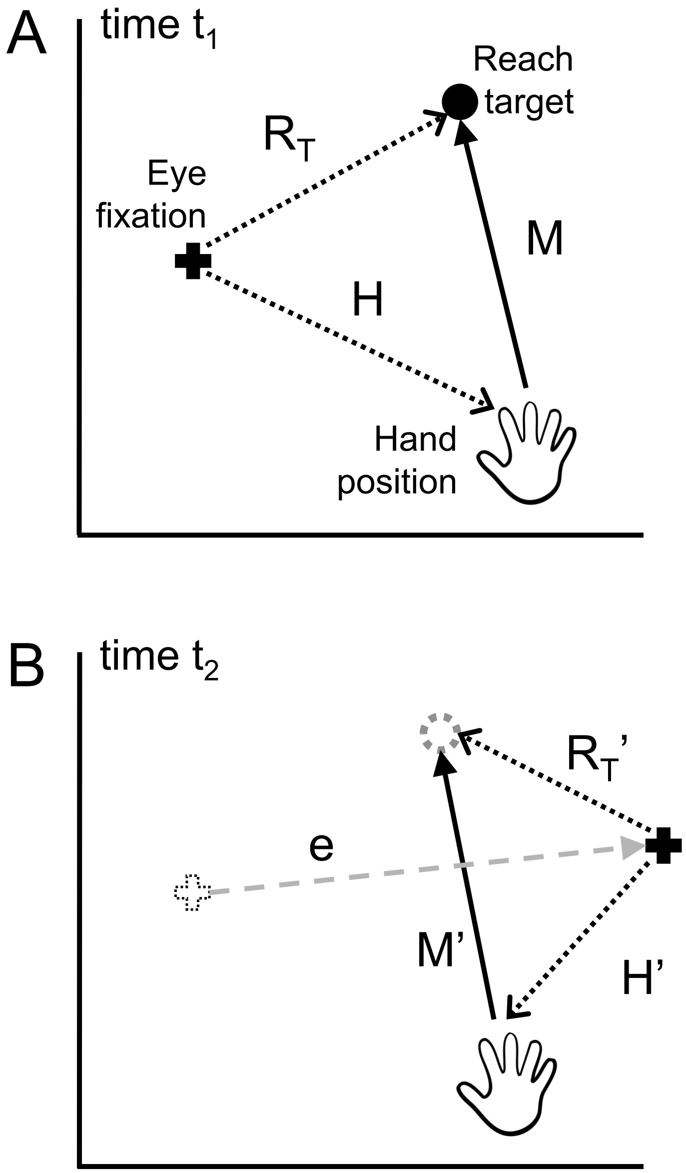

Figure 4. 2D vector arithmetic for reach plan updating. A. At an initial time (t_1), the eye is fixated at the cross and a reach target (T) is flashed at an eye-centered location R_T. H is the eye-centered hand location, and M is the reach vector to acquire the target. M can be calculated as $M = R_T - H$. B. By a later time (t_2), an eye movement e has shifted the gaze location. The new eye-centered coordinates of the reach target is $R_T' = R_T + e$, and the new eye-centered hand location is $H' = H + e$. Since the reach target is no longer visible, the reach vector M' must be calculated from information available at time t_1, i.e. R_T and H, and information about the eye movement e. (If the reach target is visible at time t_2, $\mathrm{R_T}'$ is available from visual feedback and M' can be computed identically as at time t_1.)

computed similarly: $H' = H + e$. Note that with these definitions the reach is identical both before and after the eye movement, i.e. $M' = M$, since $M = R_T - H$ and $M' = R_T' - H' = (R_T + e) - (H + e) = R_T - H$. Therefore, updating the eye-centered location of the reach target solves the problem of spatial stability.

In the brain, this can be accomplished by updating neural activity representing the reach target's eye-centered location for each eye movement. In the example laid out in Figure 4, the reach target moves from an eye-centered location "up and to the right" of the fovea at time t_1, to a location "up and to the left" at time t_2. In this case neural activity representing the initial eye-centered position, encoded by cells with receptive fields "up and to the right", is remapped to cells with receptive fields "up and to the left". In this way the readout of these eye-centered neurons by downstream areas provides the correct eye-centered position. Importantly, updating like this requires the brain to know the vector e, i.e. the amount that the eye movement will displace visual space.

The third mechanism for spatial stability is that the brain computes and stores the reach plan M in non-eye-centered coordinates, such as hand-centered coordinates. This could also be considered as the "null case", where, due to the reference frame, eye movements have no effect on reach plans. The transformation of visual information to a reference frame insensitive to gaze location could be accomplished by immediately computing reach vector M and storing it at time t_1, rather than storing and updating the eye-centered location of the target (R_T). Note that M is the final product computed by both the direct and indirect visuomotor transformations and is expressed in hand-centered coordinates. Because M is in hand-centered coordinates, changes to eye position are rendered irrelevant and no updating is required when an eye movement is made. Again, this solution provides a spatially accurate reach vector M before and after the eye movement, and therefore solves the problem of spatial stability.

It's important to note that at some level both updating and using non-eye-centered coordinates are equivalent, in that they both compute M as the difference between target and hand positions. However, they differ in their predictions of how reach planning neurons in areas like the PPC and PMd encode reach information. In the updating scheme neurons encode the target and hand vectors separably in eye-centered coordinates; for the second, non-eye-centered model, neurons encode the movement vector inseparably in hand-centered coordinates (Buneo and Andersen, 2006). Some interpretations make a definite distinction between these two models (Colby and Goldberg, 1999, Wurtz, 2008, Schneegans and Schöner, 2012, Xu et al., 2012). However, it's also possible that they are part of the same "pipeline" for visuomotor transformation, where reach information is stored in an eye-centered reference frame prior to being transferred into a hand-centered scheme. Indeed, the fact that the same reach target can be represented in eye-centered coordinates in one brain area and hand-centered coordinates in another, shows that the different mechanisms for visual stability are likely at play in different areas. That is, across brain areas, eye-centered representations stored at the time of an eye movement are updated according to the above discussion, while the hand-centered representations target are not.

***Gain field theory*.** The above vector arithmetic allows us to conceptualize the computations required to update. The accurate motor vector is generally computed as a difference vector between the hand and the reach target. However, how do networks of neurons compute such a vector subtraction? The neural network theory of "gain fields" was initially posited as a biologically plausible way that neural networks could compute visuomotor transformations (Zipser and Andersen, 1988). Because these transformations involve computing a difference vector between, say, target and hand position (Fig. 2), gain fields also provide a biologically plausible mechanism for computing the vector arithmetic required for remapping (Cassanello and Ferrera, 2007a, b). Since its inception by Zipser and Andersen (1988), gain field theory has been demonstrated to be a computationally tractable, biologically plausible solution to visuomotor transformations (Pouget and Sejnowski, 1994, Salinas and Abbott, 1995, Pouget and Sejnowski, 1997, Pouget and Snyder, 2000, Pouget et al., 2002a, Chang et al., 2009, Xu et al., 2012).

In the gain field model, single neuron firing rates have a multiplicative (i.e. "gain") relationship with certain postural signals, such as eye-in-orbit (Zipser and Andersen, 1988) or hand-on-body position (Chang et al., 2009). Gain field models are typically in the form of neural networks. Pouget and colleagues (2002a) give an excellent summary of how a three layer neural network can use eye position gain fields compute a coordinate transformation, in particular the transformation from a location in eye-centered to head-centered coordinates. This example transformation is the first step in the indirect visuomotor transformation (Fig. 2B). At first glance, the head-centered location of a target (T_h) can be calculated by summing the target's eye-centered location (T_e) with the position of the eyes in the head (E): $T_h = T_e + E$.

How can this transformation be accomplished using a biologically plausible neural network model? The first layer of the model mimics sensory input, where two distinct populations of neurons encode the eye-centered location of the target (T_e) and the position of the eyes (E). These neurons encode the sensory stimuli with bell-shaped (Gaussian) tuning curves, thus responding with maximum firing rate to a preferred stimulus: $fr = G(E)$ or $fr = G(T_e)$, where G is the Gaussian function. Each neuron in the intermediate layer receives input from a unique set of input neurons. In this simplified example, the original tuning curves of the input layers are 1D Gaussians, meaning each intermediate neuron responds with a 2D Gaussian tuning curve with a preferred T_e and E. This 2D Gaussian means that eye position E acts as the gain on eye-centered target position T_e.

In order for this model to compute the transformation to head-centered coordinates, it suffices that neurons in the third (output) layer respond preferentially to a given head-centered location. For example, neuron i in the output layer responds to a preferred head-centered location T_h^i. These neurons in the output layer receive input from all intermediate neurons, with a weighting for each connection mimicking synaptic connection strength between neurons. Therefore, in simplest terms, output neuron i will have a firing rate $fr^{(i)} \propto w^{i1} * fr^{(1)} + w^{i2} * fr^{(2)} + \ldots$, where $fr^{(1)}$ is the firing rate from the first intermediate neuron, w^{i1} is the weighting between neuron i in the output layer and neuron 1 in the intermediate layer, and so on. In order for neuron i to compute the head-centered location $T_h{}^i$, then, all that's required is for neuron i to receive input from intermediate neurons with the appropriate preferred eye-centered location $T_e{}^j$ and preferred eye position E_k, such that $T_h{}^i = T_e{}^j + E^k$. Therefore weightings for inputs from these appropriate intermediate neurons can be hand picked and set to 1, with weightings from all other neurons set to 0. (In practice these weightings are set by training the network.) In essence, the intermediate, hidden layer forms a set of basis vectors which can be summed to compute the required head-centered representation (Pouget and Sejnowski, 1997).

This example given here computed the first step in the indirect visuomotor transformation. That is, an eye-centered location was transformed into a head-centered location using postural information about eye position (Fig. 2B). However by providing the appropriate input variables, gain fields can theoretically compute other vector operations, including the direct visuomotor transformation: subtracting eye-centered hand and target positions to compute the direct visuomotor transformation (Fig. 2A) (Buneo et al., 2002, Buneo and Andersen, 2006). Therefore gain fields are a general model for how the brain may transform visual information into a motor vector.

1.3.5 Updating reach plans versus saccade plans

The theory of remapping and gain fields form the backbone of how reach plan updating is understood to be computed by the brain. However, most updating studies over the last 40 years, and most papers cited in this thesis, investigated updating in the saccadic system rather than the reach system. This is the case for behavioral studies, such as the double-step saccade task (Hallett and Lightstone, 1976a), and electrophysiology recordings in areas like LIP and FEF, e.g. (Duhamel et al., 1992). The differences in updating reach and saccade plans are not well understood. One argument in favor of their similarity is that reach and saccade plans share a similar eye-centered reference frame (Cohen and Andersen, 2002), meaning that the same operation could potentially serve to update either plan. In line with this, evidence from both reach and saccade studies tends to be presented together, and most reach updating reviews use evidence from both systems interchangeably, e.g. (Crawford et al., 2004, Crawford et al., 2011).

Saccades and reaches differ, at least biomechanically, in a number of ways. First, the sensory organ and the effector (i.e. the body part that moves) are dissociated for reaches but are one and the same for saccades. Therefore, a location in visual space is sufficient information to drive a saccade, while a reach requires the additional information about the starting hand location. Therefore mechanisms unique to reaching must come into play when calculating the hand displacement vector. However, the initial stages of movement planning are, generally, positions in visual space, and are therefore similar between reaches and saccades.

In comparison to the number of saccade plan updating studies in the literature, evidence specific to the reach system is sometimes lacking. For example, there is little or no direct evidence for the involvement of efference copy in the reach system. Indeed, predictive updating, e.g. (Duhamel et al., 1992), has not been demonstrated in reach planning neurons, despite a number of studies investigating updating at the single-neuron level in reach areas MIP (Batista et al., 1999, Cisek and Kalaska, 2002). Similarly, stimulation experiments in support of efference copy, like those conducted by Sparks and Mays (1983), have not been conducted for reaches.

1.3.6 Updating by smooth pursuit eye movements

Eye-centered movement plans must update for eye movements in order to maintain spatial stability. In addition to saccades, updating has been investigated behaviorally for other eye movement types, such as vergence eye movements where the eyes rotate toward or away from each other in order to focus in depth (Van Pelt and Medendorp, 2008), and eye movements that result from whole body (Klier et al., 2005) and head movements (Medendorp et al., 2002). (Updating for whole body and head movements is discussed in more depth in section 1.3.3.) A number of studies also investigated updating using smooth pursuit eye movements, which are tracking eye movements that maintain focus on a moving object. In contrast to saccades, pursuit eye movements can last multiple seconds and rely on visual feedback to control the eye movement (Krauzlis and Lisberger, 1989, Krauzlis, 2004).

Two early studies questioned whether updating occurred in response to smooth pursuits at all, since both primates (McKenzie and Lisberger, 1986) and humans (Gellman and Fletcher, 1992) showed inaccurate movements after a smooth pursuit, consistent with a failure to update the eye-centered representation of the target, e.g. Figure 3B. However, it was subsequently discovered that at least partial updating was possible for smooth pursuits (Schlag et al., 1990, Herter and Guitton, 1998, Baker et al., 2003) and that, at least behaviorally in humans, updating tended to lag the eye movement (Blohm et al., 2003, 2005), perhaps explaining initial negative results. A recent behavioral study found that reaching behavior was similar whether reaches were updated by saccades or pursuits (Thompson and Henriques, 2008a).

Since the double-step saccade task (Hallett and Lightstone, 1976a), many studies have focused on how updating occurs in response to saccades. As mentioned in the previous section, this means examining how saccade plans are updated. In addition to updating *of* saccade plans, it also means the focus has tended to be on updating *by* saccades. In particular, there have been no electrophysiology studies of how cortical movement planning neurons in areas like the PPC and the premotor cortex change their activity during smooth pursuits. Indeed, electrophysiology studies are warranted, since it is questionable whether mechanisms responsible for saccade updating would apply to pursuit updating, given the extreme difference in temporal properties of the two eye movements. However, recent evidence suggests that the neural mechanisms driving saccades and pursuits are more similar than previously thought (Krauzlis, 2004).

1.4 Summary and outlook

This thesis is primarily concerned with how the brain maintains spatially accurate reaching in the face of constant changes to eye position. Because of the open questions surrounding updating by smooth pursuit eye movements, Chapter 2 proceeds to examine whether effects of updating smooth pursuit and saccade eye movements are similar at the neural level, or whether neural responses differ for the two eye movements.

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Chapter 2

Brain areas MIP and PMd update reach targets for eye movements but do not discriminate by eye movement type

2.1 Abstract

In order to make visually guided movements, primates must transform visual information into a motor command. However, because the eyes are often in motion, inflowing signals from the retina are subject to change multiple times a second. Therefore, there have evolved mechanisms to compensate for self-caused changes to visual information. Neurons in brain areas responsible for the planning of reaching movements, such as the medial intraparietal cortex (MIP) and dorsal premotor cortex (PMd), update their activity for each change to eye position in order to keep the spatial goal of the reach stable. One implication of this is that changes to eye position that result from different types of eye movements will yield precisely the same updated signal. To test this, we recorded from MIP and PMd while monkeys planned and executed reaches. Reach planning activity was perturbed by both saccade and smooth pursuit eye movements. Neurons in both areas changed activity consistently with updating the reach target location for the change to eye position. Importantly, for the majority of neurons, changes to firing rates were identical whether a saccade or smooth pursuit eye movement was made. This confirms previous results showing that activity in MIP and PMd encode reach target locations relative to visual space and are likely involved in the transformation of visual signals for reaching. Further, it suggests that results from saccadic updating studies, which are the majority, can be generalized to updating by other eye movements such as smooth pursuit.

2.2 Introduction

Visual information about the location of objects in space changes with each eye movement. Despite the continual displacement of images on the retina, primates still use visual information to accurately guide reaching behavior. Multiple studies in electrophysiology and reach behaviour suggest that internally represented targets for reaching (reach plans) are encoded in retinal (eye-centered) coordinates (Henriques et al., 1998, Batista et al., 1999, Heiser and Colby, 2006, Thompson et al., 2014) or in hybrid systems that combine eye-centered and body-centered coordinates (Schlack et al., 2005, Mullette-Gillman et al., 2009). To maintain spatial accuracy, eye-centered and hybrid movement plans must account for each shift in gaze. This process, whereby the brain accounts for eye movements in order to maintain spatial accuracy of targets is called updating (Duhamel et al., 1992, Henriques et al., 1998). The activity of single neurons in two brain areas responsible for encoding reach plans, the medial intraparietal sulcus (MIP) and dorsal premotor cortex (PMd) (Boussaoud, 2001, Quian Quiroga et al., 2006), have been shown to encode reach plans relative to gaze location (Cohen and Andersen, 2002, Pesaran et al., 2006) and therefore update for saccade eye movements (Batista et al., 1999, Jouffrais and Boussaoud, 1999).

Since the classic double-step saccade experiment (Hallett and Lightstone, 1976b), most studies investigating updating use saccades (Mays and Sparks, 1980, Gnadt and Andersen, 1988, Duhamel et al., 1992, Nakamura and Colby, 2002a, Burr and Morrone, 2005, Heiser and Colby, 2006, Sommer and Wurtz, 2006, Sommer and Wurtz, 2008a). Studies have shown that reach plans can update for gaze changes caused by saccades (Henriques et al., 1998, Batista et al., 1999, Thompson et al., 2014), even if auditory or proprioceptive cues were used to localize the target (Cohen and Andersen, 2000, Pouget et al., 2002b). Less is known about how reach plans update for other eye movement types, such as smooth pursuit. While behavioral results show that the brain is capable of updating for pursuit eye movements (Schlag et al., 1990, Blohm et al., 2005), and specifically capable of updating reach targets for pursuits (Thompson and Henriques, 2008a), it is not yet clear whether the neural mechanisms underlying updating are similar between pursuit and saccade eye movements. Updating for saccades must operate in short bursts, whereas updating during pursuits can potentially be sustained for many seconds and cannot rely on saccade-specific mechanisms such as saccadic suppression (Bridgeman, 2011). Unlike saccades, which are ballistic and pre-programmed, pursuit generation relies heavily on a closed loop negative feedback system (Churchland and Lisberger, 2001, Lisberger, 2010). Because of saccadic compression of space, simple mathematical translation of the coordinate system is an unlikely mechanism for updating shifts due to saccades (Ross et al., 1997, Kaiser and Lappe, 2004). Pursuit has no such restriction, as compression of space during pursuit has not been reported. Nevertheless, recent evidence suggests that the architecture for pursuit and saccades are much more similar than previously thought (Krauzlis, 2004) . Indeed, recent studies reported that reaches preceded by pursuits and saccades yield similar patterns of reaching errors that were consistent with an eye centered reference frame (Thompson and Henriques, 2008a).

Despite the differences between pursuits and saccades, the finding that reaches are updated in eye centered coordinates following saccades and pursuits implies a similar updating mechanism for both eye movements. If reach neurons encode and update reach plans relative to eye position, then performing a smooth pursuit or a saccade to the same eye position should elicit the same change in neural activity. We hypothesized that the activity of reach neurons that encode reaches in eye-centered coordinates is only dependent on the final eye position, and not on the type of eye movement used to attain that position. To test this hypothesis, we recorded firing rates from reach planning neurons in MIP and PMd while monkeys performed a memory reach task. This task included intervening saccades and pursuits that changed the relative position of the gaze and reach target. Our results show that, for eye movements to the same location, firing rates of MIP and PMd neurons were generally the same regardless of whether the eye was moved by a saccade or a smooth pursuit. This suggests that eye centered updating is a dominant mechanism in neurons in MIP and PMd.

2.3 Methods

2.3.1 Subjects and surgical procedures

We recorded from two awake, behaving male monkeys (*Macaca mullata,* M and H) weighing 6.5 kg and 11.9 kg, respectively, using implanted multi-electrode arrays. Sterile conditions were maintained for all surgical procedures, and all experiments complied with the Canadian Council of Animal Care guidelines and were approved by the McGill animal care committee.

Monkeys were implanted with an MRI compatible head post (Rogue Research) and thoroughly trained on the task before electrode implantation. In both animals, the left medial intraparietal area (MIP) and left dorsal premotor cortex (PMd) were localized for microelectrode array implantation (MicroProbe, Gaithersburg, MD) using MRI-based software (Brainsight, Rogue Research) (Figure 1).

Monkeys were given Glycopyrrolate intramuscularly at a dose of 0.005 mg/kg followed by a dose of Ketamine at 10 mg/kg for the induction of general anesthesia. Isoflurane gas (1-4%) was given to maintain general anesthesia. A technician monitored the anesthesia and vital signs throughout the surgery. After the surgical procedures, analgesia was administered to the monkeys for pain control for 10 days. Experiments began at least 14 days after surgery to allow for recovery. We measured the monkeys' body weights on a daily basis to monitor health and growth. Throughout the period of experimental sessions, the animals were pair-housed and had access to exercise via a jungle gym. Monkeys were given fresh fruits after all completed sessions.

2.3.2 Behavioral task

The two monkeys were trained to perform a modified center-out memory reach task. All experiments were performed in a grounded Farraday copper cage. The behavioral tasks were run by a real-time system (LabVIEW RT, National Instruments). The monkey's head was held stationary by the implanted headpost. An infrared reflection camera monitored eye position (ISCAN, Boston). The monkey's two-dimensional hand position was monitored by an acoustic touch screen (ELO Touch, California) coupled to a monitor.

Monkeys sat approximately 45 cm in front of the touch screen oriented along the fronto-parallel plane. Monkeys were trained to reach to targets located 7 cm (8.8 deg) from the center of the touch screen. Monkeys were rewarded with juice for each successful reach. Once the trial was initiated, the eye and hand positions were constrained within 2 cm radius windows until the reward was delivered. Monkeys were trained on three tasks, each a variant of the memory reach task (Figure 1A). The three tasks were named according to the eye behavior instructed in the memory period: Fixation Condition, Saccade Condition and Pursuit Condition.

Trials from all conditions were initiated when the animal visually fixated a red central eye target and touched a green central reach target for 700 ms (Fig 1A, panel I). A peripheral reach cue was then flashed for 600ms, indicating one of four reach target locations (panel II). The time from the disappearance of the peripheral reach cue until the instruction to reach was defined as the memory period (Fig 1A, panel III). After holding the correct reach target for 500 ms, the monkey was rewarded with juice. All cues and targets were solid color circles approximately 1 cm in diameter.

I. ***Fixation condition.*** During *Fixation* trials, animals performed a memory reach task with eye position fixed centrally throughout the trial (Fig. 1A). Trials were initiated as described above. In all Fixation trials, the memory period lasted between 1.2 and 1.6 s. Animals were instructed to reach to the remembered location of the reach cue by extinguishing the central reach target (Fig. 1A, panel IVa).

II. ***Saccade condition.*** On *Saccade* trials, trials were initiated as described above. 600-800 ms after the start of the memory period (Fig. 1A, panel IIIc) animals were instructed to perform a saccade during the memory period (panel IIId). The central eye target was extinguished and an eye target appeared at a location in one of the four reach target directions: up, down, right or left (Fig. 1C). On most trials saccades were instructed in the same direction as the reach, although on three recordings saccades were also instructed in the opposite direction of the reach. These three sessions were analyzed separately as a control. The saccade targets were 10 cm from the central eye target. The monkey had 250 ms to initiate the saccade or the trial was aborted. The memory period lasted the same length of time as in the fixation condition, and all other trial periods were identical.

III. ***Pursuit condition**. Pursuit* trials were initiated as described above*.* In the Pursuit condition, the animals were instructed to perform a pursuit eye movement during the memory period. 700-900ms after the start of the memory period (Fig 1A, panel IIIe) the central eye target moved smoothly to an endpoint 10cm away (panel IIIf). The pursuit endpoints were the same as the saccade targets used in the Saccade condition. On the majority of trials, pursuits were instructed in the same direction as the reach, although on three recordings pursuits were also instructed in the opposite direction of the reach. The pursuit eye movement lasted approximately 1250 ms. The memory period ended a variable amount of time after the pursuit ended (200-700 ms).

The number of successful trials was approximately evenly distributed among conditions and reach directions. All reach cues were presented at a distance of 7 cm from the central fixation, whereas all eye movement targets were at a distance of 10 cm (Fig. 1A). The spatial separation of reach and saccade targets was chosen such that reaches on both eye movement and Fixation trials were made to peripheral (i.e. non-foveated) reach targets. All datasets consisted of at least 240 successful trials (3 trial conditions x 4 directions x 20 trials each). Unless specified, all analyses use trials where the direction of eye movement and the direction of reach were the same. On three recordings monkeys also performed trials with two reach directions associated with each eye movement. These sessions were performed to examine whether eye movement modulations depended on the reach plan.

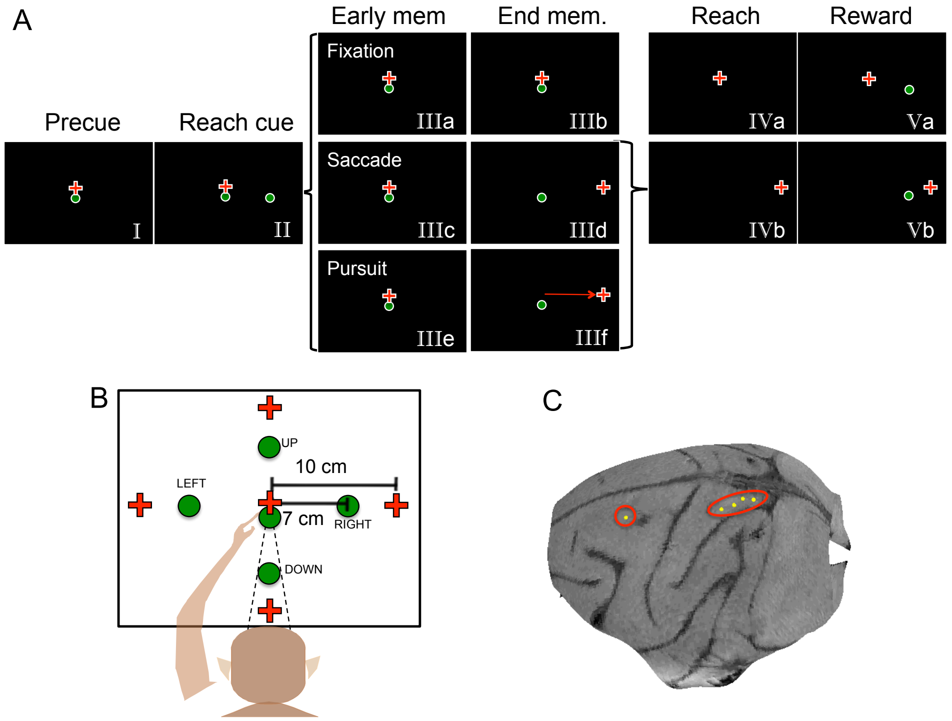

Figure 1. A. Schematic of Pursuit, Saccade and Fixation experiments. Red crosses are eye position, and green dots are hand position. All trials began by fixating central hand and eye targets (I) followed by a reach cue at one of four peripheral locations (II). On Fixation trials the eye was not instructed to move and after the memory period (IIIa-b) the animal reached to the remembered location of the reach cue (IVa) for a reward (Va). On Saccade and Pursuit trials, an eye movement was instructed in the memory period (IIIc-f), after which the animal reached to the remember target (IVb) for a reward (Vb). B. Schematic of reach targets (green circles) and eye targets (red crosses). All hand targets are 7 cm from central fixation, and all eye targets are 10 cm from the centre. Movements are made in one of four directions: RIGHT, UP, LEFT or DOWN. C. Array locations in monkey M.

2.3.3 Electrophysiology

We used multi-electrode array recordings to record neural activity from monkeys M and H. Monkey M was implanted with four 16-channel floating microelectrode arrays along the bank of the medial intraparietal sulcus (MIP) and one 32-channel array in the dorsal premotor cortex (PMd) (MicroProbe, Gaithersburg, MD) (Fig. 1B). Monkey H was implanted with one 32-channel array along the bank of MIP and one 32-channel array in PMd. In both animals, electrodes in MIP had lengths ranging from 1-9 mm in order to sample the depth of the sulcus, and electrodes in PMd varied between 0.5-1.5 mm. Electrode impedances ranged between 0.4 MOhms and 0.6 MOhms. As reaches were made with the right arm, arrays were implanted in the left hemisphere of both monkeys. Three arrays (48 channels) were recorded from simultaneously. Signals were initially amplified using a 20x headstage (Plexon, Inc). All spike waveforms were sampled at 40kHz using a Plexon acquisition system (Plexon, Inc). Spike waveforms were initially sorted online with the Plexon system and additionally sorted offline using custom software.

2.3.4 Data analysis

Firing rate alignment and calculation. We analyzed firing rates from two 300 ms time periods. The *early memory period* was defined as 200 to 500 ms after the start of the memory period (reach cue offset). The *end memory period* was a 300 ms window centered on the end of the memory period (extinguishing the central reach target). All trial-by-trial firing rates used in statistical tests (t-test and ANOVA) were calculated as binned spike counts in one of these windows divided by the window width. Firing rates in other time periods were also calculated, but these were used only for visualization in peristimulus time histogram (PSTH) traces.

To assess how eye movements changed firing rates, ΔFR was calculated as the difference in firing rate between the early and end memory periods: $\Delta FR = FR_{end} - FR_{early}$, where FR_{end} and FR_{early} are the firing rates in the end and early memory periods, respectively. ΔFR was calculated separately for each combination of trial condition and movement direction. ΔFR_p is the change in firing rate on Pursuit trials for a given direction, and ΔFR_s is the same quantity for Saccade trials.

In order to maximize the signal-to-noise ratio, we identified the eye movement direction that led to the greatest change in firing rate. We defined this direction (D_{max}) as the eye movement direction (RIGHT, UP, LEFT, or DOWN) with the greatest absolute ΔFR. In order to have a single value D_{max} was defined using only Pursuit trials. D_{max} could also have been defined using Saccade trials, or an average of Saccade and Pursuit, although Pursuit trials were chosen here for simplicity.

Task-selective neurons. We recorded from 283 MIP units (220 monkey M, 63 monkey H) and 651 PMd units (549 monkey M, 102 monkey H). Units were defined using a combination of visual sorting and custom spike-sorting software. Although we strove for well-isolated single neurons, it is likely that multi-unit data is included as well. Units were selected for analysis if they were i) modulated by the upcoming reach in the early memory period and ii) modulated by eye movements. The early memory period is common to all trials. Reach modulation was defined using a 1-way ANOVA on reach direction ($p < 0.05$) using trial-by-trial firing rates in the early memory period of all successful trials (Fixation, Saccade and Pursuit). A neuron was determined to modulate for eye position if firing rates in the end memory period on Pursuit or Saccade trials were different from firing rates from the same period on Fixation trials (unpaired t-test, $p < 0.05$). Therefore neurons could modulate for either eye movement and be defined as responding to eye movements. Only a single direction (D_{max}) was used to determine eye movement modulation. From our population, 127 MIP (91 monkey M, 36 monkey H) and 313 PMd units (275 monkey M, 38 monkey H) were task-selective.

Preferred direction (PD). A neuron's preferred direction (PD) was calculated using a vector average method (Georgopoulos, 1982, Gail and Andersen, 2006):

$$PD = \sum_{i=1}^{4} r_i u_i .$$

PD was calculated in the end memory period separately for the three trial conditions. Argument *i* denotes indices for the 4 movement directions. u_i is the center-out unit vector for each of the 4 directions, and r_i is a neuron's mean firing rate on corresponding trials. This method calculates *PD* as the sum of the 4 center-out unit vectors weighted by mean firing rate. u_i was defined in screen-centered coordinates, and therefore *PD* measures the screen-centered preferred direction.

The change in PD caused by eye movements (ΔPD) was calculated as the difference between PD on Saccade versus Fixation trials or Pursuit versus Fixation trials. Since PD was calculated in the end memory period, this compared PD after an eye movement to PD after no eye movement was made. Since we were concerned with the magnitude of PD change, we used the absolute value of ΔPD, i.e. $0° \leq \Delta PD \leq 180°$. 95% confidence intervals for each ΔPD value were calculated by randomly sampling trials with replacement (bootstrap, 1000 iterations).

Modeling ΔPD distributions. In order to explain the observed distributions of ΔPD (see Fig 4 A and B), we used Monte-Carlo simulations of two models with receptive fields that shift with eye position (Fig. 2). This model, where neurons have a spatially limited movement receptive field, has been shown extensively for neurons in the saccadic system [for review, see (Klier and Angelaki, 2008)], and a number of studies support the validity of this model for parietal reach neurons (Duhamel et al., 1997, Pouget et al., 2002a). Although to our knowledge no studies document receptive field models for reach neurons in PMd, we apply this model to PMd neurons for two reasons. First, other premotor neurons such as those in the frontal eye fields can be described by movement receptive fields, and second, this model adequately describes our data.

The first receptive field model assumed that all neurons encoded the eye-centered position of the reach target, and therefore the receptive field shifted by the

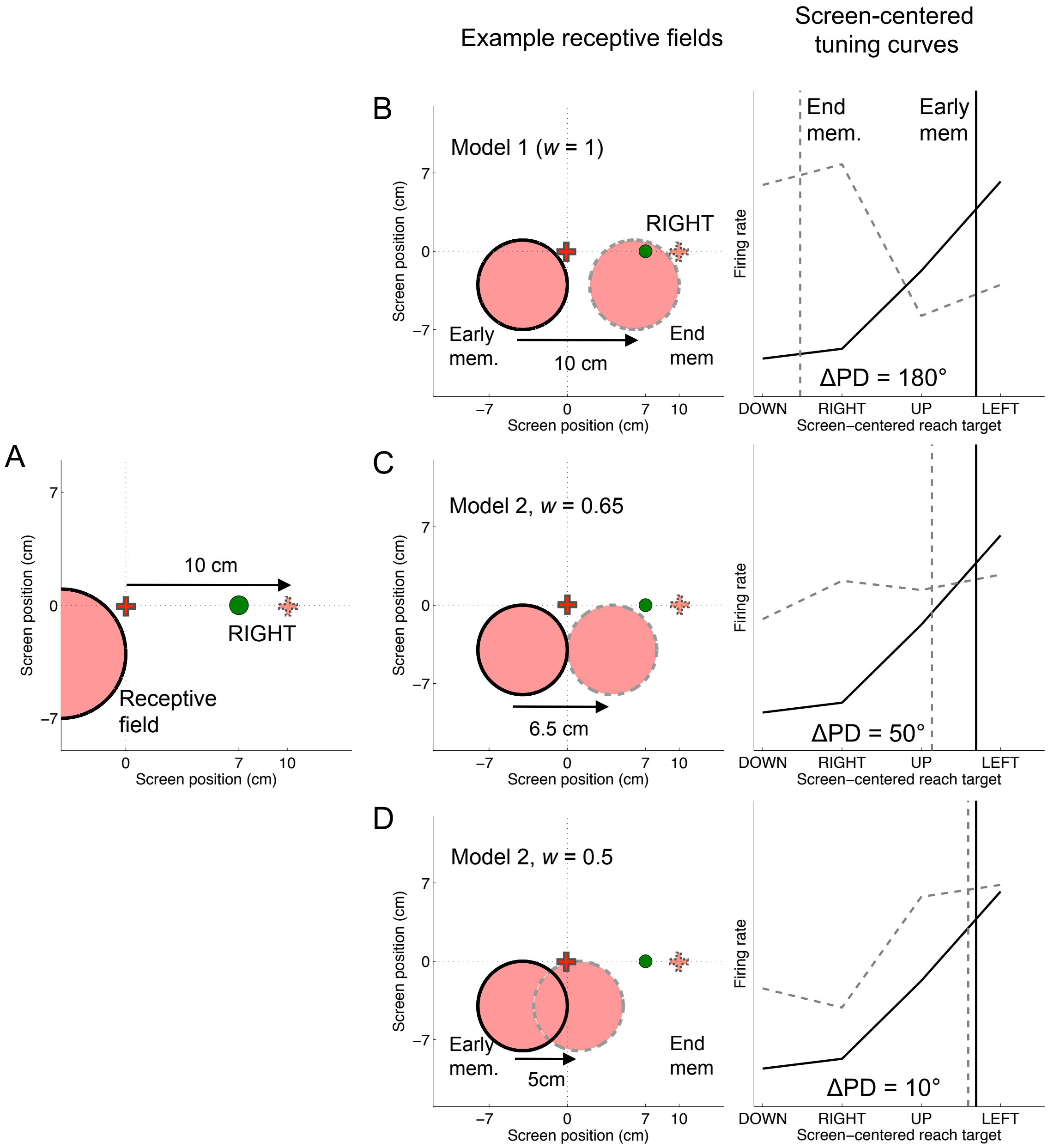

Figure 2. A model of eye-centered, hand-centered, and intermediate reference frames. A. Diagram showing the RIGHT reach target with the early (solid red cross, left) and end memory eye positions (dashed red cross, right). The 2/3-maximum width of a hypothetical receptive field is shown relative to the initial eye position (pink circle). B. For a hypothetical Model 1 neuron, the receptive field in A shifts by an amount identical to gaze, i.e. 10 cm. Using the hypothetical receptive field in A, this brings the RIGHT target into the receptive field. Activity on RIGHT reach trials is increased by the eye movement, while activity on LEFT trials decreases as the target is brought out of the receptive field (right column). This results in a shift in

screen-centered PD of 180°. Vertical lines show PD for early (solid) and end memory period (dashed). Because the eye movements in this experiment result in LEFT and RIGHT targets switching visual hemispheres, as do the DOWN and UP targets, fully eye-centered neurons will shift PD by 180°. C. If neurons have partially shifting receptive fields, eye movements in this experiment can lead to a range of ΔPD. This figure shows an example neuron whose receptive field shifts by 65% of the gaze shift (*w* = 0.65). After eye movements on RIGHT trials, the reach target is further from the receptive field center than in A. Correspondingly, firing rates on RIGHT trials increase slightly (right), and across all directions the change in screen-centered PD is intermediate (ΔPD=50°). D. Similar to C, but *w*=0.5. Solid black: early memory gaze location. Dashed grey: end memory. Right plots show tuning curves for model neurons.

same amount as the gaze (Model 1). In this case, receptive fields were modeled as a Gaussian hill function:

$$FR = \exp(-\frac{((T-E)-\mu)^2}{2\sigma^2}) + \varepsilon,$$

where T-E is the two-dimensional location of the reach target *T* relative to gaze location *E*, i.e. T-E is the eye-centered target location. The Gaussian peak locations *m* was drawn from the interval [-20° 20°], which is the approximate extent of the visual field in this experiment. Gaussian width s was 10°. ε was a Gaussian white noise term with a standard deviation of 0.07, which was determined from neural data.

The second model assumed that receptive fields partially shifted with changes to the gaze (Model 2):

$$FR = \exp(-\frac{((T-wE)-\mu)^2}{2\sigma^2}) + \varepsilon,$$

where *w* determines the extent to which the receptive field shifts with changes to gaze position *E*. *w* was drawn from the interval [0 1], representing an even distribution from hand-/head-/body-centered to eye-centered. (Note that hand-, head-, body-, and screen-centered are equivalent for this experiment.) Values for *w* come from previous experiments showing a full range of partially shifting receptive fields in movement planning neurons (Duhamel et al., 1997, Pouget et al., 2002a). The other parameters in Model 2 are identical to Model 1. Note that Model 1 is a special case of Model 2, since *w=1* corresponds to the full eye-centered encoding in Model 1.

Model distributions of ΔPD were calculated similarly to actual distributions of ΔPD. That is, for each parameter set, two 4-point tuning curves were calculated: one using the peripheral eye position in the end memory period on Saccade and Pursuit trials (E = ±10 cm), and the other using the central eye position in the end memory period on Fixation trials (E = 0 cm). ΔPD was calculated as the difference in PD between the two model tuning curves. The procedure was repeated 1,000 times with randomized parameter sets (μ and *w*) to compute model ΔPD distributions.

In order to compare the output of these simulations to our neural data, we compared the probability densities of ΔPD distributions from model and real data. Probability densities were computed by counting the fraction of each distribution within a 10° bin. In practice this process was identical to calculating normalized histogram bin heights. Probability densities were calculated identically for real and model distributions.

Reach plan-dependent ΔFR. In order to test whether ΔFR on eye movement trials represented reach plan updating or a reach-independent eye position signal, we compared ΔFR between trials with the same eye movement but different reach plan. If eye movement modulations represent reach plan updating, ΔFR for the same eye movement should differ depending on the reach plan. To test this, we used three datasets from monkey M where reaches were made in either the same direction (ipsilateral) or the opposite direction from the eye movement (contralateral). For each eye movement direction, we computed an unpaired t-test between ΔFR from trials with ipsilateral and contralateral reaches. A significant difference ($p<0.05$) was taken as evidence that ΔFR was dependent on the reach plan.

Eye movement onset. The start of eye movement was detected using custom software in Matlab. Eye speed was calculated by first filtering eye position using a 200 ms boxcar filter and then differentiating (Fig. 1C). As a threshold for saccade onset, we calculated the average eye speed during the early memory period, i.e. during a period when the eye was confined to the center of the screen. Instructed saccade onset was defined as the first time at which eye speed was greater than five times this threshold speed for at least 20 ms. Pursuit onset was detected using a combination of eye speed and eye position. A distribution of eye positions was calculated during a baseline period 300 ms to 0 ms before pursuit instruction. Pursuit onset was defined as the first time that eye position was greater than one z-score relative to the baseline distribution, and eye speed was greater than one quarter the average speed across the memory period. This method allowed reliable detection of pursuit onsets with and without catchup saccades. The parameters of this method, including thresholds and baseline periods, were optimized to ensure correct eye movement onset detection. Onset times for all trials were confirmed visually.

2.4 Results

2.4.1 Reach error is similar following a saccade or a pursuit

To investigate the effects of smooth pursuit and saccade eye movements on reach behavior, we first compared reaching error for all three conditions (Fig. 3). The mean reach error across all Fixation, Pursuit and Saccade trials was 0.17° (SD 1.01°), -0.13 (SD 1.07°) and -0.17 (SD 1.13°). Positive reach error values meant the reaches had greater amplitude than the reach target, while negative values meant that reaches undershot the reach target. Reaching error was not significantly different between Saccade and Pursuit trials (Wilcoxon rank-sum, $p=0.65$), but was significantly different between Fixation and Saccade trials ($p<0.001$) and Fixation and Pursuit trials ($p<0.001$). These results show that the monkeys could accurately

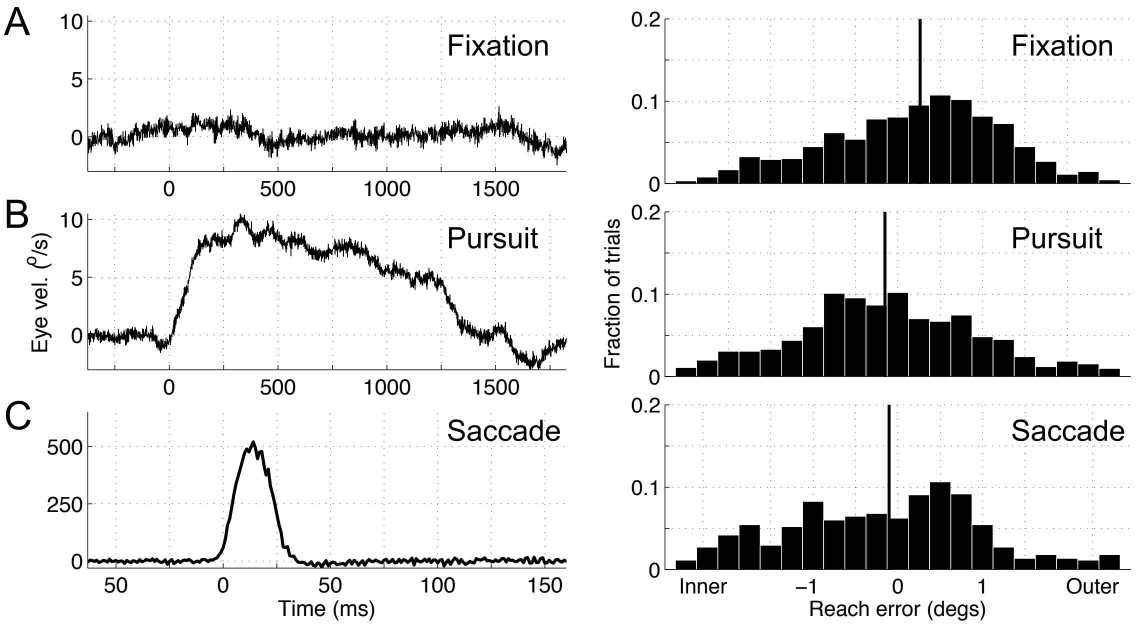

Figure 3. Reaching error was similar after both eye movements. A. Mean eye velocity (left) and reach error (right) during Fixation trials. Reach error was combined across all recordings, and was measured in the direction parallel to the fixation-reach target line. Positive ("outer") errors fell more peripherally than the reach target, while negative ("inner") errors fell closer to the central fixation, consistent with an overreaching to peripheral reach targets (Bock, 1986) on Saccade and Pursuit trials. B. Pursuit trials. C. Saccade trials. Fixation and Pursuit eye positions were filtered with a 25 ms boxcar filter before differentiating, while Saccade eye positions were filtered with a 5 ms boxcar to limit low-pass filtering.

perform all trial conditions, and that both eye movements subtly changed reaching behavior. The pattern of reach error is consistent with a retinal eccentricity effect where reaches overshoot targets in the visual periphery (Bock, 1986, Thompson and Henriques, 2008a).

2.4.2 Saccades and pursuit produce similar effects on PD

We next sought to characterize the effect of eye movements on the activity of reach planning neurons in MIP and PMd. An example MIP neuron is shown in Figure 4. During the early memory period, which occurred while the eye was centrally fixated on all trials, the neuron had equal firing rates on Saccade (Fig. 4B), Pursuit (Fig. 4C), and Fixation trials (Fig. 4D). After the monkey made an upward saccade, the neuron rapidly increased firing rate (Fig 4B). It similarly increased for an upward pursuit (Fig 4C), although the firing rate remained relatively constant throughout the memory period on Fixation trials (Fig. 4D).

Across all four movement directions, the effect of eye movements on this neuron can be interpreted as a change in the screen-centered preferred direction (PD). Between the early and end memory periods on Saccade and Pursuit trials, PD changed from approximately down and to the left of central fixation to a direction approximately up from central fixation (Fig. 4E). PD on Fixation trials changed minimally between early and end memory periods (Fig. 4E,F, black). Measuring relative to Fixation, eye movements led to a change in PD, i.e. ΔPD, of 161° and 169° on Saccade and Pursuit trials, respectively. This pattern of PD is consistent with the neuron encoding the reach target location relative to gaze location. That is, the neuron fires maximally when the reach target is slightly (3 to 7 cm) below the gaze location.

Similar results were obtained for the populations of neurons. MIP neurons changed PD by 65° (SD 49°) (circular mean and SD) on Pursuit trials and 70.6° (SD 45°) on Saccade trials, a non-significant difference ($p=0.43$, Watson-Williams test; Fig. 5A). Similarly, PMd neurons had a broad range of ΔPD that did not significantly

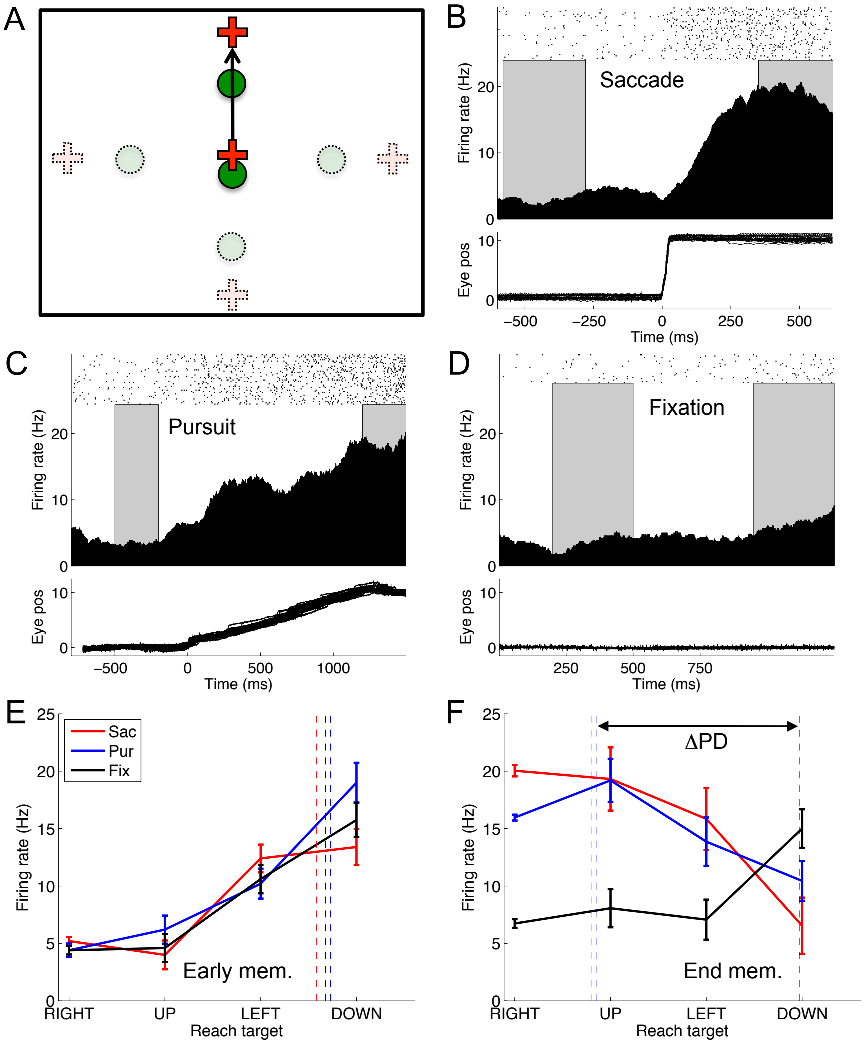

Figure 4. Eye movements change the firing rate and tuning curve of an example MIP neuron. A. Diagram showing the reach/eye movement direction (UP) used in panels B, C and D. B. Activity (rasters and PSTH) from an example MIP neuron in response to an UP saccade (bottom, vertical eye position). Data were aligned to the start of the saccade. C. Activity from the same neuron during the memory period on Pursuit trials. Data were aligned to the start of pursuit. D. Activity during the memory period from the same example neuron on Fixation trials. Alignment was to the start of memory period. Gray patches show the average times of early and end memory periods relative to alignment. E. Early memory tuning curve for the same neuron measured in screen-centered coordinates for the three trial conditions. The early memory period occurs before any eye movements were made. Vertical dashed lines show the PD for the three conditions. F. The same as E, but using data from

the end memory period. ΔPD is calculated as the difference between PD on Fixation and eye movement trials in the end memory period.

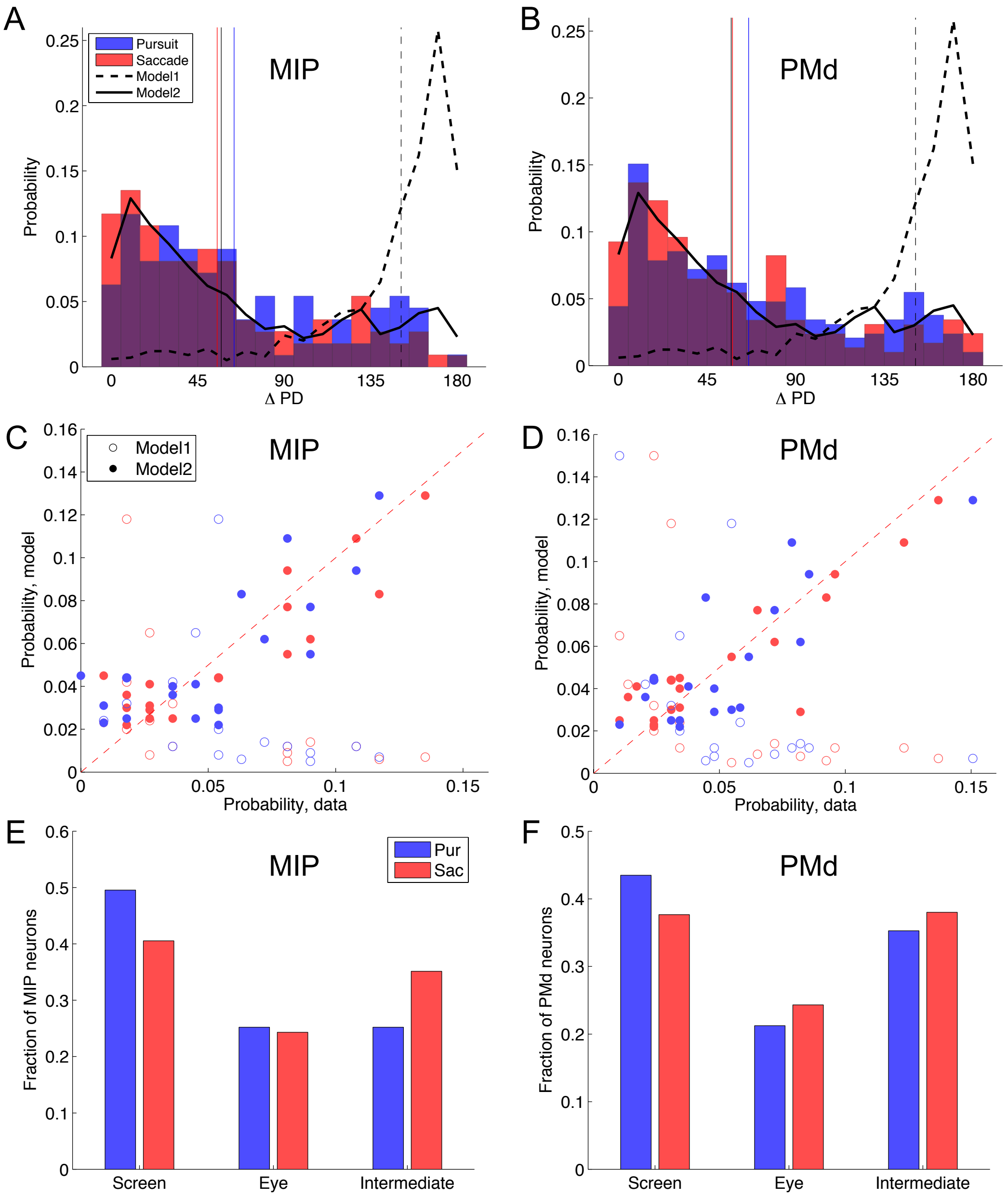

Figure 5. Effects of eye movements on PD, population. A. The normalized histogram (probability density) of ΔPD for all MIP neurons. The predictions of Model 1 and Model 2 are shown. Vertical lines show the circular mean ΔPD for Pursuit trials (blue), Saccade trials (red), Model 1 (dashed black), and Model 2 (solid black). B. PMd neurons. C. ΔPD probability calculated from real MIP neurons versus model

predictions. One data point for Model 1 is outside the bounds of the graph for clarity. Blue: Pursuit. Red: Saccade. D. PMd neurons. E. The fraction of MIP neurons with hand-centered, eye-centered, and intermediate reference frames, as determined by ΔPD. F. PMd neurons.

differ between Pursuit and Saccade trials (Pursuit mean ΔPD = 66° (SD 47°), Saccade mean ΔPD = 60° (SD 47°), p=0.08; Fig. 5B). ΔPD circular means did not differ between MIP and PMd (Saccade, p=0.62; Pursuit, p=0.07). Note that since all neurons analyzed responded to eye movements, ΔPD=0° means that firing rates increased or decreased by the same amount on all four movement directions.

Since eye movements in this experiment inverted the relative positions of gaze and reach target, if neurons were encoding the eye-centered reach targets in a purely eye-centered reference frame, ΔPD would be clustered around 180° (Fig. 5A,B, Model 1). This was not what we saw. Instead, both eye movements led to a range of ΔPD between 0° and 180°. In order to explain this, we modeled the probability density of ΔPD distributions using a second model that used even distribution from hand-/head-/body-centered to eye-centered (Fig. 5A,B, Model 2; see Figure 2 for model description). This leads to partially shifting receptive fields similar to those documented in a number of parietal movement planning brain areas (Stricanne et al., 1996b, Duhamel et al., 1997). A Monte-Carlo simulation was used to generate model ΔPD distributions (see Methods). Model 2 (partially shifting receptive fields) accurately predicted ΔPD probability for MIP neurons on Pursuit (Pearson R^2=0.53, p=0.0004) and Saccade trials (R^2=0.55, p=0.0003; Fig. 5C), and similarly for PMd neurons (Pursuit, R^2=0.57, p=0.0002; Saccade, R^2=0.49, p=0.0008; Fig. 5D). In contrast, Model 1 (strictly eye-centered) poorly predicted ΔPD probability (Fig. 5C,D).

We used each neuron's ΔPD value to determine whether it encoded the reach target in eye-centered, hand-centered, or an intermediate reference frame. (Note that "hand-centered" here could also refer to body-centered or screen-centered.)

95% confidence intervals were computed for each ΔPD via bootstrap (1000 iterations). Neurons with ΔPD not distinguishable from 0° (i.e. 0° within 95% CI) were classified as hand-centered, while those with ΔPD not distinguishable from 180° were classified as eye-centered. The remaining neurons, i.e. those with a partial shift in PD, were classified as encoding in an intermediate reference frame. In both MIP (Fig. 5E) and PMd (Fig. 5F), determining the reference frame with either Saccade or Pursuit trials yielded similar fractions of neurons. Taking the average between Saccade and Pursuit conditions, 45% of MIP neurons were screen-centered, 24% were eye-centered, and 31% had an intermediate reference frame (Fig. 5E). PMd had slightly fewer eye-centered cells (41% screen-centered, 21% eye-centered, 38% intermediate; Fig. 5F).

2.4.3 ΔFR due to saccades and pursuits were similar

The analysis above suggests that saccades and smooth pursuit eye movements to the same location produce a similar change in PD. Since measuring PD potentially obscures changes to raw firing rate, for example if all movement directions change firing rate by the same amount, we next examined the effect of eye movements on firing rate. Figure 6 shows an example neuron recorded from PMd. Initially, the direction of the impending reach conveyed by the reach cue is the only modulating variable (Fig 6A). Subsequent saccades and pursuits made in the memory period caused additional modulation (Fig 6B-E).

In order to quantify these firing rate changes due to eye movements, we calculated the difference in firing rates between early and late memory period on Pursuit (ΔFR_p) and Saccade trials (ΔFR_s). When planning a reach to the RIGHT reach target and making an eye movement in the same direction, the example neuron decreased firing rates by 11.0 Hz (SD 4.9) on Pursuit trials and 9.1 Hz (SD 7.1) on Saccade trials, a non-significant difference (p=0.24, unpaired t-test). Similarly, ΔFR_p and ΔFR_s were not significantly different for UP [7.9 Hz (SD 9.3), 11.6 Hz (SD 9.5), respectively, p=0.29], LEFT [-2.9 Hz (SD 7.6), -2.8 Hz (SD 7.4), p=0.93], and DOWN reaches/eye movements [-15.8 Hz (SD 6.4), -12.9 Hz (SD 5.9), p=0.07]. For this

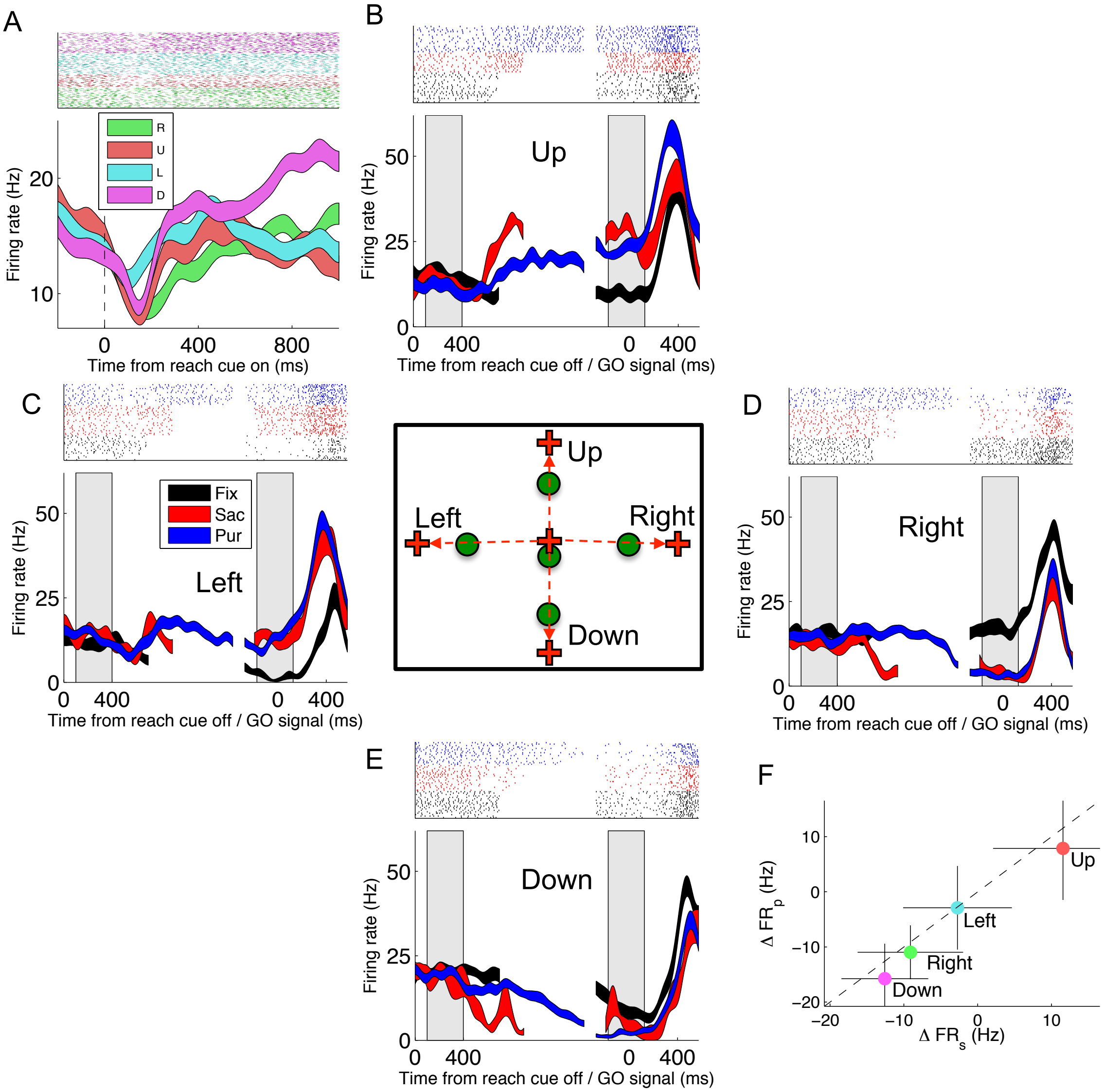

Figure 6. An example neuron with similar ΔFR on Saccade and Pursuit trials. A. PSTHs aligned to the onset of the reach target, using trials from Fixation, Saccade and Pursuit conditions (green-RIGHT reaches, red-UP, blue-LEFT, magenta-DOWN). B. PSTHs aligned to the start of memory period on Fixation trials (black), saccade onset on Saccade trials (red), and pursuit onset on Pursuit trials (blue) (left). PSTHs were also aligned to the reach cue (right). Grey vertical bars show the mean early and end memory periods. All trials are from reaches in the UP direction. C. LEFT reaches and eye movements. D. RIGHT reaches and eye movements. E. DOWN reaches and eye movements. F. ΔFR_s vs ΔFR_p for the same example neuron. Colors correspond to A, and error bars show standard deviation. The unity line is shown (dashed).

example neuron, ΔFR_s and ΔFR_p were not significantly different for any movement direction (Figure 6F). Therefore, the change in firing rate between pre and post eye movements was modulated by the eye movement but was not affected by how gaze arrived at its final position.

Similarly to the example neuron, the populations of MIP and PMd neurons did not have significantly different ΔFR_p and ΔFR_s. Examining the populations of MIP neurons as a whole, mean ΔFR_p was not significantly different from mean ΔFR_s across MIP units [1.8 Hz (SD 11.4) versus 3.5 Hz (SD 11.1), respectively; p=0.24, paired t-test]. Note that ΔFR_p and ΔFR_s distributions contain positive and negative values. Similarly for PMd units, across the population mean ΔFR_p was not significantly different from mean ΔFR_s [21.2 Hz (SD 29.7) versus 23.9 (SD 31.5), respectively; p=0.27]. As can be seen, both MIP (Fig. 7A) and PMd (Fig. 7B) neurons tended to have equivalent responses to for saccades and pursuits. Indeed, 80% (102/127) of MIP and 79% (248/313) of PMd units had no significant difference between ΔFR_s and ΔFR_p, as calculated for the D_{max} direction (unpaired t-test, p>0.05, Fig. 7C). Results were similar when analyzing only eye-centered (MIP: 23/30, 77%; PMd: 56/73, 77%), hand-centered (MIP: 41/51, 80%; PMd: 89/115, 75%), or intermediate neurons (MIP: 35/46, 76%; PMd: 93/122, 76%) as determined by ΔPD. Therefore, for most MIP and PMd neurons an eye movement to the same location resulted in the same firing rate change regardless of the eye movement type.

2.4.4 ΔFR represents reach plan updating

It is possible that the observed firing rate changes were simply an eye position signal as seen in other brain areas, e.g. (Wang et al., 2007), and did not represent updating *per se*. To test this, we compared firing rates for the same eye movement but different reach plans (ipsi- or contralateral to the eye movement). If the firing rate changes reflect updating, changes in firing rates due to eye movements (ΔFR) will depend on the reach plan, whereas an eye position-only signal will be independent of the reach plan. This was measured by comparing ΔFR

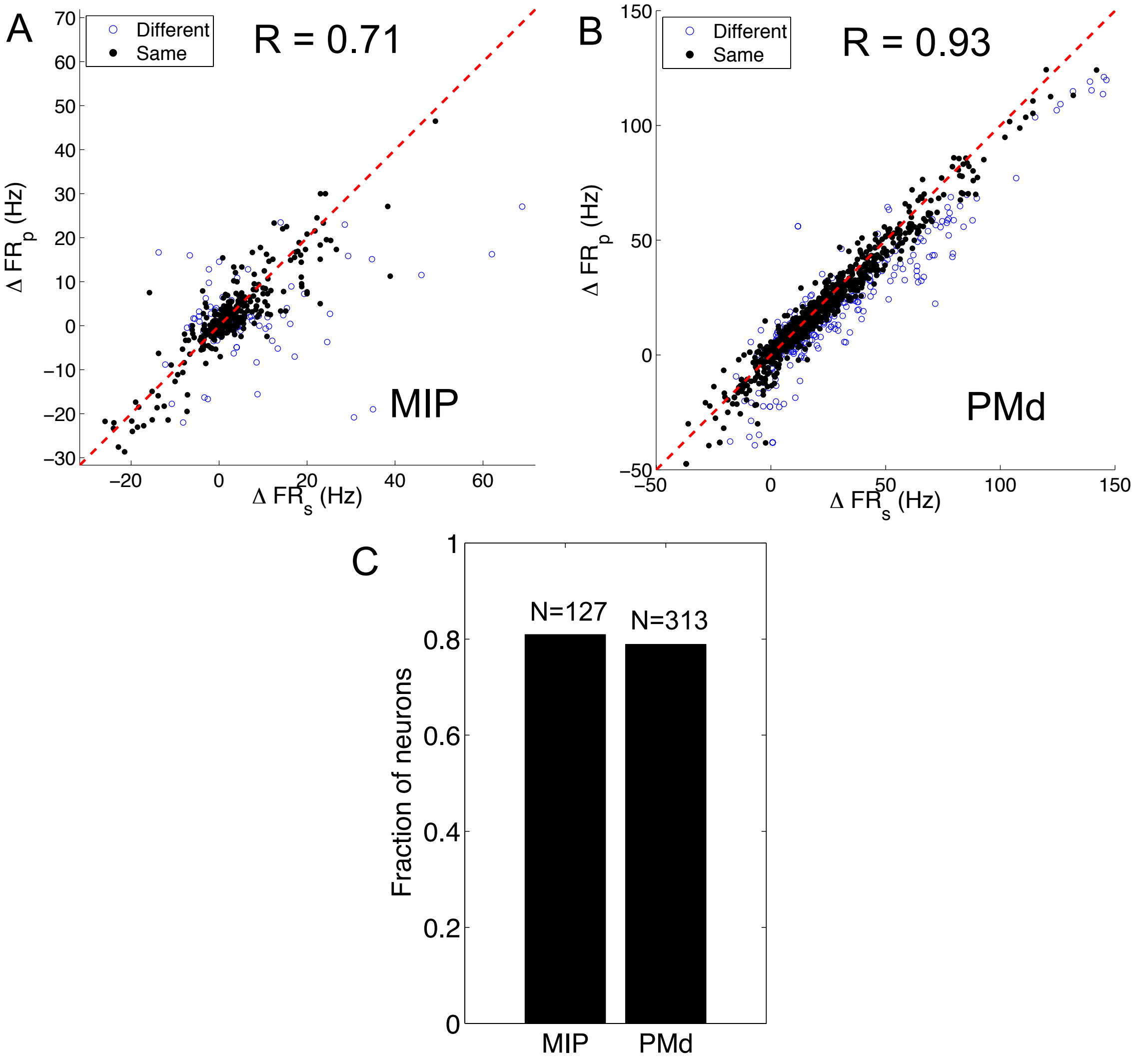

Figure 7. ΔFR_s and ΔFR_p are similar for most MIP and PMd neurons. A. Scatter plot of ΔFR_s and ΔFR_p for all MIP neurons. Each point represents the mean firing rate change (ΔFR) for one neuron on Saccade (x-axis) or Pursuit trials (y-axis). Open circles denote significant difference between ΔFR_s and ΔFR_p (t-test, $p<0.05$), and filled circles denote no difference ($p>0.05$). ΔFR for all four movement directions is plotted, meaning there are 127x4=508 data points. B. Same for PMd neurons. C. Fraction of neurons with no significant difference between ΔFR_s and ΔFR_p (unpaired t-test, $p < 0.05$), calculated for a single direction (D_{max}).

for each eye movement direction between trials with an ipsilateral and contralateral reach. This required datasets where multiple eye movements were made for the same reach. Using three such datasets from monkey M we had a total of 43 task-selective MIP neurons and 103 task-selective MIP neurons. Figure 8 shows an example MIP neuron responding to the same saccade but different reaches. When planning a reach to the left, the effect of the saccade was to decrease firing rates, whereas when planning a reach to the right the same eye movement increased firing rates, which constituted a significant difference in ΔFR ($p=0.0006$, unpaired t-test; Fig. 8B). (This is consistent with the neuron having an eye-centered receptive field for reach targets to the left of gaze location.) This effect – eye movement modulation depends on ongoing reach plans – was true for 79% (34/43) of MIP neurons and 87% (90/103) of PMd neurons (Fig. 8C). Similar results were obtained for pursuit eye movements (73% MIP, 84% PMd).

2.4.5 A minority of neurons had greater responses for saccades than pursuits

We sought an explanation for the minority of neurons that did have a significant difference between ΔFR_s and ΔFR_p. Across PMd neurons with a significant difference between ΔFR_s and ΔFR_p (65/313), mean ΔFR_s was significantly greater than mean ΔFR_p [32.2 Hz (SD 37.5) versus 26.2 Hz (SD 32.3), respectively; $p=2e-5$, paired t-test]. Of these 65 neurons, 50 had significantly greater ΔFR_s than ΔFR_p , while 15 showed the opposite relationship (unpaired t-test, $p<0.05$). For MIP neurons with unequal responses to eye movements (25/127), there were similarly significantly greater responses on Saccade trials [mean ΔFR_s = 6.2 Hz (SD 12.2), mean ΔFR_p = 0.2 Hz (SD 12.0); $p = 0.02$]. Of these 25 neurons, 19 had significantly greater ΔFR_s than ΔFR_p (unpaired t-test, $p<0.05$). Therefore, neurons with unequal responses tended to have greater responses to saccades.

We next investigated whether there were differences in either visual or motor responses for the two populations (equal ΔFR and unequal ΔFR). Defining a 300 ms window at the time of the appearance of the reach cue, there was not a significant difference in reach cue firing rates between the two populations for MIP

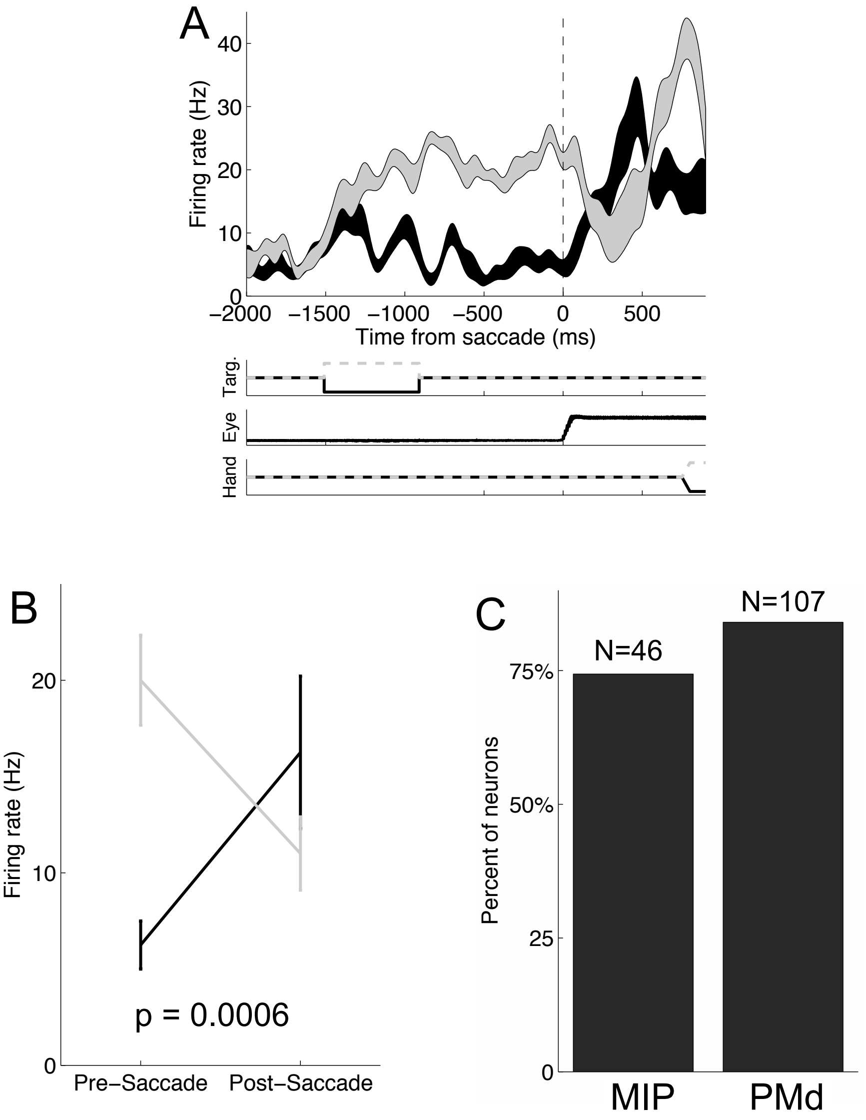

Figure 8. Activity changes due to eye movements reflects updating. A. Single PRR neuron responding to the same rightward saccade while planning a rightward (black) or leftward reach (gray). The effect of the eye movement, either an increase or decrease in firing rate, depends on the ongoing reach plan. Firing rate changes are consistent with the neuron preferentially encoding reach targets to the left of gaze location. Timing of reach target, eye movement and reach are shown in bottom panels. B. Mean firing rates in the early memory movement and post-eye movement epochs for neuron in A (same color scheme). ΔFR_s is the difference between post- and pre-saccade firing rates. The reported p-value was computed by comparing ΔFR_s between contra- and ipsilateral conditions (unpaired t-test). C.

Fraction of PRR and PMd neurons that have reach-dependent responses to eye movements, as indicated by a significant interaction term p-value (p<0.05).

neurons (p=0.36, unpaired t-test) or PMd neurons (p=0.59). Similarly, in a 300 ms window at the start of the reach, there was no difference in firing rates between the two populations for MIP or PMd neurons (p=0.66, p=0.71, respectively). Therefore, for a minority neurons there was a trend to respond with a greater change in firing rate on Saccade trials, although this did not correlate with differences in either visual or motor responses.

2.5 Discussion

Our primary goal was to characterize how reach planning brain areas updated activity for smooth pursuit eye movements at the single neuron level. In particular, we compared the modulation of reach neurons to pursuit and saccadic eye movements. The two types of eye movements have significantly different dynamics, since smooth pursuit eye movements are slower and generated by a closed loop feedback system, while saccades are faster, ballistic, and pre-programmed. While primates are able to update movement targets for pursuit eye movements (Blohm et al., 2005), there is conflicting evidence whether updating in response to a pursuit eye movement occurs similarly (Thompson and Henriques, 2008a) or differently from saccades (Baker et al., 2003). However, if firing rates in reach planning areas encode the relative positions of eye, target, and hand position, then neurons should be updated similarly by pursuit and saccade movements that end at the same final gaze location.

We first confirmed that reaching error following saccades and pursuits did not differ. Both animals in this study were able to accurately reach to remembered targets after either eye movement. Consistent with a behavioral effect to overreach when moving the hand to targets in the visual periphery (Bock, 1986), reaches slightly shifted toward the center of the screen after a saccade or pursuit that brought the gaze to the periphery of the screen (Fig. 3). This result has been used before as evidence that internally represented locations of reach targets shift with eye movements (Henriques et al., 1998, Thompson et al., 2014). Consistent with the behavior, we saw that the majority of MIP (102/127, 80%) and PMd neurons (248/313, 79%; Fig. 7C) responded to both eye movements with similar changes to firing rate. These results show that although there are considerable differences in the mechanics of the two eye movements, the consequences for neural encoding are the same.

2.5.1 The nature of screen-centered tuning curve changes in response to eye movements

The responses of neurons to eye movements in this study were consistent with neurons encoding reach targets relative to gaze location, although responses for the majority of neurons differed from strict eye-centered encoding. Because eye movements in this experiment inverted the visual hemisphere of the reach targets, screen-centered tuning curves should similarly shift by 180° if neurons encoded the target in eye-centered coordinates. This is not what we saw (Fig. 5). Instead, screen-centered tuning curves tended to shift partially for both pursuits (MIP 65°, PMd 66°) and saccades (MIP 71°, PMd 60°). Both MIP and PMd had similar broad ranges of shifts. This partial shift could be explained by a mixture of eye-centered and body-centered reference frames that lead to partially shifting receptive fields in parietal areas (Stricanne et al., 1996a, Duhamel et al., 1997) and the premotor cortex (Graziano et al., 1997). In particular, Duhamel and colleagues (1997) showed that activity from neurons in the ventral intraparietal area shifted with eye position, although the magnitude of the shift varied greatly between neurons. Some neurons encoded the stimuli in a head-centered reference frame and were entirely invariant for eye movements, while others had a strict eye-centered scheme, shifting by an amount equal to the eye movement. Since hand-centered neurons should not encode changes to gaze position, it is not immediately clear why many hand-centered cells responded to eye movements, i.e. non-zero ΔFR. However, it is plausible that these firing rate changes for hand-centered cells are due to eye position gain fields (Zipser and Andersen, 1988, Pouget and Snyder, 2000).

Modeling this with a scheme previously used elsewhere (Chang et al., 2009), we used simulations in which individual neurons had a mix of eye- and body-centered encoding (Model 2). As opposed to strict eye-centered encoding (Model 1), a mix of eye- and body-centered encoding accurately reproduced the shape of ΔPD distributions obtained from MIP and PMd neurons (Fig. 5). These results support the idea that even within the same localized brain region, parietal and premotor neurons encode space with a range of reference frames that weight eye position to varying degrees. This encoding likely does not represent an end-stage computation. Instead, theoretical studies suggest that these partially shifting receptive fields are an intermediate step in the coordinate transformation process, in this case between eye- and body-centered coordinates (Pouget et al., 2002a). This is consistent with MIP and PMd's putative roles in transforming eye-centered visual information into a more arm- or hand-centered encoding scheme suitable for driving a reach (Boussaoud et al., 1998, Buneo and Andersen, 2006).

2.5.2 Implications of equal firing rate changes caused by saccades and pursuits

It is important to note that assessing the main goal of this study ("Do saccades and pursuit update reach planning neurons similarly?") does not require us to know the underlying encoding scheme. Instead, it is sufficient for neurons to i) encode the reach target relative to gaze location in some way and ii) update for changes to gaze location. The changes to firing rate, which form the neural substrate of visual updating, can then be compared between the two eye movements. Doing so, we saw that both measures of updating (ΔPD and ΔFR) did not differ between the two eye movements. Therefore, both the magnitude of firing rate changes and the relative shift in firing rates between the four movement directions were the same for saccades and pursuits.

Note that while changes to firing rate due to spatial updating implies that neural activity changes in a systematic manner with gaze direction, we did not test that explicitly here. While we did confirm that changes in preferred direction were consistent with an accepted model (partially shifting receptive fields), it's possible that other models, such as a combination of eye-centered encoding and eye position gain fields (Chang et al., 2009), could equally explain our data. A future experiment with different starting hand, eye, and target positions is likely required to differentiate between these two models.

Our results are consistent with previous single neuron studies showing that PMd and MIP encode either the relative gaze and reach target positions (Batista et al., 1999, Pouget et al., 2002b) or the relative positions of gaze, target and hand (Pesaran et al., 2006, 2010). Given these past findings, discrepant firing rates following either eye movement would have suggested that the internal representation of the gaze-target relationship differs after pursuits and saccades. This discrepancy would lead to differences between reach endpoints following either eye movement, i.e. different reaching error, which we did not observe (Fig. 3). Therefore both behavioral and single neuron results in this study support the idea that MIP and PMd participate in transforming visual information into signals that subserve reaching behavior.

However, caution should be taken when interpreting PMd modulations for eye position during reaching tasks. Cisek and Kalaska (2002) found that gaze-dependent modulation in single PMd neurons was much more modest when the animals were not trained to fixate and instead made natural, spontaneous eye movements. Therefore an alternate interpretation is that gaze-related modulations in PMd seen in some studies may reflect rewarded, instructed motor acts rather than an explicit spatial encoding. Given that eye positions in this experiment were instructed, we do not test this alternate interpretation here.

Although only a minority of neurons in MIP (25/127, 20%) and PMd (65/313, 21%) had different firing rate changes for saccade and pursuit, the fraction was still greater than chance levels. These neurons tended to respond with greater firing rates for saccades relative to pursuits. A recent modeling paper showed that neural networks trained to store and update locations across eye movements used signals related to the velocity of the gaze change rather than gaze position *per se* (White and Snyder, 2004, 2007). Greater activation in response to saccades could therefore represent the differing velocity components of the two eye movements, although it is unclear how this would affect the neuron's ability to encode the gaze-target relationship.

2.6 Conclusions

In this Chapter, we investigated whether the consequences of updating by pursuit and saccade eye movements differ at the neural level. We recorded from neurons in brain areas MIP and PMd, which are known to encode the locations of reach targets relative to gaze location, while monkeys executed reaches after intervening eye movements. We showed that neural activity updated for these eye movements in a manner consistent with encoding the reach target wholly or partially relative to gaze location. Changes to firing rates induced by saccades or pursuits were similar for approximately 80% of neurons in both MIP and PMd. This is consistent with neurons updating similarly regardless of how the eye position was changed.

The results here do not address any temporal differences between updating for the two eye movements. Given the great differences in saccade and pursuit biomechanics, most noticeably the difference in their duration, there are likely significant differences in the time courses of pursuit and saccade updating. The time course of reach plan updating during pursuit has not been investigated at the neural level. This Chapter investigated updating using periods of fixed eye position around the eye movements. Chapter 3 analyzes data during the pursuit eye movement in order to investigate the temporal components of updating in response to pursuit eye movements.

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Chapter 3

Predictive and dynamic reach plan updating during saccade and smooth pursuit eye movements

3.1 Abstract

Primates have the ability to reach to the location of previously viewed objects after an intervening movement. Internal representations of the reach target location, encoded in areas such as the medial intraparietal sulcus (MIP) and the dorsal premotor cortex (PMd), are known to update their activity for these intervening movements, particularly for saccadic eye movements. However, it is poorly understood how updating occurs during slower movements, like smooth pursuit eye movements. To investigate this, we recorded from MIP and PMd while monkeys planned a reach, made an intervening smooth pursuit eye movement, and then executed the reach. A subset of neurons in PMd were found to begin to update predictively, while updating was delayed relative to the eye movement in nearly all MIP neurons. Neurons in both areas updated dynamically during the eye movement. That is, neurons appeared to encode the reach target relative to the transient eye positions during smooth pursuit. This is the first demonstration of predictive updating in the reach system. These results support efference copy as a driving signal of reach plan updating, at least for PMd neurons, and confirms previously reported temporal delays during visuomotor tasks between MIP and PMd. Further, this is the first finding of dynamic updating in cortical neurons.

3.2 Introduction

Primates are capable of accurately reaching to the remembered visual location of a target. Neurophysiological evidence from the last two decades shows that the neural representations of such reach goals are encoded in a coordinate system centered on gaze location (Batista et al., 1999) or in a hybrid coordinate system including gaze location (Mullette-Gillman et al., 2005, Pesaran et al., 2006). This means that neurons in brain areas such as the medial intraparietal sulcus (MIP) and the dorsal premotor cortex (PMd), which are known to encode the location of reach goals or "reach plans" (Boussaoud, 2001, Andersen and Buneo, 2002), modulate their activity relative to gaze (Batista et al., 1999, Cisek and Kalaska, 2002). Therefore, to keep representations of reach targets accurate in natural, dynamic environments, the brain must account for eye movements and correspondingly update the response properties of neurons in reach planning areas like MIP and PMd. To date, it is still unclear how updating occurs in reach planning neurons.

Updating is most often investigated using periods of fixed eye position between fast, saccadic eye movements, e.g. (Goldberg and Bruce, 1990). In this context, saccadic eye movements induce a discontinuous remapping of response properties of neurons in cortical eye movement planning areas (Kusunoki and Goldberg, 2003). In the superior colliculus (SC), an area that updates for eye movements and that likely contributes signals for cortical updating, only the pre- and post-saccade locations are encoded, and the intermediate locations of the target as it is smeared across the retina are ignored (Sommer and Wurtz, 2006). Driven by a copy of the eye movement command ("efference copy"), updating in eye movement planning areas can occur predictively up to 250 ms in advance of the eye movement (Duhamel et al., 1992, Umeno and Goldberg, 1997b, Kusunoki and Goldberg, 2003). Given the similarities between eye movements and reaches, it is hypothesized that reach movement plans are similarly updated by saccades, although predictive updating has not been shown in the reach system.

In contrast, it is less clear how neurons update for other eye movement types, such as smooth pursuits. Given that pursuit eye movements are used for tracking unpredictable movements in the real world and can last many seconds, the final eye position is typically unknown at the onset of pursuit. Thus, it is impossible that movement plans predictively remap relative to the final eye position, as is the case with saccades. If movement planning neurons do not immediately remap relative to the final eye position, what eye position is referenced by the movement plan during the pursuit? We imagine two scenarios.

If, like saccades, pursuit updating does not process intermediate eye positions, then activity relative to the initial eye position should linger throughout the pursuit ("static updating"). "Static" here would describe updating not occurring as a continuous, gradual process, but rather as a discrete transition. The second option is that, unlike transsaccadic updating, activity is continuously remapped for intermediate pursuit eye positions during the pursuit ("dynamic updating").

In this study we addressed two temporal components of reach plan updating. Our first goal was to investigate whether reach plans can update predictively for saccades and pursuits. Since efference copy is a likely source of reach plan updating, we hypothesized that some reach planning neurons should exhibit predictive updating. Second, we wanted to differentiate between static and dynamic updating during pursuits. Given that static updating renders reach plans inaccurate during the pursuit, we hypothesized that the reach system is updated dynamically with the pursuit gaze change. In order to investigate this, we trained primates to execute a memory reach task with intervening saccade and pursuit eye movements. We simultaneously recorded from neurons in brain areas MIP and PMd. Our results showed that predictive updating arose in PMd neurons but not MIP. Further, both MIP and PMd updated dynamically during pursuit eye movements by encoding the intermediate gaze-target relationships during the pursuit. These results imply that the brain continually monitors the relationship between gaze and reach target locations during slow tracking eye movements, a process that does not occur for transsaccadic updating.

3.3 Methods

3.3.1 Subjects and surgical procedures

We collected data from two awake, behaving male monkeys (Macaca mullata, M and H), weighing 6.5 kg and 11.9 kg. Monkeys were first implanted with an MRI compatible head post (Rogue Research). We localized the left medial intraparietal area (MIP) and left dorsal premotor cortex (PMd) for microelectrode array implantation (MicroProbe, Gaithersburg, MD) using the

MRI-based Brainsight (Rogue Research). Monkeys were given Glycopyrrolate intramuscularly at a dose of 0.005 mg/kg followed by a dose of Ketamine at 10 mg/kg for the induction of general anesthesia. Isoflurane gas (1-4%) was given to maintain general anesthesia. All surgical procedures were carried out under sterile conditions. After the surgical procedures, analgesia was administered to the monkeys for pain control for 10 days. The monkeys were given 14 days to recover before starting experiments. We measured the monkeys' body weight on a daily basis to monitor health and growth. Throughout the testing period the animals were pair-housed and could exercise in a jungle gym. Monkeys were given fresh fruits after all completed sessions. All experimental procedures complied with the Canadian Council of Animal Care guidelines and were approved by the McGill animal care committee.

3.3.2 Behavioral task

The monkeys were trained to perform modified center-out memory reach tasks. Animals were mechanically headfixed and seated in a Farraday cage. Behaviour was controlled using a real time system (LabVIEW RT, National Instruments). We used an infrared reflection camera to record eye position (ISCAN, Boston). Two-dimensional hand position was monitored using a frontoparallel acoustic touch screen (ELO Touch, California) that was coupled to a monitor. Monkeys sat 45 cm in front of the touch screen. Once a trial was initiated, eye and hand positions were constrained within 2.5° radius windows until the trial was completed. Unsuccessful trials were those in which the monkey failed to maintain accurate eye and hand positions before the reward was delivered. Both trial condition and movement directions were randomly interleaved, and the number of successful trials was approximately evenly distributed among conditions and directions.

Experiment 1. Data for Experiment 1 (Fig. 1A) was collected from two animals (M and H) over 18 recording sessions. All trials began when the animal visually fixated a red central eye fixation target and touched a central green reach target for 600 ms. A peripheral reach cue was then flashed for 600ms at one of four locations (Fig. 1B). The disappearance of the peripheral reach cue initiated the memory period. The memory period involved one of three conditions.

I. ***Fixation condition*** *("Fix").* Fixation trials provided a control condition without eye movements. During the memory period the monkey fixated on the central eye target for 1200-1600 ms (uniform distribution). At the end of the memory period the central green hand target disappeared, instructing the monkey to reach.

II. ***Saccade condition*** *("Sac").* 600-800 ms after the start of the memory period the central eye target was extinguished and a peripheral saccade target was simultaneously illuminated at a distance 10 cm away. The monkey initiated a saccade to the saccade target within 400 ms or the trial was aborted. The animal held the new eye position until the reach was completed. Memory periods lasted 1200-1600 ms (uniform distribution) and the saccade was instructed halfway through the memory period.

III. ***Pursuit condition*** *("Pur").* 700-900 ms (uniform distribution) after the start of the memory period the central red eye target began moving at 9.4°/s. The monkeys tracked the pursuit target by reflexively generating a smooth pursuit eye movement. After reaching the endpoint the eye target stopped and the monkey held the new eye position until the reach was completed. The pursuit eye movements ended at the same locations as the saccades in the Saccade condition.

On all trials the memory period was ended by extinguishing of the central green reach target, which instructed the animal to reach to the remembered location of the reach cue. If the monkey reached within 2.5° of the reach target, the target was re-illuminated and the animal received a juice reward. On Saccade

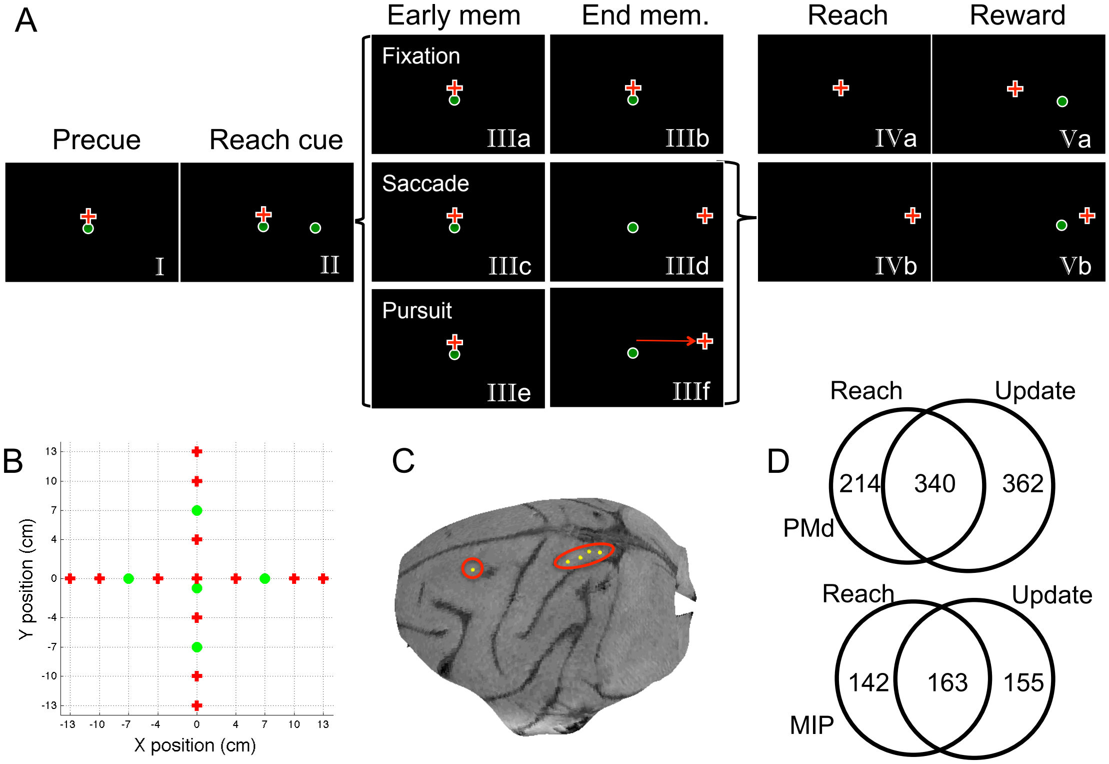

Figure 1. A. Schematic of Fixation, Saccade and Pursuit experiment paradigms. Red crosses are eye position, and green dots are hand position. All trials began by looking at and touching central targets (I) followed by a 600 ms reach cue (II). During the memory period eye position was either held constant (Fixation condition, IIIa,b) or moved by a saccade (Saccade condition, IIIc,d) or pursuit eye movement (Pursuit condition, IIIe,f). At the end of the memory period the central hand target disappeared (IVa,b) instructing the animal to reach to the remembered target location. B. Schematic showing the eye and hand target locations on the display screen. Most recordings only instructed eye movements with a 10 cm amplitude (Experiment 1), although three recordings had additional eye movements to targets at 4 cm and 13 cm (Experiment 2). Red cross: eye. Green circle: hand. Eye and hand position always started centrally. C. Array locations in monkey M. D. Total numbers of neurons that encoded reach targets and updated for eye movements.

and Pursuit trials the eye movement was always in the same direction as the reach. Eye movements were always 10 cm in amplitude. Datasets from Experiment 1 had at least 180 trials (3 conditions x 4 directions x 15 repetitions), although we continued collecting data until the animal had reached its minimum fluid allowance or stopped working (mean trials per recording: 364).

Experiment 2 - Multiple amplitude pursuit. During three recording sessions for Experiment 1 we also collected data for Experiment 2 from monkey M. In this second experiment, animals made pursuit eye movements to multiple amplitudes (Fig. 1B). These trials were identical to Pursuit trials in Experiment 1 except that in Experiment 2 pursuits were made to two other amplitudes: 4 cm and 13 cm. Trials were initiated and completed in the same way. Directions and amplitudes were randomly interleaved. The pursuit target moved at 9.4°/s to one of 3 endpoints in the direction parallel to the reach. Neural activity occurring after the pursuit, i.e. when eye position was fixated at one of the three endpoints (4 cm, 10 cm or 13 cm), was compared to activity during the pursuit when the eye transiently passed through the same position. Data from Experiment 2 was used to test dynamic versus static updating at amplitudes 4 cm, 10 cm or 13 cm.

3.3.3 Electrophysiology

We used multi-electrode array recordings to record neural activity from monkeys M and H. Monkey M was implanted with four 16-channel floating microelectrode arrays in MIP and one 32-channel microelectrode array in PMd (MicroProbe, Gaithersburg, MD). Monkey H was implanted with two 32-channel arrays, one in MIP and one in PMd. Three arrays (48 channels) were recorded from in each session, and MIP and PMd neurons were recorded simultaneously. The lengths of electrodes in MIP ranged from 1-9 mm in both monkeys in order to sample the depth of the intraparietal sulcus. Electrodes in PMd varied from 0.5-1.5 mm. Electrode impedances ranged from 0.4 MOhms to 0.6 MOhms. Since both animals were trained to reach with the right arm, all arrays were implanted in the left hemisphere. Signals were initially amplified using a 20x headstage

(Plexon, Inc). All spike waveforms were sampled at 40kHz using a Plexon acquisition system (Plexon, Inc). Spike waveforms were initially sorted online and additionally sorted offline using custom software.

3.3.4 Data analysis

Neuron selection and trial periods. Since our goal was to analyze the time course of reach plan updating, we required that neurons analyzed in this study i) encode the location of reach targets and ii) update for eye movements in the memory period. The first criterion (reach encoding) was assessed in the *early memory period* across all trials (1-way ANOVA, $p<0.05$). The *early memory period* epoch was defined as the first 300 ms of the memory period, occurring after the presentation of the reach cue but before any eye or hand movements.

We assessed the second criterion (updating) by testing for a significant change in firing rate before and after the smooth pursuit eye movement (paired t-test, $p<0.05$). This second criterion was assessed using only firing rates on Pursuit trials from one movement direction (D_{max}, see below) and amplitude (10 cm). The two time periods used were the early memory period and *end memory period*. The *end memory period* was a 300 ms window centered on the end of the memory period. We selected a single population of neurons that satisfied both these criteria.

During Experiment 1 we recorded from 163 MIP and 340 PMd neurons that met our two criteria for task-selectiveness. These task-selective neurons comprise all the neurons reported in the rest of this study and include 35 MIP and 37 PMd neurons recorded during Experiment 2. For completeness, the numbers of neurons that satisfied only one criterion are shown in Figure 1D. Units were defined using a combination of visual sorting and custom spike-sorting software. Although we strove for well-isolated single neurons, it is likely that multi-unit data is included as well.

Defining D_{max}. For some analyses a subset of trials with movements in a single direction were used. Per neuron, we chose the direction on which there was the maximum absolute change in firing rate between early and end memory periods on Pursuit trials. This direction was defined as "D_{max}". We defined D_{max} in this way in order to maximize the signal to noise ratio by picking the movement direction (right, up, left or down) for which the effects of updating were most prominent.

Updating onset time (t_{ons}). We performed a sliding window analysis in order to determine the earliest time that individual neurons began updating (Crapse and Sommer, 2012). Updating onset was assessed separately for Pursuit and Saccade trials. No trials from Experiment 2 were used. For both eye movements, only trials in a single movement direction were used (D_{max}). Time windows were 300 ms wide and incremented by 50 ms. Alignment was to the start of the saccade or pursuit. All time windows were "causal". We assessed updating by comparing firing rates in each time window to the earliest window, defined as the baseline, which was 800 to 500 ms before the start of the eye movement (paired t-test). The time of updating onset (t_{ons}) was defined as the first of three consecutive bins with a significant difference from the baseline bin ($p<0.05$). As a control, the same analysis was computed on Fixation trials, during which there should be no detectable updating.

Testing for dynamic versus static updating. Data from Experiment 2 was used to test whether neurons updated dynamically or statically during pursuit eye movements. To do so, firing rates during periods of post-pursuit fixation were compared to firing rates when the same eye position was transiently passed through during a pursuit with larger amplitude. Because the activity of dynamically updating neurons reflects the current eye position even during an eye movement, neurons that update dynamically will have comparable post-pursuit fixation and mid-pursuit firing rates for the same eye position.

Post-pursuit fixation firing rates were calculated during 200 ms windows occurring 100 to 300 ms after the end of the pursuit movement. Any trials with reaches beginning less than 100 ms after this post-pursuit fixation window (i.e. less than 400ms after the end of pursuit) were excluded, although in practice few trials were excluded (5% of trials over three recordings). During post-pursuit fixation periods, eye position was held at locations 4 cm, 10 cm, or 13 cm from the central fixation point in one of the four movement directions (Fig. 1B). In order to calculate mid-pursuit firing rates, we found the times when mid-pursuit eye positions during pursuits of the largest amplitude (13 cm) first intersected the eye position of the fixation periods, that is 4 cm, 10 cm, or 13 cm. We defined *time from intersection* (t_{int}) such that t_{int}=0 ms was the time that mid-pursuit eye position on 13 cm trials was equal to post-pursuit fixation eye position (either 4 cm, 10 cm or 13 cm). We included the intersection at 13 cm because pursuits tended to overshoot slightly and then correct, meaning that the 13 cm post-pursuit fixation after t_{int}=0 ms. Firing rates were calculated in sliding windows around t_{int}=0 ms. Sliding windows were 200 ms and incremented by 50 ms.

ROC analysis: t_4, t_{10}, and t_{13}. We sought to estimate whether firing rates during pursuit led or lagged the eye movement for individual neurons. To do so, we computed a receiver operating characteristic (ROC) between mid-pursuit firing rates and post-pursuit fixation firing rates for each neuron. The mid-pursuit firing rates were calculated in 200 ms bins aligned to t_{int}=0 ms as described above. We computed an ROC curve between each mid-pursuit firing rate bin and one of the three post-pursuit fixation firing rates (4 cm, 10 cm, or 13 cm). Only the mid-pursuit bins were shifted. For each ROC curve we calculated the area under the curve (AUC). Therefore for each neuron, we calculated three AUC time-series aligned to either t_{int}=0 ms for 4 cm, 10 cm, or 13 cm.

For example, on each pursuit to 13 cm we found the times that eye position first transiently reached 4 cm, i.e. t_{int}=0 ms, and computed firing rates in bins aligned to that time. We then computed the AUC between firing rates in these bins and firing rates during the post-pursuit fixation at 4 cm. The time of the lowest AUC value was taken to be the time that mid-pursuit and fixation firing rates were most similar. This time was defined as t_4. Similar times were calculated for eye positions at 10 cm (t_{10}) and 13 cm (t_{13}). Note that t_4, t_{10}, and t_{13} are relative to t_{int}=0 ms. For example, t_4=100 ms means that mid-pursuit and fixation firing rates were most similar 100 ms after the pursuit eye position passed through 4 cm.

We therefore calculated four timing variables for each neuron:

- t_{ons} – Updating onset time, aligned to either the saccade or pursuit.
- t_4 – Time when mid-pursuit firing rates are most similar to 4 cm post-pursuit fixation firing rates, aligned to t_{int}=0 ms.
- t_{10} – The same as t_4 but for eye position = 10 cm.
- t_{13} – The same as t_4 and t_{10} but for eye position = 13 cm.

Note that positive values for t_{ons}, t_4, t_{10}, and t_{13} mean that firing rates lag eye position. Negative values mean that firing rates lead eye position.

Detecting the start of eye movements. The start of either eye movement was first detected using custom software in Matlab and then confirmed with visual inspection. All parameters of this software, including thresholds and baseline periods, were optimized to ensure optimal eye movement onset detection. First, eye speed was calculated from the raw eye position signal by filtering it using a 200 ms boxcar filter and then computing its derivative. As a threshold for saccade onset, we calculated the average eye speed during the early memory period, i.e. during a period when the eye was held within a central 2.5° window on all trials. Instructed saccade onset was defined as the first time at which eye speed was greater than five times this threshold speed for at least 20 ms. Pursuit onset was detected using a combination of eye speed and eye position. A distribution of eye positions was calculated during a baseline period 300 ms to 0 ms before pursuit instruction. Pursuit onset was defined as the first time that eye position was greater than one standard deviation from the mean of the baseline distribution, and eye speed was greater than one quarter of the average speed across the memory period. This method allowed reliable detection of pursuit onsets with and without a catchup saccade.

3.4 Results

3.4.1 PMd neurons begin to update predictively for pursuits and saccades

Our first step was to confirm that MIP and PMd neurons updated reach plans in response to eye movements. This was accomplished by selecting neurons that both encoded the reach target and changed firing rate between the early and late memory periods in the D_{max} movement direction on Pursuit trials ($p<0.05$, paired t-test). Of the 305 MIP neurons that were tuned for the reach, 163 (53%) updated in response to eye movements. In PMd, the proportion was slightly higher (340/554, 61%; Fig. 1D).

We next wanted to determine whether neurons updated reach plans predictively. To do so, we computed the time that neurons first changed firing rates relative to the start of the eye movement ("updating onset time"). Aligning firing rates to the start of saccade and pursuit eye movements, we saw that a number of PMd neurons had firing rates that changed in advance of the eye movement, i.e. updated predictively. Figure 2A shows an example PMd neuron that updated predictively for both saccades and pursuits by approximately 100 ms. Importantly, updating began before the eye movement was made but after the eye movement was instructed (Fig. 2A asterisks; mean ± st.d. pursuit latency 271 ± 59 ms, mean ± st.d. saccade latency 229 ± 41 ms). In contrast, an example MIP neuron (Fig. 2B) had firing rates that changed only after the eye movement started (Fig. 2C) and therefore did not update predictively.

To assess predictive updating for the populations of MIP and PMd neurons, we performed a sliding window analysis (Crapse and Sommer, 2012). For each task-selective neuron, we computed a t-test between firing rates around

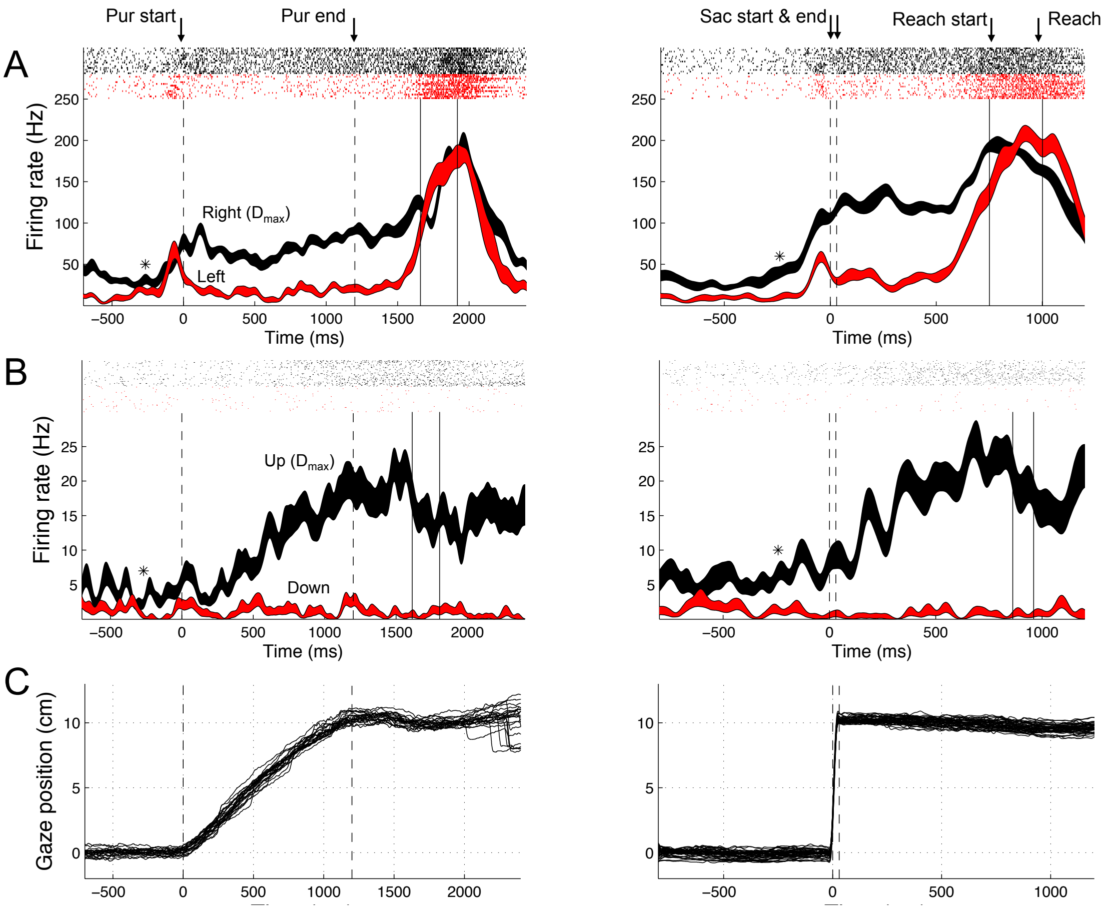

Figure 2. PMd neurons update predictively. A. Mean firing rate from an example PMd neuron during Pursuit (left) and Saccade trials (right). Vertical dashed lines show the start and end time of each eye movement. Vertical solid lines show the mean times for the start and end of the reach. Data was aligned to the start of the eye movement. PSTHs were calculated by convolving spike times with a 20 ms Gaussian kernel. Asterisks show the average time that the pursuit or saccade was instructed relative to the actual start of the eye movement. B. An example MIP neuron does not update predictively. C. Raw eye position traces during Pursuit and Saccade trials.

the start of the eye movement and a baseline 500 ms earlier (Fig. 3). Updating onset was the time of the first significant difference that was maintained over at least 3 time bins. We found that approximately one third of PMd neurons started to update before the pursuit began, i.e. predictively: 37% of PMd neurons had $t_{ons} \leq 0$ ms, i.e. before or equal to the time the pursuit started (126/340; paired t-test, $p<0.05$; Fig. 3A). In contrast, only chance levels of MIP neurons updated predictively: 4% of MIP neurons (7/163) had $t_{ons} \leq 0$ ms. Large t_{ons} values may be partially due to a low signal-to-noise ratio, since noisy firing rates will delay t_{ons}. It's also possible that these neurons had broad receptive fields, and that an eye movement of a few degrees was required to shift the reach target in or out of the receptive field. The mean latency of updating was 280 ± 40 ms (mean ± st.d.) earlier for PMd than MIP neurons, a highly significant difference (unpaired t-test, p=2e-10; Fig. 2A). Therefore MIP did not appear to update predictively, while more than one third of PMd neurons updated predictively for pursuit eye movements.

Because their velocity is relatively low, detecting the onset of pursuit eye movements precisely can be difficult, e.g. (Vidal et al., 2012). Therefore, we also confirmed that PMd neurons updated predictively using saccades, an eye movement whose timing is much easier to detect. 26% of PMd neurons had $t_{ons}<=0$ ms on saccade trials (88/340; paired t-test, $p<0.05$; Fig. 3B). MIP neurons did not update predictively for saccades, as only 1% of MIP neurons had $t_{ons}<=0$ ms on saccade trials. Similar to updating onset measured on Pursuit trials, t_{ons} for PMd neurons was 147 ± 16 ms (mean ± st.d.) faster than for MIP neurons on saccade trials (unpaired t-test, p=2e-17). On a per neuron basis, updating onset times were relatively conserved across the two eye movements in both areas: pursuit and saccade t_{ons} times were significantly correlated for MIP (Pearson R=0.29, p=0.012) and PMd neurons (R=0.25, p=0.0003), meaning that neurons that updated predictively for saccades tended to update predictively for pursuits as well.

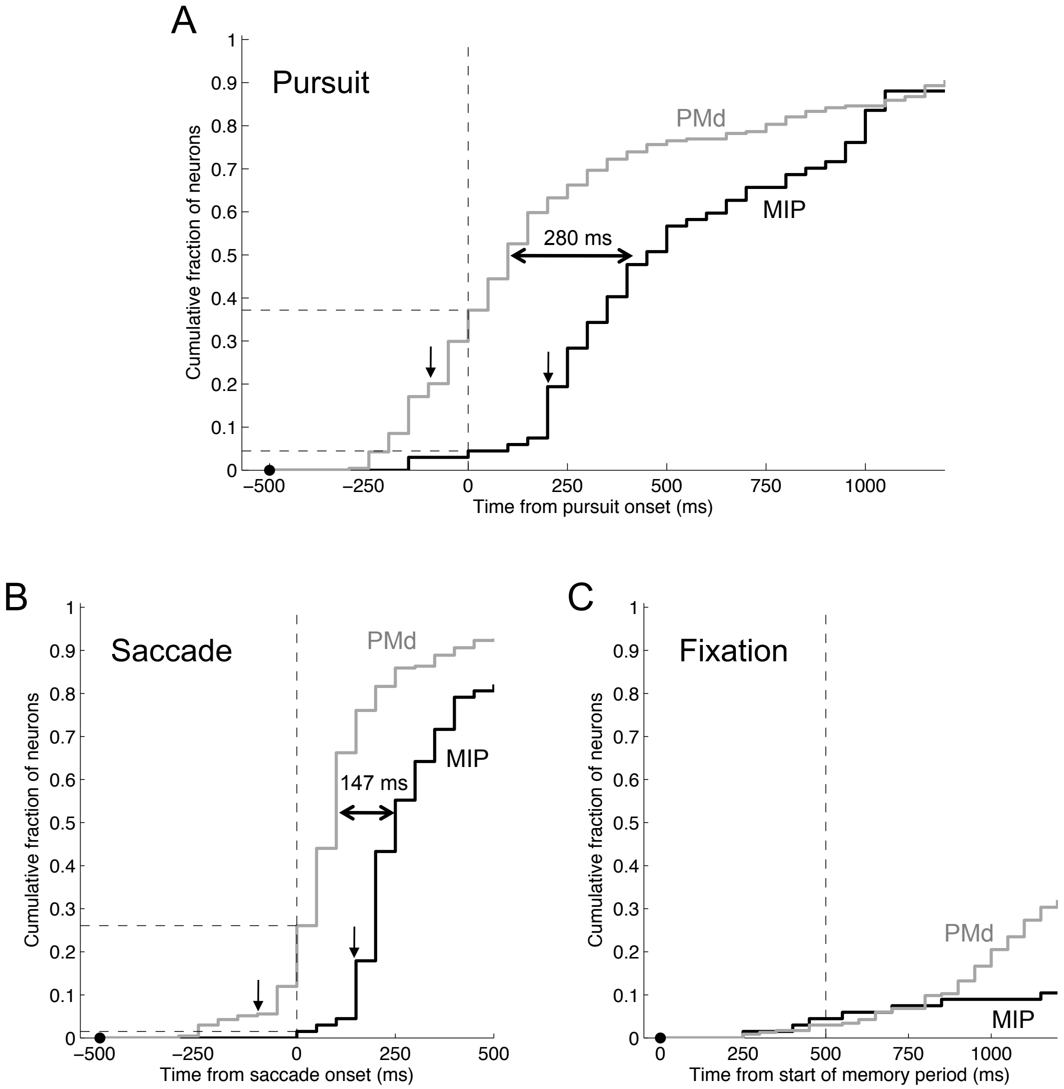

Figure 3. A subset of neurons updated predictively. A. Pursuit updating onset. 37% of PMd neurons (126/340) began updating by the time of pursuit initiation (t=0 ms), compared with 4% of MIP neurons (7/163). Arrows show the updating onset time for the example neurons in Figure 2. Cumulative fractions do not reach exactly one because updating onset was defined as a significant difference on three consecutive significant time windows (paired t-test, $p<0.05$), whereas task-selective neurons were defined slightly differently (see Methods). The pre-eye movement baseline time is shown with a black circle. B. Saccade updating onset. 26% of PMd neurons began updating by the time the saccade was initiated, compared to 1% of MIP neurons (2/163). E. "Updating onset" control using Fixation trials. Without an eye movement, few neurons had a significant change in firing rate after 500 ms of memory period (MIP: 7/163, PMd: 10/340).

In order to ensure that the observed changes in firing rate resulted from the eye movement, we repeated the same analysis on Fixation trials (Fig. 3E). The baseline period was defined at the start of the Fixation memory period. Few neurons had a measurable t_{ons} 500 ms after the baseline period (MIP: 4%, 7/163; PMd: 3%, 10/340). Therefore t_{ons} calculated on Saccade and Pursuit trials likely reflect firing rate changes due to the instructed eye movements.

3.4.2 Both MIP and PMd neurons update dynamically

Our next step was to assess how firing rates changed throughout the pursuit. The goal of this was to determine whether individual neurons and the populations of neurons changed dynamically or statically during pursuit eye movements. To answer this question, we compared mid-pursuit firing rates during longer pursuits (13 cm amplitude) to firing rates during post-pursuit fixation periods at 4 cm, 10 cm, and 13 cm. We predicted that neurons that update dynamically should have comparable firing rates when gaze is at a given position, regardless of whether the eye is fixating or pursuing. On the other hand, statically updating neurons should have different post-pursuit fixation and mid-pursuit firing rates for the same gaze position (Fig. 4).

Figure 5 shows an example MIP neuron that exhibits dynamic updating. This neuron increased its firing rate while pursuit was ongoing but stopped changing once the eye movement ended (Fig. 5B). If the neuron updated statically, the change in firing rate would occur after the eye movement. This was not the case. Instead, the neuron appeared to update for the changing eye position dynamically throughout the pursuit. To quantify this, and therefore to test dynamic versus static updating, mid-pursuit firing rates were aligned to the times that eye position transiently intersected 4 cm, 10 cm, and 13 cm (i.e. $t_{int}=0$ ms; Fig. 5C). For the neuron in Figure 5B, firing rates during post-pursuit fixation were not significantly different from mid-pursuit firing rates when the eye was at 4 cm (unpaired t-test, $p=0.78$), 10 cm ($p=0.12$), or 13 cm ($p=0.33$; Fig. 5D).

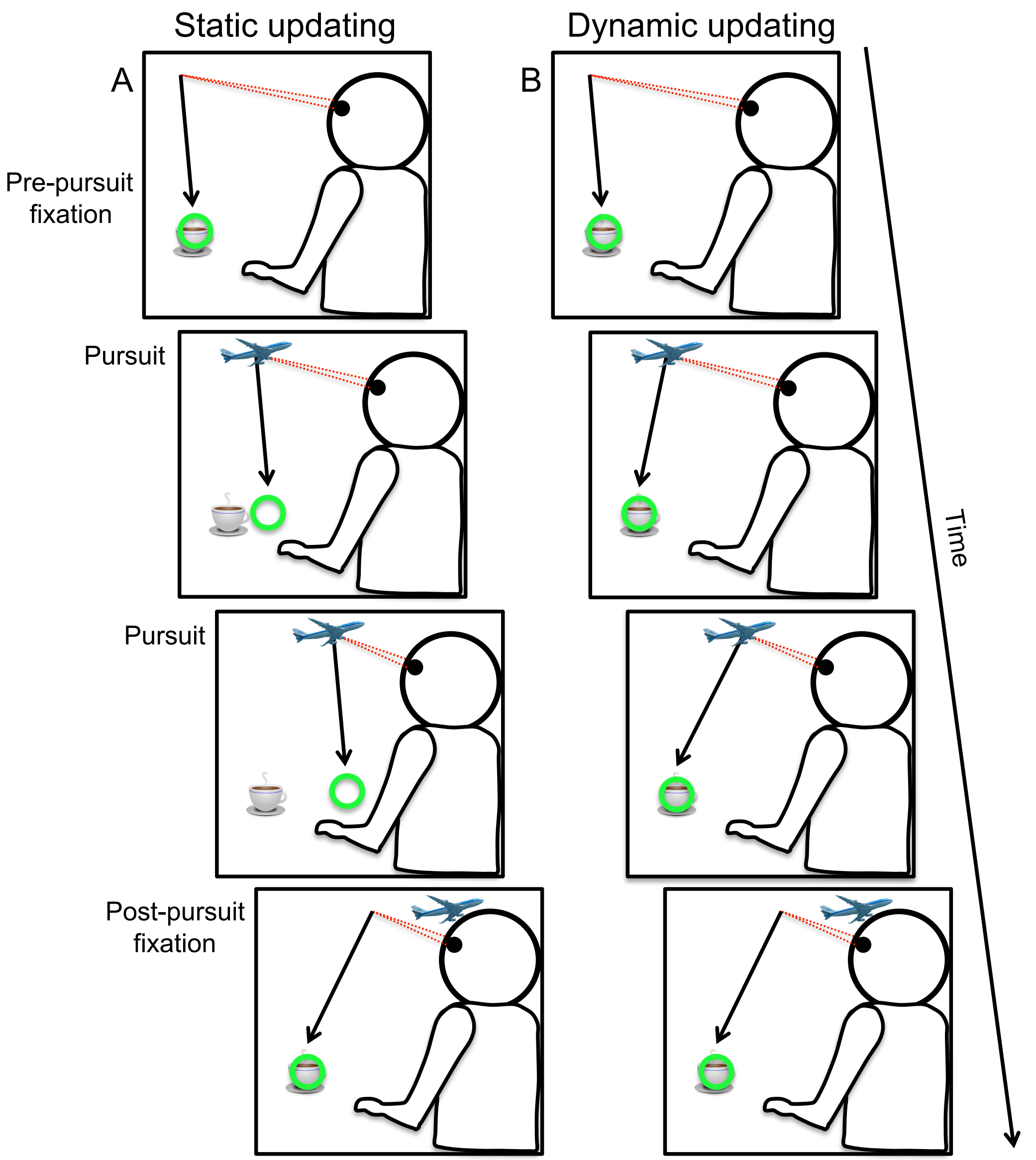

Figure 4. Static versus dynamic updating. A. In the static updating case, neurons update for new eye positions during periods of fixation. Eye-centered spatial locations encoded by these neurons are therefore inaccurate during the pursuit. B. Neurons update continuously throughout the eye movement in the dynamic case, and therefore the spatial accuracy of the reach target is maintained. The panels show gaze location (intersection of red lines) and the spatial location of the eye-centered reach plan (green circle).

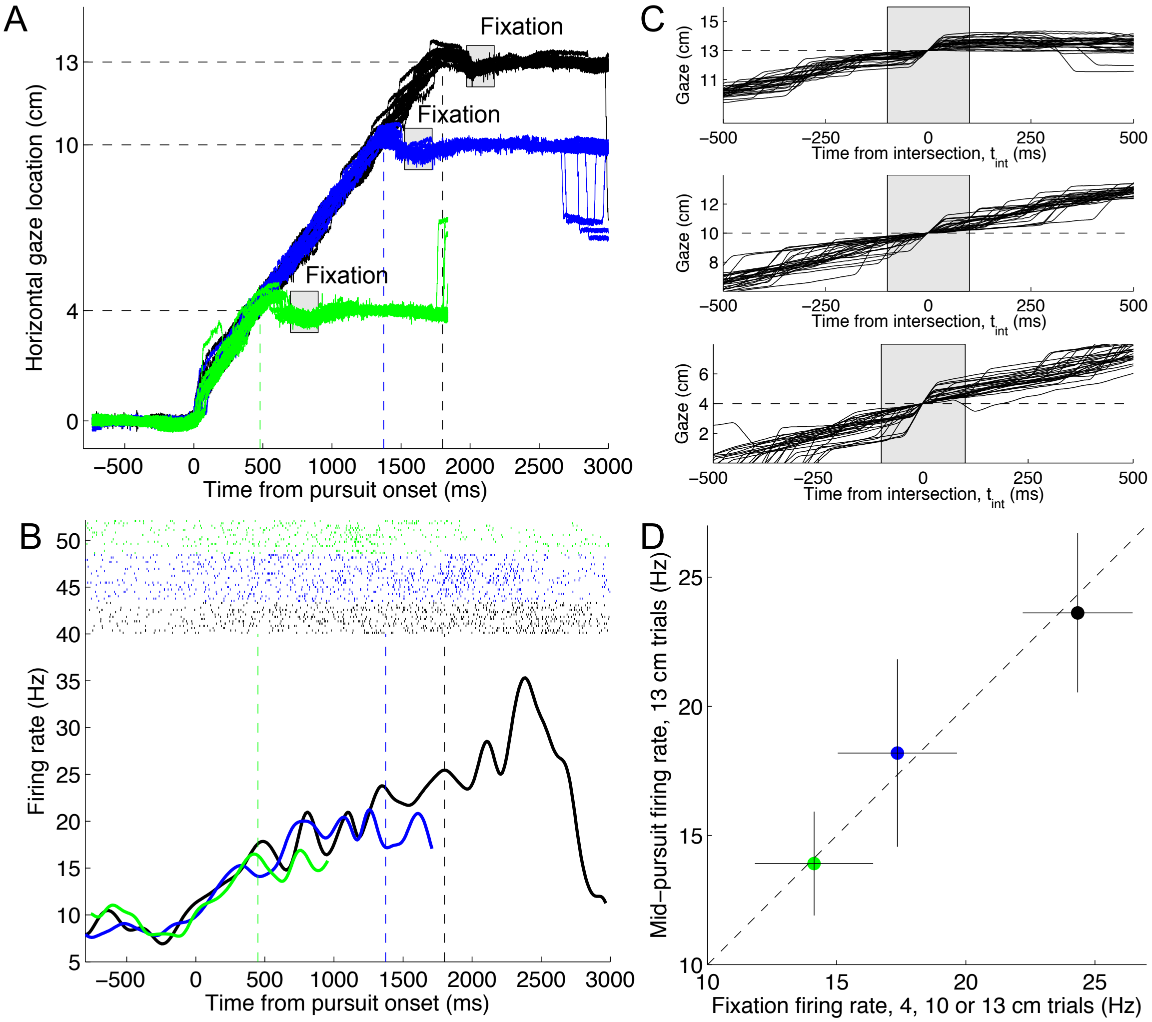

Figure 5. Using multi-amplitude pursuits to assess dynamic updating. A. Pursuit eye movement traces to 4 cm, 10 cm and 13 cm. Grey boxes show post-pursuit fixation periods. Vertical dashed lines show when the pursuit target during 13 cm trials (black) first reached 4 cm, 10 cm and 13 cm, i.e. when post-pursuit fixation and mid-pursuit eye positions are approximately equal. B. An example PMd neuron responding to multiple amplitude pursuits. Timing is the same as A. C. Since there was some variability in eye position, firing rates were aligned to the trial-by-trial times that the largest-amplitude pursuit first intersected 4 cm (bottom), 10 cm (middle), and 13 cm (top). Grey boxes show 200 ms windows during which mid-pursuit firing rates were calculated. D. Post-pursuit fixation versus mid-pursuit firing rates for the example neuron in B. Colors correspond to A and B. Errorbars show s.e.

Figure 6 repeats this analysis for all MIP and PMd neurons. The scatter plot compares the transient mid-pursuit responses to firing rates during the corresponding post-pursuit fixation. Similar firing rates in this context are evidence for dynamic updating, since they show that neurons respond to eye position similarly whether the eyes are moving (mid-pursuit) or stationary (post-pursuit fixation). In order to normalize for each neuron's basal activity, firing rate responses were measured as a difference from baseline firing rate, defined as the early memory period on Fixation trials. We observed that the responses were highly correlated between these two gaze conditions ($R^2 = 0.78$, $p < 1e\text{-}32$, MIP, Fig. 6A; $R^2 = 0.95$, $p = 3e\text{-}71$, PMd, Fig. 6B). Since correlation measures the degree to which variables covary but not whether they are equal in value, we also compared mid-pursuit firing rates with post-pursuit firing rates via a t-test. Only 2% of all comparisons for MIP neurons showed significant differences when eye position was equal, i.e. $t_{int}=0$ ms (unpaired t-test, $p<0.05$, Fig. 6C; the two significant data points are highlighted in Fig. 6A). In PMd, no comparisons between mid-pursuit and post-pursuit firing rates were significantly different at $t_{int}=0$ ms. Taken together, this suggests that neuronal firing rates during mid-pursuit matched those during the corresponding post-pursuit fixation, as predicted by dynamic updating.

We also compared firing rate responses to the two gaze conditions across the population at various time lags. Using sliding windows aligned to $t_{int}=0$ ms, we computed the fraction of neurons that had mid-pursuit firing rates significantly different from post-pursuit fixation in each time window (unpaired t-test, $p<0.05$). Pooling over three eye amplitudes, PMd neurons were best matched between these two conditions at a time lag of 0 ms (Fig. 6C), whereas the optimal lag for MIP neurons was between 50 and 150 ms (Fig. 6D). This result was confirmed via a correlation analysis, where the mean responses to the two gaze conditions were best correlated across the populations at time lags of 0 ms and 100 ms for PMd and MIP, respectively (Fig. 6E). These data suggest that

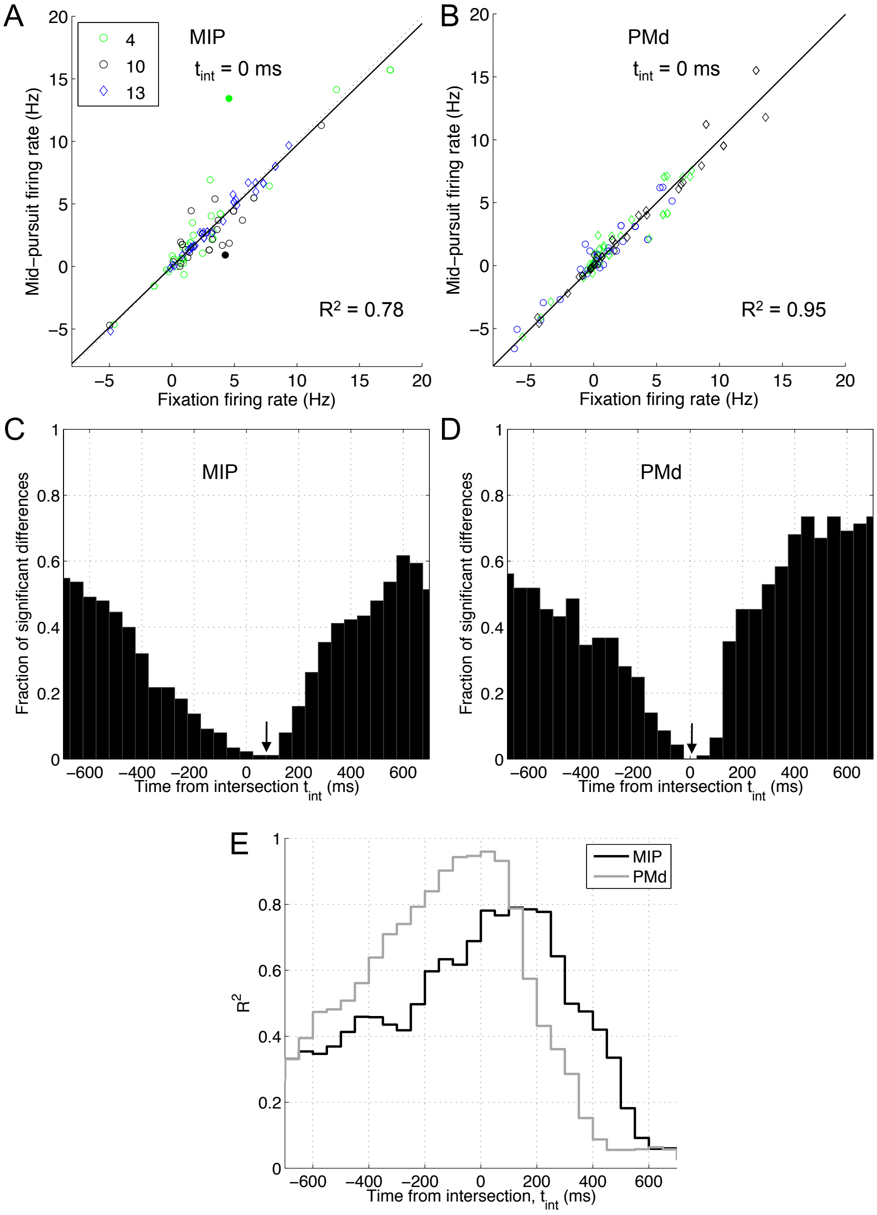

Figure 6. Mid-pursuit and fixation firing rates are similar when eye position is equal. A. Fixation versus mid-pursuit firing rates for MIP at each of the three eye amplitudes (t_{int}=0 ms). Filled circles show the two data points that had a significant difference between fixation and pursuit firing rates (unpaired t-test, $p<0.05$). Each neuron (n=35) had 3 data points corresponding to the three eye amplitudes. R^2 was calculated using a Pearson correlation. B. The same as A for PMd neurons (n=37). C. The fraction of MIP firing rates that had a significant difference between fixation and pursuit as a function of t_{int}. The three amplitudes were combined such that the total count was n=35 * 3. The arrow shows the time with the fewest significant differences (50 ms <= t_{int} <= 150 ms). D. The same as

C for PMd neurons. The arrow again shows the time with the fewest significant differences (t_{int}=0 ms). E. Correlation analysis. R^2 as a function of t_{int} for MIP (black) and PMd neurons (grey). PMd R^2 was maximum at t_{int}=0 ms. MIP R^2 was maximum slightly later (t_{int}=100 ms).

MIP and PMd both update dynamically, but at different time lags with respect to the instantaneous eye position signal: average MIP firing rates slightly lagged eye position while average PMd firing rates did not.

In order to characterize the time-dependent dynamic updating at the single neuron level, we calculated lag times t_4, t_{10} and t_{13} for each individual neuron. For each neuron, we measured the time, relative to t_{int}=0ms, when post-pursuit fixation and mid-pursuit firing rates were most similar, based on an ROC analysis (see Methods). Figure 7A shows an example MIP neuron whose firing rates consistently led eye position by 200 ms (t_4=t_{10}=t_{13}=200 ms). That is, post-pursuit fixation and mid-pursuit firing rates were most similar 200 ms after eye positions were equal. Indeed, MIP firing rates from individual neurons tended to lag pursuit eye position: t_4 and t_{10} distributions were significantly positive for MIP neurons (p=0.0029, p=0.0034, respectively, one-tailed t-test), although t_{13} was not (p=0.53) (Fig. 8B). PMd lag distributions were not significantly different from 0 ms (p=0.21, 0.33, 0.14 for t_4, t_{10} and t_{13}, respectively; two-tailed t-test; Fig. 7C). Comparing the combined t_4, t_{10}, and t_{13} distributions between areas, lag times were significantly more positive in MIP than PMd (one-tail t-test, p=0.0004).

3.5 Discussion

After viewing an object, primates are capable of remembering its location and reaching to that location even when the object is no longer visible. These internal representations of reach target locations are stored relative to visual space. Thus, in order to remain spatially accurate, the representation of the reach plan must be updated with each eye movement. In this study, we investigated the

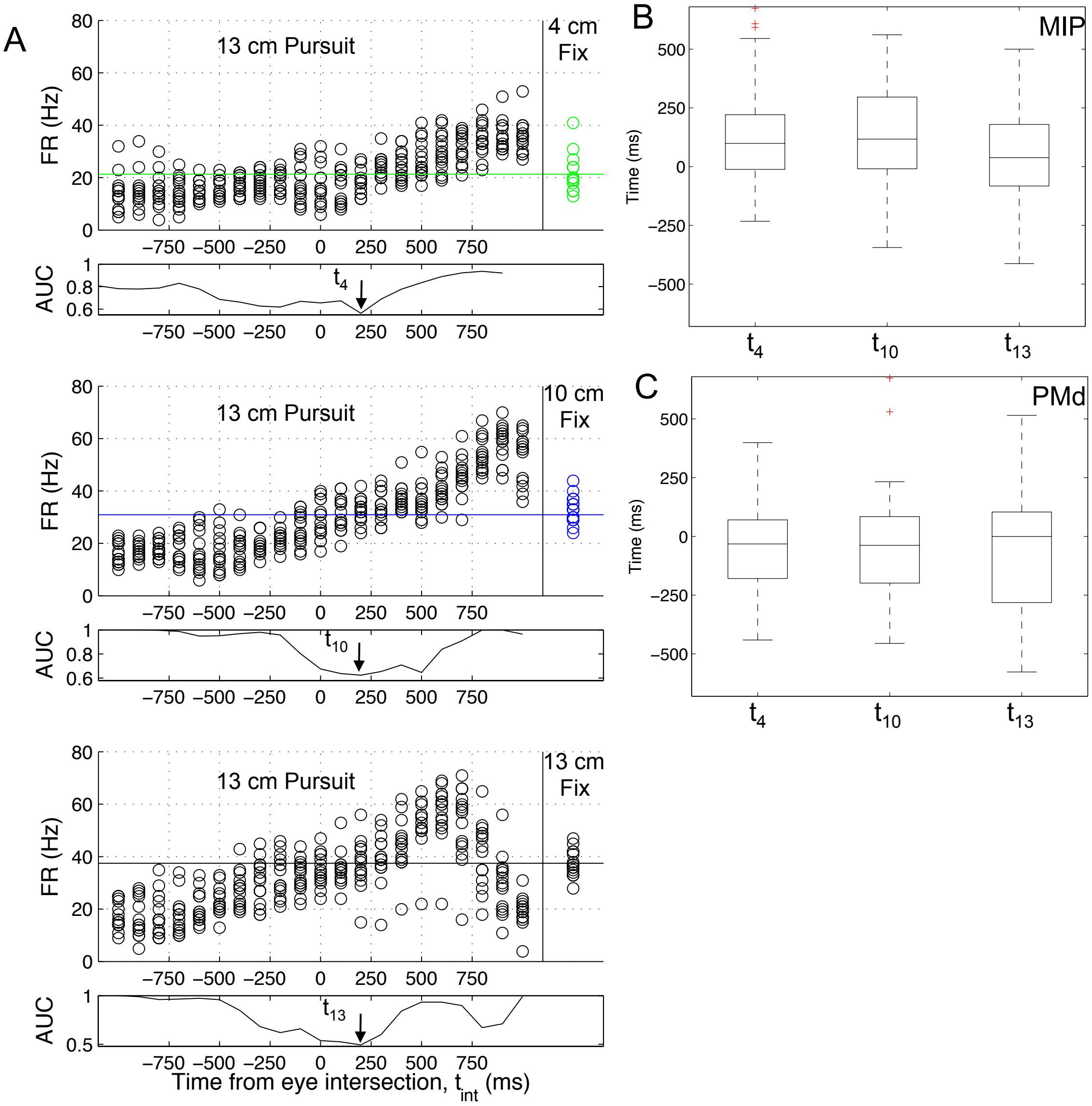

Figure 7. Calculating t_4, t_{10}, and t_{13}. A. An example neuron increases firing rates for pursuits to the left side of the screen. Open black circles show firing rates during pursuits to the leftward 13 cm target. Firing rates are in bins aligned to the time that mid-pursuit eye position first reached 4 cm (top), 10 cm (middle), and 13 cm (bottom). These are compared to firing rates when the eye was fixated at 4 cm (green), 10 cm (blue), and 13 cm to the left (black). Horizontal lines show the mean firing rates during fixation. Below each firing rate plot a time-series of AUC value was calculated by computing an ROC analysis between each mid-pursuit firing rate bin and fixation. The times that mid-pursuit firing rates most resembled fixation firing rates at the same eye position are marked (t_4, t_{10}, t_{13}). B.

The distribution of t_4, t_{10}, and t_{13} times for MIP (top) and PMd neurons (bottom). Boxplots show the 25th-75th percentiles, means, and full range of distributions. Outliers, plotted in red, are defined as greater than q3 + 1.5*(q3 - q1) or smaller than q1 – 1.5*(q3 - q1), where q1 and q3 are the 25th and 75th percentiles, respectively.

time course of reach plan updating by recording from single neurons while monkeys performed a reach updating task. In particular, we looked at two temporal components of updating: the earliest time that updating could be detected relative to the start of the eye movement ("updating onset"), and the progression of updating during smooth pursuit eye movements ("static" vs. "dynamic" updating).

To date, it is not clear how neurons in movement planning areas update in response to eye movements. In the lateral intraparietal sulcus (LIP), a brain area that has gaze-centered encoding (Cohen and Andersen, 2002) and updates for eye movements (Duhamel et al., 1992), saccades caused neuronal receptive fields to simultaneously increase sensitivity relative to the post-saccade location while decreasing sensitivity relative to the pre-saccade location (Kusunoki and Goldberg, 2003). Neurons in the superior colliculus (SC), an area that similarly updates for saccades (Walker et al., 1995), had receptive fields that effectively underwent a static and discrete remapping in response to saccades (Sommer and Wurtz, 2006). Our study shows that a different process likely occurs for slow, pursuit eye movements. By comparing mid-pursuit and fixation firing rates, we saw that neurons encoded the reach target relative to instantaneous eye positions during the pursuit. Therefore neurons in both MIP and PMd updated dynamically rather than statically. In addition, a minority of PMd neurons (Saccade 88/340, 26%; Pursuit 126/340, 37%) updated predictively by at most 250 ms. MIP neurons in contrast tended to lag the eye movement by 100-200 ms. This is the first observation of predictive updating in the reach system.

3.5.1 The temporal nature of reach plan updating

Taken together, our results show that neurons in both MIP and PMd update in response to eye movements, and that there is a temporal delay between the two areas. Updated firing rates appeared earlier in PMd than in MIP for pursuits (280 ms earlier) and saccades (147 ms). During the pursuit, a similar delay was seen: the activity of an average MIP neuron lagged pursuit eye position while the average PMd neuron had no appreciable lag with eye position (Figs. 6, 7). Therefore, at the level of population activity, the data are self-consistent between updating onset times and mid-pursuit updating lags.

There are previous observations of frontoparietal latency differences during other reaching tasks. In particular, MIP and area 5, another parietal reach-related area neighboring MIP, are also delayed relative to PMd at the time of the reach onset (Kalaska et al., 1983, Johnson et al., 1996, Archambault et al., 2011), a time period which was not investigated here. Latency differences between PMd and parietal neurons during the memory period appear to depend on whether the task requires decision making. A shorter latency difference between MIP and PMd was noted in an anti-reach task that required reaching in the opposite direction of the cue, where tuning occurred 25 ms earlier in PMd than MIP (Westendorff et al., 2010). This delay was not observed when the reach was made in the same direction as the cue, supporting findings that MIP and PMd lags are context-dependent (Pesaran et al., 2008). Taken together with our observations of latency delays between PMd and MIP neurons (Fig. 3), these observations are consistent with a context-dependent flow of information from PMd to the parietal cortex.

If receptive fields in some brain areas exhibit discrete remapping during transsaccadic updating (Sommer and Wurtz, 2006), why do they appear to update dynamically during smooth pursuits? The answer probably lies in the nature of the two eye movements. Saccades are pre-programmed: saccade endpoints are known prior to the movement, and it is possible for the receptive field to remap for the saccade endpoint without waiting for feedback. Visual processing is also shut down during saccades to limit the perception of motion blur (Bridgeman et al., 1975, Wurtz et al., 2011). In contrast, smooth pursuit is a tracking eye movements that relies on mid-pursuit visual processing to stabilize the tracked target (Robinson, 1965, Krauzlis, 2004), and the endpoint of the pursuit is typically unknown until the end of the movement. This is consistent with a dynamic updating of the relative gaze-target relationship during pursuit.

3.5.2 Computing a spatially correct reach plan with MIP and PMd

The question of how updating progresses throughout slow eye movements is important because brain areas like MIP and PMd are thought to transform visual information into motor commands (Buneo et al., 2002). If their representation of eye position is inaccurate, motor commands computed using that eye position will be inaccurate. Indeed, Xu et al. (Xu et al., 2012) recently found that eye position gain fields in LIP lag eye movements considerably, questioning the role of gain fields in transsaccadic updating. However, our findings here show that PMd and MIP neurons represent mid-pursuit eye positions dynamically.

Behaviorally, there is evidence for dynamic updating. The fact that primates can visually pursue an object and make an accurate reach at the same time (e.g. catching a ball), a movement that implies an accurate, updated reach plan during a pursuit, argues for dynamic updating. Indeed there is a large amount of literature demonstrating that humans are adept at both pursuing to targets while simultaneously tracking them with a hand movement, e.g. (Bock, 1987). However, oculomanual tracking tasks like these differ from the experimental paradigm used here, as the pursuit target and reaching target are the same, and arm movements are made while the pursuit is ongoing.

Finally, the sluggish response of MIP is interesting. If reach plans in the posterior parietal cortex lag eye movements by 100-200 ms, then given the fact that primates make 3-4 saccades a second, reach plans are almost always inaccurate for the current eye position. One obvious solution is that PMd neurons, which on average do not lag eye position, are more responsible for encoding the spatially accurate reach plan. Indeed, it is unclear what role a reach plan with delayed updating would serve. It is possible that MIP updating arises from the activity of eye position gain fields which are reported to lag eye position by the same extent (Xu 2012). Slower signals like this might calibrate updating, for example to correct for the accumulation of errors over successive remappings (Lewis et al., 1994, Xu et al., 2012, Graf and Andersen, 2014). An alternate explanation is that activity in PMd is more closely connected to the feedforward motor command, while MIP activity is more closely connected to a feedforward internal model of the limb state. The latter would require sensory feedback of the arm, contributing to the delayed representation of body state (i.e. eye position) measured here.

3.5.3 Eye movement efference copy in the reach system

Predictive updating is well established in some saccade planning brain areas such as the lateral intraparietal sulcus (LIP) (Duhamel et al., 1992) and the frontal eye fields (FEF) (Umeno and Goldberg, 1997b, Sommer and Wurtz, 2006). However predictive updating has not been observed in reach planning brain areas. This is curious since updating is likely driven by efference copy. Indeed, along with stimulation studies of the SC (Mays and Sparks, 1980) and ocular nerve (Sparks and Mays, 1983), predictive updating is one of the primary pieces of evidence that efference copy drives saccade plan updating (Klier and Angelaki, 2008, Sommer and Wurtz, 2008a). Therefore our study provides evidence for efference copy driving reach plan updating. These results support the interpretation that efference copy is a common updating signal for self-generated movements. However, further work is required to provide direct evidence of efference copy of the eye movement command in the reach system.

While evidence from this study argues for efference copy driving updating in PMd, we did not find similar predictive updating in MIP (Fig. 3). One possible explanation for this difference in updating onset times between the two areas is that it takes the efference copy longer to reach MIP and PMd. The putative pathway that efference copy takes to reach the cortex is from the superior colliculus, to the medial dorsal nucleus of the thalamus, and finally to the frontal eye fields (FEF). The FEF is anatomically closer to PMd than MIP. PMd is also anatomically close to the frontal pursuit area (FPA), an area of the frontal cortex posterior and adjacent to FEF that shows selective activation for pursuit eye movements (MacAvoy et al., 1991, Tanaka and Lisberger, 2001). Therefore it is plausible that efference signals or other eye-movement signals from FEF and FPA reach PMd first. However, the difference in updating onset between the two areas (150-300 ms) was much larger than a single conduction delay, implying that the delay arises from a multisynaptic network.

In summary, our findings provide the first direct study of the temporal dynamics of reach plan updating for eye movements. In general we found that updating in PMd neurons updated earlier than MIP neurons, a result that was consistent for updating onset times as well updating during pursuit. In contrast to previous results that showed static updating in response to saccades, both MIP and PMd in this study updated dynamically during pursuit eye movements.

3.6 Conclusions

This Chapter investigated the temporal nature of reach plan updating in response to smooth pursuit eye movements. We analyzed neural data from the same recording sessions as Chapter 2, where MIP and PMd neurons were recorded while monkeys executed reaches following intervening pursuits and saccades. (The criteria for task-selective neurons differed slightly between Chapter 2 and Chapter 3, so many, although not all, neurons overlap between studies.) Rather than analyzing data during fixation times around the eye movements, in this Chapter we additionally investigated how updating proceeds during the pursuit eye movement. We documented two temporal components of reach plan updating. First, it was found that a subset of PMd neurons began updating in advance of the pursuit eye movement, that is predictively. In contrast, MIP neurons only began updating after the eye movement. These results were confirmed for saccades as well. Given that the predictive nature of updating in PMd is inconsistent with a feedback signal, this result shows that efference copy likely drives reach plan updating as it does saccade plan (Duhamel et al., 1992). Second, we found that neurons in both MIP and PMd change their activity continuously throughout the pursuit, consistent with a constant updating of the reach target. These results provide insight into the temporal nature of updating during slow eye movements.

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Chapter 4

Knowledge of eye targets prior to smooth pursuit eye movements can be used to update reach plans

4.1 Abstract

Previous studies have shown that reach movements are initially coded in eye-centered coordinates and continuously updated after eye movements. Updating signals are generated by combining available efferent or afferent information from multiple sources. We propose that knowledge of the goal of the intervening eye movement can also contribute to updating. We recorded the eye and hand positions of human participants as they reached to remembered locations in the dark after making intervening pursuit eye movements. In order to investigate the contribution of the eye movement goal to updating, the intervening eye movement either stopped unpredictably (no goal) or stopped predictably at a cued location. Reaches to remember targets were more accurate and precise when the goal of the eye movement was known. Information about the eye movement goal also reduced reach reaction times. These results demonstrate that information about the final gaze location can contribute to reach plan updating.

4.2 Introduction

To perform a visually guided reach, the brain must transform incoming sensory information into appropriate commands for reaching. The position of the reach target, initially encoded in retinal coordinates, must be translated into a series of muscle activations that yield the desired hand movement (Kalaska et al., 1997). Reach targets are coded relative to multiple body parts, depending on the integrity and availability of sensory information (Schlack et al., 2005, Mullette-Gillman et al., 2009, McGuire and Sabes, 2011b). Studies in monkeys and humans suggest that reach targets are initially coded in eye-centered coordinates (Batista et al., 1999, Pouget et al., 2002b, Medendorp et al., 2003, Beurze et al., 2010, Thompson et al., 2014). The brain must actively update this representation as intervening movements of the eyes or head can corrupt the integrity of eye-centered reach plans. Studies have shown that reach plans are updated in eye-centered coordinates (Henriques et al., 1998, Batista et al., 1999, Medendorp et al., 2003, Khan et al., 2005b).

Neurons in several areas involved in the generation of eye movements anticipate the effect of upcoming saccades on the spatial representation of targets by predictively updating the representation of visual space (Duhamel et al., 1992, Umeno and Goldberg, 1997a, Nakamura and Colby, 2002b, Sommer and Wurtz, 2006). This early updating implies that these neurons have access to information about the dynamics of the upcoming eye movement, consistent with the proposal that the updating signal comes from the outgoing eye movement command ("efference copy") (Mays and Sparks, 1980, Sparks and Mays, 1983, Sommer and Wurtz, 2008b). Updating also occurs when efference copy signals do not exist, such as after passive whole body rotations or translations (Bresciani et al., 2002b, Li and Angelaki, 2005b, Li et al., 2005b, Klier et al., 2008a). The implication of these studies is that both sensory and motor signals can be combined to maintain spatial constancy (Ernst and Banks, 2002, Sabes, 2011).

Vaziri et al. (2006) recently reported that visual feedback of the position of a reach target following a saccade improved reach accuracy. Similarly, in a multiple saccade task, combining efference copy signals with visual feedback following the first saccade improved subsequent target localization (Munuera et al., 2009). In these studies, the visual feedback provides information following the eye movements. We wondered whether visual feedback of the eye movement goal presented before the eye movement can contribute to updating. We hypothesized that sensory information specifying the goal of an intervening eye movement can improve reach accuracy. Efference copy signals and visual information about the eye movement goal both contain the same information encoded in different modalities. Thus, following the appearance of the reach target and the eye target, it is possible that reach plans are predictively updated without processing the efference copy. More likely, however, information from both sources is combined to optimize the updating signal (Poletti et al., 2013).

Figure 1 illustrates the relationship between sensory information about the eye target and efference copy. The hand target (HT) and eye target (ET) are both flashed in the periphery of the screen (Fig 1A). The subject is instructed to make an eye movement to the ET followed by a reach to the remembered location HT. $R_{HT}(t1)$ is the retinal location of HT viewed from the initial central fixation (Fx) at time t1 (Fig 1B). In this situation, updating the representation of the reach target HT amounts to computing $R_{HT}(t2)$, i.e. the eye-centered location of HT following the eye movement. Therefore, the initial retinal location of the eye target (R_{ET}) has the necessary information for updating because $R_{HT}(t2) = R_{HT}(t1) – R_{ET}$. $R_{HT}(t2)$ can also be computed by combining $R_{HT}(t1)$ with information about the eye movement obtained from the efference copy (EC): $R_{HT} (t2) = R_{HT} (t1) – EC$ (Fig 1C). Note that this vector subtraction is equivalent to remembering the relative spatial locations of the eye and hand targets. Once $R_{HT}(t2)$ is known, the reach vector M can be computed: $M = R_{HT}(t2) – R_H$ (Fig 1D). Therefore, when reaching to targets after an eye movement, both efference copy (EC) and visual information about the eye target (R_{ET}) can update the reach plan.

To test our hypothesis, we examined whether the presence or absence of visual information about the eye target affected reach performance. Since saccades are ballistic and are directed towards a goal, we used smooth pursuit eye movements to disrupt reach plans. If visual information about the eye target contributes to updating, then reaches following a pursuit to a known goal should have reduced error when compared to reaches following a pursuit without a goal. Reaches preceded by eye movements with a predictable endpoint had lower errors than reaches preceded by eye movements without an eye target. These results suggest that eye targets can be used to update motor plans.

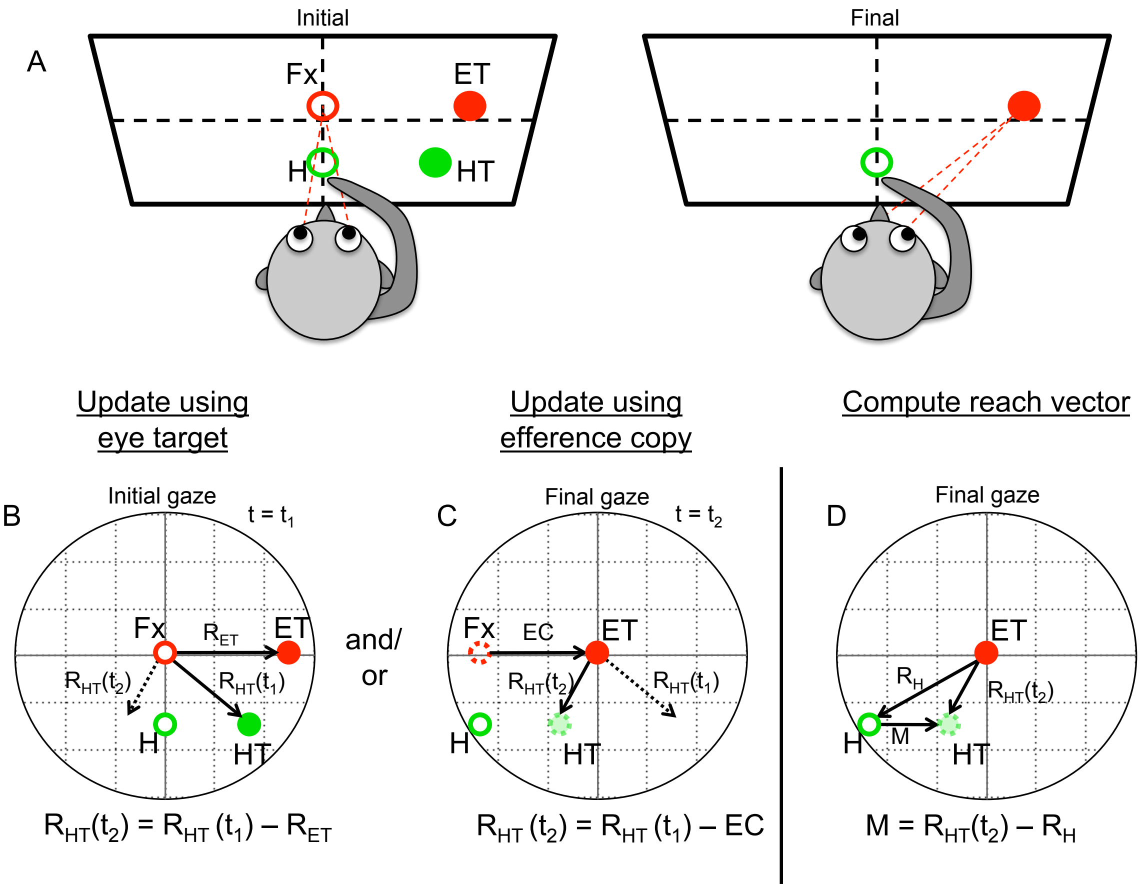

Figure 1. Solving the problem of spatial stability for eye-centered reach plans. A. Schematic showing our experimental setup. Participants began by looking at and touching central targets on a computer screen. Depending on the condition, reach target T and eye target ET were both flashed in the periphery of the screen. The subject then made an eye movement to ET followed by a reach to the remembered location of T. Pictures are not to scale. B. Updating reach target with eye target. The eye-centered location of T after an eye movement to ET can be computed using initial retinal information. R_{HT} (t_1) is the retinal location of T viewed from the initial central fixation (Fx) at time t_1. Since updating amounts to computing R_{HT} (t_2), i.e. the eye-centered location of T following the eye movement, it can be computed as a vector difference: $R_{HT}(t_2) = R_{HT}(t_1) - R_{ET}$. C. Updating reach target with efference copy. R_{HT} (t_2) can also be computed by combining R_{HT} (t_1) with information about the eye movement obtained from the efference copy: $R_{HT}(t_2) = R_{HT}(t_1) - EC$. D. Updated reach plan. Once R_{HT} (t_2) is known, the reach vector M can be computed as its difference from the eye-centered hand location R_H: $M = R_{HT}(t_2) - R_H$. Dashed circles show targets that are no longer visible. Dashed lines show R_{HT} vectors that are correct for a later or earlier eye position. Abbreviations: Fx – central eye

fixation, ET – eye target, H – hand, HT – reach target, $R_{HT}(t_1)$ – retinal location of the reach target at the initial eye position, $R_{HT}(t_2)$ – retinal location of the reach target at final eye position, EC – efference copy of the eye movement command to ET. R_{ET} – retinal location of the eye target.

4.3 Methods

4.3.1 Participants

Thirteen human subjects aged 20-34 (mean age 26) participated in this study. All participants were healthy, right-handed individuals with no knowledge of the specific hypothesis of the experiment. They had normal or corrected-to-normal vision, and no history of claustrophobia or jaw soreness (to prevent pain due to the bite bar). Participants received $20 /hour compensation for their time. They provided informed consent in accordance with the ethical guidelines of McGill University's Research Ethics and Compliance Board.

4.3.2 Apparatus

Participants sat in a completely dark chamber where the only source of light was the luminance of a vertical monitor located 42.5cm away from their eyes. To remove the effect of screen cues, we placed a transparency with a light to dark gradient between the monitor and the participant (Fig 2C). By creating a progressive transition into the screen, the gradient eliminated spatial cues given by the edge of the monitor. A bite bar made from single use molded dental putty stabilized the subject's heads. An adjustable chin rest further minimized shifting. An infrared eye-tracking camera (Eyelink II, SR Research: Complete Eye Tracking Solutions, Mississauga, ON) tracked the participants' right eye, and an acoustic pulse recognition touch screen (Tyco Electronics, Menlo Park, CA) recorded the reach end points. Data acquisition occurred at a sampling rate of 1000Hz. The touch screen and eye camera were calibrated at the beginning of every testing session and after any head movement. The targets were presented on an LCD computer monitor located directly behind the touch screen.

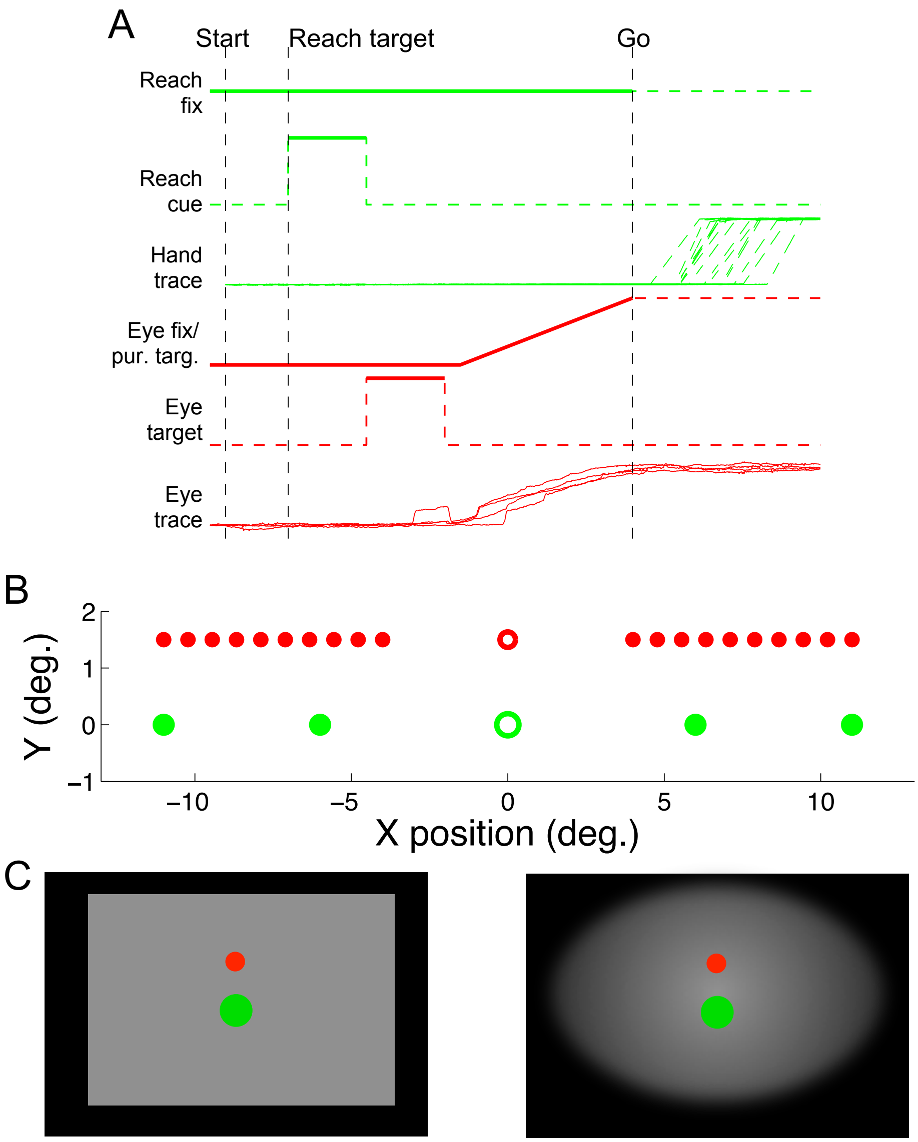

Figure 2. Experimental design. A. Timeline of a cued goal (CG) smooth pursuit trial. The trial is initiated when both hand and eye enter the central fixation windows. After holding fixation for 600 ms a peripheral reach target is flashed at one of four locations for 500 ms. The memory period begins immediately after the reach target is extinguished. On CG and stop short (SS) trials, an eye target is flashed for 500 ms at one of the 20 endpoint locations immediately after the peripheral reach target is extinguished. 100 ms after the eye target is extinguished, the central eye fixation moves smoothly to the pursuit endpoint. On SS trials, he pursuit stops 10% of the location indicated by the eye target. The reach is instructed by simultaneously extinguishing the reach fixation and eye targets immediately after the pursuit

reaches its endpoint. On CG trials, the pursuit endpoint is the location indicated by the eye target, whereas on SS trials the pursuit stops 10% short of the eye target. NG trials are identical to CG trials except that the eye target is not illuminated. On Saccade trials, 800-1600 ms after the start of the memory period the eye fixation jumps to one of the 20 eye endpoints. Once the instructed saccade is made, the reach and eye cue are extinguished, which is the instruction to reach. Solid lines denote visible targets. B. Location of eye (red) and reach (green) targets. Reach targets are at ±6° and ±11°. Fixation targets are shown by open circles. C. The participants' visual screen with and without the display gradient designed to eliminate allocentric cues.

4.3.3 Experimental paradigms

We asked subjects to perform memory reaches with and without intervening eye movements. There were five trial conditions named for the type of eye movement executed during the memory period: 1) Fixation (no-eye movement), 2) Saccade, 3) Pursuit No Goal, 4) Pursuit Cued Goal, and 5) Pursuit Stop Short. Each of the eye movement conditions was performed to 20 eye targets: 10 on the right side of the screen between 5° and 11°, equally incremented by 2/3°, and 10 on the left side with identical distribution. Eye targets were at eye height for each subject, and the reach targets were 1.5° below the eye targets. Eye positions were constrained to be within 2° of the instructed locations, and hand position was constrained to be within 4° of the reach target. We use the term "eye target" or "eye movement goal" to refer to the end location of the instructed eye movement. Similarly, we use the term "reach target" to indicate the goal of a reach.

On all trials, subjects initiated the trial by touching a central green reach target and fixating their gaze on a central red eye target for 600ms ("reach fix.", "eye fix."; Fig. 2A). A reach cue indicating the location of the impending reach was then flashed for 500ms at one of four positions located at ±6° or ±11° away from center (Fig. 2B). The memory period followed involving one of the following conditions:

I. ***Fixation condition (Fixation).*** The eye remained stationary on the central fixation target. Fixation trials served as a measure of performance in the absence of eye movements. Memory periods in this condition varied between 1200-2000 ms.

II. ***Saccade condition (Saccade)***. 800-1600 ms after the start of the memory period, one of the 20 eye targets was illuminated indicating the target of the instructed saccade. Simultaneously, the central eye fixation target was extinguished instructing execution of the saccade. Reaches were instructed immediately after the saccade was completed. The length of the memory period of Saccade trials was approximately equal to the length of the memory period in Fixation trials. Gaze was restricted to the saccade target during the reach. This condition was used to compare smooth pursuit updating with saccade updating.

III. ***Smooth pursuit – Cued goal condition (CG)***. At the start of the memory period, one of the 20 eye targets was illuminated for 500ms indicating the end location of the smooth pursuit eye movement. 100 ms after the eye target was extinguished (600ms after the start of the memory period), the central eye fixation target moved horizontally away from the center at 9.4°/s towards the extinguished eye target (Fig. 2B). Upon reaching the eye target, the tracked fixation point disappeared immediately, cuing the participant to reach to the remembered reach target while they kept their gaze on the eye target's final location.

IV. ***Smooth pursuit – No goal condition (NG)***. In this condition, the end location of the smooth pursuit eye movement was not revealed. 600ms after the start of the memory period, the central eye target moved horizontally away from the center at 9.4°/s towards one of the 20 gaze locations (Fig. 2B). Upon reaching the gaze target, the eye target disappeared, cuing the participant to reach to the remembered reach targets while they kept their gaze on the eye target's final location. NG trials were identical to CG trials aside from the absence of information about the eye target. The amplitude of eye movements instructed in the NG condition was the same as in the CG condition.

V. ***Smooth pursuit – Stop short condition (SS)***. This condition was identical to the CG condition, except that the smooth pursuit eye movement was terminated after travelling 90% of the distance to the cued eye target. Specifically, at the start of the memory period, one of the 20 eye targets was illuminated for 500ms. 100 ms after the eye target was extinguished, the central eye target moved horizontally away from center at 9.4°/s towards the extinguished eye target, but stopped short after travelling 90% of the distance. Thus, the motor signals and information from the eye target were incongruent. Following the experiment, subjects indicated whether they noticed the discrepancy between the eye target and real pursuit endpoint. 8 out of 13 participants completed this condition.

For all trials, reaches were instructed by extinguishing the fixated target, which was located at the center of the screen on Fixation trials or at the endpoint of the eye movement on Saccade, CG, NG and SS trials. After a successful reach, the reach target was re-illuminated and paired with an audible tone for reinforcement.

4.3.4 Data analysis

Eye and hand position were calibrated before the start of each session and halfway through the recording. The calibration of eye data during smooth pursuit was confirmed offline by assuming that catchup saccades landed on target (Kang and Malpeli, 2003). Final eye position was defined to be the position of the eye 50 ms after the instruction to reach. Reaction time was calculated as the time between the instruction to reach (disappearance of the eye target) and lifting of the hand from the touch screen. We defined reach error as the horizontal displacement from the location of the reach target to the location of the participants' hand during the first 15ms of touching the screen. Only horizontal displacement was used since both reach targets and eye movements were located on a horizontal axis. Reach precision measured the spread of touches to each target. Trials with reaction time less than 80 ms or greater than 600 ms were excluded from further analysis.

4.4 Results

We examined whether reaches preceded by smooth pursuit eye movements are affected by the knowledge of the eye target. In the CG condition, the goal of the smooth pursuit eye movement was flashed on the screen. In the NG condition, subjects pursued targets without knowing the end position. The SS condition created a mismatch between the visual information and motor program. The reach error and reaction time were measured and compared across conditions.

4.4.1 Reach errors are consistent with eye-centered target encoding

Our first goal was to confirm that reaches are updated following smooth pursuit eye movements. We also used the retinal eccentricity effect to uncover the reference frame used for updating (Bock, 1986, Henriques et al., 1998). We inferred the reference frame by measuring the pattern of reach errors for reaches to eccentric targets (Henriques et al., 1998). As shown in Figure 3, reach errors for conditions with and without eye movements were consistent with a retinal eccentricity effect. Subjects tended to overreach the target relative to the gaze location: when gaze was to the right of the reach target ($G-HT > 0$), reach error tended to be negative ($H-HT < 0$), while a gaze to the left of the reach target elicited positive reach errors. This was seen for both single participants (Fig 3A) and across participants (Fig. 3B). Across eye movement conditions, 11/13 subjects had similar patterns of reach error, where reaches overshot the target relative to the direction of the final gaze location (one-tailed t-test, $p<0.05$). Because this effect was relative to the final gaze location, this suggests that internal representations of the reach target were stored relative to the gaze location and updated for the eye movement. These results are consistent with previous reach studies (Henriques et al., 1998, Thompson and Henriques, 2008b).

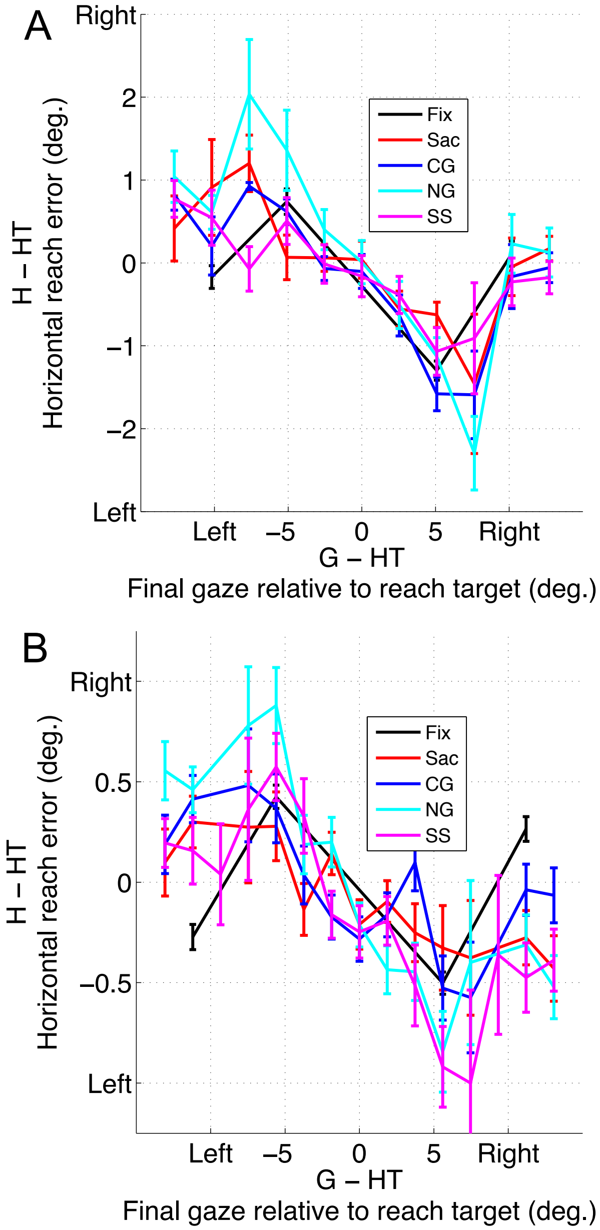

Figure 3. Reaching errors (H-HT) demonstrate retinal magnification. A. An individual participant's horizontal each error as a function of final gaze position relative to the reach target. Consistent with the retinal magnification effect, reaches overshot the reach target relative to the final gaze location at the end of the eye movement (Bock, 1986, Henriques et al., 1998). This effect was seen across all conditions. B. This plot is the same as A, but averaged across all participants. H-HT = 0° indicates accurate reaching. Abbreviations: G – gaze location, HT – hand (reach) target location, HT – hand location. Fix – Fixation condition. Sac – Saccade. CG – Cued Goal. NG – No Goal. SS – Stop Short.

4.4.2 Reach Error increased for the Smooth Pursuit No-Goal condition

If knowledge of the eye target contributes to updating, then we predict that the reach error and reach variance during the CG condition should be smaller than the error and variance during the NG trials. To test this prediction, we compared the absolute horizontal reach error and reach precision (variance of the signed reach error) of the NG condition with the CG condition. For the population, there was a highly significant effect of condition on reach error (1-way ANOVA, p = 9e-8) (Fig 4A). NG trials had significantly higher reach error than CG and Saccade trials (unpaired t-test, p=0.0002 and p=0.0003, respectively). Trials with correct eye target information (Saccade and CG) had an average reach error of 1.34° (SD 0.97°) [Saccade – 1.35° (SD 0.97°), CG – 1.34° (SD 0.97°)], while NG trials had an average reach error of 1.49° (SD 1.02°). Fixation trials had the lowest reach error with 1.17° (SD 0.92°), significantly lower than Saccade trials (unpaired t-test, p=2e-6) and CG trials (p=3e-6).

The magnitude of reach error varied across reach targets (Fig. 4B). The error on NG trials was higher than the error for CG trials for all targets (unpaired t-test, p<0.05) except for reaches to targets at 6°. For the 6° target, reach error on NG trials was not significantly greater than CG trials (1.15° vs. 1.17°, respectively, p=0.58). However for the target at -6°, reach error on NG trials was greater than errors on CG (1.39° vs. 1.19°, respectively, p=0.007). Similarly NG error was greater than CG error for reaches to targets at -11° (p=0.002) and 11° (p=0.03).

Comparing Saccade and NG, reaches to the 6° target had higher error on NG trials than Saccade trials (1.16° vs. 1.04°, p=0.047). For the target at -6°, there was no difference between NG and saccade trials (1.39° vs. 1.37°, p=0.74). The error during NG trials was greater than Saccade trials for reaches to targets at -11° (p=0.008) and 11° (p=0.0005). While reach error differed strongly when reaching to different targets on eye movement trials, Fixation trials did not have significantly different error across reach targets (1-way ANOVA, p=0.07) (Fig. 4B). This suggests

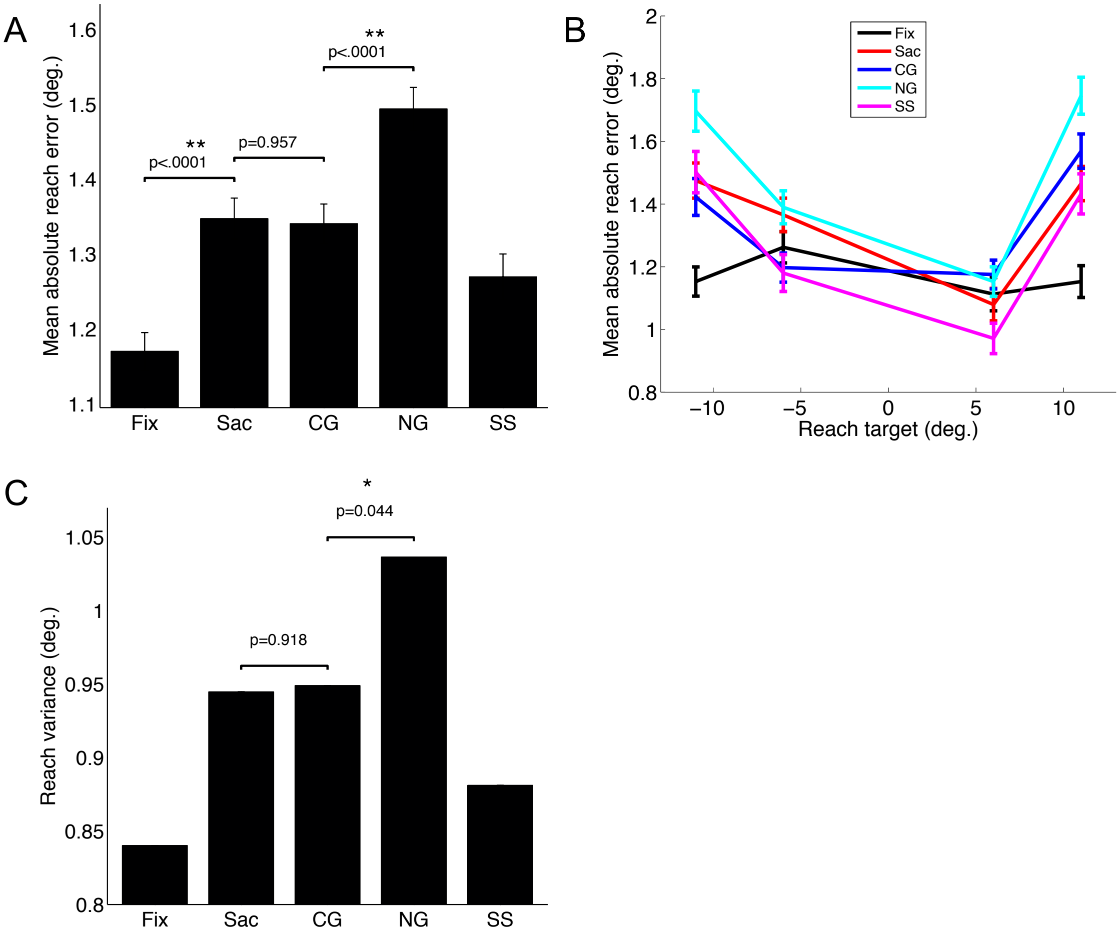

Figure 4. Reaching error and variance are greatest for the no goal (NG) condition. A. Absolute reaching error as a function of condition. Data was combined across all participants. Reported p-values are from unpaired t-tests. Reach error was highest for NG trials, intermediate for Saccade, CG and SS trials, and least for Fixation trials. B. Absolute reaching error as a function of reach target, combined across participants. All error bars show standard error. Increased error on NG trials was most prominent for the reach targets at ±11°. C. Reach variance as a function of reach target, combined across participants.

that the tendency for higher error when reaching to the outer targets (±11°) is due to the instructed eye movements.

The pattern of reach errors in the population was generally consistent with reach errors made by individual participants. Comparing CG to NG trials for reaches to the -11° target, 7/13 participants had significantly higher error on NG trials (unpaired t-test, $p<0.05$). The same was true for reaches to the rightward target at 11° (6/13). Across all targets, 8/13 participants had significantly higher error on NG trials relative to CG. Importantly, no subjects had CG error significantly greater than NG error ($p > 0.05$). Therefore the effect of the eye target on reach errors was evident both within and across participants.

We found a similar pattern for reach variance, where trials with correct eye target information had the most precise reaches (lowest variance) (Fig. 4D). Across all participants, we found a significant difference in reach variance between conditions (p=3e-5, Levene's test). NG trials had the highest variance in reach error, while CG and Saccade trials had the lowest variance. The variance of reach error on NG trials was 1.03°, while CG and Saccade trials combined had a significantly lower variance of 0.94° ($p=0.012$, Levene's test). Thus, trials where gaze endpoint was known had both decreased reach error and increased reach precision.

4.4.3 The discrepancy on SS trials did not affect reach error

Reaches tended to overshoot the target relative to gaze during the CG condition. In the SS condition sensory (eye movement goal) and motor signals (efference copy) of the eye movement were dissociated. Trials in this condition were identical to CG, except that the pursuit ended 10% short of the position signaled by the eye target. If the visual information is discarded, then updating using the efference copy signal alone should yield increased overshoot as the shorter eye movement increases the distance between the final gaze and the reach target. In contrast, using the visual information will result in an overcompensated updating resulting in an undershoot.

We first confirmed that the eye was traveling less in the SS condition. Indeed, the mean eye displacement was 8.2° on CG trials and 7.2° on SS trials (11% decrease). In general, trials with incorrect eye target information (SS) did not have reaching errors significantly different from trials with correct eye target information (Fig. 4B). Absolute reaching errors on SS trials were on average 1.27° (SD 0.94°), not significantly different from either Saccade or CG trial reaching errors ($p=0.08$ and $p=0.06$, respectively; unpaired t-test). No participants had a significant difference in reach error between CG and SS conditions (unpaired t-test, $p<0.05$); 1/8 had significantly lower error on Saccade trials compared to SS ($p<0.05$), and a further participant showed the opposite (SS > Saccade, $p<0.05$). Similarly, reach variance was not significantly different between CG and SS conditions either across participants (Levene's test, $p=0.13$) or within participants (0/8, $p<0.05$). In a post-recording questionnaire, 3/8 participants reported that they noticed the discrepancy between cued endpoints and real pursuit endpoints on SS trials. Reach error was lower for participants that noticed that the cued eye target was incorrect, but not significantly (noticed: 1.25° +/- 0.93° SD, did not notice: 1.29° +/- 0.95° SD; $p=0.12$, unpaired t-test). Similarly reach variance was not significantly different between these two groups (noticed: 0.87°, did not notice: 90°; $p=0.68$, Levene's test). Therefore, the discrepancy between eye targets and real pursuit endpoints did not appear to have a significant effect on reach error or variance.

4.4.4 Reaction times were lower on smooth pursuit trials with an accurate eye target

Since the eye target was presented before the eye movement, it could potentially be used to update reach plans earlier than would be possible using feedback or efference copy signals. Therefore, we measured whether reaches made on CG trials required less preparatory time by measuring the reach reaction time. In general, reaction times differed significantly between trial conditions (1-way ANOVA, $p=1e-15$). The magnitude of the reaction time is used to indicate differences in the preparatory processes while reach errors indicate errors in the estimates of target position (Riehle and Requin, 1989, Crammond and Kalaska, 2000).

Among the smooth pursuit conditions (NG, CG and SS), correct eye target information significantly lowered reach reaction time (Fig. 5). Across participants, NG reach reaction times had a mean of 375 ms whereas CG trials had a mean reach reaction time of 318 ms (p = 4e-90, rank-sum test). Thus, the presence of correct eye target information on pursuit trials reduced reaction time by 15%. Looking at participants individually, 10/13 showed this pattern significantly ($p<0.05$) and all participants had lower reaction times on CG compared to NG trials.

SS trials had significantly shorter reach reaction times than NG trials (SS: 329 ms, NG: 375 ms; p=5e-51, rank-sum test), indicating that the discrepant eye target still provided information that resulted in reduced reaction times. For individual participants, 6/8 had shorter reaction times on SS trials relative to NG trials ($p<0.05$, rank-sum test). Across participants reaction times on SS trials were also significantly longer than on CG trials (CG: 318 ms; p=2e-6, rank-sum test), a pattern that was also shown for individual participants (CG < SS, 6/8, $p<0.05$). This increased RT may indicate an effort to resolve the discrepancy between visual and motor information.

4.4.5 Lower reaction times are not explained by attentional facilitation

We tested whether lower reaction times in the CG condition were a result of attentional facilitation by the eye target cue. Previous studies showed that a visual stimulus such as the eye target cue can facilitate attention to that location and reduce reaction times for saccades (Bell et al., 2004, Fecteau et al., 2004). We tested for this by regressing reaction time against the distance between eye target and reach target: if spatial attention to the eye target lowered reaction times, then reaction times should be shortest when eye target and reach target are close. Pooled CG trials showed no correlation between reaction time and eye-to-reach-target distance (Pearson correlation coefficient, R=0.0309, p=0.115, on 2120 trials).

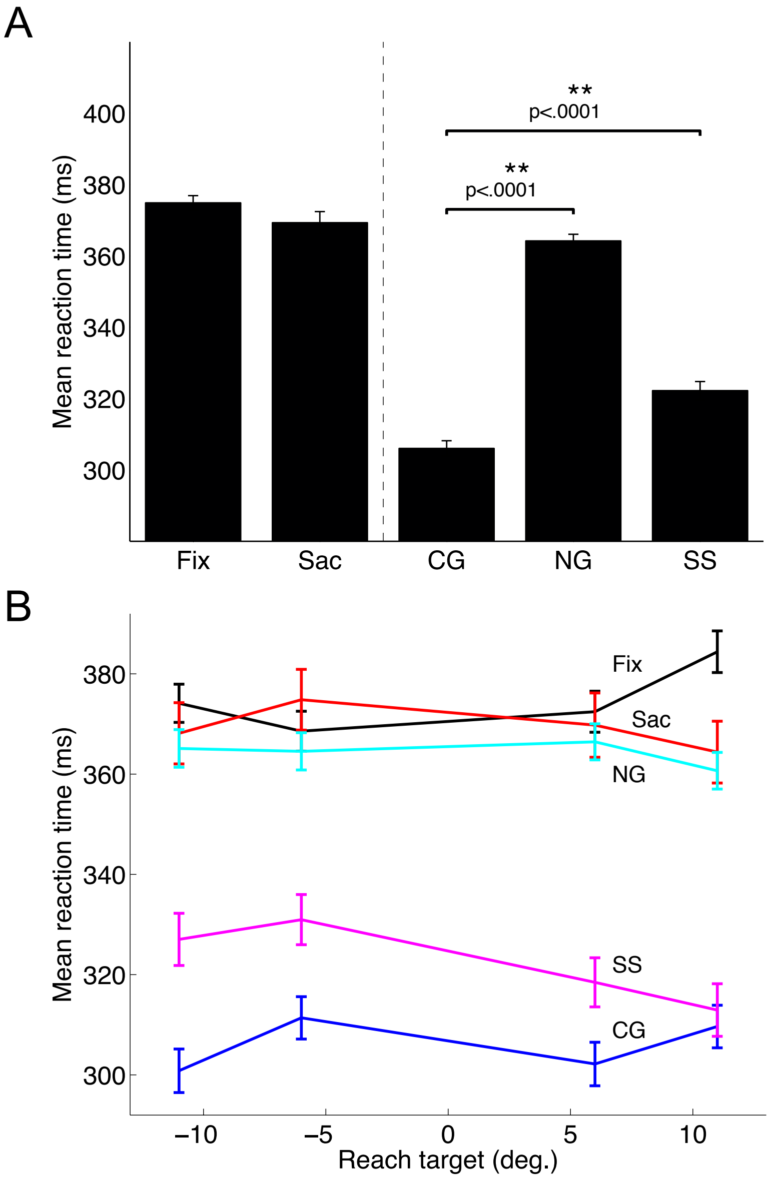

Figure 5. Reaction time was lowest on cued goal (CG) trials. A. Reaction time as a function of trial condition. Among pursuit trials, reaction time was greatest for NG trials, intermediate for SS, and lowest for CG. Fixation and Saccade trials had reaction times similar to NG trials. Data was combined across all participants. B. Reaction time as a function of reach target. Reaction time varied only weakly with reach target and was mostly a function of trial condition. Reported p-values are from Wilcoxon rank-sum tests. All error bars show standard error.

Indeed, only 1/13 participants showed a significant, negative relationship, i.e. lower reaction time when the eye targets appeared nearer the reach target ($p<0.05$). Thus, it is unlikely that shorter reaction times for CG trials were a result of attentional mechanisms.

4.5 Discussion

4.5.1 The effect of eye target on reaching behavior

We investigated whether visual information about the endpoint of the upcoming eye movement (eye target) could be used to update reach targets. We examined the accuracy and reaction time of reaches made when the eye endpoint was known (Saccade or CG) versus when the endpoint was unpredictable (NG). We first confirmed that participants in this study planned reaches relative to gaze location and therefore updated reach plans for eye movements (Fig. 3) (Bock, 1986, Henriques et al., 1998). We found that error was higher and precision was lower when the intervening eye movement ended at an unpredictable location. Reach errors on NG trials were about 10% higher than on trials where the eye target was known before the eye movement was made (Saccade and CG; Fig. 4). Reach reaction time also decreased when the eye target was not known. Therefore, when the eye target of the updating eye movement was known, reaches were more accurate, precise, and were executed more quickly.

Reach error was not affected when we dissociated the visual and motor information in the SS condition. The absolute horizontal reaching errors on SS trials were not significantly greater than on CG trials (Fig. 4). If information from the eye target was the sole updating source, the 10% error in the eye target position should have translated into errors in reaching. Using the efference copy could also increase reach error as shorter gaze shifts can increase the eye-centered eccentricity of the reach target, although this effect is likely to be small given that a 10% increase in reach target eccentricity would have a small effect on reach error on average (Fig. 3). Therefore, one possibility is that greater errors on SS trials were canceled by weighting motor signals more heavily. In addition, given that the discrepancy on SS trials was constrained to be small in order to minimize detection, it is also possible that a greater discrepancy between the visual and motor signal is needed.

It is also possible that the pursuit system used temporal dynamics to improve updating. Since the eye target eliciting the smooth pursuit moved at a constant speed across trials, the pursuit system could easily learn the temporal dynamics (Medina et al., 2005). With a constant velocity, the only other variable required for computing the duration of the eye movement was its magnitude. In the CG condition, the pursuit system had all the information it needed to predict the end of the smooth pursuit and the cue to reach. The reach could be prepared without waiting for an external reach cue. However, it seems unlikely that the reach system is extracting only temporal information from the flashed endpoint. Even if the brain knows when to reach thanks to the temporal information, it still needs to know by how much to update the reach plan, which requires spatial information. In addition, since the temporal properties of the eye target would have to be learned in our paradigm, a negative relationship between trial number and reaction time should emerge. This pattern did not exist in our data.

Since knowledge of final eye position produces shorter latencies for subsequent memory-guided reaches, we expected saccades, where that knowledge is present, to have shorter latencies than the smooth pursuit condition without eye endpoint information. We did not observe this in our data. It is important to remember that most animals reach to where they are looking, and the reach and saccade systems are strongly interlinked. Some work has shown that it is very difficult to saccade away from a pointing target during the arm movement, a phenomenon known as gaze anchoring (Neggers and Bekkering, 2000, 2001, 2002). In our study, participants had to reach directly after they finished the saccade, which may have introduced a latency while the attention system disengaged from the saccade task.

From these findings, we propose that updating by eye targets – that is, the spatial endpoint of the eye movement irrespective of the eye movement kinetics –

may be a common mechanism for updating by eye movements. While pursuit eye movements with known eye targets are a special case, saccades are ballistic eye movements that require an eye target for initiation. Indeed, saccade efference copy could potentially carry two pieces of information: i) online, dynamic information about the eye movement, and ii) information about the final, resultant gaze location.

4.5.2 Updating using information about the eye movement goal

How is information about the eye target used to update? Figure 1 lays out our proposed scheme. The presence of the eye target can allow the brain to anticipate the degree of retinal shift between the relative gaze-hand-target positions at the initial gaze location and the gaze-hand-target positions at the time of the reach. The eye-hand distance modulates firing rates in cortical areas involved with reach planning (Chang et al., 2009), as does the relative location of the target and the eye position, i.e. eye-centered target location (Batista et al., 1999). Therefore, it seems plausible that knowledge of the eye endpoint has sufficient information to generate an updated reach plan. Updating using efference copy requires that efference copy be passed through a forward model of the eye. Similarly updating using visual information about the eye target would require an interior model that predicts the consequences of an eye movement to that location.

Note that while our proposed scheme for updating using the eye target is formalized as a vector subtraction (Fig. 1), the neural mechanism for updating in this fashion is unclear. Given that the brain integrates signals from various sources to compute a spatially accurate reach vector, such as feedforward motor commands and sensory feedback (Klier and Angelaki, 2008, Sabes, 2011), it is likely that feedback from the eye target signal is combined with other updating signals such as efference copy. Therefore reach target improves in the CG case because there is additional noisy information about the gaze-centered location of the reach target following the eye movement. This is consistent with other studies finding that introducing multiple updating signals improves reaching accuracy in an updating task (Avillac et al., 2005, Schütz et al., 2013).

It is possible that subjects used other cues to gauge the extent of the eye movement. We eliminated external reference points by placing a transparency with a light to dark gradient between the monitor and the participants. Since the participant is sitting in the dark, and in the absence of other spatial markers, it is unlikely updating was computed using allocentric cues.

While these results are consistent with eye targets allowing for earlier updating, they do not make strong claims about when updating by eye target information occurs. Updating could potentially occur before the eye movement, since eye target information was available approximately 2000 ms before a complete efference copy signals was available. However, in comparison, the 57 ms decrease in reaction times from NG to CG trials is slight, and does not by itself imply predictive updating. It is unlikely that an updated reach plan was computed seconds before the reach was initiated. A more likely option is that the eye target signal is combined with the incoming eye movement efference copy. The mechanism for this is unclear, and in general more work remains to determine how the brain integrates signals from various sources, such as motor and feedback, to compute a spatially accurate reach vector (Klier and Angelaki, 2008).

The decrease in reach error, reach variance and reaction times on trials with a known eye endpoint provides evidence for our initial hypothesis that prior knowledge of the final eye position contributes to updating. That is, updating is improved and reaches are therefore more accurate when the intervening eye movement is predictable. Our findings show that knowledge of the target of an eye movement that disrupts spatial constancy can reduce reach errors and reach reaction time, although more work is required to understand how that signals is integrated with other updating signals, such as efference copy.

4.6 Conclusions

This Chapter investigated reaching behavior following updating by predictable (CG and Saccade) and unpredictable eye movements (NG). The goal was to determine whether visual signals related to the endpoint of the eye movement, which carry the necessary information to update internal representations of the reach target in visual space, can indeed be used to update. Predictability was manipulated by either presenting or not presenting the endpoint of the updating pursuit eye movement before the pursuit began. If eye endpoint signals do not contribute to updating, these two conditions should lead to identical reaching behavior. We used pursuit eye movements, since unlike saccades, pursuits can be initiated without knowing the next fixation point. Using a previously demonstrated effect where reach behavior shifts with eye movements (Henriques et al., 1998), we first confirmed that reach updating was likely to be occurring in this experiment. Reach error and variance were subsequently shown to be lower following pursuits with a cued endpoint, i.e. after predictably terminating pursuits, versus pursuits that ended unpredictably. These results are consistent with visual information about the eye endpoint being used to update the reach target for the change to eye position.

Combined with results from Chapter 3, the findings here show that reach updating is likely computed by combining multiple signals depending on the context. Chapter 3 showed that some neurons in brain area PMd began updating predictively with respect to the eye movement, a result that demonstrates updating by internal signals of the eye movement command. Results in this Chapter show that a different signal (visual feedback of the eye endpoint) also contributes to updating. This is consistent with recent findings that a number of signals, such as vestibular cues (Klier et al., 2008a), can update movement plans. How these multiple signals are combined in order to compute an update reach plan is unknown.

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Chapter 5

Summary and Future Directions

5.1 Overview of main findings

Understanding how the brain maintains stable models of space has been a longstanding problem in neuroscience. This issue of spatial stability is a problem for perception, and especially visual perception, which must stitch together brief, narrow glimpses of the world into a unified and stable visual scene. Spatial stability is also an issue for motor control, since motor systems require an accurate model of external space in order to plan and generate correct movements. This thesis focuses on the problem of spatial stability for accurate motor control.

Spatially stable motor plans for reaching likely arise in the posterior parietal and dorsal premotor cortices (PPC and PMd), since these brain areas display a range of reference frames, from eye-centered neurons that retain the native coordinate system of the retina to body-centered coding (Avillac et al., 2005, Pesaran et al., 2006, Sereno and Huang, 2014). As seen in Chapter 2 and other studies of PPC (Stricanne et al., 1996b, Duhamel et al., 1997) and PMd (Graziano et al., 1997), these two coding schemes can even exist within the same brain area. Indeed, a recent study showed that area 7a, a subdivision of the PPC, briefly encodes information in retinocentric coordinates before switching to a spatially stable coordinate system after 100 ms (Crowe et al., 2008). Therefore, PPC and PMd appear to be the dividing line between spatially dependent sensory reference frames and spatially stable motor reference frames. If these brain areas do indeed solve the problem of spatial stability, how do they do it?

An internal model that flawlessly represents space is a heroic task of neural computation. While researchers are still far from understanding neural mechanisms that give rise to spatial stability, there have been significant advances in the last few decades. Two general paradigms describe most spatial stability strategies. First, spatial stability is solved when sensory information is transformed into a coordinate system independent from motion of the sensory organ. This sensorimotor transformation can be computed by gain field mechanisms. A number of theoretical studies show that a gain, i.e. multiplicative relationship between firing rates and postural positions, like eye position, is a predicted feature of neurons that transform information between coordinate systems (Zipser and Andersen, 1988, Pouget and Sejnowski, 1997). Neurons that encode an eye-centered position and have a multiplicative relationship with eye position can act as a middle layer whose activity can be integrated by downstream areas to compute a head-centered position (Pouget and Snyder, 2000). This head-centered representation is then invariant for eye movements. Other combinations of postural signals can potentially compute a number of eye-invariant reference frames, e.g. (Buneo et al., 2002).

The bulk of this thesis, however, deals with a second mechanism: spatial updating. Since many neurons encode movement goals relative to visual space, in order to maintain the correct registry between the movement goal and the location in real external space to which the goal is directed, neurons must shift their activity for each eye movement. In this process, activity representing the movement goal is shifted from one group of neurons encoding it relative to the initial eye position to a second group relative to the final eye position. This shift ("update") in activity cannot be a result from simple visual feedback, since it occurs for remembered movement targets (Gnadt and Andersen, 1988, Duhamel et al., 1992). Correctly remapping between neurons like this can solve the problem of spatial stability.

Despite recent advances, there are a number of open questions about the underlying mechanisms of spatial updating. In particular, this thesis addresses how the brain updates across slow, tracking eye movements (smooth pursuit). While a number of behavioral studies show that humans (Herter and Guitton, 1998, Thompson and Henriques, 2008a) are capable of updating for pursuits, it's not clear what neural correlates underlie this ability. Specifically, it's not known whether mechanisms investigated for transsaccadic updating are common to smooth pursuit updating. If updating is driven by efference copy, and since efference copy varies significantly between saccades and pursuits, it's possible that saccades and pursuits will lead to different updating. Further, the time course of reach plan updating during pursuit eye movements is not known. Finally, this thesis addresses which neural signals contribute to reach plan updating.

5.1.1 Reach updating by slow eye movements

The majority of updating studies use saccades to update motor plans, although in the last two decades there has been relatively more focus on updating by slow movements. This recent work has tended to focus on slow, passive movements, such as rotation by a turntable (Klier et al., 2005, Klier et al., 2008b). Compared to updating induced by saccades, studies investigating updating in response to smooth pursuits are under represented in the literature. Indeed, due to the mislocalization of flashed target targets during a pursuit (Nijhawan, 1994), it was contentious that motor plans could be updated accurately by pursuit eye movements at all. Since reach plan updating is itself a subset of the updating literature, reach plan updating by pursuit eye movements is particularly poorly understood. All three studies in this thesis address this deficit.

One of the main pursuit updating issues tackled here, and the focus of Chapter 2, is whether neurons update similarly for saccade and pursuit eye movements. The main finding of Chapter 2 is that reach planning neurons have the same magnitude of firing rate change when updated by saccades and pursuit. That is, reach planning neurons that are updated by eye movements don't discriminate for the eye movement type. This is consistent with a human behavioral study that found similar patterns of reaching errors after updating by the two eye movements (Thompson and Henriques, 2008a). The observed similarity between saccade and pursuit updating is important because it implies that, temporal dynamics aside, insight into spatial stability gleaned from saccade updating studies can be applied to pursuit updating and vice versa.

At first glance, Chapter 2 and Chapter 3 appear to arrive at different conclusions. While the results from Chapter 2 show pursuit and saccade updating are equivalent, Chapter 3 finds that they differ in a significant way. Specifically, the results from Chapter 3 show that pursuit updating occurs dynamically throughout the eye movement, rather than the discontinuous "jump" that transsaccadic updating resembles in LIP (Kusunoki and Goldberg, 2003) and the superior colliculus (Sommer and Wurtz, 2006). These two findings are not inconsistent, however. That is, while the temporal dynamics of saccade and pursuit updating differ, the final result of remapping is equivalent. Further, both of these results are generally consistent with the model that firing rates in MIP and PMd represent the relative locations of the reach target and gaze location (Batista et al., 1999, Pesaran et al., 2006).

If transsaccadic updating resembles a discontinuous remapping (static updating), why is pursuit updating dynamic? One possible answer is the difference in knowledge of the eye movement goal, as highlighted in Chapter 4. That is static updating, where activity is discontinuously remapped from one fixation eye position to the next, is possible when the next fixation eye position is known. In the case of saccades, which are ballistic eye movements, the final eye position is pre-programmed, meaning that discontinuous updating between fixation eye positions is possible. In the case of pursuits where the next fixation point remains to be determined, the options are to update dynamically or fail to update for the change in eye position. This is supported by the results from Chapter 4 which found that when information about the endpoint of a pursuit eye movement is provided experimentally, reaches are faster and more accurate, suggesting that visual information about the pursuit endpoint is indeed used to update. Exactly how information about the pursuit goal can be used to update, however, remains to be investigated.

5.1.2 Signals for reach updating

While much work has examined spatial updating, there remains to be found a unified understanding of the mechanisms are behind it. One important approach for understanding how the brain computes accurate spatial updating is to determine the internal signals underlying its computation (Klier et al., 2008b). These signals include feedback from sensory organs, like visual feedback from retinal cells or proprioceptive feedback from muscle mechanoreceptors, as well as feedforward signals about our own movement commands, i.e. efference copy. Efference copy signals provide information about our movements through the external world, and therefore they predict reafferent (self-caused) sensory information. Accumulating evidence from the last 40 years has highlighted their importance in updating (Mays and Sparks, 1980, Sparks and Mays, 1983, Duhamel et al., 1992).

Most of the evidence for the involvement of efference copy in updating comes from saccade updating literature. Although many sophisticated variations exist, the general template for these studies is similar to the double-step saccade paradigm (Hallett and Lightstone, 1976a), where saccadic eye movements perturb ongoing movement plans to a remembered target. Again similar to the double-step saccade task, the ongoing movement plan is itself most often a saccade plan. It is common for studies to implicitly assume that evidence from updating in the saccade system applies to updating in the reach systems. However, given that reach and saccade plans are encoded separately in different brain areas (Snyder et al., 2000, Quian Quiroga et al., 2006), it is plausible to imagine that there are different updating mechanisms (Medendorp, 2011). Therefore in general the signals contributing to reach plan updating are not as well understood as the signals involved in saccade plan updating. The findings in this thesis address that deficit.

Efference copy in the reach system. Aside from a study showing that reach stability does not require extraocular muscle proprioception (Lewis et al., 1998), there is little evidence for the direct involvement of efference copy in maintaining spatial stability in the reach system [see discussion in (Thompson and Henriques, 2011)]. The results of Chapter 3, where PMd neurons were predictively updated by saccades and pursuits, are the first direct evidence that efference copy can drive reach plan updating. Approximately a quarter to a third of PMd neurons began updating before the eye movement started by at most 250 ms (Chapter 3, Fig. 3). Because updating occurred in advance of the eye movement, it could not have resulted from feedback signals related to the eye movement. This temporal argument is one of the main criteria for determining the presence of efference copy signals (Duhamel et al., 1992, Klier and Angelaki, 2008, Sommer and Wurtz, 2008a).

Visual signals for reach updating*.* Using behavioral evidence in an updating task, Chapter 4 identified a novel signal that is capable of driving updating. Namely, the presence of an "eye movement goal", a visual signal providing the endpoint of the updating eye movement, led to reaches that were more accurate and precise and were executed faster. We concluded that the information provided by the eye movement goal was used to compute spatially accurate reach plans, resulting in improved reaching behavior. When reach plans are updated by an intervening eye movement, the spatial goal of the updating eye movement is capable of providing the same basic information as efference copy, since it can be used to compute the displacement vector between the initial and final eye position. This information is sufficient to compute the relative positions of gaze, hand and reach target at the time of the reach – that is, to update. In essence intervening eye movements made when the eye movement goal is known are predictable; intervening eye movements made without an eye movement goal terminate unpredictably.

How does the brain use the predictability of eye movements to update? Since the eye target, reach target and hand are all viewed in the same visual reference frame, one possibility is that the brain computes something akin to a vector subtraction using the visual location of the eye movement goal (Chapter 4, Fig. 1). Further, given that the inaccuracies in the eye movement goal did not translate into inaccuracies in the reach (Chapter 4, Fig. 4, SS condition), updating by this signal is unlikely to be the sole mechanism. A more probable mechanism is that the predictability provided by the eye movement goal makes integrating signals like efference copy more accurate. However, more work is needed to determine exactly when and how this signal is used to update the reach plan.

5.2 Future directions

Directly building off of the studies presented here, there are a number of experiments that are warranted. In particular, the novel updating signal investigated in Chapter 4 presents several open questions. First, when are visual signals about the pursuit endpoint used to update reach planning neurons? Second, if reach plans don't immediately update based on eye endpoint, in what brain area is endpoint information stored and what reference frame is it encoded in? Third and finally, is this signal sufficient to update, or does it facilitate updating by other signals like eye movement efference copy? These questions can be directly answered via primate electrophysiology during an experiment similar to that in Chapter 4. One difficulty would be to communicate the significance of the eye movement endpoint stimulus, something that may be difficult to test. However the behavioral changes (decreased error and reaction time) would be evidence that it was communicated sufficiently, and the experimental design could be changed to require the animal to stop pursuing at the location signaled by the endpoint stimulus. This design could answer the first two questions in this paragraph. In particular, an updating onset analysis similar to that in Chapter 3 could be used to assess the time course of updating by this signal.

Using a stimulation experiment, it may be possible to answer whether an eye endpoint signal is sufficient to update. Sparks and Mays (1983) showed that eye movement plans are not correctly updated when eye movements are produced by trochlear nerve stimulation, since the saccade made after the stimulation was inaccurate. That is, at least in the context of the experiment, efference copy was a necessary updating signal. However, could updating be rescued by signaling the location of the upcoming gaze shift (eye endpoint) before the stimulation is applied, similar to the Cued Goal condition in Chapter 4? If so, this would be evidence that eye endpoint information is sufficient to update.

Other open questions remain about how the brain updates for slow, pursuit eye movements. A design similar to that used by Kusunoki and Goldberg (2003) could be used to probe the extent of reach receptive fields during pursuit. In this experiment, 'probe' stimuli are flashed at times around the eye movement, and the neural response can be compared to times when the eye position is fixed. This is used to examine how receptive fields momentarily update around the time of the eye movement. A similar experiment that replaces probe stimuli flashed around the time of a saccade with reach targets flashed during a pursuit could greatly expand the understanding of the time course of updating during a pursuit.

In a broader scope, certain fundamental questions about spatial updating may be difficult to answer using primate studies. The ability to train primates to perform a wide range of behavioral tasks, and the fact that they are our closest relatives, means that primate electrophysiology will likely remain an important piece of the puzzle. However, two limitations warrant investigation with other models. First, the primate cortex is complex and activity is modulated by many variables. Primate brain areas involved in visuomotor transformations, especially neurons in the PPC, vary their activity with the cognitive state of the animal, such as the reward the animal is expecting (Musallam et al., 2004, Rajalingham et al., 2014). These cognitive changes obscure mechanisms related solely to neural computations underlying spatial stability.

Second, primate studies are, in general, restricted to either correlating activity with stimuli and movements, or perturbing the brain (electrically, chemically, or via a lesion) and measuring the effect on behavior. In order to understand the neural hardware and software that underlie spatial updating, however, experiments likely require selective activation and inactivation of single neurons and neural circuits, a task which current stimulation techniques are not capable of. Although recent advances in using optogenetics to alter visuomotor behavior holds the promise of controlling single neurons in a behaving primate (Cavanaugh et al., 2012), the complexity of the primate brain remains a major stumbling block. Therefore it may be worthwhile to investigate the neural mechanisms behind spatial updating using simpler animal models.

Insects face the same fundamental sensorimotor problem as primates: how to transform sensory information, which is subject to stimulation by the animal's own movement, into accurate movements. They also face the same issue of integrating signals from different modalities, for example mechanoreceptor information from the antennae and visual feedback. However, unlike primates, in insects these problems can be investigated at the level of single, uniquely identifiable neurons that are common between all individuals of the species, and many of which can be linked to specific behaviors (Hoyle and Wiersma, 1977, Comer and Robertson, 2001).

Perhaps surprisingly, *Drosophila* have the ability to remember spatial locations of visual targets in short term memory (Ofstad et al., 2011). In an experiment analogous to the double-step saccade task, which demonstrates spatial updating in primates (see section 1.3.1), a recent study showed that *Drosophila* can remember their orientation relative to a target even when the target is removed from sight and, importantly, even when the animal has moved relative to the target (Neuser et al., 2008). The orientation memory is localized in the central complex of the *Drosophila* brain and requires functioning ring neurons (Ofstad et al., 2011, Kuntz et al., 2012), cells that likely extract and encode visual features in an eye-centered reference frame (Seelig and Jayaraman, 2013).

Similarly to primate spatial updating investigated in this thesis, orientation memory in *Drosophila* takes an initial visual signal and stores it in a spatially stable way. The neuronal mechanisms underlying this ability are yet to be understood. Does the framework of reference frames apply? If so, what reference frame is the memory stored in? How is it updated for changes to the fly's orientation? What are the effects of active versus passive changes, i.e. those with and without efference copies? Do the theories of gain fields and remapping apply to *Drosophila* spatial stability? A protocol involving tethered, head-fixed flies in a spatial learning experiment similar to that of Neuser et al. (Neuser et al., 2008) combined with calcium imaging of ring neurons (Seelig and Jayaraman, 2013) may be able to answer these questions with a more controlled, less complex model than primate cortical brain areas. Coupling this with genetic mutants, ablation studies, or optogenetics would allow for causal testing of any potential theory.

Although this is just a single example, it highlights the universality of spatial updating across species. Indeed, problems of sensorimotor transformation and spatial updating are likely fundamental to any organism using variable sensory information to spatially orient itself. Whether the mechanisms are common between organisms, and the degree to which they could shed light on our own, human neural mechanisms remain to be seen.

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