Contributions of Parietal Cortex to Reach Planning

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Dedication

For my stepmother Nancy, for her years of encouragement and education.

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Abstract

Sensory-motor circuits course through the parietal cortex of the human and monkey brain. How parietal cortex manipulates these signals has been an important question in behavioral neuroscience. This thesis presents experiments that explore the contributions of monkey parietal cortex to sensory-motor processing, with an emphasis on the area's contributions to reaching. First, it is shown that parietal cortex is organized into subregions devoted to specific movements. Area LIP encodes plans to make saccadic eye movements. A nearby area, the parietal reach region (PRR), plans reaches. A series of experiments are then described which explore the contributions of PRR to reach planning. Reach plans are represented in an eye-centered reference frame in PRR. This representation is shown to be stable across eye movements. When a sequence of reaches is planned, only the impending movement is represented in PRR, showing that the area is more related to movement planning than to storing the memory of reach targets. PRR resembles area LIP in each of these properties: the two areas may provide a substrate for hand-eye coordination. These findings yield new perspectives on the functions of the parietal cortex and on the organization of sensory-motor processing in primate brains.

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Chapter 1 Introduction

> *The whole neural organism, it will be remembered, is, physiologically considered, but a machine for converting stimuli into reactions; and the intellectual part of our life is knit up with but the middle or 'central' portion of the machine's operations.*
>
> William James, The Principles of Psychology, 1890

The ease and speed of our movements mask the complexity of the underlying neural processing. In the perfected movements of a dancer, the diving catch of a baseball infielder, or the pouring of milk by a scientist into his morning coffee, we see smooth, accurate movements, coordinating many parts of the body, and perfectly adjusted to the particulars of the environment. Billions of neurons in many different regions of the brain's sensory systems and motor systems, connected in intricate branching and looping networks, mediate these behaviors. Out of the distribution of neuronal action potentials across intricate patterns of connectivity emerge accurate representations of the sensory environment, the will to execute a movement, and a smooth and efficient motion of the body.

A behavior that interacts with the environment consists of at least three conceptually distinct processes. A target must be selected. Natural environments present many objects which might be acted upon at a given time, and each action requires selecting one object. The type of action must be chosen. A person or animal may simply look at an object. Or, he or she might want to pick it up. Or, if it is distant, walk toward it. Finally, the movement must be executed. How fast? How smooth and direct will the movement be? Information about the position of the body in space must be integrated with information about the location of the goal in order to specify the particulars of the movement.

Aspects of each of these components of sensory-motor processing were studied in the experiments presented in chapters 2, 3, 4 and 5. First, this chapter will describe and discuss some of the existing knowledge about the neural processes of target selection, movement choice, and sensory-motor transformation. This information is germane to the experiments to follow. Chapters 2 through 5 motivate, describe, and discuss the experiments we have performed. The final chapter will offer an interpretation of how these experiments advance and alter the existing body of knowledge outlined in this chapter, and will end with a discussion of some of the new avenues that have opened for study as a result of the experiments described here.

1.1 The primate model

The study of the brain of the Rhesus monkey (*Macaca mulatta*) is an essential branch of neuroscience. These animals can perform complex, occasionally humanlike, behaviors, and at the same time, it is possible to study their brains directly. With rare exception, the human brain cannot be studied in this manner. Investigation of the monkey brain is an effective substitute for direct studies of the human brain.

In addition to studies of brain physiology, all that is known of the patterns of connectivity between different brain areas and the local anatomy of circuits within brain areas comes from studies of monkeys and other mammals with a neocortex.

Physiological studies of individual neurons in the monkey brain provide the most direct means of establishing the functions of brain areas. Other methods of studying the brain's control of behavior do exist. Studies of human beings who have suffered brain trauma can yield perspectives on the function of various brain regions. The studies of human sensory discrimination and behavior can generate clues as to the internal structure of brain processing. Recently, noninvasive studies of blood flow in the human brain during cognitive tasks have implicated different brain areas in various tasks. However, none of these methodologies can rival the spatial and temporal resolution of the picture of the brain that primate neurophysiology provides.

1.2 Functional inferences from brain lesions

The principle of localization of functions in the brain came from studies of human beings who had suffered lesions to specific areas of the brain, resulting in specific behavioral or perceptual deficits (Damasio 1994). While lesions of the visual areas can produce blindness (and occasionally blindsight) and lesions of motor areas can produce paralysis, lesions to the parietal cortex produce more complex syndromes. Inabilities to perceive regions of space or parts of the body, or to initiate deliberate actions, characterize parietal lesions. In contrast, lesions to the temporal lobes of cortex produce deficits in the ability to identify objects. Thus, it has been proposed that the cortex is divided into separate processing streams for perception and for action (Goodale and Milner 1992).

The image of parietal function that emerges from lesion studies is that the area is involved in spatial and body awareness, and in movement initiation. *Optic ataxia*, first described by Balint in a patient that had suffered damage to both parietal lobes (1909; reported in Milner and Goodale 1993) is an inability to initiate reaching movements under visual guidance. When asked to reach to an object placed in front of him with his right hand, Balint's patient would grope. Residual abilities of the patient demonstrated that the deficit was in visually guided reaching, and not simply in vision or in movement. He could accurately reach the object with the left hand, or direct gaze at it. And, with his right hand, the patient could accurately touch parts of his body which Balint indicated by touching. This observation was recently reinforced by Mattingley et al. (1998). These authors found that patients with parietal damage had difficulty initiating movements to the contralesional side of space that was exacerbated when the target was also contralesional with respect to the hand.

Neglect is a common disorder resulting from right parietal damage. It is an insensitivity to the left half of space. Patients do not initiate movements there, and when asked to describe their surroundings, patients omit objects on their left (Bisiach and Luzzatti 1978). Interestingly, the "left half of space" which is neglected can be quite different in different patients. It can be the left half of space defined retinotopically, with respect to the body (Karnath, Schenkel, and Fischer 1991), and even with respect to objects in the world (Driver, Baylis, Goodrich, and Rafal 1994). This concept of the reference frames for representing space in parietal cortex will recur.

Neglect can occur in a milder form, called *extinction*. In this deficit, the contralesional half of space is less strongly represented than the ipsilesional space. For example, when asked to report the number of objects in front of him, a person will respond correctly when one object is presented, regardless of where it is positioned. But, when two objects are presented, one in the "good" visual field, and the other in the "bad" visual field, the patient erroneously says one object has been presented.

Deficits in body awareness sometimes result from parietal damage, particularly to the superior parietal lobule. Wolpert, Goodbody, and Husain (1998) reported a patient with left superior parietal damage who would experience proprioceptive fading. When asked to maintain grip on an object, her grip force would weaken within a few seconds. When asked to estimate the position of her contralesional hand while it was held still, her perception of its location would drift, reliably up and away from her body. These deficits were not apparent whenever vision of the limb was permitted.

A striking component of parietal damage is that the patient is not aware of his or her deficits. Whereas a patient with partial damage to primary visual cortex is fully aware that he is blind in one part of space, and will continually reorient his eyes and body in order to see what is out there, patients with parietal damage are not aware that there is even a region of space which they cannot see.

Two confounds in studies of human beings with lesions are that no two patterns of brain damage in different patients are alike, and brain damage is rarely localized to all and only a particular area. Thus, many intriguing observations often cannot be replicated, and no ascription of a function to an area can be made unambiguously. Deliberately placed lesions in the brains of monkeys offers the opportunities to collect more than one data point, and to induce circumscribed damage. Milner and Goodale (1993) report an early lesion study, conducted by David Ferrier in 1890, that precedes and augments Balint's observation of optic ataxia. Ferrier lesioned both parietal cortices in a monkey, and observed that the animal was unable to reach accurately for raisins. This was a deficit in initiating spatially directed reaches, and not a deficit in perception, since the monkey could clearly see the raisins (he would attempt to reach). It was also not a deficit in movement, since the animal could bring the raisin to its mouth, once he had managed to pick it up.

A more recent lesion study in monkeys has had widespread influence. (Ungerleider and Mishkin 1982) proposed that visual cortex is organized into two distinct processing streams, a ventral pathway necessary for object identification, and a dorsal pathway needed for spatial localization. This dichotomy is widely accepted, with refinement by Goodale and Milner (1992). These authors have proposed that the dorsal stream is for controlling actions, and not merely for perceiving spatial locations. Their evidence stems from observations made on a brain damaged patient who is incapable of describing the orientation of a slit cut into a piece of cardboard, although she is capable of putting her hand into it. The intact portions of her brain allow her to reach accurately, although she has lost the ability to accurately perceive the target.

Parietal cortex, which includes the areas studied in this thesis, comprises most of the dorsal visual stream. As the following two sections will make clear, the anatomy and physiology of the primate brain are consistent with Goodale and Milner's proposal that the dorsal visual stream is important for action.

1.3 Anatomy

This section is an overview of the locations of and connectivity between areas of the primate brain that are involved in arm and eye movements. It is not exhaustive of what is known, but instead emphasizes the areas that will be most important for interpreting the experiments discussed in this thesis. The focus is on the cortical areas and their connections thought to be the principal neural substrates for performing actions under the guidance of sensory stimuli.

1.3.1 Concepts and methods in anatomy

Like the early studies of brain lesioned human beings explored in the previous section, early studies of brain anatomy underscored the concept of functional specialization in the brain. *Cytoarchetectonics*, the study of cell morphology, provided the initial ground to establish functional differences between cortical areas. Cortex is typically divided into six layers, sometimes with sublayers present or layers absent. Inputs to an area generally enter in cortical layer 4. Layers 2 and 3 contain cells that project to higher cortical areas. Layers 5 and 6 contain cells which project to subcortical structures, or which feed back onto lower cortical areas. Layer 1 consists of fibers for local processing. Sensory areas contain small, densely packed neurons in layer 4, thus are referred to in general as *granular cortex.* For example, *primary visual cortex,* also known as area *V1*, contains an exaggerated layer 4, comprised of four distinct sublayers. The dense packing of cells in this layer forms a stripe visible in stained tissue to the unaided eye, and is termed the "striatum of Gennari." Thus the term *striate cortex* is often used for V1. In contrast, area *M1*, (*primary motor cortex*), contains an enlarged layer 5, with giant pyramidal cells whose cell bodies can be up to 50 μm in diameter (in contrast to the more typical 5-25μm). These cells form a powerful connection with motor neurons in the spinal cord. Layer 4 is almost absent in M1, thus it is referred to as "agranular cortex."

A heirarchy of cortical areas can be ascribed, based on the pattern of connections between areas (Felleman and Essen 1991). Cells with bodies in layers 2 and 3 project to cells with bodies in layer 4 in higher cortical areas, while layer 5 and 6 cells send feedback projections to cells outside layer 4 in lower cortical areas. Not only is cortex intricately looped in this manner, it is also vastly interconnected. Cortical cells generally receive an estimated 5000 synaptic inputs (Douglas and Martin 1998). A weak but reliable trend exists for nearby cortical areas to be connected (Young 1992).

Pathways between cortical areas are traced by injecting a chemical which is taken up by neurons, and transported into their processes. A common tracer, wheat germ agglutinin conjugated to horseradish peroxidase *(WGA-HRP)*, is picked up by cell bodies or terminals, and spreads to fill the cells. Once an injection has been made in one area, and the chemical is given several days to act, the animal is killed, and the brain is sliced into thin (typically 50μm) sections. Slices are searched for areas where label is found. The pattern of labelled neurons in other areas indicates the type of connectivity. If labelled cell bodies are found in a region, that demonstrates a projection from that region to the site of injection. If labelled axon terminals are found, that site receives projections from neurons with cell bodies in the injected area. An older method (Jones and Powell 1970) involved ablating a cortical area. When a cell is damaged, its processes wither. These damaged processes can be identified in other areas, to illustrate the connectivity of the lesioned areas.

Many names often exist for the same cortical area, since they have been designated by different researchers, using different methods, and holding different perspectives. Although it can be confusing, the presence of multiple names for the same area does indicate that the borders are reliable enough to be detectable by independent groups, often using different methods. In the areal descriptions which follow, I will generally use the more commonly used name for each area, and I will occasionally mention alternate names. In 1905, Brodmann assigned numerical designations to cortical areas in the order in which he studied them (for example area 7). Many of the names I will use come from Brodmann's system. Other names reflect the location of the area (for example, the region in the lateral bank of the intraparietal sulcus devoted to eye movements is named *LIP*). If a new area was identified functionally in its first report, its functional name is often retained (for example, the frontal eye fields, *FEF*). A similar functional nomenclature is used for frank sensory and motor areas, with the visual areas being named as V1 through V6, primary motor cortex named M1, and somatosensory cortices names S1 and S2.

In the cortical areas more remote from the sensory and motor peripheries, cytoarchitectonics often fails to locate areal borders. In these cases, areas can be differentiated based on complete representations of the visual hemifield, or by representation of the vertical meridian (Zeki 1993), as revealed by detecting the locations of cells or terminals that connect across the corpus callosum. In higher areas, where retinotopy often breaks down, different areas are often ascribed in part based on differences in function revealed physiologically (Colby and Duhamel 1991). Thus, this section together with the following one yield a fuller picture of the organization of parietal and frontal cortices.

1.3.2 Anatomy of various parietal and frontal areas

A recurring observation (Cavada and Goldman-Rakic 1989; Johnson, Ferraina, Bianchi, and Caminiti 1996) in both anatomical and functional studies of the parietal and frontal cortices is the presence of segregated networks for eye movements, arm movements, and hand movements. Parietal areas involved in eye movements are connected with areas in frontal cortex that are also functionally acti-

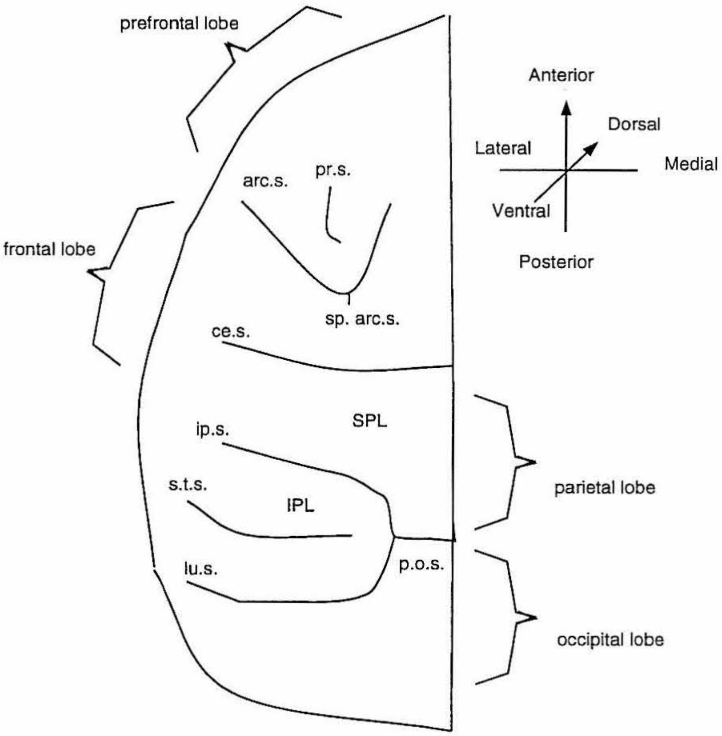

Figure 1.1: Schematic of the dorsal view of the brain of a macaque monkey. Sulci are labelled with lowercase letters. arc.s.:arcuate sulcus; ce.s.:central sulcus; ip.s.:intraparietal sulcus; lu.s.:lunate sulcus; po.s.:parieto-occipital sulcus; pr.s.:principal sulcus; sp.arc.s.:spur of the arcuate sulcus; s.t.s.:superior temporal sulcus. The parietal lobe is divided into the inferior parietal lobule (IPL) and the superior parietal lobule (SPL).

vated during saccades (rapid changes in eye position). Parietal and frontal areas involved in reaching are connected, and areas that are involved in grasping share connections. Although there is certainly cross-talk between these networks, they seem largely segregated.

Figures 1.1 and 1.2 illustrates the locations of areas described in this section and the next.

Parietal areas

Caudal area 5

The caudalmost portion of area 5 has been anatomically divided into four separate areas: PO/V6, V6A, MIP, and 7m. Tracer injections reveal these areas are interconnected but distinct. A distinct projection across the corpus callosum, a connection to an area to which the others do not connect, or a pattern of labelling indicative of differing levels in the cortical heirarchy, demonstrate these areas are distinct.

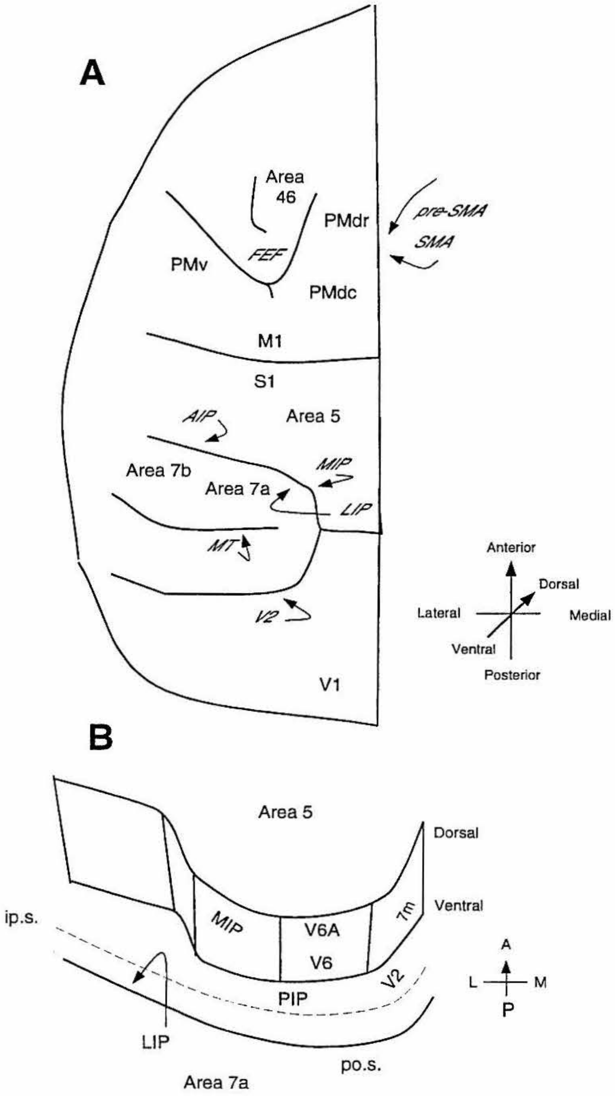

Figure 1.2: Some cortical areas. AIP: anterior intraparietal area; FEF: frontal eye fields; LIP: lateral intraparietal area; MIP: medial intraparietal area; MT: middle temporal area; M1: primary motor cortex; PMv,PMdc,PMdr: ventral, dorsal caudal, and dorsal rostral aspects of premotor cortex; SMA: supplementary motor area; S1: primary somatosensory cortex; V1: primary visual cortex. **A**, Dorsal view of the brain. Italicized names indicate the area is not visible in this surface view, but is buried within a sulcus or on the medial wall of the hemisphere. Arrows denote the position of such areas. **B**, Coronal view of the posterior wall of the opened parieto-occipital sulcus, showing the areas that comprise the caudal portion of area 5.

Area V6 (Shipp, Blanton, and Zeki 1998), or PO (Colby, Gattass, Olson, and Gross 1988), occupies the ventral part of the rostral bank of the parieto-occipital sulcus *(p.o.s.)*. Its dominant input is from V2, a visual area whose dominant input is from V1. V6 collects inputs from visual areas V2, V3, MT, and according to some anatomists, V1 and V4 (Shipp et al. found no labelling in these areas after injecting tracer in V6, while Colby et al. did observe labelling). All projections from visual areas are from portions representing the visual periphery. Correspondingly, in recordings from V6/PO, neurons have response fields that rarely include the fovea (Galletti, Fattori, Kutz, and Gamberini 1998; Colby, Gattass, Olson, and Gross 1988). This is one of the few visual cortical area that do not over-represent the fovea. Colby et al. and Galletti et al. (1998) reported that the representation of the upper visual field in V6 is on the medial wall of the hemisphere, and the representation of lower visual space is lateral to that, in the portion of the p.o.s. that wraps into the intraparietal sulcus *(ip.s.)*. This indicates that the horizontal meridian runs dorsoventrally. However, Shipp et al. found that the representation of the *vertical* meridian, as revealed by the pattern of transcallosal fibers, runs dorsoventrally.

V6's projections implicate the area in reaching: its major projection to frontal cortex is to the dorsal aspect of the premotor cortex *(PMd)*, an area known to be involved in the movement of the shoulder and upper arm during reaching. Weaker projections exist to PMv and SMA, areas implicated in grasping and in reach sequencing, respectively. V6 also has projections indicative of a role in saccadic eye movements, including area LIP, the frontal eye fields (*FEF*) (Shipp, Blanton, and Zeki 1998; Schall, Morel, King, and Bullier 1995), and the deep layers of the superior colliculus (Zeki 1986) (all three areas are active during saccades). Other areas which receive V6 projections include area 7a.

Three separate areas have been named near V6: V6A, MIP, and 7m. They each have been reported to receive input from V6, and to be interconnected with each other, with other parietal areas, notably LIP, and with PMd in the frontal lobe. Thus, they are well suited to utilize visual information for reaching or eye/hand coordination. Figure 1.2B shows the relative positions of these areas.

Dorsal to V6 is area V6A. It receives its dominant input from area V6, and unlike V6, V6A does not receive a projection from area V2, although it does receive input from other extrastriate visual areas, including V3 and MT (Shipp, Blanton, and Zeki 1998). It projects to PMd (Jones and Powell 1970; Matelli, Luppino, D'Amelio, Fattori, and Galletti 1995) which implicates the area in reaching. One report found a connection between M1 (Johnson, Ferraina, Bianchi, and Caminiti

1996) and V6A, although Shipp et al. do not report a connection to M1. Unlike V6, area V6A does not project to the frontal eye fields (Shipp, Blanton, and Zeki 1998), perhaps suggesting less involvement in eye movements for V6A than for V6.

Area 7m is located on the medial wall of the hemisphere, at the medial border of V6A. It is connected to area 5, which could provide a source of proprioceptive signals (Caminiti, Ferraina, and Johnson 1996).

Area MIP abuts V6 at V6's lateral edge, and lines the medial bank of the intraparietal sulcus. Its pattern of input and output resembles that of V6A: it receives input from V6, and from somatosensory areas, and connects with PMd (Johnson, Ferraina, Bianchi, and Caminiti 1996). In contrast to V6A, MIP does not receive input from extrastriate visual areas (Blatt, Andersen, and Stoner 1990).

In summary, despite differences between them in details, a number of studies converge to suggest that there is an anatomic pathway devoted to reaching. It begins in the extrastriate visual areas, notably area V6/PO. It progresses through areas V6A, MIP, and 7m that comprise the medial, caudal portion of the superior parietal lobe. In these areas, proprioceptive information from area 5 converges with the visual information. The output from this network of parietal areas is primarily to the dorsal aspect of premotor cortex, also to the supplementary motor and other premotor areas, and perhaps directly to M1. PMd, SMA, and PMv then project to M1, the final cortical stage in reach processing.

Area 5

Area 5 lies just anterior to the intraparietal sulcus, on the surface of the cortex (figure 1.2). Its anterior border is at the somatosensory cortices, which are in turn bordered anteriorly by the central sulcus. Area 5 receives inputs from primary somatosensory cortex, S1 (Jones and Powell 1970), but receives much weaker visual inputs than the areas that lie caudal to the intraparietal sulcus. Area 5 projects to M1, and to premotor areas (Jones and Powell 1970; Strick and Kim 1978; Johnson, Ferraina, Bianchi, and Caminiti 1996), and receives reciprocal connections from these areas. Thus, area 5 is also a reach area, perhaps more involved in the proprioceptive components of reaching than in the visual.

LIP

LIP projects to FEF (Blatt, Andersen, and Stoner 1990; Schall, Morel, King, and Bullier 1995; Stanton, Bruce, and Goldberg 1995), and to the deep layers of the superior colliculus (Lynch, Graybiel, and Lobeck 1985), both structures important for eye movements (Schiller, True, and Conway 1980). Its inputs arise primarily from extrastriate visual areas. Thus, the area is the parietal nexus in the eye movement pathway.

This network is segregated from the reach circuit described above; there is no projection from LIP anywhere behind the arcuate sulcus, where are located M1 and the other frontal areas involved in reach and grasp.

AIP

AIP, located anteriorly in the lateral bank of the intraparietal sulcus, projects to the finger representation in M1 (Tokuno and Tanji 1993), and to the ventral aspect of the premotor cortex (Matelli, Camarda, Glickstein, and Rizzolatti 1986). Area PMv, in turn, projects to the hand region of M1. Thus, AIP is the principle parietal node in an anatomic network for grasping.

Frontal areas

M1

MI is primary motor cortex, the final common pathway for much cortical control of movement. M1 is marked by the presence of giant pyramidals, neurons in layer 5 with cell bodies larger than $30\mu m$ across. M1 collects inputs from premotor areas, S1, and area 5. It projects to motoneurons in the spinal cord (He, Dum, and Strick 1993).

M1 is divided into separate regions controlling the movement of different body parts (the *motor homunculus* of Penfield and Rasmussen (1950)). Leg movements can be elicited by microstimulation in the dorsal, medial aspect of M1, then progressing laterally and ventrally, shoulder movements are elicited, then elbow, wrist, and hand movements, followed by regions controlling movements of each digit, then the face and mouth. Anatomy supports the observation of the motor homunculus, with the M1 regions of densest projection to the spinal cord segments controlling the hand largely separated from the regions of M1 that project to the spinal segments controlling the shoulder musculature (He, Dum, and Strick 1993).

Areas PMd and PMv preserve this segregation of function in their connection to MI: PMv connects to the finger region of M1, and PMd projects to the shoulder representation (Tokuno and Tanji 1993).

Premotor cortex

Premotor cortex is the area lying between M1 and the arcuate sulcus. It is divided into a dorsal aspect (*PMd*), medial and dorsal to the spur of the arcuate sulcus, and a ventral aspect (*PMv*), ventral and lateral to the spur (figures 1.1 and 1.2). A closer look reveals that each area is subdivided, based on differences in connectivity and function. The transition from premotor cortex to MI is gradual (Johnson, Ferraina, Bianchi, and Caminiti 1996; Godschalk, Lemon, Kuypers, and Ronday 1984), marked best by a gradual increase in the size of pyramidal cells, with some large ($> 30\mu m$) cell bodies found in MI but none in premotor cortex.

PMd

PMd projects principally to M1, and also to the spinal cord (He, Dum, and Strick 1993). The spinal projection indicates a large contribution to shoulder movements, and a lesser but still present contribution to hand movements. The projection to the spinal cord segments controlling shoulder movements is located in the rostral portion (He, Dum, and Strick 1993). This is the aspect of PMd to which V6/V6A projects (Shipp, Blanton, and Zeki 1998).

PMv

The ventral aspect of premotor cortex projects to regions of the spinal cord containing motoneurons that control the hand and finger (He, Dum, and Strick 1993), and to the region of primary motor cortex controlling hand movements (Tokuno and Tanji 1993). This outflow, consistent with the inflow from area AIP, poses PMv to contribute to grasping.

An important theme in these studies of anatomy of the dorsal regions of the monkey brain is that there are distinct parieto-frontal networks of areas involved in particular functions. LIP and FEF are major components in a cortical network for saccadic eye movements, V6A and PMd are the core of a network for reaching, and AIP and PMv appear linked for grasping. Connections within a network are generally reciprocal, with areas receiving projections from their targets, and densely connected, with areas themselves interconnected receiving common inputs or sending projections to the same targets. We have discussed circuits for arm, hand, and eye movements; this segregation of processing is liable to extend to networks for mouth, head, and leg movements. Since these motor systems clearly interact in the performance of coordinated movements, of eye and hand for example, cross-talk between the networks is certain to be important. The functionality of these areas, discussed in the next section, supports their different motor involvements.

1.4 Physiology

Monitoring the electrical activity of individual neurons is the most effective method of probing brain function. In particular, studying awake, behaving monkeys provides the possibility to establish tight congruences between neural activity and behavior. Further, since these animals are similar to human beings in many aspects of both brain structure and behavior, it is held that much that is learned about the monkey brain applies directly to the human brain. With the recent advent of functional imaging of the human brain, much direct evidence has been gathered to show that the human and monkey brain are indeed quite similar functionally.

This section will highlight the questions and principal findings in neurophysiology that are most relevant to the studies to be discussed later in the thesis. First, (section 1.4.1) the issues and debates in sensory-motor processing are discussed, with a brief history of the study of parietal cortex provided as an illustration of the evolution of concepts in sensory-motor processing. Second, issues of how the brain represents space (section 1.4.2), and transforms those representations for different purposes (section 1.4.3), will be discussed. Next, the question of how the brain uses internal models of the body and the world to predict changes in the positions of the body and of objects in the environment will be motivated (section 1.4.4). The final subsection (section 1.4.5) will summarize some of the fundamental neurophysiological studies of the brain areas most relevant to what will follow.

A principle of brain organization that has found wide consensus among neurophysiologists is that the visual system is divided into two separate processing streams. The ventral areas, in the temporal lobes, contain neurons involved in object identification (the "what" pathway). The ventral visual pathway leads into the entorhinal cortex and hippocampus, areas important for memory formation. The other visual processing stream is contained in the dorsal areas. The dorsal stream is thought to be concerned with object location (the "where" pathway) (*Ungerleider and Mishkin*

1982). Consistent with this, neurons in the dorsal visual areas have circumscribed receptive fields, so that a population of them can represent the positions of visual stimuli. Based on evidence new and old, the role of the dorsal stream has been recently re-cast as the "how" pathway (Goodale and Milner 1992; Mountcastle, Lynch, Georgeopoulos, Sakata, and Acuna 1975), involved in organizing and planning movements. The dorsal stream projects strongly to motor and premotor areas in the frontal lobes, consistent with a role in movement planning. The primary component of the dorsal visual stream is posterior parietal cortex (PPC). Two regions within PPC: the parietal reach region (PRR) and the lateral intraparietal area (LIP) that will be the focus of this thesis.

As explored in the previous two sections, observations of human beings with damage to parietal cortex and anatomical findings of sensory connections into and motor connections out of parietal cortex imply that the area functions in sensory-motor processing.

1.4.1 Sensory-motor processing

The nervous system is organized into hierarchical sensory-motor loops. The simplest are reflexes, fast stereotyped movements that reorient the body in response to environmental perturbations. For example, the vestibulo-ocular reflex consists of a three-neuron arc from the semicircular canals, which detect rotations of the head, to the oculomotor neurons that counter-rotates the eyes in response to head movements. Another example is the spinal cord circuitry which provides reflexes for the maintenance of posture. The next level of complexity in sensory-motor processing concerns circuits through subcortical areas. For example, the retina projects to the superficial layers of the superior colliculus. These in turn may project to the deep layers of the colliculus. The deep colliculus is known to project to eye movement centers in the brainstem. Provided the superficial-to-deep collicular projection is shown to exist, there is a short network that can generate fast eye movements. At the highest level are sensory-motor circuits that involve multiple cortical regions. Decision-making and learning from experience require these circuits. John Allman (1999) has proposed that this organization into parallel networks providing increasingly elaborate processing is a hallmark of an evolved system.

There is a parallel hierarchy in our degree of introspective volitional control over our movements. Reflexes like VOR and those involved in maintaining posture occur without our even being aware of them. At the next level up are movements that we are aware of, but that we do not feel involved in producing. For example, a person will pull his hand away from a hot stove, then only a short time after, feel the pain, which presumably was the stimulus causing him to pull back.

Similarly, complex practiced actions have an intermediate cognitive representation. Often, people will report having driven all the way home from work, but cannot recall the details of the drive. The highest introspective stage in sensory-motor processing is voluntary action, deciding between several possible routes of action, and taking one.

How can we classify a neural signal as "sensory" or "motor"? When such a classification scheme breaks down, what concepts are available to describe the signals? Sensory and motor categorizations are clearest to make at the periphery: the retina is a clear sensory structure, while motoneurons are clear motor structures. But, just one processing stage more central, feedback pathways appear. As soon as a visual area receives descending input from other brain areas, or a motor area receives sensory inputs, the dichotomy breaks down. There is a dearth of concepts to categorize these intermediate levels. Two helpful concepts that have been discussed and supported physiologically are *attention* and *intention* (or *planning*). Attention generally describes enhanced neural processing of one stimulus, usually to the exclusion of others. It is an effect that cannot be accounted for by changes in the sensory stimulation, and so must be generated within the brain, as an instantiation or trace of the animal's behavioral state. Intention describes a signal related to a movement that occurs well before the movement, and is probably not sufficient to generate the movement. Although the line between these concepts can be difficult to draw experimentally, they do help to refine our thinking about sensory-motor processing.

Physiologists have invented a variety of strategies to attempt to isolate sensory and motor signals in neurons. One influential method involved separating in time the sensory and motor components to the task (Hikosaka and Wurtz 1983). For example, in a *delayed saccade* task (Hikosaka and Wurtz 1983; Gnadt and Andersen 1988; Funahashi, Bruce, and Goldman-Rakic 1989), a target is presented briefly at a random location on the screen. It is extinguished, and the monkey must continue to hold fixation, while holding the target location in memory, through a delay period, typically about 1 s long. When the fixation point is extinguished, the animal makes a saccadic eye movement to the remembered location of the stimulus, to receive a reward. In this manner, activity related to the sensory stimulation and to the saccadic eye movement can be separated in time.

Another attempt to ascribe a sensory or motor role to an area has been to separate in space the sensory and motor components of the task. In an *antisaccade* task (Funahashi, Chafee, and Goldman-Rakic 1993), monkeys must saccade in a direction 180° away from the one in which the target was presented. Equivalent tasks has been used to dissociate sensory and motor processing in arm movement control, where a cue instructs a movement 90° away from the cue's location. Even in M1, the final cortical stage before the spinal cord, a small contingent of neurons represents the location of the sensory stimulus (Shen and Alexander 1997a).

A go/no-go task (Kalaska and Crammond 1995) was used to suggest that the dorsal premotor cortex is more involved in movement planning than is parietal area 5. In this study, monkeys were presented with a visual stimulus that could be either of two colors. One color instructed the monkey to reach to that target, while the other color instructed the animal to maintain posture, and not perform the reach. Neurons in premotor cortex were only active if the animal was planning to reach, while neurons in parietal cortex were active for either visual stimulus, regardless of whether the animal would eventually reach to it. Thus, area 5 seems to be more sensory in nature, and PMd more related to movement plans.

We used a new approach to distinguish sensory from motor processes. By using similar visual stimuli to instruct different movements, we could explore whether neurons' responses were associated with the stimulus, or with the movement being planned. Strong differences in response would implicate a neuron in motor processing, while similar responses would be consistent with the neuron's reflecting the visual stimulation, or attention to it. These experiments are discussed in chapters 2 and 3.

Area LIP: testing ground for sensory-motor concepts

Even though the conceptions of "sensory" and "motor" have proven to be too broad to map easily onto most brain regions, studies that have attempted to classify areas in this manner have been highly informative. These studies have prompted new experiments that have advanced our understandings of the areas studied, and have refined our conceptions of the neural implementation of sensory-motor processing. The history of the study of parietal cortex offers a demonstration of the useful progress that these concepts have afforded.

Vernon Mountcastle conducted groundbreaking studies of the physiology of parietal cortex in behaving monkeys. He summarized his observations in a 1975 publication:

> *Our results lead to a hypothesis of the function of the posterior parietal cortex: these regions receive afferent signals descriptive of the position and movement of the body in space, and contain a command apparatus for operation of the limbs, hands, and eyes within immediate extrapersonal space. This general command function is exercised in a holistic fashion. It relates to acts aimed at certain behavioral goals and not to the*

> *details of muscular contraction during execution* (Mountcastle, Lynch, Georgeopoulos, Sakata, and Acuna 1975).

Mountcastle observed that many area 5 neurons were far more responsive during active reaches than when the arm was moved passively through the same postures by the experimenters. Only certain categories of arm movements drove area 5 neurons: many cells were active only when the animal reached for a piece of food, or for a lever that would deliver a juice reward. When the animal moved in a less deliberate manner, such as an aggressive or aversive movement, even when similar arm movements were made, area 5 neurons were less active. Similar observations were made in area 7, where cells were more visual in nature. A neuron might be silent as an animal looked around the room, then suddenly become active once it fixated a morsel of food.

Robinson, Goldberg, and Stanton countered Mountcastle's command hypothesis of parietal function in a 1978 paper:

> *Parietal neurons respond to sensory stimulation in the absence of movement, but do not fire in association with movement in the absence of a stimulus. ... [D]ischarge is indicative of the presence of a stimulus and not predictive of movement. Our data do not support the claim that these neurons perform a "command function." We suggest that posterior parietal cortex is related to visual attention; in this context it is related to movement but dissociable from it.*

Robinson and Mountcastle did not disagree on the data: both groups observed that neurons were preferentially active during visually-guided, goal-directed movements. However, whereas Mountcastle considered those responses related to the movement, Robinson viewed them as responses to the sensory stimulation, that were perhaps enhanced due to the behavioral import of the stimulus. Clearly, experiments that could discriminate signals related to movement intention from those related to sensory attention were needed.

A few years later, Richard Andersen and colleagues (Andersen, Asanuma, and Cowan 1985; Blatt, Andersen, and Stoner 1990) discovered that the saccade neurons are contained within a subregion of posterior parietal cortex. This area, named LIP for its position lining a portion of the lateral (or, posterior) bank of the intraparietal sulcus, was identified on the basis of dense myelination (Blatt, Andersen, and Stoner 1990), and a projection (Andersen, Asanuma, and Cowan 1985) to the frontal eye fields (FEF), an area in the frontal lobes where saccadic eye movements can be elicited with low thresholds of microstimulation. Myelination along axons speeds the propagation of action potentials; dense myelination implicates an area in processes where timing information is critical: fast movements, such as saccades, or the visual perception of motion. Richard explains that he and his coworkers had expected to find columns of labelled neurons following injections of retrograde tracer in FEF, according to Mountcastle's original vision of how cortex was arranged. It was a surprise to discover label in a localized region. With the combined discovery of a function and a defining anatomic connection to a different brain area with known properties, an area becomes ideally suited for further studies. LIP has been fertile ground for asking questions about the nature of sensory-motor processing, as well as investigations of the neural representation of space, and of cognitive processing.

The sensory/motor question was pitched in a new way by Gnadt and Andersen (1989). Using the delayed saccade task described above, in which a target is flashed briefly, then after a delay period the monkey must saccade to its remembered location, they observed that individual LIP neurons contain both stimulus-locked and movement-locked components to their response. Surprisingly, neurons were also active during the delay period, as the animal sat motionless in the dark. This activity clearly cannot be either a sensory or a motor response. To gain insight into what this activity may mean, one can consider the different strategies the monkey may adopt to perform the task. The animal may be remembering the location of the target. It also might be planning a movement. Accordingly, the neural activity may be related to the sensory memory or attention to that location in space, or to the monkey's intention to look there. How can we ask which of these properties of the task the neurons are more associated with? In chapter 2, I will present our strategy to dissociate the memory/attention components of the task from the movement planning components.

1.4.2 Spatial representations in the brain

Neurons in the dorsal visual stream typically respond to light in circumscribed regions of visual space. These *receptive fields* can be large or small, from a tenth of a degree in areas like V1, to quarter fields or hemifields in extrastriate areas. They are generally contralateral, although in extrastriate areas, ipsilateral receptive fields can be found. Since each neuron represents only a small portion of the visual field, many cells are required to collectively represent the entire visual field. Neurons in motor areas also represent only small portions of space, although for many motor areas, especially those involved in arm movements, the space that is represented is not necessarily visual space, but may be the space of the joints or musculature. The region of space for which a motor neuron is active is known as the cell's *movement field* or *response field.*

One of the most fundamental question that can be asked about a brain area that represents space is, what coordinate frame does it use? That is, what sort of space is represented? Do neurons signal the spatial relationship between objects in a scene? Or do they represent the positions of objects with respect to the body? If so, to what part of the body are the response fields anchored? Visual inputs enter the brain in a reference frame anchored to the eyes, while somatosensory inputs enter the brain in a reference frame referred to the limbs, head, or torso. Thus, low-level sensory areas (V1 for vision, and S1 for somatosensation) encode space with respect to the sensory surface. At the other extreme, the brain must generate motor commands in a coordinate frame appropriate for the movement being controlled. Saccadic eye movements must be specified in a reference frame centered on the current point of fixation. Thus, the superior colliculus, involved in eye movements, represents visual targets in eye-centered coordinates. Reaches must be specified with respect to the current position of the hand, or with respect to the pattern of muscular contractions or joint rotations needed to bring the hand to the target.

The visual world remains stable as we move through it. It has long been supposed that the brain must contain neurons that represent visual space with respect to the head. Every time the eyes move, the visual input to the retina changes dramatically. Yet, our ability to move accurately is not compromised, and our perception of the world remains stable, despite eye movements. It has been argued that areas that use eye-centered encoding, as observed in the lateral geniculate nucleus, V1, and other visual areas, cannot give rise to our visual perception, since signals in these areas change dramatically whenever the eyes move. Many researchers have attempted to locate a brain area containing neurons that encode spatial locations with respect to the head.

Such a brain area has been elusive; receptive fields from the lowest to highest visual areas are generally anchored to the retina. Head-centered receptive fields have been reported in area VIP (Duhamel, Bremmer, BenHamed, and Graf 1997), where half of the cells use head-centered coding, the others have receptive fields that remain fixed to the retina as the eyes move. Head-centered neurons have been found in lesser extent (12% of neurons tested) in PO/V6A (Galletti, Fattori, Kutz, and Battaglini 1997). However, in both of these experiments, the report of head-centered coding is premature. These experiments involve changing eye position, and observing that response fields do not move. The conclusive test for head-centered coordinates is to move the head, and observe response fields that stay fixed to the head. Only rarely (Graziano, Hu, and Gross 1997) have experimenters change head position and observe neuronal responses that move with the head. Also, experimenters rarely test the effect of moving the limbs. It could be that many neurons claimed to use head centered coding actually use limb-centered coding (Graziano, Yap, and Gross 1994). Of particular concern is the report of head-centered coding in PO/V6A by Galletti et al. (1993). They did not test for limb-centered response fields, although the same group later reported reach responses among the non-visual neurons in the same area (Galletti, Fattori, Kutz, and Battaglini 1997). Even putting aside these caveats about the existing studies that purport to show head-centered coding of space, no area has been identified with a majority of neurons using head-centered receptive fields. This failure is not for lack of trying; it may be that the brain does not form an explicit head-centered representation of space at the level of individual neurons.

An influential proposal for the representation of head-centered space in the brain comes from combined physiology and modeling studies by Richard Andersen and colleagues. Andersen and Mountcastle (1983) neurons in parietal cortex that are retinotopic, but are modulated by the position of the eyes in the head (a *gain field*). Andersen proposed that signals culled from a population of neurons that represent locations in this manner could be combined to express target locations with respect to the head (Andersen, Essick, and Siegel 1985). This hypothesis was given strong support by a neural network model (Zipser and Andersen 1988). In this study, a neural network with a hidden layer was trained to convert the position of the eyes in the head and the retinal position of a target into a representation of target position with respect to the head. After the network had been trained to successfully perform this transformation, the receptive fields of the hidden layer were examined. They were found to be retinotopic with gain fields of eye-in-head position, just as had been observed in parietal neurons. Andersen and Zipser suggested that there may be no explicit head-centered code in the brain, but that target position with respect to the head may be coded throughout by eye-centered neurons with modulatory effects of eye position.

Since then, many other physiology studies have reported gain fields (Trotter and Celebrini 1999). It is now widely accepted that the brain can construct distributed representations in a variety of reference frames by using neurons that code in one reference frame, and have gain field influences of signals related to other reference frames (Andersen, Snyder, Li, and Stricanne 1993; Pouget and Sejnowski 1997).

1.4.3 Coordinate frames and coordinate transformations

How is information transformed from the spatial representation of the sensory input to a spatial representation of the motor output? This flow of information is a primary component of the process of generating a movement (Soechting and Flanders 1992).

These transformations are quite complex for reaching behaviors. This complexity is reflected in the terminology used to characterize the neural representations of movements. Reaches may be coded in *extrinsic* coordinate systems, that specify the direction and distance from a certain body part to the target. Extrinsic reference frames centered on the eyes, the shoulder, the head, and the hand find experimental support. The cortex might also represent the reach in *intrinsic* coordinate frames, that is, the pattern of joint torques or muscle activities needed to bring the hand to the target. Another pair of terms used to describe reaching is the *kinematics* of the movement: the path of the arm through space. This space can be extrinsic, such as the path of the hand through space or across the retina. Or this space can be intrinsic, such as a trajectory through the space of joint angles. In contrast to kinematics, *kinetics* refer to the mechanical features of the reach, such as the changes in muscle activity or torques around the joints. A final distinction that is noted is that between *endpoint* planning and *path* planning. Does cortex specify the target for the reach, and allow properties of the musculature to perform the specifics of the movement? Perhaps the endpoint and a few intermediate via points through which the hand must past, e.g., to avoid obstacles, are planned centrally (Sabes and Jordan 1997)? At the other extreme, the complete progress of the hand through space could be explicitly specified by the cortex (Kettner, Schwartz, and Georgopoulos 1988).

Eye movement processing is comparatively simpler than reach planning. In the oculomotor system, the most relevant issue for our purposes is the question of how information in a retinocentric coordinate frame is converted into oculocentric reference frame. These two are not always the same: in a double saccade paradigm (Hallett and Lightstone 1976; Mays and Sparks 1983), two targets are flashed within the saccadic reaction time, and human or monkey subjects must saccade to the first, then the second, target. Since the saccade to the first target intervenes between the presentation of the second target and the saccade to it, the position of the second target on the retina when presented (its *retinocentric* position) is different from the direction and distance the eyes must move to acquire it (its *oculocentric* position). Physiological investigations have shown that the superior colliculus (Mays and Sparks 1983) and LIP (Mazzoni, Bracewell, Barash, and Andersen 1996) represent the second target in its eye movement coordinate frame, and not its retinal position coordinate frame. Thus these areas code in oculocentric, not retinocentric, coordinates.

Coordinate frame questions are usually extremely well-posed; it is clear what the candidate answers may be, and they can often be easily separated experimentally. However, the results of coordinate frame studies can often be complex. Most studies report a mixture of parameters affecting neurons. The strength of these studies usually derives from comparing the relative proportions of cells between different areas that have been studied under similar conditions, thus providing an insight into the relative contributions of these areas to movement processing. These studies underscore the conception that the brain consists of distributed, interconnected areas that together perform related processing. Several distinct functional stages in sensory-motor processing often occupy a single brain area, and any given functional stage is distributed across multiple cortical areas.

Many visually-guided or visually-instructed reaching experiments in the past have been done without measuring or controlling eye position. Perhaps this was done because researchers assumed areas related to reaching would code space in at least a head-centered reference frame, and perhaps in limb-centered coordinates. The experiments that will be presented in this thesis and some other recent results in the literature demonstrate how influential can be the effect of the retinal position of the reach target or reach instruction on neurons related to reaching. As a result, the usefulness of many of the earlier experiments is severely limited. Indeed, I hope that one of the impacts of the experiments presented in this thesis is that neurophysiologists studying reaching will routinely monitor eye position in the future. Even with this problem in mind, there are still many useful concepts and facts that can be saved from previous studies on reaching.

When reading the literature on spatial representations and coordinate frames, one must take caution with interpreting the phrase, "modulated by eye position." It is used to describe quite different features of neurons. In the strong sense of the phrase, it is synonymous with a gain field: a neuron is said to be modulated by eye position if it has an eye-centered receptive field which is scaled according to the position of the eyes in the head (Andersen, Essick, and Siegel 1985; Duhamel, Bremmer, BenHamed, and Graf 1997). As discussed above, an area using this form of representation can yield information about target position with respect to the head (Zipser and Andersen 1988). However, the phrase is often used in a weaker sense, to describe neurons that change their response when the eyes are moved, and targets are presented at the same location on the screen (Mushiake, Tanatsugu, and Tanji 1997). This kind of modulation is only suggestive evidence that a neuron might have an eye-centered receptive field. Not only does this finding not demonstrate eye-centered coding, it also says nothing about whether a neuron conveys a signal of the gaze direction. One must be cautious when interpreting this term, since in some cases, it characterizes an important result (an eye-centered response field with a gain modulation of eye position), while in other cases, it is a very precursory observation (suggestive but insufficient evidence to ascertain an eye-centered response field, and no evidence about gain modulations).

An important new theory has emerged for how the brain organizes space. It has been proposed

(Rizzolatti, Riggio, and Sheliga 1994; Colby 1998) that space is represented in *action reference frames*. Neurons involved in a type of movement will represent visual stimuli in a coordinate frame appropriate for moving to them. This theory finds support in area LIP: neurons involved in eye movements code in eye movement coordinates there. Similarly, in premotor cortex, neurons have been found to code in limb-centered coordinates (Graziano, Yap, and Gross 1994). Those neurons are presumably involved in reaching, although Graziano et al. did not test their neurons for reach activity. Area VIP, which has suggested to play a role in moving the head (Colby 1998), contains neurons using head-centered coordinates (Duhamel, Bremmer, BenHamed, and Graf 1997). The theory extends to a motor theory of perception, that our perception of objects is in terms of the actions we may take on them. The same circuitry that subserves movement control, according to the theory, can also serve perception of space, and even of objects (Rizzolatti, Fadiga, and Fogassi 1997).

In the future, new technologies may provide major advances in understanding coordinate transformations. Recording simultaneously from many neurons at once could reveal functions of neural ensembles that are not readily visible in single neurons. Also, a method to observe the connectivity of the specific neuron under physiological study would be valuable (Pare and Wurtz 1997; Sommer and Wurtz 1998). It might be that in areas where multiple coordinate frames are represented, the neurons that project out of the area have different properties from those that receive stronger inputs from other areas. Even knowing the layer from which neurons are recorded could allow inferences about connectivity.

Our reach coordinate frame paradigm (presented in chapter 4) is the most thorough to date for studying relative effects of target location in eye and limb coordinates. While some studies monitor and vary eye position during reaching, (Mushiake, Tanatsugu, and Tanji 1997; Boussaoud, Jouffrais, and Bremmer 1998), and others vary hand position (Caminiti, Johnson, Galli, Ferraina, and Burnod 1991; Lacquaniti, Guigon, Bianchi, Ferraina, and Caminiti 1995), none have done both. Our results (chapter 4) demonstrate that more powerful conclusions can be drawn from coordinate frame studies by directly comparing eye, limb, and head coordinate frames. If other brain areas related to reaching are studied using similar methods in the future, a fuller picture of the neural mechanisms that generate reaches will result.

1.4.4 Compensation for movements of the body and the motion of external objects

It is critical that the brain store a representation of the body's position, and of the world relative to it. In 1975, Mountcastle (Mountcastle, Lynch, Georgeopoulos, Sakata, and Acuna 1975) speculated that parietal cortex is involved in maintaining these representations. This is what he took the term "association" cortex to designate.

Internal representations of the body and world are built up from sensory information. They might also utilize both signals for planned movements, and predictions of the movements of objects in the environment. These kinds of processing would give an enormous advantage over representations based purely on sensory inputs, since they could be much faster.

As described above in section 1.4.2, head-centered neurons are relatively rare, as are neurons coding in body- or world-centered reference frames. Eye-centered neurons, which seem to be the norm in many visual areas with different functions, face the problem of compensating for eye movements. These retinocentric representations must be combined with signals about current or anticipated eye position in order to generate an accurate representation of locations in head-centered coordinates.

Updating across eye movements has been reported by various authors, beginning with Mays and Sparks (1983) in studies of the superior colliculus. Updating has also been reported in area LIP (Gnadt and Andersen 1988; Duhamel, Colby, and Goldberg 1992; Mazzoni, Bracewell, Barash, and Andersen 1996) and in the frontal eye fields (Goldberg and Bruce 1990). Two neurons that use a head-centered coordinate frame and which update across head movements were found in the ventral aspect of the premotor cortex by Graziano, Hu, and Gross (1997).

There is evidence that parietal cortex predicts the movement of objects in the environment. In a pair of studies, John Assad and co-workers found neurons in PPC that represented the movement of an object that was known to be moving, but that was hidden behind an occluder (Assad and Maunsell 1995; Eskandar and Assad 1999). Thus, the dorsal stream seems involved in predicting changes, of both body position and objects in the environment.

1.4.5 Physiology of various areas related to reaching

The following sections review some of the studies of neurons related to reaching, in different cortical areas. This information relates directly to the anatomy described in section 1.3 and depicted in figures 1.1 and 1.2.

M1

The most important cortical motor area is M1. It projects to the spinal cord, and microstimulation in M1 generates body movements. There is a topographic map of the body in M1.

One of the most influential studies of arm movements has been the elucidation of the population vector coding hypothesis in M1. In 1982, Georgopoulos et al. observed that neurons in M1 were most active for reaches in a certain direction (the *preferred direction*), were less active for movements in slightly different directions, and were not active at all for movements in very different directions. The dependence of firing rate on the direction of the reach was well fit by a cosine function with its peak at the preferred reach direction for the neuron. Since individual neurons are active for many different reaches, it must be the case that many neurons are active for each reach. Somehow, a coarsely tuned population of neurons can precisely specify an accurate movement.

In 1986, Georgopoulos, Schwartz, and Kettner proposed a model whereby this might happen. They suggested that a weighted sum of all preferred directions is formed, with each neuron "voting for" its preferred direction with a weight given by its firing rate during that particular movement. Using a population of 224 M1 neurons, these authors were able to reconstruct the reach direction with 95% accuracy.

The most influential studies generally receive the closest scrutiny. Other, more effective population reconstruction methods have since been proposed based on probabilistic methods (Zhang, Ginzburg, McNaughton, and Sejnowski 1998; Sanger 1996). Also, the work has fallen under criticism because it fails to address the issue of coordinate frames. Loeb, Brown, and Scott (1996) point out that Georgopoulos has never made clear in what coordinate frame M1 codes reaches. The population vector method describes how neurons might signal a direction of hand movement, but does not address whether this is a direction referred to the joints, or to the muscles, or the hand position in space.

Other researchers have attempted to reveal the coordinate frames used by M1 neurons, by varying different features of the movement while recording from neurons. Kalaska et al. (1989) found that M1 neurons are sensitive to forces, as well as to directions of movements. When animals performed the same reach under different load conditions (forces either pushing against or with the hand) M1 neurons altered their responses. These cells are clearly also related to muscle activity as well as to hand movement in space. Cells were also sensitive to the arm posture used to perform reaches, even when the path of the hand was the same (Scott and Kalaska 1997). Almost all M1 neurons changed their preferred direction when the arm posture was changed. This observation was the source of the criticism levied against the population vector model by Loeb, Brown, and Scott (1996): Scott and Kalaska inferred that their findings meant M1 did not encode the path of the hand through space, but instead coded joint rotations. Georgopoulos (1995) pointed out that the population vector model can still account for the movement direction. Loeb, Brown, and Scott (1996) respond that since the population vector can be applied successfully to any situation, it is useless in deciding between theories of the coding strategy used by M1. That debate aside, it seems clear that M1 codes movements in greater detail than simply the relationship between the current position of the hand and its target.

One more coordinate frame study of M1 is worth noting for its relevance to the experiment presented in chapter 4. Mushiake, Tanatsugu, and Tanji (1997) studied the effect of the retinal position of the reach target on M1 neurons. They found virtually no effect of the retinal position of the target: only four of 110 neurons tested showed any effect. Thus, although the location of the stimulus that triggers the movement can affect M1 neurons (Georgopoulos, Lurito, Petrides, Schwartz, and Massey 1989), this effect is not in visual coordinates.

Caudal area 5

The caudalmost aspect of area 5, where the intraparietal sulcus meets the parieto-occipital sulcus, has been divided into at least four separate regions: PO/V6, V6A, MIP, and 7m. Physiology studies combine with the anatomy described in section 1.3.2 to indicate that they are involved in visually-guided reaching or eye movements. The anatomy indicates these are separate regions, though identified physiological differences between them are limited (Galletti, Fattori, Battaglini, Shipp, and Zeki 1996).

Galletti, Fattori, Kutz, and Battaglini (1997) demonstrated that area V6A is involved in arm movements. These authors had noted in previous work that V6A contained many neurons that could not be driven visually. They sought to test the hypothesis that arm movements could drive these non-visual neurons. Monkeys pushed a lever, displacing it by one centimeter, in response to a visual cue. Over half of the non-visual neurons were active in this task. Some cells became active before the earliest electromyographic *(EMG)* activity, and all cells began to fire before the movement began. These authors report that neurons were more active when monkeys reached for pieces of fruit. Thus, V6A seems related to reaching. Saccadic activity was also reported in this study. This study involved only the neurons without visual responses. However, area V6 is dominated by visual neurons. This incongruence is resolved in our experiments (presented in chapter 4) that study the visually-responsive reach neurons in and around V6A.

One physiology study (Ferraina, Johnson, Garasto, Battaglia-Mayer, Ercolani, Bianchi, Lacquaniti, and Caminiti 1997) has investigated area 7m, the area on the medial wall of the hemisphere and on the anterior border of V6. Monkeys performed a center-out reaching task to visual cues. In some trials, fixation at the center target was required throughout the trial. In other trials, the monkey was free to look at the reach target. Neurons were activated when the monkey reached, and responded differently if the reach was accompanied by a saccade. Thus, this area is affected by reaching, and is also affected by eye movements. A variety of interpretations are possible. For example, the difference in response when the eye movement occurs could be an oculomotor command signal. Or, it could be that the reach reference frame shifts when the eyes move. More rigorous studies will be needed to determine how area 7m combines eye and hand movement or position signals, and for what purpose.

Based on studies also from the Caminiti group (Johnson, Ferraina, Bianchi, and Caminiti 1996), more is understood about area MIP, the area on the medial wall of the intraparietal sulcus, abutting area V6A at its lateral border. In a delayed reach task, these researchers found that neurons located dorsally in MIP responded during the reach, while neurons positioned ventrally responded to the visual instruction cue, and during the delay period. Area MIP was first studied physiologically by Colby and Duhamel (1991), who noted visual and somatosensory responses, as well as responses during reaches. In keeping with the observations of Johnson et al., Colby and Duhamel found neurons with reach responses located more dorsally in the sulcus, and visual responses deeper within the sulcus.

A novel and intriguing type of processing has been reported in area MIP by Iriki, Tanaka, and Iwamura (1996). They found that when an animal used a tool to retrieve food, the receptive field of MIP neurons expanded to include the tool.

Area 5

Area 5 receives somatosensory inputs from nearby S1 (Jones and Powell 1970). Area 5 seems involved in planning reaches, since neurons are active during a delay period between presentation of a reach target and the signal to move (Crammond and Kalaska 1989). Unlike M1, neurons in area 5 seem more involved in specifying the direction and distance to the target from the hand or body, than in specifying the mechanics of the arm movement. For example, when the same reach is performed under different loads, cells are relatively unaffected (Kalaska, Cohen, Prud'homme, and Hyde 1990). On the other hand, this group also observed (Scott, Sergio, and Kalaska 1997) that changing the posture of the arm did affect area 5 neurons, just as it did M1 neurons.

The conception of area 5 as representing the position of a target in space, and not the mechanics of moving the arm, was supported by a recent study from a different group. Lacquaniti, Guigon, Bianchi, Ferraina, and Caminiti (1995) found that neural activity in two-thirds of area 5 cells was better described by a body-centered coordinate frame than by a hand-centered coordinate frame. However, since eye position was not monitored, they could not discriminate between eye and head or trunk coordinate frames. In this study, monkeys performed reaches to targets in a cube surrounding a central target. Three different cubes, whose centers varied in azimuth, were used. The paradigm allowed responses to be compared for the same vector of reach to different targets, and for reaches to the same endpoint from different initial hand positions. The response of most neurons was better related to the target position than to the reach vector. Also, cells seemed preferentially tuned to one spatial parameter: distance, elevation, or azimuth. These authors posited a shoulder-centered representation of the target endpoint, but eye-centered coordinates remain an open possibility.

AIP

Hand movements activate AIP neurons (Taira, Mine, Georgeopoulos, Murata, and Sakata 1990; Murata, Gallese, Kaseda, and Sakata 1996). Cells respond differently to different objects presented at the same location. Although this resembles the sort of selectivity observed in the ventral visual stream, here it does not represent object information *per se*, but is actually grasp intention activity, since different sorts of grasps are required to pick up the different objects. Thus, AIP offers a critical test between the action and location interpretations of dorsal stream: the presence of object information in the dorsal stream is consistent with the interpretation of Goodale and Milner that the area encodes movement plans, but is inconsistent with the view of Ungerleider and Mishkin that the dorsal stream is concerned with object location, to the exclusion of object identity.

Dorsal premotor cortex

The dorsal premotor cortex (*PMd*) is the region on the surface of the brain above the spur of the arcuate sulcus and bordering M1 posteriorly (figure 1.2). As detailed in section 1.3, it receives input from the areas in the rostral bank of the parieto-occipital sulcus, and from area 5. The principle target of PMd projections is M1, although the region also projects to the spinal cord directly.

An early report of the involvement of premotor cortices in visually-guided reaching comes from Moll and Kuypers (1977). They ablated all of the premotor cortex in one hemisphere (dorsal and ventral premotor cortices, the supplementary motor area, and the cortex dorsal and ventral to the principal sulcus). Animals with this ablation were presented with pieces of apple on the far side of a plastic partition with a hole in it. When they reached with the intact arm, they would reach through the hole to the apple. When the intact arm was restrained so that they had to use the arm contralateral to the ablation, they would reach straight toward the apple, hitting the partition. Based on this deficit, Moll and Kuypers offer two possible explanations for the role of the premotor cortex: the area could be critical for planning complex reach trajectories, or it could be responsible for inhibiting subcortical areas that generate direct reaches to visual targets.

Shen and Alexander (1997b) used a redirected reach task to compare PMd and M1. In each trial, a cue instructed a reach 90° away from its location. They observed that during the instructed delay period, about nine times as many PMd neurons represented the target location than the movement direction. This is in contrast to M1 (Shen and Alexander 1997a), where equal numbers of neurons represent the target location and the movement direction. Thus, PMd seems more involved in the sensory and planning aspects of a reach, while M1 is more involved in the details of the movement.

In a thorough study of reaching in PMd, (Caminiti, Johnson, Galli, Ferraina, and Burnod 1991) instructed animals to reach to targets in a variety of directions surrounding a central button. These reaches were performed in three different regions of space. It was found that cells had a preferred direction in each region. These preferred directions generally were not the same. Despite changes in the directionality of cells, a population vector computed from the population of cells still accurately described the reach. So, although the contribution of individual cells may change when the hand is moved, the population of PMd cells can still specify the movement. A severe limitation of this study is that eye position was not controlled, or even monitored. Some of the changes in preferred direction might be accounted for if the eye-centered positions of the targets were known. This study did have an important objective: dissociating the extrinsic, hand-centered position of the target from an intrinsic, muscle- or joint-based representation of the target.

The importance of monitoring eye position when studying PMd reach neurons is underscored by a study by Boussaoud et al. (1998). Many cells were modulated by eye position, and some could be retinotopic. Most cells were influenced by the direction of the reach. Their task was hindered by the fact that the instruction stimulus and the reach target bore no spatial relationship to one another.

There was no need, in principle, for the visual stimuli to be represented in limb coordinates.

Ventral premotor cortex

Rizzolatti studied PMv and found that neurons there are active for specific grasps, and for other sorts of goal-oriented actions, such as bringing food to the mouth (Rizzolatti, Camarda, Fogassi, Gentilucci, Luppino, and Matelli 1988). Considering the input from parietal area AIP, and the output to motor cortex and spinal cord regions involved in hand and finger movements, PMv seems to contribute to grasping, among other functions.

Coordinate frame studies have found limb-centered representations of space in PMv. Graziano, Hu, and Gross (1997) studied PMv neurons that had tactile receptive fields on the arm and visual receptive fields. They found that, when the arm was moved, the visual receptive field of 70% of these cells moves with it, to stay anchored to the tactile receptive field. Just over half of these neurons were modulated by the position of the eyes. Although the animals did not make movements in these studies, the authors inferred that the limb-centered coding in PMv is for reaching.

However, in a study of coordinate frames for reaching in PMv, Mushiake, Tanatsugu, and Tanji (1997) found that 41% of neurons were modulated by eye position during the reaction time period of a targeted reach task. These authors did not analyze their data to see if cells were coding in eye-centered coordinates. Some cells may have been, although alternatively, the cells could code in hand-centered space, with a modulatory influence of eye position. These possibilities were not dissociated in their study.

These two studies indicate that PMv contains a variety of eye-centered and limb-centered coordinate frames.

It seems PMv neurons may be involved both in the observation and in the production of movements. Rizzolatti and co-workers (Rizzolatti, Fadiga, Gallese, and Fogassi 1996) have found "mirror neurons" in PMv: cells that discharge both when a monkey makes a particular grasp, and when he observes an experimenter or another monkey making the same grasp. It is an unusual and striking demonstration, and it suggests that individual neurons in PMv are involved both in the programming of movements, and in the recognition of those movements when made by others. This observation is a cornerstone of Rizzolatti's hypothesis (Rizzolatti, Fadiga, and Fogassi 1997) that the same brain circuits responsible for actions are involved in perception (see section 1.4.3).

Recently, Tanji and co-workers (Fujii, Mushiake, and Tanji 1998) have found a region of PMv where eye movements can be elicited by microstimulation. This suggests PMv contains the machinery necessary to contribute to hand-eye coordination.

Taken together, these studies suggest that PMv could be involved in complex orienting behaviors of eyes and hand, such as bringing food to the mouth. Also, the diversity of function reported in PMv suggests that future studies will likely subdivide PMv into functionally distinct regions.

We have seen a variety of brain areas involved in specifying reach movements, and explored some differences in the contributions of these areas to movement planning and execution. It seems there are largely segregated networks of areas involved in reach and in grasp. And within these networks, there are a variety of levels of representation, from representations that are influenced by the visual position of targets, to signals related to different aspects of the movement. These areas are active simultaneously, working in concert to handle different aspects of a reach.

1.5 Human reaching behavior

What is specified when the brain instructs a reach? One extreme possibility would be that cortex specifies the complete pattern of muscular contractions over time. This level of control is unnecessary, since the details of the movement are often of far less importance than the final hand position. However, the possibility at the other extreme, that cortex need only signal a final position for the hand, is also unlikely. The current position of the hand, whether something is being carried, and the presence of obstructions will all affect the movement of the arm, so must all be accounted for when programming the reach. Psychophysics has sought to determine which features of a reach, between these two extremes, are programmed centrally.

Arm movements are more complicated than eye movements. There is redundancy in the muscle tensions and joint angles that can position the hand at any point in space. The eye musculature provides an extra degree of freedom, but it is rarely used: eye movements are governed by Listing's Law, which reduces the number of degrees of freedom in which the eyes can move. There is no such yoking of degrees of freedom for arm movements. Also unlike eye movements, arm movements face variable loads. In 1903, eye movements were decomposed into five basic types (saccades, smooth pursuit, vestibulo-ocular and optokinetic reflexes, and vergence; Dodge 1903, described in Goldberg, Eggers, and Gouras 1991) with separate and overlapping neural control. No such classification exists for reaches.

This section will review some psychophysical investigations of reaching. To answer the question of what aspects of reaching are planned centrally, researchers have tried to establish the coordinate frames in which targets and movements are specificed. The first section describes some of these findings. Other aspects of reaching relevant for the studies in this thesis are discussed in the following sections. The concept that the movement of the arm and the shaping of the hand are planned separately will be presented. Lastly, some studies of the coordination of the eyes and hand will be discussed.

1.5.1 Coordinate frames for reaching

In what coordinate frame do human beings plan reaches? Reach planning may occur in extrinsic coordinates, for example the cartesian coordinates of the hand in visual space. Or, reaching may be planned in intrinsic coordinates, such as the angles of the joints of the arm. What parameters of the arm movement are specificed centrally? The brain may specify only the endpoint (desired hand position or joint angles) of the reach, or the central command may instruct some or all intermediate points through which the arm must pass (again, in extrinsic or intrinsic coordinates).

Particular sorts of movements are likely to involve different planning strategies. Catching a baseball, for example, is likely to involve motor plans that specify the endpoint, while handwriting is liable to involve planning a pattern of joint movements. A hybrid of coordinate frames and parameters may be specified for every reach.

There is experimental support for a variety of strategies for reach planning. The results are not necessarily incompatible; they may highlight different aspects of movement planning. A model for reach planning offered by Flanders, Tillery, and Soechting (1992) proposes that targeted arm movements are processed through a series of discrete stages. First, retinocentric information about target position is converted to a head-centered representation. This is then converted to a shoulder-centered representation. At that stage, movement kinematics (direction and distance) are computed. Finally, activation of the arm muscles occurs.

Studies that seek to establish the coordinate frames used for reach planning employ a variety of techniques, including searching for invariances in the movement, analyzing the pattern of errors that subjects make, and observing the effects of perturbations on reaching. Studies that employ each of these methodologies, the logic behind them, and the conclusions that can be drawn from them will be discussed.

Some studies seek invariances in the movement. These studies argue that if some property of the movement is reliably reproduced, this property is likely to be explicitly controlled. Soechting and Lacquaniti (1981) studied the path of the hand and the rotations of the elbow and shoulder joints as subjects reached to different targets. They observed that the velocities of rotations at the elbow and shoulder joints were linearly related, even for different speeds and directions of reaches. This invariance would be most readily attained if the joint rotations were explicitly planned. Since joint rotations are intrinsic parameters, this finding suggested that reach planning occurs in the intrinsic coordinates of the arm. However, the path of the hand through cartesian space was also reliably straight, so it could be that that was the explicitly planned parameter (Hollerbach and Atkeson 1986). Also, the invariances in joint trajectory could conceivably emerge from properties of the arm or lower-level controllers (Sabes 1996).

Analysis of errors provides another method to ascertain coordinate frames for reach planning. The logic behind these studies is that coordinate transformations proceed through a series of stages, with errors potentially introduced at each stage. If the distribution of errors has some structure to it, that structure indicates the form of one of the representational stages. For example, Soechting and Flanders (1989) analyzed errors in a memory-guided reach task. They found that errors were greatest in the radial distance from the shoulder (subjects consistently reached short of the target), and smaller in the azimuth and elevation. This indicated that distance and direction of the reach are coded separately, and that reaches are planned in a shoulder-centered coordinate frame. In an additional experiment, these authors observed that the errors in distance were reduced if subjects indicated the position of the target with a 1 m long pointer, instead of pointing with their finger. They interpreted this to mean that the errors in pointing were introduced in the motor stages of processing, and not in the sensory memory of target location.

Of particular relevance to the experiments presented in chapter 4 is the study performed by Henriques et al. (1998) using the method of error analysis. These authors attempted to dissociate between a head-centered and an eye-centered scheme for reach target storage. They made use of a known observation that reaching to targets in the visual periphery is less accurate than reaching to targets that are at the point of foveation (Bock 1986; Enright 1995). In their experiment, three conditions were contrasted. In the first, subjects looked straight ahead. Reach targets were presented briefly at the point of fixation. After a delay, subjects would reach to the memorized target location. In the second condition, subjects looked off to one side. The same reach target was presented. Errors were larger when the eyes were deviated, consistent with earlier findings. In the experimental condition, subjects began trials by fixating straight ahead, and a reach target was presented at the point of foveation. Then, before the reach could be performed, subjects were instructed to saccade to the peripheral fixation point. The logic behind the experiment was that if targets were stored in a head-centered reference frame, then the errors should be small, consistent with the retinal position where the target was presented. On the other hand, if targets were stored in an eye-centered reference frame, then reach errors should be large, consistent with the retinal position of the remembered target after the saccade at the time the reach was performed. They found that errors were large, consistent with the eye-centered model for target storage, and inconsistent with the head-centered model.

Perturbation studies offer a third window into the internal representations for reach planning. When a distortion is introduced between the visible endpoint and the kinesthetic position of the hand, as with prisms, humans will misreach, then learn to reach accurately (Held and Hein 1958). Interestingly, it was recently shown that human parietal cortex is uniquely activated during prism adaptation (Clower, Hoffman, Votaw, Faber, Woods, and Alexander 1996), suggesting that this area is the critical site for learning the new visual-kinesthetic mapping. In a psychophysical study, Vetter, Goodbody, and Wolpert (1999) introduced a distortion at one point in the visual field. After subjects had learned to adapt their reaches at that location, they were tested for effects of the adaptation on reaches made at other locations. It was found that the adaptation generalized to other locations, and that the pattern of adaptation was best described in a spherical coordinate frame centered on the eyes. Thus, the central representation of reach targets appeared eye-centered.

Other perturbation studies present evidence that the path of the arm movement (that is, the hand's position throughout the reach), and not just the endpoint of the reach, is planned in eye coordinates (Wolpert, Ghahramani, and Jordan 1995; Flanagan and Rao 1995). In these studies, visual feedback about the hand position during point-to-point reaching movements was perturbed. Subjects altered their hand path to restore a visually straight trajectory, although there was no need to make such a change: the unaltered reach would successfully bring the hand to the target. In one study, subject were not aware of the alterations in the hand path (Wolpert, Ghahramani, and Jordan 1995). Thus, path planning appears to occur in visual coordinates.

The different techniques used in these studies (arguments from invariance, analysis of errors, and adaptations to perturbations) provide evidence in favor of different coordinate frames used for reach planning. Probably, the brain can employ different planning strategies in different situations, and even for different components of the same task. One viable hypothesis for the coordinate frame for movement planning is that movement endpoint and a few key intermediate points are specified in a visual reference frame, then these points are modified into intrinsic signals in a joint reference frame, in order to perform the movement (Sabes and Jordan 1997).

1.5.2 Transport and grasp components to a reach

There are two distinct components to a reach: moving the arm and shaping the hand. These components have been termed the *proximal* (or *transport*) and *distal* (or *grasp*) components of the reach, respectively. They are performed simultaneously, as can be seen in the fact the hand adopts an appropriate position for the grasp while it is still near the body, as the arm is beginning to move (Jeannerod 1988, p. 63). As we explored in previous sections (section 1.3 and 1.4), the transport and grasp components of a reach are likely to involve disjoint neural circuits.

1.5.3 Eye-hand coordination

In natural circumstances, movements of the eyes routinely accompany movements of the hand to visible targets. The relationship between the hand and eyes is flexible; it is not the case that reaches must be performed to a point being fixated. Arm movement often begins while the eyes are in mid-saccade (Jeannerod 1988, p. 48). The eyes move with a faster latency and duration than the arm. A common pattern of eye and hand movements is for the reach to be performed to a target that was recently fixated, but is no longer at the center of gaze (Ballard, Hayhoe, Li, and Whitehead 1992).

Since we are able to reach and saccade simultaneously in different directions, the movements must be controlled independently. We might expect to find separate neural circuits dedicated to moving the eyes and hand. Further, since the endpoints are so precisely orchestrated, we might imagine that these circuits are capable of exchanging information about target position, and eye and limb position. One effective way to do this would be to use a common scheme for representing space.

This chapter has described some prominent studies of the neuropsychology, anatomy, physiology, and behavior of the control of reaching. The following four chapters will present our studies of movement planning and reach control in the parietal cortex.

Chapter 2 Sensory-Motor Processing in Parietal Cortex

2.1 Coding of intention in the posterior parietal cortex[1]

2.1.1 Introduction

To look at or reach for what we see, spatial information from the visual system must be transformed into a motor plan. The posterior parietal cortex (PPC) is well-placed to perform this function, because it lies between visual areas, which encode spatial information (Ungerleider and Mishkin 1982; Goodale and Milner 1992), and motor cortical areas. The PPC contains several subdivisions, which are generally conceived as high-order sensory areas (Hyvärinen and Poranen 1974; Gross 1994). Neurons in area 7a and the lateral intraparietal area (LIP) fire before and during visually guided saccades. Other neurons in areas 7a and 5 are active before and during visually-guided arm movements (Hartje and Ettlinger 1974; Mountcastle, Lynch, Georgeopoulos, Sakata, and Acuna 1975; Seal and Commenges 1985; Shibutani, Sakata, and Hyvärinen 1984; Andersen, Essick, and Siegel 1987; Murata, Gallese, Kaseda, and Sakata 1996). These areas are also active during memory tasks in which the animal remembers the location of a target for hundreds of millisceonds before making an eye or arm movement. Such activity could reflect either visual attentions (Robinson, Goldberg, and Stanton 1978; Bushnell, Goldberg, and Robinson 1981; Duhamel, Colby, and Goldberg 1992; Steinmetz, Connor, Constantinidis, and McLaughlin 1994; Colby, Duhamel, and Goldberg 1995) or the intention to make movements (Gnadt and Andersen 1988; Andersen 1989; Thier and Andersen 1996; Shadlen and Newsome 1996; Mazzoni, Bracewell, Barash, and Andersen 1996; Andersen 1995; Bracewell, Mazzoni, Barash, and Andersen 1996). This question is difficult to resolve, because even if the animal maintains fixation while directing attention to a peripheral location, the observed neuronal activity could reflect movements that are planned but not executed (Bracewell, Mazzoni, Barash, and Andersen 1996). To address this, we recoreded from the PPC while monkeys planned either reaches or saccades to a single remembered location. We now report that, for most neurons, activity before the movement depended on the type of movement being planned. We conclude that PPC contains signals related to what the animal intends to do.

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[1] Section 2.1 has been published as Snyder, Batista, and Andersen (1997). Subsection headings have been added.

2.1.2 Methods

Animals faced an array of nine buttons 3.7 cm in diameter at 28 cm distance. Each button contained a red and a green light emitting diode (LED) side by side behind a 1.2 cm translucent lens. The animal pressed buttons illuminated green using its right arm, and fixated buttons illuminated red. No other lights were present. All trials began with fixation (± 2.7 deg) and depression of the illuminated central button. After 750 ms, a red (saccade task) or green (reach task) peripheral LED was flashed for 150 ms. After a 1-1.6 s delay, the central LEDs were extinguished and the monkey saccaded (latency mean ± SD: 182 ± 36 ms) or reached (269 ± 45 ms) to the remembered peripheral location in complete darkness. The animal maintained central fixation during reach trials, and maintained central button depression during saccade trials. Eight delayed saccade and eight delayed reach trials were performed in each of eight directions. For most neurons, the best direction was determined from this first block of trials and then a second block of interleaved delayed saccade, delayed reach, and delayed dissociation movements was performed in the best and the opposite directions (8 or 16 trials per task per direction). The dissociation task was similar to the simple tasks, but now simultaneous red and green flashes were delivered on opposite sides of the fovea, and the animal responded with a near-simultaneous reach and saccade in opposite directions when the central fixation light was extinguished. The animal typically performed over 90% of the trials successfully. Results (table 2.1.3) were based primarily on data from the second block of trials.

2.1.3 Results

Neurons in PPC were recorded from three hemispheres of two adult macaque monkeys during interleaved delayed saccade and delayed reach trials (figure 2.1). Delay activity (measured 150-600 ms after target extinction) was significantly modulated by direction of movement during either or both tasks in 373 of 652 neurons for which complete data were collected (Students' t test, $P<0.05$). Of these, 68% were motor intention specific: 21% were significantly modulated before eye but not arm movements, while 47% were significantly modulated before arm but not eye movements. Surprisingly, activity during the cue interval (50 ms before to 150 ms after extinction) was intention specific in 44% of the 443 active neurons. Specificity so early after target presentation suggests that these findings apply during saccades and reaches made without delays, that is, during saccades and reaches to visible targets.

A dissociation task was introduced to control for the possibility that the animal planned both a

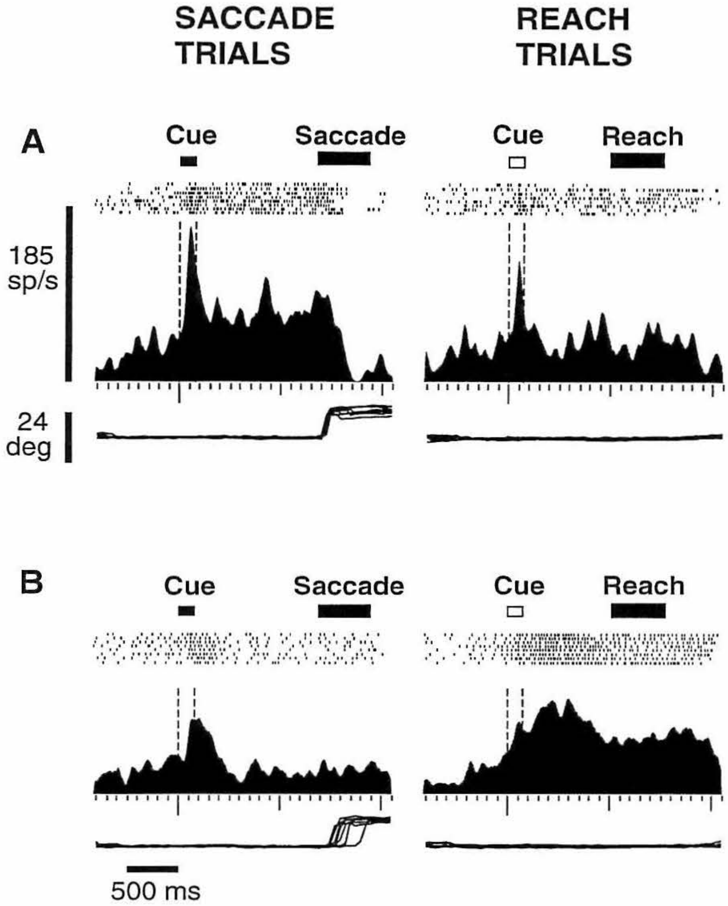


Figure 2.1: Responses of two intention specific neurons in the delayed saccade (left) and delayed reach (right) tasks. Each panel shows timing of peripheral flash ("Cue": red flashes indicated by filled bars, green flashes by open bars) and response ("Saccade" or "Reach"); eight rows of rasters corresponding to every third action potential recorded during each of eight trials; a spike density histogram of neuronal activity, generated by convolution with a triangular kernel (Scott 1985) aligned on cue presentation, with cue onset and offset indicated by dashed lines; and eight overlaid traces showing vertical eye position. Neuronal responses in the cue interval (50 ms before to 150 ms after cue offset) were non-specific. However, during the delay interval (150 to 600 ms), firing depended specifically on motor intent. **A** A cell showing elevated delay period firing prior to a saccade (left) but not prior to a reach (right). For illustration purposes, data for this cell were collected using a fixed delay interval. **B** A second cell which showed reach rather than saccade specificity during the delay interval.

reach and a saccade to a target even when only a single movement was instructed (figure 2.2). In fact, in a previous pair of studies (Bushnell, Goldberg, and Robinson 1981; Goldberg and Bushnell 1981) which reported no specificity for saccades compared to reaching movements in PPC, animals trained to reach toward targets without looking at them nonetheless looked toward the target at the end of the trial. It is likely that plans for both eye and arm movements to the target were formed simultaneously, with the execution of the eye movement delayed until the end of the trial. Delayed and even entirely unexecuted plans for movement may influence LIP firing (Bracewell, Mazzoni, Barash, and Andersen 1996). Similarly, in a delayed "go/no go" task, neurons in area 5 code target location regardless of whether or not a movement is made (Kalaska and Crammond 1995). The dissociation task eliminates plans for movements that will not be executed by explicitly instructing eye and arm movements in opposite directions. Of neurons with non-specific delay activity in the single movement tasks (delayed reach or delayed saccade) that were tested in the dissociation task, 62% were revealed to be intention specific, bringing the total percentage of specific neurons to 84% (table 2.1.3). In the cue interval, corresponding percentages were 45% and 63%.

Anatomic location of neurons

Neurons specific for eye and arm movements were anatomically segregated (table 2.1.3 and figure 2.3). While cells throughout PPC showed motor specific responses, cells in two subregions (area LIP and a reach area medial and posterior to LIP) tended to have strong, prolonged delay activity. In the middle third of the longitudinal extent of the intraparietal sulcus, intended eye movement cells outnumbered intended arm movement cells by 5:1. Of 47 cells active during the delay period, 28 were eye specific and only 5 arm specific in the simple tasks, with an additional 4 eye specific and only 1 arm specific cell revealed by the dissociation task. In a second area, medial and posterior to LIP, arm cells outnumbered eye cells 9:1. Of 95 active cells, 68 were arm specific and only 9 eye specific in the simple tasks, with an additional 12 arm specific cells revealed by the dissociation task. This anatomical segregation argues against chromatic tuning as a basis for our results, since clustering of red- or green-preferring neurons over many square millimeters of cortex is unlikely. The dissociation task revealed neurons specific for saccades as well as reaches. This helps to rule out the possibility that different activity levels reflect differential allocations of attention; if reaching, for example, required greater attention, then all cells should have appeared reach specific.

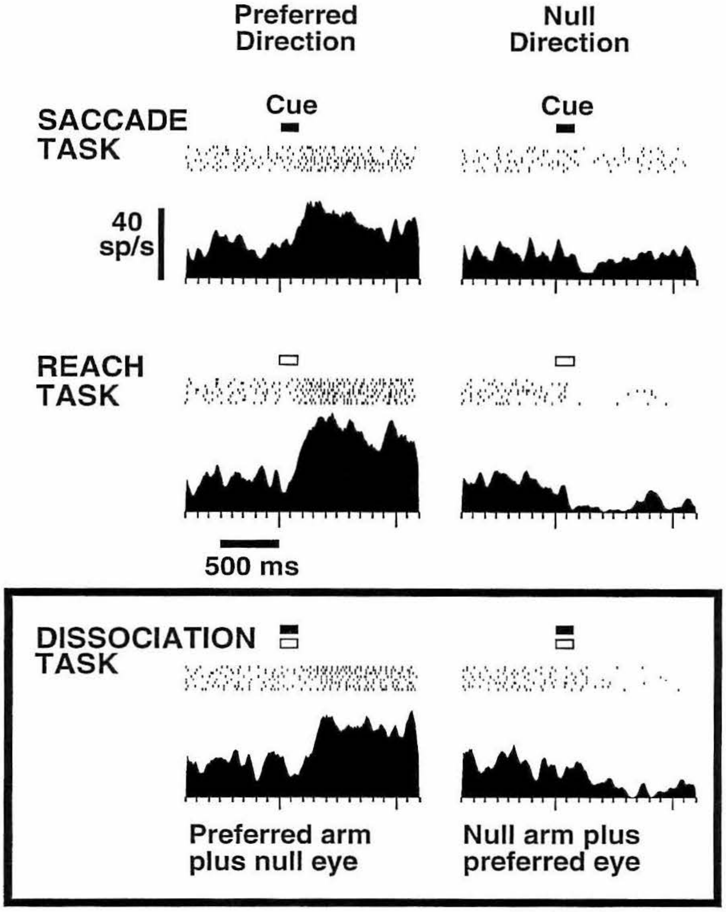


Figure 2.2: An intention specific neuron whose motor specificity was revealed by the dissociation task. Delay activity was greater prior to movements towards the receptive field (preferred direction, left column) compared to away (null direction, right column) in both delayed saccade (upper row) and reach (middle row) tasks. Thus in single movement tasks, the neuron appears to code remembered target location independent of motor intent. However, motor specificity was revealed in the dissociation task. Firing was vigorous prior to a preferred reach combined with a null saccade (lower left), but nearly absent prior to a preferred saccade plus null reach (lower right). Thus when both a reach and a saccade were planned, delay activity reflected the intended reach and not the intended saccade. Panel formats are similar to figure 2.1. Every other action potential is indicated by one raster mark.

	All areas	Area LIP		Reach area	
	Both	M1	M2	M1	M2
Cue interval (100-300 ms from cue onset)					
Saccade specific	104 (23%)	17 (40)	12 (39)	17 (24)	1 (4)
Plus dissociation	161 (36%)	26 (62)	22 (71)	18 (26)	1 (4)
Reach specific	91 (21%)	4 (10)	1 (3)	13 (19)	13 (50)
Plus dissociation	119 (27%)	4 (10)	1 (3)	17 (24)	17 (65)
Non-specific	163 (37%)	12 (29)	8 (26)	35 (50)	8 (31)
Total active cells	443	42	31	70	26
Delay interval (150-600 ms from cue offset)					
Saccade specific	79 (21%)	17 (59)	11 (61)	9 (13)	0 (0)
Plus dissociation	87 (23%)	18 (62)	14 (78)	9 (13)	0 (0)
Reach specific	175 (47%)	3 (10)	2 (11)	47 (68)	21 (81)
Plus dissociation	227 (61%)	4 (14)	2 (11)	55 (80)	25 (96)
Non-specific	59 (16%)	7 (24)	2 (11)	5 (7)	1 (4)
Total active cells	373	29	18	69	26

Table 2.1: Summary of neurons. Most active cells were intention specific in both cue and delay intervals. Data for the cue interval (during and immediately after stimulus presentation) are shown above, and for the delay interval (after stimulus presentation but well before movement) below. Columns show cell counts and percentages for cells in all areas, LIP cells in the first and second monkey (M1 and M2), and reach area cells in M1 and M2. Effects of movement intention were assayed by comparing activity prior to movements in the best and opposite directions (determined in a previous block of trials). If activity was modulated only by the intention to saccade in opposite directions (Students' two tailed t test, $p < 0.05$), the cell was classified as saccade specific (first row). If activity was modulated only by the intention to reach in opposite directions, the cell was classified as reach specific (third row). If activity was modulated by either movement, the cell was classified as non-specific (fifth row). Rows labelled "plus dissociation" (second and fourth rows) include cells active in both the simple saccade and reach tasks whose firing depended on movement direction in the dissociation task. Inactive cells and cells without directionally selective activity were excluded. Not all cells were tested in the dissociation task.

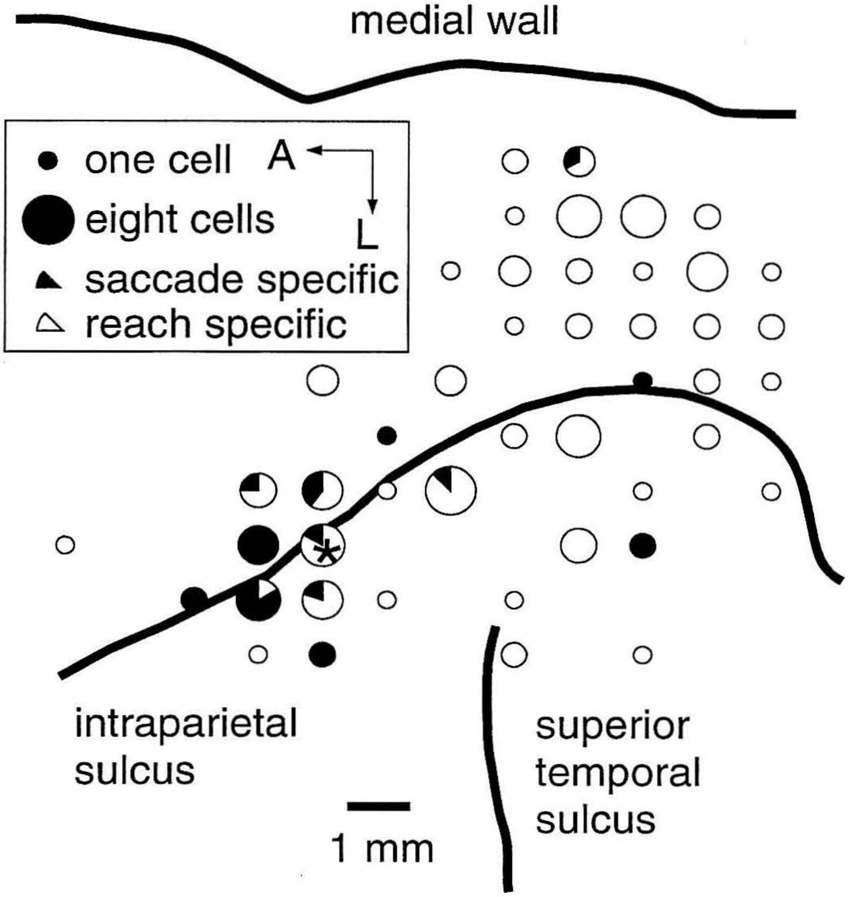
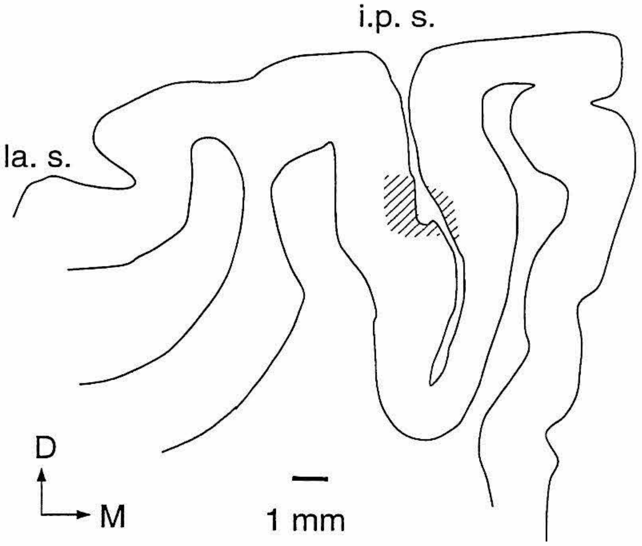


Figure 2.3: Neurons specific for the intention to make eye and arm movements were anatomically segregated. Surface map showing the locations of motor specific cells relative to the intraparietal and superior temporal sulci in the left hemisphere of one animal. The area of each pie chart corresponds to the number of cells with saccade-specific (filled) and reach-specific (open) delay activity at each location. Only cells with robust delay activity are shown (16 spikes/s or more in one or both task delay intervals). The excluded cells are primarily located in and around areas 7a, VIP and MST. Because the x-y positioning apparatus for single neuron recording and for dye injection were not identical, the placement of tracks may be misaligned by up to ±1 mm.

Figure 2.4: Electrode penetration in area LIP. Coronal section showing a nuclear yellow dye injection made into the center of the cluster of eye-specific cells in the first animal (indicated by * in figure 2.3). The injection was visualized midway down the lateral bank of the intraparietal sulcus (ip. s.), in area LIP. la. s.: lateral sulcus.



2.1.4 Discussion

Our results reveal separate intended reach and intended saccade pathways in PPC. This demonstrates that the decision of how to utilize a particular sensory stimulus is reflected in PPC firing. Attention may still be present in PPC (Robinson, Goldberg, and Stanton 1978; Bushnell, Goldberg, and Robinson 1981; Steinmetz, Connor, Constantinidis, and McLaughlin 1994; Lynch, Mountcastle, Talbot, and Yin 1977), encoded by the small number of cells that are not specific for one type of movement, or in the non-specific cue responses of the cells that are movement-specific in the delay period, or in the weak response of the specific neurons prior to their non-preferred movement. Alternatively, non-specific neurons may reflect plans for moving body parts other than the eyes or arms, e.g., pinna movement, that we did not test (Bon and Lucchetti 1994). Some saccade-specific neurons are active before arm movements and some reach-specific neurons are active before saccades. We propose that this activity reflects plans for movements not explicitly called for by the task, but formed automatically in response to target appearance. When these default plans are countermanded by explicit instructions, as in the dissociation task, intention specificity is revealed. The mechanism may involve inhibition between neurons in the same movement pathway coding different directions. Functionally, this coupling of saccade and reach activity may reflect the fact that these movements are often coupled.

The idea that PPC plays a role in motor planning is consistent with previous experiments in LIP. In a delayed double saccade task, animals memorized two flashed locations and then, after a delay, saccaded to them sequentially. Most LIP delay activity coded the goal of the first saccade (target 1) rather than the location of the most recently presented stimulus (target 2). At the time of the first saccade, firing changed to code the goal of the second saccade (target 2). These two observations, taken together, rule out a strictly sensory role for LIP, and support the motor planning hypothesis (Mazzoni, Bracewell, Barash, and Andersen 1996; Andersen 1995; Bracewell, Mazzoni, Barash, and Andersen 1996). The appearance of activity coding target 2 after the first saccade, alternatively, can be explained as sensory remapping of a remembered stimulus in retinal coordinates. The observation that this activity sometimes anticipates the completion of the first saccade has been proposed to support the sensory remapping hypothesis (Duhamel, Colby, and Goldberg 1992). However, predictive behavior is as likely to occur in motor planning as in sensory pathways, and so the observation of anticipatory activity does not favor either hypothesis. In contrast, we have now directly shown that the majority of the delay activity in LIP as well as in the neighboring reach area is related to specific motor intention and not to either sensory stimuli or spatial attention.

Other instances of task requirements influencing PPC responses have been reported, and have been ascribed to attentional processes (Robinson, Goldberg, and Stanton 1978; Bushnell, Goldberg, and Robinson 1981). In the dorsal visual stream, posited to be dedicated to action (Goodale and Milner 1992; Mountcastle, Lynch, Georgeopoulos, Sakata, and Acuna 1975), attention and intention can be difficult to distinguish. Even when a given task does not require an action, plans for movements not explicitly required by the task can nonetheless be formed, producing potentially deceptive results. The current results indicate that it is important to rule out intention related signals (using controls like the dissociation task) before concluding that task dependent modulation in PPC reflects an attentional process.

2.2 Further considerations

2.2.1 Crosstalk between LIP and PRR?

Neurons in LIP tended to exhibit a weak but reliable response to a target for a reach, and cells in the parietal reach region, *PRR*, responded weakly before saccades. It would appear that LIP contributes somewhat to reach planning, and PRR contributes slightly to saccade planning. In other words, this residual processing could be an attentional component of the response. Alternatively, it could be that a reach target becomes a candidate for a saccade, if the saccade system is not currently engaged in orienting toward another stimulus. The dissociation task, where an eye and arm movement are planned concurrently to different targets, provided a means to test between these possibilities. Specifically, what would happen to the residual response in PRR to a saccade target, if a reach were planned to a different location?

We tested these alternatives by examining the response of neurons in the dissociation task. As discussed above (figure 2.2), the dissociation task was able to reveal that some nonselective cells became selective when an eye movement and a reach were planned in different directions. This effect also appeared in the neurons that were selective in the one-movement task: their low level of response to the non-preferred movement was reduced even further when the preferred movement was planned in the null direction. Concretely, consider a PRR neuron that is more active before a reach than before a saccade. It may still have a small increase in response when a saccade is planned into the response field. However, that response would be abolished if the same saccade were planned, but a reach were planned in the cell's null direction. This means that the residual activity before a saccade is more likely to represent a default reach plan (that is formed because the reach planning system is not otherwise engaged) than a contribution of this neuron to the saccade.

Across the population of PRR and LIP neurons, the dissociation task lowered response to the non-preferred movement even further. Figure 2.5 shows a population histogram of all neurons tested, in the four tasks: reaches or saccades into the response field, either performed alone, or made concurrently with a saccade or reach, respectively, in the opposite direction. Consider first the PRR response (panel A). The solid black trace shows the population response as a function of time for reaches in the preferred direction: activity is high. The solid gray trace is the response for saccades. The response is low, but above the pre-cue baseline. The dotted curves show the response for the dissociation tasks. For the black dotted curve, the reach is planned into the response field, and the saccade out. The response of the neuron is equivalent to its response when the reach into the response field is planned alone (solid black). Next, compare the dotted gray trace to the solid gray trace. Both represent the response when a saccade is planned into the response field. For the solid curve, that movement is made alone. For the dotted curve, a reach away from the response field is also planned. The activity is lower in this case, even though the same saccade is performed. That difference is due to the reach planned in the opposite direction. This shows that when a reach is planned, PRR cells tuned to other directions are suppressed. Therefore, the small level of activity when a saccade alone is planned is due to the formation of a weak reach plan to that location, and

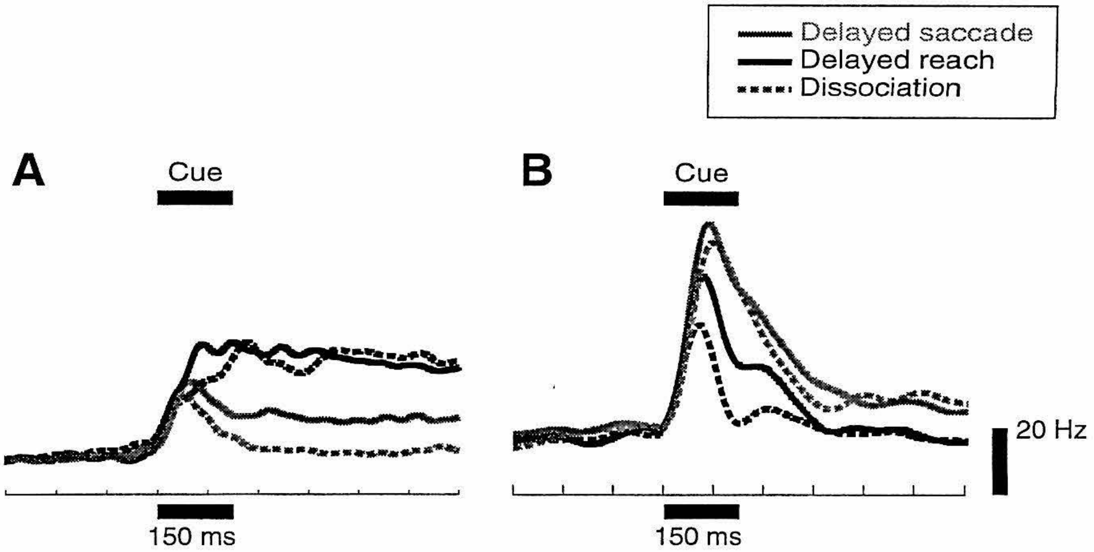


Figure 2.5: Population histograms of PPC neurons in one-movement and dissociation tasks. PRR and LIP cells are grouped separately. Figure courteousy of Larry Snyder.

not to the saccade plan itself.

The same trends can be observed in the LIP data, in panel B of figure 2.5. A saccade planned out of the response field eliminates the weak response when a reach is planned into the response field, although this effect disappears later in the delay period.

2.2.2 Timing of selectivity

The observation (table 2.1.3) that half of the parietal neurons are selective in their response to the cue while two-thirds are selective during the delay period indicates that movement selectivity evolves with time during a trial. That the earliest parietal responses are selective in half the cells may suggest that the initial movement selection process occurs directly in parietal cortex, or in areas antecedent. On the other hand, the fact that some cells become selective later in the trial could indicate that a feedback signal onto those neurons generates the selectivity. That feedback could be from an area outside parietal cortex, perhaps the frontal eye fields and premotor cortex, or it could arise locally within LIP and PRR themselves.

2.2.3 Stimulus generality in PRR

Responses in PRR seemed insensitive to dramatic changes in the stimulus that instructed the reach. A striking example of this stimulus generality is that auditory and visual cues did not elicit different

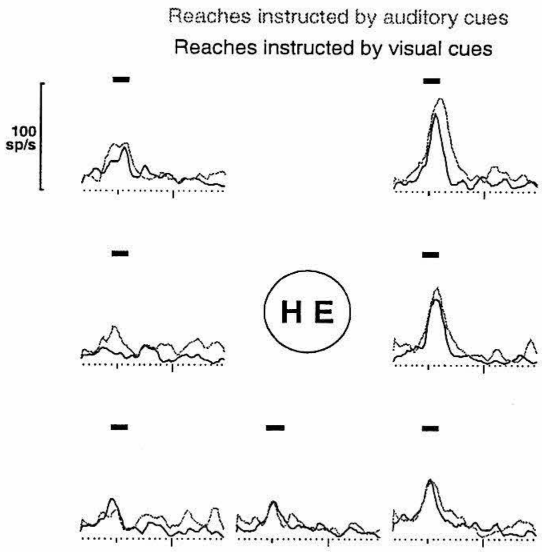


Figure 2.6: Stimulus generality in the cue response. A PRR neuron exhibiting similar responses to auditory and visual cues that instruct a reach. Eye position and initial hand position is in the center (indicated by circled E and H); reaches are made to seven targets, with the reach instructed by an auditory cue (gray PSTHs) or visual cue (black PSTHs) at the target location. Bars above histograms indicate timing of cue presentation.

responses from PRR neurons. Figures 2.6 and 2.7 show two PRR neurons tested in tasks where reach target locations are indicated by 300 ms bursts of sound or light. The cell in figure 2.6 exhibited a brief response to the cue, and very little sustained memory response. This made it well-suited for testing for stimulus effects in the cue response. The cell did not respond differently to cues of very different sensory nature. Some other cells with responses primarily during the cue epoch were tested with stimuli of different durations or different intensities; these manipulations also did not alter neurons' responses.

The neuron pictured in figure 2.7 had a sustained response during the delay period. This allowed for a comparison of stimulus effect in the memory period. Again, the cell responded in a similar manner regardless of whether an auditory or visual cue had instructed the reach.

Another test revealed a similar absence of stimulus effects during the memory period. Two cells were tested in a task where the visual cue for the reach remained on throughout the delay period. Cells responded at a similar rate regardless of whether the target remained illuminated throughout the delay period.

The intention to reach, and not aspects of the instruction signal, account for the activity of these neurons. This stimulus generality suggests PRR neurons do not convey much information about the

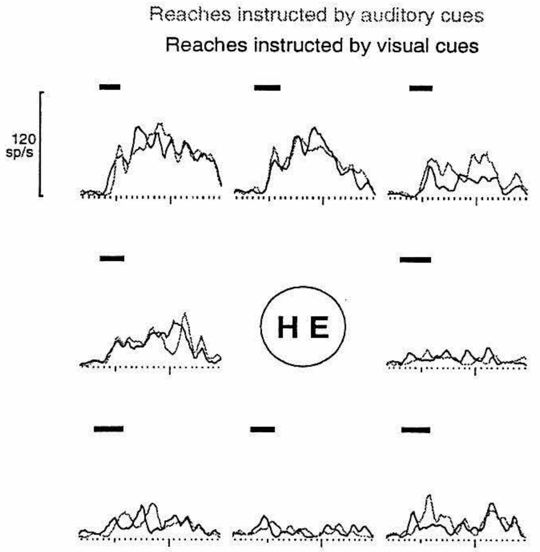


Figure 2.7: Stimulus generality in the delay period. A PRR neuron exhibiting similar responses during the delay period before auditory and visual cues that instruct a reach. Reaches were performed in eight directions. Symbols as described in figure 2.6 caption. Note that this neuron was tested with a variable delay period, and data are aligned on the time of the "go" signal, so differences in latency cannot be inferred from the plots, and the cue durations, indicated by the bars above histograms, have been blurred.

stimulus, but instead reflect the animal's intention to reach.

2.2.4 Errors

Once animals had been trained, they were generally very good at the delayed saccade and delayed reach tasks. When errors were made, they were almost never an error in the type of movement performed. However, due to an unusual training schedule, monkey G did make errors of movement type one day in training. This animal was proficient at the auditory delayed reach task before he was trained to execute delayed reaches and saccades to visible targets. He had learned to make each movement, but had not yet learned the color code of the cues. We recorded one day while he was erroneously saccading to the location of green targets and reaching to red targets. The result of the handful of error trials we were able to observe while recording from a PRR neuron is shown below. Successful and erroneous movements to the target location for which the neuron was most reach-selective is shown in figure 2.8. The neuron is active before reaches made to the location of *red* cues, and not active for saccades made to the memorized location of *green* cues. Thus, for this neuron, the only one we observed, responses predict the type of movement that will be made, and not the color of the stimulus.

2.2.5 Conclusion

Posterior parietal cortex is involved in specifying the movement to be made to a target, and not simply the behavioral salience of a target. This is perhaps the most conclusive evidence so far in favor of Mountcastle's original command hypothesis for parietal function.

It has often been reported (see, for example, Ballard, Hayhoe, Li, and Whitehead 1992; Jeannerod 1988) that eye and hand movements can be made simultaneously in different directions. This indicates that there are independent neural circuits controlling eye and hand movements. Our findings show that these separate circuits originate quite early in cortical processing. While it has long been accepted that the frontal lobe is divided into separate movement planning regions (*e.g.*, the frontal eye fields for saccadic eye movements, and primary motor cortex for body movements), the concept of separate regions dedicated to different movements in the parietal lobe has been slower to gain acceptance.

This result also casts new light on how physiologists conceive of sensory-motor processing. Physiologists often use "attention" to refer to extra-visual signals in visual neurons. The behavioral significance of those sharpened or enhanced response is often glossed. We can now propose that other "attention" signals might also be revealed to be related to task-specific processing, such as motor planning, long-term memory formation, or the animal's understanding of his task. Although the initial findings of attention in the brain were noteworthy, now it is time to probe the functional significance of that processing, as we have done in this experiment.

Perhaps one of the most important outcomes of this experiment will be that it discovered an important new cortical area: we established the existence of the parietal reach region, an area specialized for reach planning. What we have since learned about this new area is the focus of the majority of the remainder of my thesis; but first, in chapter 3 a related experiment that refines and extends the observations of this experiment will be presented.

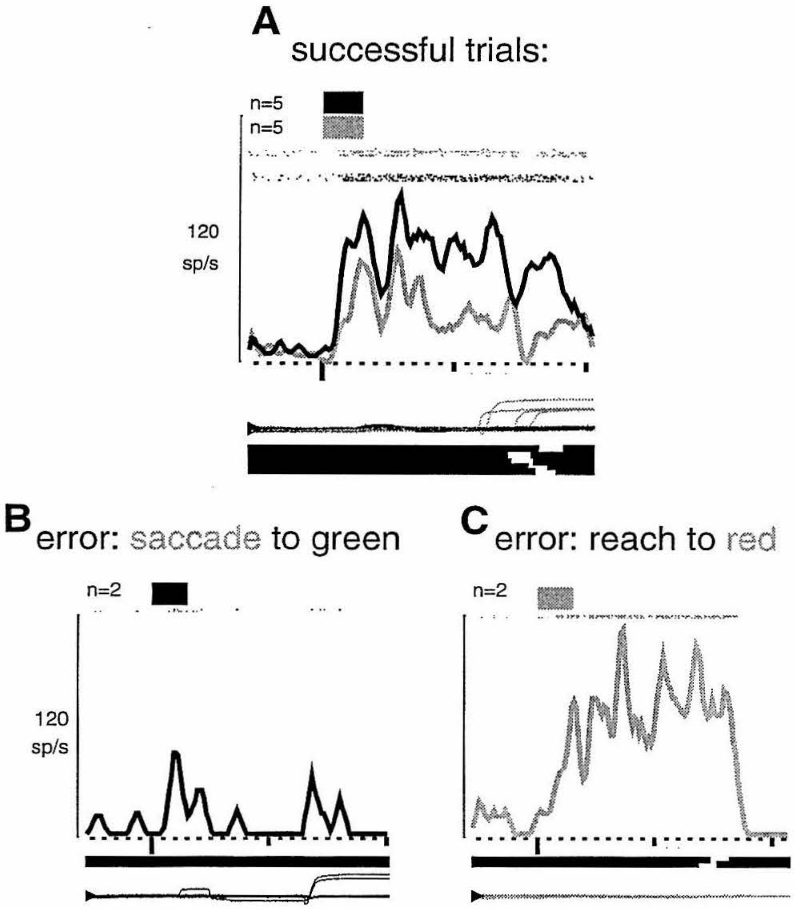


Figure 2.8: A PRR neuron that predicts movement choice during errors. **A**, successful delayed saccades and delayed reaches to the same target. Pictured from top to bottom are cue timings, rasters, spike density functions, eye position for saccade (gray) and reach (black) trials, hand position traces for reach trials. Five movements of each type were performed. **B**, erroneous saccades to green targets. Response is low, consistent with the saccade plan, but not the reach cue. The two errors of this type to this location are shown. **C**, erroneous reaches to the location of a red target. Response indicates the movement, not the cue. Two errors of this type to this location were made.

Chapter 3 Change in Motor Plan, Without a Change in the Spatial Locus of Attention, Modulates Activity in Posterior Parietal Cortex[1]

3.1 Abstract

The lateral intraparietal area (LIP) of macaque monkey, and a parietal reach region (PRR) medial and posterior to LIP, code the intention to make visually-guided eye and arm movements, respectively. We studied the effect of changing the motor plan, without changing the locus of attention, on single neurons in these two areas. A central target was fixated while one or two sequential flashes occurred in the periphery. The first appeared either within the response field of the neuron being recorded or else on the opposite side of the fixation point. Animals planned a saccade (red flash) or reach (green flash) to the flash location. In some trials, a second flash 750 ms later could change the motor plan, but never shifted attention: second flashes always occurred at the same location as the preceding first flash. Responses in LIP were larger when a saccade was instructed (n = 20 cells), while responses in PRR were larger when a reach was instructed (n=17). This motor preference was observed for both first flashes and second flashes. In addition, the response to a second flash depended on whether it affirmed or countermanded the first flash; second flash responses were diminished only in the former case. Control experiments indicated that this differential effect was not due to stimulus novelty. These findings support a role for posterior parietal cortex in coding specific motor intention, and are consistent with a possible role in the non-spatial shifting of motor intention.

3.2 Introduction

Neural responses in the lateral intraparietal area (LIP) and an adjacent parietal reach region (PRR) of macaque monkey are specifically related to rapid goal-directed movements of the eyes and arms, respectively (Bracewell et al. 1996; Mazzoni et al. 1996; Snyder et al. 1997). Previous studies suggest that portions of the parietal cortex may encode the spatial locus of visual attention or play a role in shifting visual attention (Lynch et al. 1977; Yin and Mountcastle 1977; Robinson et al. 1978; Bushnell et al. 1981; Bowman et al. 1993; Steinmetz et al. 1994, 1995; Robinson et al. 1995). In

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[1] This chapter has been published as Snyder, Batista, and Andersen (1998).

the current study we tested whether a shift in motor intention, exclusive of a shift in spatial attention, might also modulate activity in LIP and PRR.

3.3 Methods

Equipment, training and surgery have been previously described (Snyder et al. 1997). Briefly, eye movements (scleral search coil technique, 500 Hz sampling rate), button press and release times (2 ms resolution) and single unit activity (0.4 ms resolution) were recorded for off-line analysis. A square array of eight 3.2 cm buttons surrounding a central fixation button, each of which could be lit by a red or green LED, was located 28 cm from the eyes, subtending 30 x 30 degree of visual angle. Extracellular potentials were recorded using tungsten electrodes, inserted through a recording cylinder centered at 5 mm posterior and 12 mm lateral (Horsley-Clarke coordinates). Single cells were isolated while animals performed delayed saccades and reaches to one of the eight peripheral red or green LEDs. Data were collected from cells that had excitatory responses prior to movement to at least one target.

The effect of changes in motor intention was studied in two adult male rhesus macaques. Trials began with 750 ms of central light fixation in an otherwise dark room (figure 3.1). A peripheral flash on opposite sides of the fixation point and either inside or outside the receptive field instructed a saccade (red) or a reach (green). On half of trials, a second flash occurred at the same location as the first, either affirming or countermanding the type of movement to be made. (Never, during training or data collection, did an animal experience a trial with sequential flashes in two different locations.) Thus the first flash oriented the animal's attention in space and instructed the direction and modality of an upcoming movement. The second flash always occurred at an attended location and so never shifted attention, but sometimes instructed a change in movement type. Finally, the fixation light was extinguished, signalling the animal to execute the planned movement (see figure 3.1 for timing). The delay periods of single flash trials and double flash trials were 2500 ms and 1600 ms, respectively.

Eight to twelve repetitions of each trial type were performed. Trials with premature or incorrect movements were aborted and the data discarded. On randomly interleaved trials, movements opposite to the neuron's response field were instructed so that the location of the first flash, unlike that of the second, could not be predicted. Data from these catch trials are not presented. Greater than 90% of trials were completed successfully. In each recording session, either the ipsilateral arm

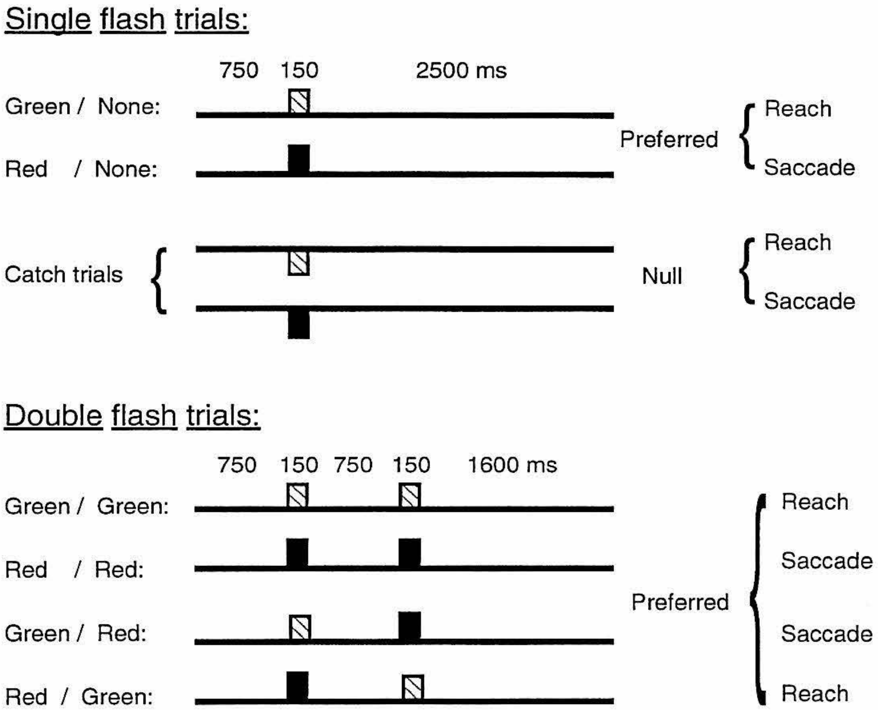

Figure 3.1: Time course of 8 single and double flash delayed movement trials. The experiment was designed to force the animal to attend to the spatial location and color of both flashes. A 150 ms flash appeared 750 ms after fixation began. Red and green flashes instructed saccades and reaches, respectively. On half of trials, a second flash occurred 750 ms later at the same location as the first, sometimes instructing a change in the motor plan but never shifting spatial attention. Fixation light offset, 2.5 s after the first flash, signalled the animal to perform the most recently instructed movement. For one animal, double flash trials also occurred for the null direction (not shown).

(PRR recording: 13 cells; LIP: 6 cells) or contralateral arm (4 PRR cells, 14 LIP cells) was used, and the other was lightly restrained. Although this study was not designed to address this issue and quantitative data were not obtained, no systematic effect of laterality on the proportion of responsive cells was observed.

Statistical significance was calculated using a paired Students' T test (population data, $p < 0.01$) or unpaired T test (single cell data, $p < 0.05$). In LIP, data was obtained 100-450 ms after flash onset. In PRR, peak second flash responses were delayed up to 150 ms compared to first flash responses, and sustained activity from the first flash often continued up until and slightly beyond the time of the second flash (figures 3.2A and 3.3A, middle panel). To avoid contamination from this sustained first flash response, and to compensate for the slowed response to the second flash, PRR activity was measured 350-550 ms after second flash onsets but 200-400 ms after first flashes. These intervals were chosen to begin at the approximate peak transient PRR response time. Since data from LIP and PRR were never directly compared, there was no compelling reason to use corresponding epochs in the two areas.

3.4 Results

Data are reported for 20 LIP and 17 PRR neurons with excitatory responses to intended movements collected from two monkeys. This includes all cells with directional cue or delay period responses in a memory saccade task, recorded from nine consecutive tracks in one animal (10 cells in LIP, 15 cells in PRR; histology shown in figure 2.3 of chapter 2), and from eight consecutive tracks in a second animal (ten cells in LIP, two cells in PRR).

If parietal cortex encodes only the locus of spatial attention, then the response to a flash should not depend on the movement instructed by the flash. Furthermore, if shifts in attention are encoded, then a flash at an attended location should elicit a diminished response, regardless of what it signifies (Steinmetz et al. 1994). Neither finding was observed. Figure 3.2 shows averaged responses of one PRR neuron (A) and one LIP neuron (B) to red followed by green flashes (light traces) and to green followed by red flashes (dark traces). Each pair of flashes was presented inside the response field at the same location.

In PRR, an initial flash instructing a saccade evoked a transient response (S1), while the instruction to reach evoked a transient plus sustained response (R1). A second flash of opposite color was then presented at the same location, instructing a change of plan from a saccade to a reach or

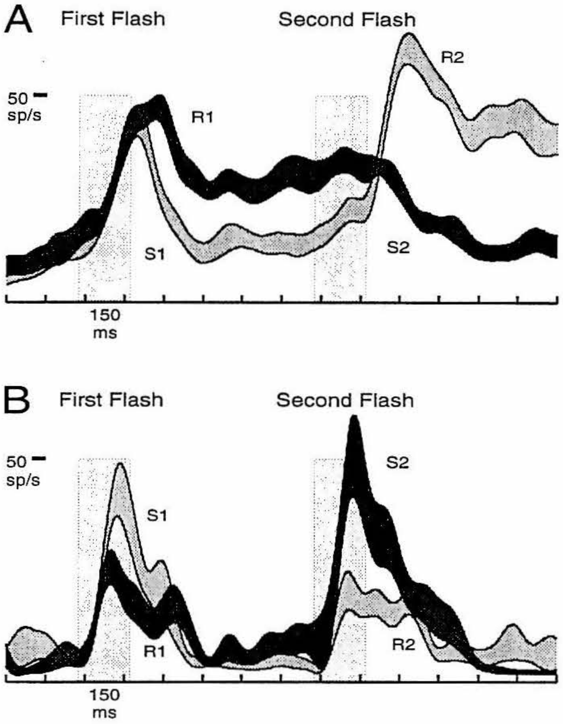

Figure 3.2: **A**. Intention-selective responses of a PRR neuron to a change in motor plan, from a saccade to a reach (dark trace) or from a reach to a saccade (light trace). Sustained activity resulting from an instruction to plan a reach (R1) was abolished when a second flash changed the plan to a saccade (S2). An initial instruction to plan a saccade elicited only a transient response (S1), but when the plan was changed to a reach, activity increased (R2). The instruction to plan a reach elicited a larger response when countermanding a previous plan than when presented alone (R2 transient and sustained responses are larger than R1 responses). The reverse was true for a flash instructing a saccade (S2 transient less than S1 transient). Each flash was presented at the same location inside the response field, so that second flashes changed motor intention without shifting spatial attention. All data shown were obtained before movement was cued to begin. **B**. Intention-selective responses from an LIP neuron, complementary to the neuron of A. Flashes instructing saccades elicited larger responses than those instructing reaches (S1 versus R1 and S2 versus R2), with still larger transient responses when the instruction to saccade countermanded a previous instruction (S2 versus S1). Each ribbon is the mean response of 8-12 trials 1 standard error. Shading indicates the time of one 150 ms flash. Data were smoothed prior to plotting (191 point digital low pass filter, transition band 20- 32 Hz), but all reported values were obtained before smoothing.

vice versa. A flash instructing a change from a saccade to a reach evoked a much larger response (R2) than did the same flash presented first (R1). Conversely, a flash instructing a change from a reach to a saccade produced almost no transient response, and a decrease in sustained activity (S2). These reciprocal activity changes are reminiscent of those produced by Bracewell and colleagues (1996). However, those changes were produced by changing the direction of intended movement; the modulations shown here were produced by changing the type of intended movement.

A complementary pattern was observed in LIP (figure 3.2B). The instruction to plan a saccade evoked a larger response than the instruction to plan a reach (S1 versus R1). This differential response occurred not just for first but also for second flashes (S2 versus R2). Furthermore, the instruction to change the plan from a reach to a saccade (S2) resulted in a larger response than an initial saccade instruction (S1).

Figure 3.3 shows averaged data from PRR (A) and LIP (B). Left panels show first flash responses, sorted by instruction. In PRR, reach instructions elicited larger responses than saccade instructions: 26.2 ± 2.3 versus 16.1 ± 1.8 sp/s (traces 1 versus 2, mean ± SEM for 17 cells; equal responses can be rejected with $p < 0.01$). In the majority of neurons, elevated firing continued throughout the delay period prior to a reach. The reverse pattern occurred in LIP: saccade instructions were preferred (30.8 ± 2.1 versus 18.2 ± 1.5 sp/s (n=20, $p < 0.01$). Single cell data confirmed these patterns. Reach responses were greater in all but 1 PRR cell, and saccade responses were greater in all 20 LIP cells (table 3.1, P vs N). These data confirm the findings of Snyder et al. (1997).

In the remaining four panels, responses to second flashes are sorted by whether they instructed a preferred (center) or non-preferred (right) movement type, and by whether they affirmed (dashed) or countermanded (solid) the previous instruction. Responses were larger when the second flash instructed a preferred movement (traces 3+4) compared to a non-preferred movement (traces 5+6): 23.3 ± 3.4 versus 12.9 ± 2.6 sp/s in PRR and 31.2 ± 3.5 versus 20.8 ± 3.0 sp/s in LIP, both significant at $p \leq 0.01$. Preferred and non-preferred here refer to movement type, not direction; all data presented are for movements planned into the response field.

Responses in the center and right panels are further split according to whether the second flash countermanded (solid traces 3+5) or affirmed (dashed traces 4+6) the previous instruction. A countermanding, preferred second flash (trace 3) elicited a response comparable to or larger than the same flash presented first (trace 1): 30.4 ± 3.8 versus 26.2 ± 2.3 sp/s in PRR, and 33.6 ± 3.8 versus 30.8 ± 2.1 sp/s in LIP (both $p < 0.05$). This was the case despite the fact that first but not second

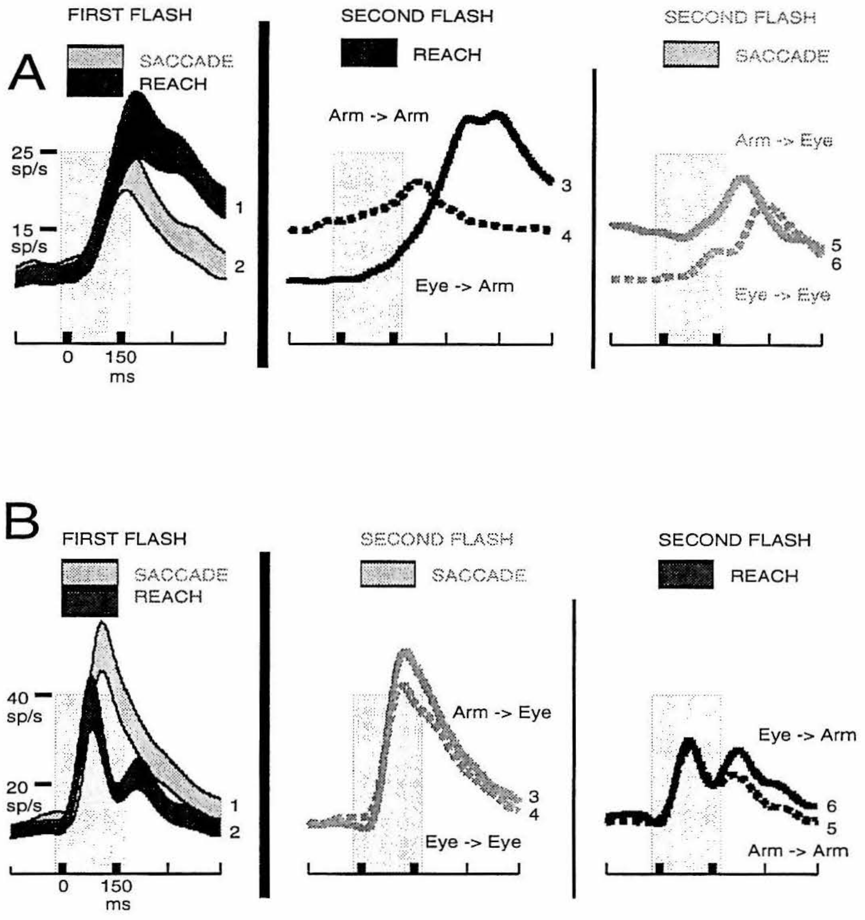

Figure 3.3: Population data from PRR (**A**; average of 17 cells) and LIP (**B**; average of 20 cells). Responses to first (left) and second (right and center) flashes, instructing either a saccade (light) or a reach (dark) are shown. Second flashes could instruct a preferred (center) or non-preferred (right) movement, and this instruction could countermand (solid traces 3+5) or affirm (dashed traces 4+6) the original instruction. The response to a preferred countermanding flash was larger than to a preferred affirming flash (traces 3 versus 4) and comparable to the response to a preferred first flash (trace 1). For non-preferred movements, countermanding and affirming flashes elicited similar comparatively small responses (traces 5 versus 6). Format as in figure 3.2, except that standard error was calculated across cells rather than across trials (left panels).

	PRR		LIP	
Movement Instructed	Responses	No. of cells > vs. < No. of significantly > No. of significantly <	Responses	No. of cells > vs. < No. of significantly > No. of significantly <
Preferred vs. **N**ull	26.2±2.3** vs. 16.1±1.8	16 vs. 1 15* 1*	30.8±2.1** vs. 18.2±1.5	20 vs. 0 14* 0
-/**P** vs -/**N**	23.3±3.4** vs. 12.9±2.6	15 vs. 2 11* 1*	31.2±3.5** vs. 20.8±3.0	20 vs. 0 9* 0
N/**P** vs **P**/-	30.4±3.8 vs. 26.2±2.3	12 vs. 5 6* 0	33.6±3.8 vs. 30.8±2.1	13 vs. 7 4* 1*
P/**P** vs **P**/-	16.1±3.1** vs. 26.1±2.3	2 vs. 15 1* 13	28.9±3.3 vs. 30.8±2.1	10 vs. 10 1* 4*
N/**P** vs P/**P**	30.4±3.8** vs. 16.1±3.1	15 vs. 2 13* 1	33.6±3.8** vs. 28.9±3.3	13 vs. 7 1* 0
P/**N** vs N/**N**	12.3±2.6 vs. 13.4±2.7	5 vs. 12 1* 2*	22.6±2.8 vs. 19.0±3.2	13 vs. 7 4* 1*

Table 3.1: Population firing rate (spikes per second; columns 2 and 4) and cell counts (columns 3 and 5) from PRR ($n = 17$) and LIP ($n = 20$) showing responses to first or second flashes instructing movements of a preferred (P) or non-preferred type (N). In PRR, reaches were preferred, whereas in LIP, saccades were preferred. This held for responses to both first (row 1) and second (row 2) responses. The next two rows compare second versus first flash responses, where each instructed the same perferred movement but the second flash either countermanded (row 3) or affirmed (row 4) the first flash. The final two rows compare the response to a countermanding versus affirming second flash, instructing either a preferred (row 5) or non-preferred (row 6) movement. Population data shows mean ± 1 SE under each condition, with ** indicating a significance level of $p \leq 0.01$. First line of single cell data shows the number of cells in which first condition responses were greater than second condition responses, versus the number in which the second responses were greater than first. The next two lines show the number of cells for which these two inequalities were significant at $p < .05$ (*), respectively. See text for details.

flashes shifted the locus of attention, suggesting that a component of LIP and PRR activity reflects the setting up of specific motor plans, and not the location of spatial attention.

Steinmetz and colleagues reported a very different effect in 7a: repeated flashes at the same location elicited reduced responses (Steinmetz et al. 1994, 1995). In PRR and LIP, responses to a second flash were reduced if the two flashes instructed the same movement (figure 3.3, A and B, trace 4 vs. 1): 16.1 ± 3.1 versus 26.2 ± 2.3 in PRR, and 28.9 ± 3.3 versus 30.8 ± 2.1 in LIP ($p <$ 0.01 in PRR). Single cell data confirm these findings, with stronger effects in PRR than in LIP. An affirming second flash elicited a significantly decreased response (compared to that elicited by the same flash presented first) in 16 cells and an increased response in only 2 (table 3.1, P/P vs P). In contrast, a countermanding second target elicited significantly decreased responses in only 3 cells, but significantly increased responses in 10. Therefore, the decrement seen by Steinmetz et al. in 7a, whereby responses to stimuli presented at an attended location were reduced, was evident in LIP and PRR only when the stimulus affirmed the existing motor plan. If the stimulus signalled a change in motor plan, the effect was reversed, and a similar or even increased response occurred. This is again consistent with the idea that a large component of LIP and PRR activity reflects specific motor intention, and not the location of spatial attention.

A strong test of the motor intention hypothesis is to compare responses to the same second flash when it either affirms (dashed traces) or countermands (solid traces) the first instruction. A flash instructing a preferred movement evoked a greater response when it countermanded rather than affirmed the preceding flash (traces 3 versus 4: 30.4 ± 3.8 versus 16.1 ± 3.1 sp/s in PRR, 33.6 ± 3.8 versus 28.9 ± 3.3 in LIP; both $P < 0.01$). The small but significant effect in LIP was consistent across the two animals. This suggests that LIP and PRR activities are modulated by changes in the intended motor plan.

From these data alone, we cannot rule out an alternative explanation: a novel color elicits a greater response than a familiar color. However, responses to second flashes instructing non-preferred movements do not support a role of novelty, as they did not depend on the preceding flash (traces 5 versus 6: 12.3 2.6 versus 13.4 2.7 sp/s in PRR; 22.6 2.8 versus 19.0 3.2 sp/s in LIP; both p >0.05). Two points are worth noting. There is a late divergence of LIP responses, although the early responses are almost identical. Second, in PRR, the peak response to a countermanding non-preferred flash was greater than that to an affirming non-preferred flash, but this only reflects the higher sustained activity following the first flash and preceding the second; the relative increases from the two different baselines are similar. The 350-550 ms measurement interval for second flashes was chosen to avoid baseline contamination.

A cell by cell analysis confirmed the population data. A second flash instructing a preferred movement evoked a significantly larger response in 14 of 37 cells when it countermanded rather than affirmed the first flash, with no cells showing a significant decrease (table 3.1, N/P vs P/P). If increased responses to countermanding flashes were an effect of stimulus novelty, we would expect a similar increase for countermanding non-preferred flashes. Instead, similar numbers of cells showed increased and decreased responses, exactly as would be predicted if there were no systematic effect of novelty (table 3.1, P/N versus N/N). Therefore, novelty alone cannot explain why a preferred second flash elicits a greater response when it countermands rather than affirms the first flash.

3.5 Discussion

There has been considerable investigation examining the degree to which posterior parietal activity is better described as encoding sensory responses, spatial attention, or motor intention (Mountcastle et al. 1975; Lynch et al. 1977; Robinson et al. 1978; Gnadt and Andersen 1988; Andersen 1995; Colby et al. 1995). Two recent findings inspired the current study. First, cells in LIP and PRR encode specifically (though not exclusively) the intention to saccade and reach, respectively (Snyder et al. 1997). Second, in 7a, responses to targets appearing at attended locations were diminished relative to responses to targets at non-attended locations, consistent with a role for 7a in shifting spatial attention (Steinmetz et al. 1994, 1995).

In our task, a direct comparison of first and second flash responses was problematic, since the animal was in a different behavioral state in each case. Prior to the first flash, the animal did not know which of the two possible directions to attend to, and no movement plan had been instructed. The second flash, on the other hand, either affirmed or countermanded a previously established plan, and did not shift the locus of attention. Despite this difference, responses to preferred, countermanding second flashes were comparable to or greater than responses to preferred first flashes, consistent with the idea that shifts in motor intention are at least as important as shifts in attention. Another demonstration of this idea was the fact that the response to a second flash instructing a preferred movement was greater when it countermanded rather than affirmed the preceding flash (figure 3.3). Similar patterns were seen in both LIP and PRR, although the magnitude of the effects were larger in PRR.

If LIP and PRR are inhibited by non-preferred motor plans, as suggested by the data of Snyder et al. (1997), then the larger response to a countermanding second flash could reflect a rebound from inhibition. Alternatively, the smaller response to an affirming second flash could reflect the fact that an affirming flash carries no new information and is therefore filtered out at an early stage. Additional processing that occurs only when there is already an existing motor plan could account for the increased latency of PRR responses to the second compared to the first flash. The two explanations (rebound from inhibition or filtering out of superfluous information) are not mutually exclusive, and both are consistent with a role of LIP and PRR in establishing and changing motor plans.

Temporal properties of LIP and PRR responses were not identical. In this data set, large, brisk transients were common in LIP, while sustained responses were more common in PRR. Response latencies to first and second flashes differed by ~150 ms in PRR, but were similar in LIP. These properties could be interpreted to suggest that LIP may be more closely related to the visual event, and PRR to the intended reaching movement. However, many PRR neurons have brisk transient responses, while many LIP neurons have been shown in previous studies to have long sustained activity (Gnadt et al. 1988, Snyder et al. 1997). Furthermore, intention affected even the earliest transient responses in some cells in both regions (Snyder et al. 1997; unpublished observations). Finally, the principal findings – selective response to flashes that shift motor intention but not attention, and differential responses dependent on whether motor intention is countermanded or affirmed – occurred in both PRR and LIP. Keeping in mind that PRR comprises several anatomically distinct areas, perhaps each playing a different role in the visual-motor transformation, the evidence suggests that both LIP and PRR process visual information for the purpose of specific motor planning.

Chapter 4 Reference Frames for Reaching in PRR

The experiments of the previous two chapters were designed to address a long-standing question about the sensory-motor role of area LIP. In that experiment, we used reaching as a task that would have similar attentional demands to an eye movement task, but very different intentional demands. The outcome of the experiment was unambiguous: it showed that area LIP is involved in the intention to saccade, and reflected sensory attention to a much lesser extent. A fortuitous outcome of these experiments was that we discovered the parietal reach region, PRR, a nearby area of parietal cortex that reflects the intention to reach.

This area, part of the dorsal processing stream, represents space for the purpose of making arm movements. Neurons are most active for reaches made in one direction, less active for reaches to nearby directions, and not responsive at all when the reach is directed opposite to the preferred direction. Different neurons have different preferred directions, so that all of PRR together represents space for the purpose of reaching. One of the most fundamental pieces of information to learn about an area that represents space is to describe that representation. That is, what coordinate frame do neurons use to represent space? This chapter presents our study of the coordinate frames used by PRR to represent reach plans.

The main component of this chapter is a paper recently submitted. It is presented in section 4.2. To give a fuller description of our studies, two extra sections are included here. An introductory section motivates and poses the question we asked in our coordinate frame experiment. After the section detailing the main results, a final section discusses some further results that were not included in the paper.

4.1 Prologue on coordinate frames for reaching

In the next section, an experiment is presented in which we attempted to isolate several candidates for the coordinate frame that PRR may employ to guide reaches. This section will motivate the possibilities for the coordinate frame used by PRR, and our methods of establishing which are used.

In visually-guided reaching, the hand is directed toward a seen target. The target's position enters the brain in the coordinates of the retina. The output of cortical processing must be a specification of the direction and distance the hand must move to reach the target. This output may perhaps also specify the path the hand must take, or the speed and force with which it must move. Some limb-centered reference frame is required for this specification. The reach could be coded cortically as signals related to intrinsic parameters of the movement, such as muscular contractions or joint rotations. Or extrinsic limb-centered coding could be used: the vector from the hand's current position to its target position could be represented cortically, with circuitry in the spinal cord and the properties of the arm muscles handling the details of the reach.

Between the retinal and limb-centered encoding of the reach, the plan may pass through a variety of processing stages. One intermediate coordinate frame that is commonly proposed is head-centered coding of the position of the target. This would be computed by adding eye position information to the retinal position of the target. The target-s position in trunk- or shoulder-centered coordinates could be computed by adding in the position of the head on the body. At last, the position of the limb must be added to compute a limb-centered representation of the target.

Clearly, all these signals must be combined to perform the reach. We sought to determine which coordinate frames PRR employs. And, from that result, to learn how the brain combines these signals. Are they all combined at once in a single stage of processing? Or is the transformation gradual, with different cortical areas performing progressive elaborations of the reach plan?

Our experiment tested between two hypotheses explicitly: that PRR uses an eye-centered representation, and that the area employs a limb-centered representation of target location. Within limb-centered coding, two general classes of coding are possible: either an extrinsic representation (the direction and distance from the hand to the target) or an intrinsic representation (the joint rotations or muscular contractions needed to bring the hand to the target). We designed the experiment to avoid confounding these. Finally, the paradigm allowed the possibility that head-centered coding would be discovered.

The principle of the experiment was to map out reach tuning curves in four different conditions, then compare those tuning curves. A *tuning curve* here means the firing rate of the neuron as a function of reach endpoint. The four conditions resolved into two pairs, each testing a different possible influence on the neuron. In one pair, we varied the initial position of the hand, and explored what effect it would produce on neurons. If the tuning curves did not differ, that would show the cell was unaffected by the limb-centered position of the target, and would suggest the cell coded in eye coordinates.

In the other pair of tuning curves, the eye position was changed, and the initial hand position was the same. If the cell did not respond differently, we could conclude it was unaffected by the retinal position of the target. The neuron was likely, then, to code in limb coordinates.

If both pairs of tuning curves were very similar, that would show the cell was insensitive to both the retinal and limb-centered positions of the target, and could be coding in head-centered coordinates.

Thus, similarity between two tuning curves would allow us to conclude that the variable that had been manipulated did not influence the neuron. We computed the correlation coefficient (equation 4.1) between the tuning curves as the measure of their similarity.

A more direct test for eye-centered coordinates was to see if the tuning curves remained fixed to the eyes, when gaze was directed differently. To measure this, we compared the two tuning curves that were collected when gaze was different, and observed whether they were highly correlated when shifted into alignment on the eyes, so that the target positions on the retina were the same.

An equivalent comparison for limb coordinates was not possible. Varying the initial position of the hand while the animal performs a reach of the same direction and distance has been found to change the response of neurons in M1 and PMd, areas clearly related to reaching. This is because cells in these areas code intrinsic parameters of the arm movement. By changing the initial hand position, the muscle contractions and joint rotations needed to reach a target at the same position relative to the hand will change. Extrinsic limb-centered coordinates are rare in cortex. Only in PMv have been found neurons with response fields that stay anchored to the limb as it moves. It was possible that PRR coded in intrinsic limb-centered coordinates. If so, by changing the initial hand position and instructing the same reach, we would see quite different responses, leading us to mistakenly conclude that the neuron did not use limb-centered coordinates. Only if PRR coded in extrinsic limb coordinates, as does PMv, would the preferred reach endpoint remain a fixed direction and distance from the hand when the initial hand position was changed. Because of the difficulty in dissociating extrinsic and intrinsic limb-centered coordinates, our test for limb-centered coding involved observing no change in neurons' responses when the initial hand position was kept constant and the other parameter likely to affect the cells (retinal position of the target) was changed. A consequence of this was that, in our paradigm, it was possible that limb-centered and head-centered coordinates would not be differentiable. Further experiments to dissociate these possibilities by changing the head position were envisioned, if necessary.

In summary, no change in the response of a neuron when the eye position was changed suggested the cell used limb-centered coordinates for representing reach targets. No change when the initial hand position changed was evidence for eye-centered coding of reach goals. Conclusive evidence for eye-centered coding was to observe that the preferred reach endpoint was constant relative to the point of fixation. Head- or body-centered coding of reaches would be evident as similarity between all four tuning curves, showing an insensitivity to both the eye and hand positions of the target.

4.2 Reach Plans in Eye-Centered Coordinates[1]

4.2.1 Abstract

Visually guided reaching begins with an image on the retina and ends with neural impulses to the muscles. In between a plan to reach is formed. This plan could be in the coordinates of the limb, specifying the direction and amplitude of the movement, or it could be in one of a number of other coordinate frames. We found that a reach planning area in the posterior parietal cortex codes reach targets in eye-centered coordinates. This finding is the first physiological demonstration of reaching planned in eye coordinates. Such a coding of limb movements in this visual frame of reference is advantageous because both obstacles that affect planning and errors in reaching are registered in this reference frame. Also, eye movements are planned in eye coordinates, and the use of similar coordinates for reaching may facilitate hand-eye coordination.

4.2.2 Introduction

To reach to an object, information about its location must first be obtained from the retinal image. Early visual cortical areas contain topographic maps of the retina, and as a result the target is originally represented in eye-centered coordinates. However, targets for reaches should ultimately be represented in limb coordinates, specifying the direction and amplitude the limb must move (so-called motor error) in order to obtain its goal. Thus, for the brain to specify an appropriate reach command, coordinate transformations must take place. Transformation of signals from eye to limb coordinates requires information about eye, head, and limb position. These signals could be combined all at once to accomplish this transformation, or in serial order to form intermediate representations in head-centered coordinates (by adding eye position information) and body-centered coordinates (by adding eye and head position information) (Jeannerod 1988). At some point in this process a plan to make the movement is formed, and knowing how reach plans are represented in

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[1] Section 4.2 has been submitted for publication (Batista, Buneo, Snyder, and Andersen 1999). Figure 4.2, included here, was not included in the submission. Section headings have been added.

the brain can tell us much about the mechanisms and strategies the brain uses to generate reaches.

The major anatomical pathway for visually guided reaching begins in visual cortex and passes through the posterior parietal cortex (PPC) to the frontal lobe. Different regions of PPC have recently been shown to be specialized for planning different types of movements (Snyder, Batista, and Andersen 1997; Murata, Gallese, Kaseda, and Sakata 1996), including areas specialized for saccadic eye movements (the lateral intraparietal area, LIP), for reaches (the parietal reach region, PRR), and for grasping (the anterior intraparietal area, AIP). In other words, by this level of the visual-motor pathway the pattern of neural activity reflects the outcome of a movement selection process. Since PPC is partitioned into planning regions for different actions, it has been proposed that each subdivision should code its respective movement in the coordinate frame appropriate for making the movement (Colby 1998; Rizzolatti, Riggio, and Sheliga 1994). This proposal predicts that targets for reaches should be coded in limb coordinates in PRR. Here we show that the reach-specific neurons in PRR code reach targets in eye-centered coordinates, not in limb coordinates, showing that, at least in PRR, early reach plans are coded in terms of visual space rather than in terms of the limb.

4.2.3 Results

Single cell recordings were made in PRR (see section 4.2.5: "Delayed reach and saccade tasks"). We tested neurons in four conditions; in two conditions different reaches were performed to targets at the same retinal location, and in the other two conditions the same reach was made to targets that were now at different retinal locations. This paradigm allowed us to observe independently the effects on PRR neurons of manipulating target location in eye and limb reference frames (see section 4.2.5: "Coordinate frame task"). Figure 4.1 shows a reach-specific neuron tested in these four conditions. Panels A and B illustrate the effect of varying the initial hand position: the cell's spatial tuning is similar in the two cases, showing that the cell is largely insensitive to the limb-centered position of the target. Panels C and D illustrate the effect of changing the direction of gaze, which markedly changes the spatial tuning of the neuron. In all cases, the cell's preferred reach endpoint is constant relative to the direction of gaze, i.e., down with respect to fixation. This neuron is selectively active for reaches (figure 4.2), but encodes target location in an eye-centered reference frame.

This neuron was exemplary of the population of 74 neurons from three monkeys tested in this experiment. Figure 4.3A summarizes the data from all neurons, using a correlation analysis (de-

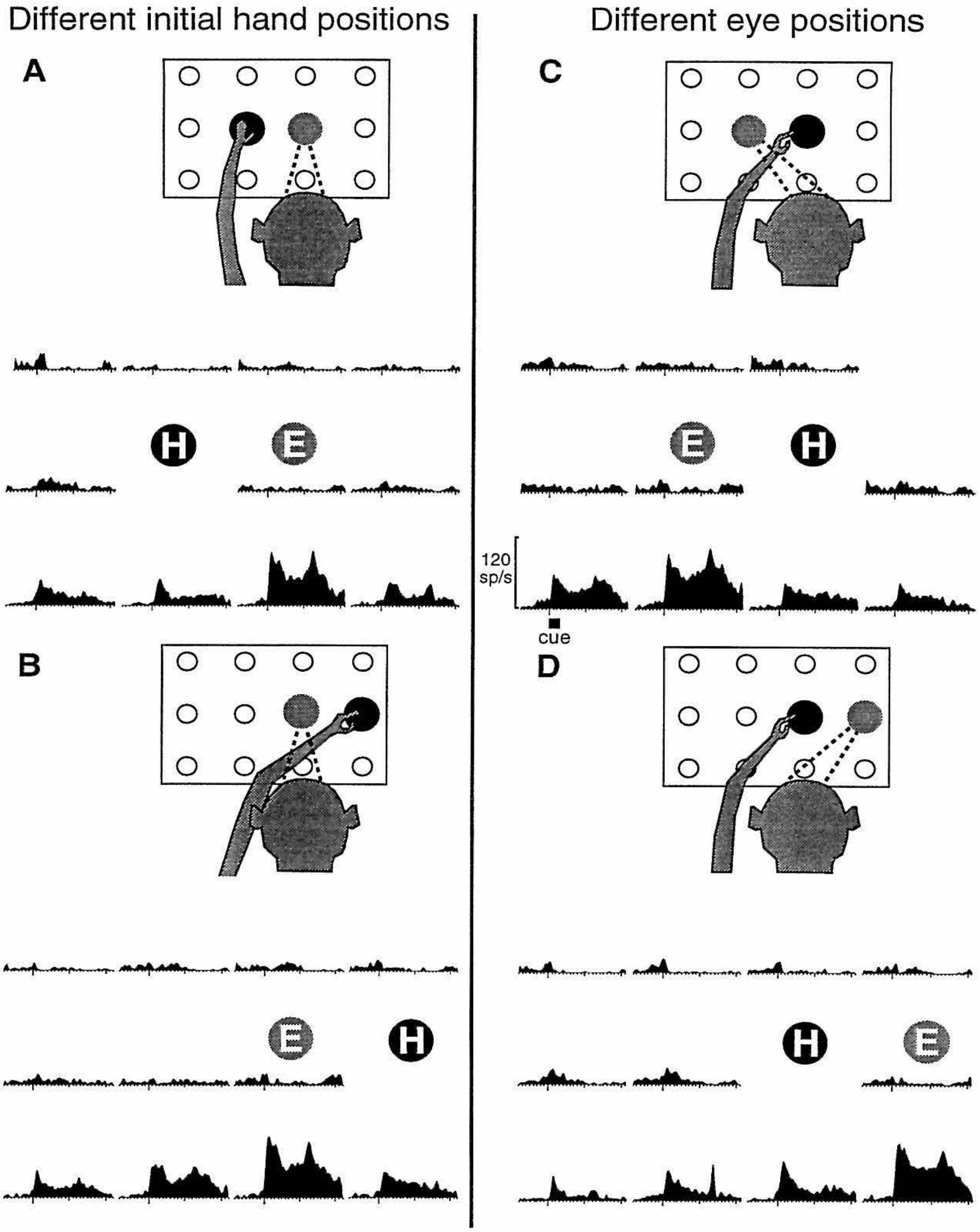

Figure 4.1: Behavior of a PRR neuron in the coordinate frame experiment. Each panel (**A**-**D**) shows the response of the cell for reaches made from one configuration of eye position and initial hand position. Spike density histograms are plotted at a position corresponding to the target button's location on the board. Histograms are aligned on the time of cue onset, indicated by the long tic on the time axis. The cue was illuminated for 300 ms, its duration is marked in panel C. Tic marks, 100 ms. The icon in each panel shows the array of push buttons on the board, with the button the monkey pushes at the beginning of the trial (initial hand position) highlighted in black and the button the monkey fixates highlighted in gray.

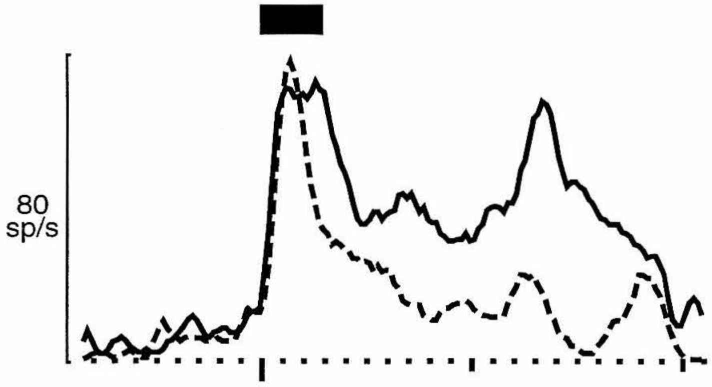

Figure 4.2: Behavior of the neuron of figure 4.1 in the delayed reach and delayed saccade experiments. Two histograms of the neuron's firing rate as a function of time are shown. The *solid trace* is activity during the delayed reach task; the *dotted trace* is activity during the delayed saccade task. Data shown are for movements straight down, the direction of movement that maximally activated the neuron in both tasks. Histograms are aligned on the time of cue onset, indicated by the long tic on the time axis. The reach occurs around the time of the second peak of activity in the solid trace. Tic marks, 100 ms.

scribed in section 4.2.5: "Analysis for CF task"). Each point represents one neuron; a point's position along the horizontal axis represents the correlation between the cell's two tuning curves measured with targets at the same retinal location (configurations shown in figure 4.1, A and B). The position along the vertical axis represents the correlation between that neuron's tuning curves measured with targets at the same limb-centered location (configurations shown in figure 4.1, C and D). Eighty-four percent of the neurons lie below the line of equal correlation[1], showing a better correlation in an eye-centered reference frame than in a limb-centered reference frame. A second test was used in which the two tuning curves measured with the same initial hand position but with different eye positions were shifted into alignment in eye-centered coordinates (figure 4.3B). With this analysis 81% of neurons had a correlation that was greater when the tuning curves are shifted into eye-centered alignment than when they were not shifted. These two analyses show that most PRR neurons code reaches in an eye centered, rather than a limb centered, reference frame. Head- and body-centered reference frames can also be ruled out, since the target location in these reference frames does not change across the four conditions, although the neural responses do when the direction of gaze is changed.

An eye-centered representation of a reach plan may potentially be disrupted if the eyes move before the reach can be executed, particularly in the case in which the reach is to a remembered

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[1] 91% of neurons in monkey D (42 were tested), 78% in monkey O (18 tested), and 71% in monkey C (14 tested) show a greater correlation in eye-centered coordinates than in limb-centered coordinates.

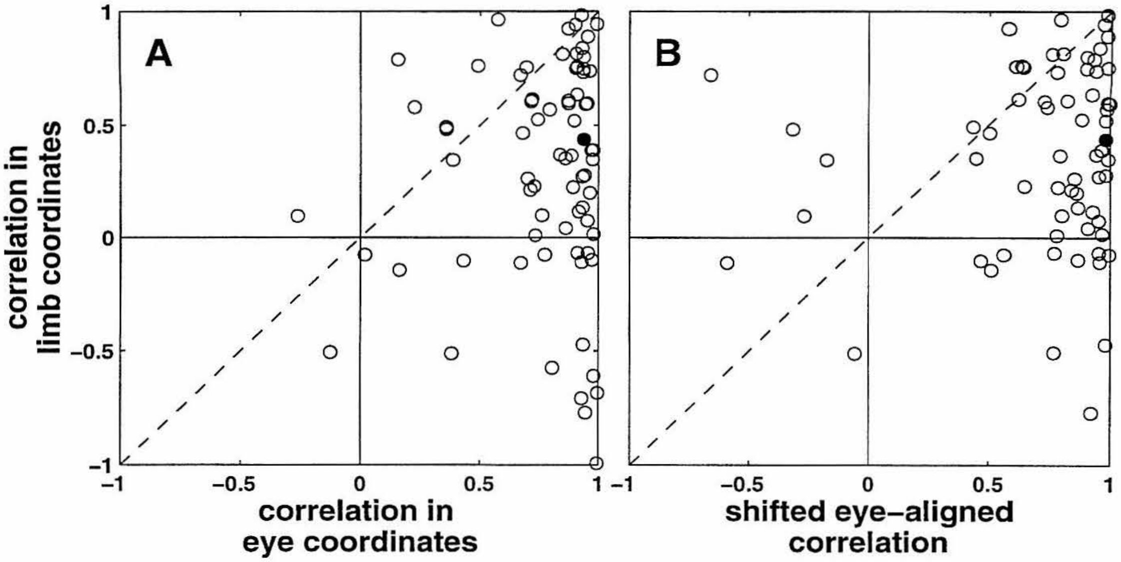


Figure 4.3: Reference frame analysis for the population of reach neurons. (**A**) For each neuron (○), the correlation between the two tuning curves that have a common initial hand position (figure 4.1C and D) is plotted on the vertical axis, and the correlation between the two tuning curves that have a common eye position (figure 4.1A and B) is plotted on the horizontal axis. Seventy-four neurons are shown. The diagonal line represents equal correlation in limb-centered and eye-centered coordinates. The filled circle represents the neuron shown in figure 4.1. (**B**) The vertical axis is the same as A; the horizontal axis is the correlation for the tuning curves collected with the same initial hand position, but shifted into the same eye-centered alignment (e.g., data in figure 4.1C correlated with data in figure 4.1D, shifted two buttons to the left).

location in the dark. Other brain areas involved in movement planning have been shown to update their spatial representations across saccades and head movements (Mays and Sparks 1983; Gnadt and Andersen 1988; Duhamel, Colby, and Goldberg 1992; Walker, Fitzgibbon, and Goldberg 1995; Graziano, Hu, and Gross 1997). To test whether PRR can compensate for a saccade, we trained animals to make a saccade while planning a reach (see section 4.2.5: "Intervening saccade task"). The reach target was presented outside of or on the edge of the response field, and then, after the target was turned off, a saccade was instructed which brought the reach goal into the center of the response field. Figure 4.4C shows a neuron tested in this task. Before the monkey makes a saccade, the neuron's response is low, indicating the target is out of the response field (figure 4.4A). After the saccade, the neuron responds at a higher rate, similar to its response when the target actually appears in the response field (figure 4.4B). All 34 reach-specific neurons tested in this task showed a significant increase in response after a saccade brought the remembered target location into the response field 4.2.5 (figure 4.4D). Thus, PRR compensates for saccades in order to preserve correct

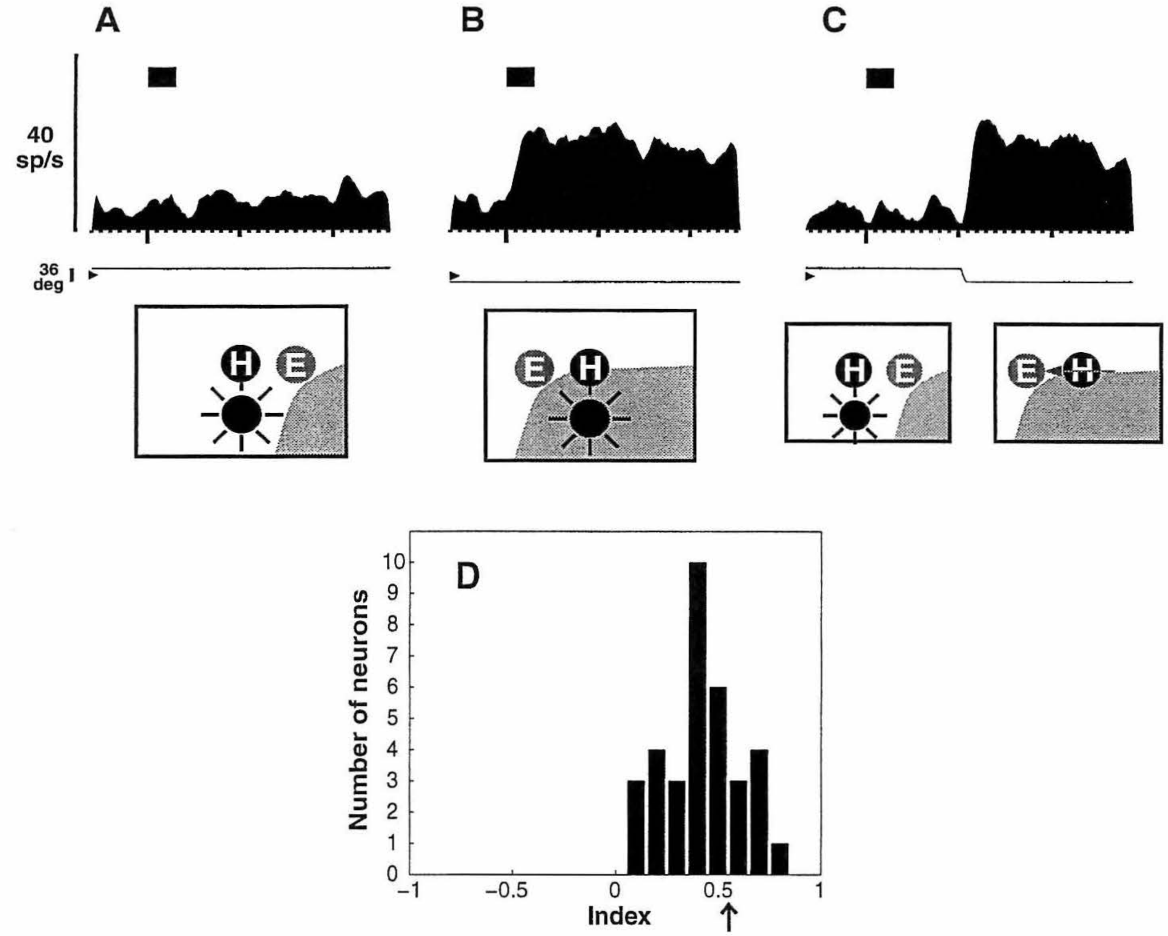


Figure 4.4: (**A**-**C**) Behavior of one neuron tested in the intervening saccade experiment. The three spike density histograms show the response for reaches to the same target in the three tasks. The position of the response field is indicated by the gray region. (**A**) Delayed reach (*DR*) task (with no eye movement) with gaze directed so that the target is out of the response field. (**B**) DR task with the target in the response field. (**C**) Intervening saccade (IS) task. The eye movement carries the reach goal into the neuron's response field. Below each histogram is a trace of the horizontal component of eye position during one trial. Bars above histograms, timing of cue. Histograms are aligned on time of cue presentation. (**D**) Population analysis. Index is $\frac{after\ saccade - target\ out}{after\ saccade + target\ out}$ where *after saccade* is the mean firing rate in the IS task during the 500 ms epoch from 100 ms after the saccade to the "go" signal, and *target out* is the mean firing rate in the DR task configuration with the target out of the response field (i.e., figure 4.4A) during the 500 ms before the "go" signal. The index value for the cell in figure 4.4A-C is indicated by the arrow.

encoding of reach targets in an eye-centered reference frame.

4.2.4 Discussion

Psychophysical studies have provided evidence for a number of extrinsic coordinate frames for reach planning including eye-, head-, and shoulder-centered coordinates (Henriques, Klier, Smith, Lowy, and Crawford 1998; Vetter, Goodbody, and Wolpert 1999; Soetching, Helms-Tillery, and Flanders 1990; McIntyre, Stratta, and Lacquaniti 1997). Presumably the studies which find eye-centered effects are probing early planning stages in areas like PRR which code in eye coordinates.

There is suggestive evidence that PRR may work in conjunction with other areas to specify reach plans in eye coordinates. Lacquaniti et al. (Lacquaniti, Guigon, Bianchi, Ferraina, and Caminiti 1995) found some area 5 neurons with reach activity that was more closely linked to the spatial location of the goal than the direction of limb movement, although the paradigm they used did not allow them to determine the reference frame used by these cells. Although cells with response fields that are spatially invariant when the direction of gaze changes have been found in area VIP (which has been suggested to play a role in head movements (Colby 1998)), this is true only of about half the cells in VIP(Duhamel, Bremmer, BenHamed, and Graf 1997); the other cells in this area code in an eye-centered frame. Even in the premotor cortex, where limb-centered (Graziano, Yap, and Gross 1994) and other non-retinal (Fogassi, Gallese, Fadiga, Luppino, Matelli, and Rizzolatti 1996) response fields are found, approximately half of the cells are still modulated by eye position(Mushiake, Tanatsugu, and Tanji 1997; Boussaoud, Jouffrais, and Bremmer 1998), although it has yet to be established whether the response fields are in eye coordinates.

Recent studies have emphasized that two largely non-overlapping circuits, distributed through multiple brain regions, are responsible for eye movements (Cavada and Goldman-Rakic 1989; Blatt, Andersen, and Stoner 1990) and reach movements (Johnson et al. 1996). We propose that there is an initial stage in the multi-area reach circuit in which reaches are coded in eye-centered coordinates (see figure 4.5). Response fields in a variety of areas in this presumed reach network, which includes PRR, area 5, PO/V6A, and premotor cortex, are gain modulated by eye, head, and limb position signals. These gain fields can provide the mechanism necessary for the transformation (Zipser and Andersen 1988) to later effector-centered reference frames such as limb-centered coordinates (figure 4.5). The few cells we did find in PRR that were better correlated to a limb reference frame than to an eye reference frame, along with the cells with non-retinotopic and limb-centered fields in other reach areas, could reflect these later stages of movement processing. A prediction of this

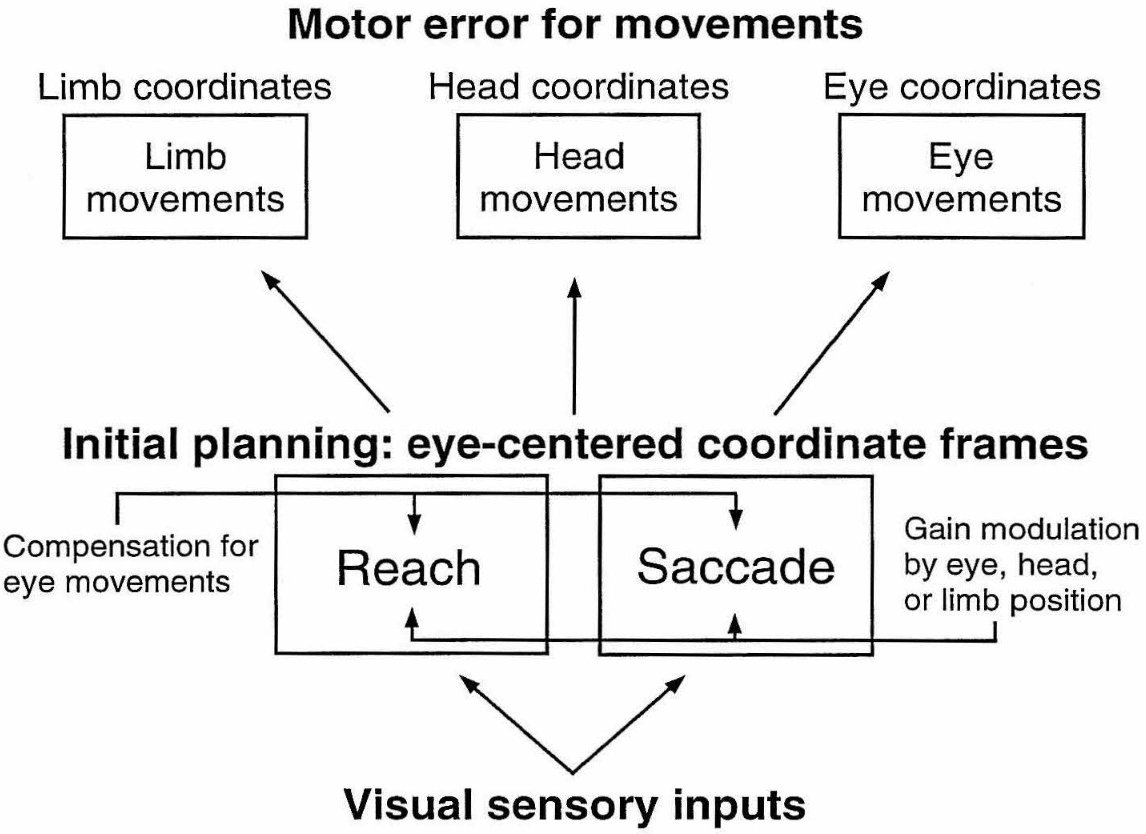


Figure 4.5: Summary of pathways for sensory-motor control. Putative flow of information is from bottom to top.

model, borne out by this study, is that for the transformation to operate correctly, neurons with eye-centered response fields must compensate for intervening saccades, since eye position gains will necessarily change after the saccade. In summary, our model proposes that initial plans to reach or make a saccade to a target are formed within distinct networks in eye-centered coordinates; these plans are updated if disrupted by intervening saccades; and finally, later stages of reach processing in head, body and limb coordinates are achieved through gain modulations of the eye-centered representation.

There are several possible reasons why early reach plans are made in eye coordinates. First, natural scenes are cluttered with many potential reach goals as well as obstacles to reaching. If every object had to be converted to limb coordinates prior to the formation of a planned reach, considerably more computation would be required than if the initial planning is performed in visual coordinates (Sabes and Jordan 1997). Second, reach movements can be modified in flight by visual cues and cortical motor activity is correlated with these modifications (Georgopoulos, Kalaska, Caminiti, and Massey 1983). Since the hand is usually visible during reaching, it would be most parsimonious to make corrections to the reach plan in the same coordinates as on-line visual error signals. Third, the reach system is plastic, as has been demonstrated in adaptation experiments in which the visual feedback during reaching is perturbed with prisms (Held and Hein 1958). Clower et al. (1996) have shown that parietal cortex is uniquely involved in prismatic adaptation for reaches. Again the errors detected for adaptation are in eye coordinates, and this would be a most natural coordinate frame in which to recalibrate reach plans. Finally, planning reaches in eye coordinates may facilitate hand-eye coordination. Even in simple tasks, there is a complex orchestration of eye and hand movements, with the eyes and hand often moving independently to different locations (Ballard, Hayhoe, Li, and Whitehead 1992). Nearby parietal area LIP is involved in planning eye movements, and shares many similarities with PRR including eye-centered response fields, compensation for intervening saccades, and gain field modulation by eye position (see figure 4.5). These two areas may use a similar encoding of space to enable fast and computationally inexpensive communication between them for simultaneous, coordinated movements of the eyes and arms. The above four considerations lead to the conclusion that the findings of this study, which at first glance appear quite surprising, are perhaps not so surprising after all.

4.2.5 Methods

Delayed reach and saccade tasks

All recordings were made in a region medial and posterior to LIP, presumably overlapping with areas V6A (Galletti, Fattori, Kutz, and Battaglini 1997) and MIP (Johnson, Ferraina, Bianchi, and Caminiti 1996; Colby and Duhamel 1991). Recording sites have been reconstructed in one animal, the other three are involved in other experiments. Eye movements were recorded using scleral search coils. A vertically-oriented 3X4 array of touch-sensitive buttons was placed 24 cm in front of the animal. Each button was 3.7 cm in diameter and contained a red and a green LED behind a translucent window 1.2 cm in diameter. Neurons were first tested in a delayed reach and saccade paradigm (Snyder et al. 1997). A trial began with the illumination of a red and a green LED at the button straight ahead. The animal would look at and touch this button. A cue was presented (300 ms for monkeys D, G and O; 150 ms for monkey C) at one of the eight locations surrounding the straight-ahead button, 18 or 26° from it. A red cue signaled an eventual saccade (*DS task*), and a green cue signaled a reach (*DR task*). After a delay period (800 ms or longer), the central LEDs were extinguished as a "go" signal. The animal would then make a saccade or reach to the remembered location of the target. Importantly, during saccade trials, the monkey could not move its hand, and during reach trials, the animal had to maintain fixation at the location of the now-extinguished red LED. The contralateral limb was used in all experiments. The animal's room was dark; there was no vision of the hand during the reach.

To test whether neurons were reach-specific, delay period activity (from 100 ms after the cue was extinguished until the "go" signal) was compared between the reach and saccade tasks. If the greatest reach planning response was significantly larger than the greatest saccade planning response (Mann-Whitney test, $p<0.05$), the neuron was considered reach-specific. Only reach-specific neurons were analyzed further.

Coordinate frame task

The coordinate frame (*CF*) task was a variant of the DR task. The position of either the red or green LED was varied. Four different configurations of eye and initial hand positions were used. In two conditions, the red LED instructing visual fixation was at the button located straight ahead, and the green LED instructing the initial button press was 18° (36° for 11 neurons in monkey C) to the left or right. In the other two conditions, the green LED was at the straight-ahead button, and the red LED was 18° to the left or right. For each neuron, the four initial configurations were randomly interleaved for five repetitions of reaches to each target.

Analysis for CF task

The average firing rate during the delay interval (from 100 ms after cue offset to the "go" signal) was used to compute the correlations. The formula employed was

$$correlation(x,y) = \frac{\sum_{i=1}^{n}(x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \overline{x})^2}\sqrt{\sum_{i=1}^{n}(y_i - \overline{y})^2}} \tag{4.1}$$

To compute the correlation in eye-centered coordinates, x_i is the average firing rate for a reach to a given target i from an initial hand position to the left, and y_i is a reach to the same target from an initial hand position to the right, $\overline{x}$ is the average of the x_i, and n is the number of targets that overlapped in the two configurations. To compute the correlation in hand-centered coordinates, x_i

and y_i are the average firing rates for reaches to target i, with the eyes fixating to the left (x) or to the right (y). For most cells, there were between eight and 11 overlapping locations. If there were fewer than three overlapping locations, the cell was not included in the correlation analysis.

Intervening saccade task

The intervening saccade (*IS*) task was a modification of the CF task. Five hundred milliseconds into the delay period, the visual fixation point jumped. The monkey responded by making a saccade to the new location of the red LED. Another 600 ms of delay period ensued before both fixation LEDs were extinguished to trigger the reach. This task was interleaved with two different configurations of the CF task: In one configuration, gaze was directed at the initial eye position for the intervening saccade trials. In the other configuration, gaze was directed at the final eye position for the intervening saccade trials. The delay epochs for the two CF tasks were lengthened to 1100 ms, to more closely match the overall delay period in the IS task. In all three tasks the initial hand position was at the center button, so the same reach was always performed. Typically, ten repetitions of each task were performed.

Analysis for IS task

Neurons that showed a significantly different response (Mann-Whitney test, $p<0.05$) during the final 500 ms of the delay period for the two CF tasks were analyzed further. A cell was considered to update if its response during the 500 ms period after the saccade and before the reach in the IS task was significantly greater (Mann-Whitney test, $p<0.05$) than its response during the 500 ms before the reach for the CF task with the target out of the response field. 15 neurons from monkey D, 3 from monkey G, and 16 from monkey O were studied.

4.3 Further considerations on coordinate frames for reaching

4.3.1 Comparison of coordinate frames during different epochs

Coordinate transformations unfold in time. It is possible that the process could be observed in individual neurons. PRR neurons possess responses to visual stimuli and responses just before the reach; it is possible that the visual activation in these neurons is encoded in retinal coordinates, and the reach activity is in limb-centered coordinates. When designing this experiment, we hypothesized that the process of coordinate transformation might occur in individual neurons, across time. If so, the early activity would be in retinocentric coordinates, and the late activity in limb-centered coordinates. Figure 4.6 tests this possibility, by showing the correlation analysis on different time epochs. The analysis is shown separately for each monkey, thus the effects can be compared across animals. To give a measure of the baseline value of the correlation metric, correlations were computed during the 500 ms before cue presentation, for all three animals (figure 4.7). There should be no structure to this correlation, since no spatial information has been presented yet. Although the spread of correlation values is large, the values are clustered around zero, and most of the correlation values shown in figure 4.6 exceed these correlations in background activity.

No trend from eye-centered coordinates to limb-centered coordinates as a function of time is evident. In fact, for two animals (O and D), the degree of eye-centered correlation in the population actually increases later in the trial. Rather, it seems that a reference frame is largely a static property of a neuron, and not something that changes rapidly in time.

4.3.2 Comparison of coordinate frames between animals

Figure 4.6 also allows a comparison between animals. The result of the coordinate frame experiment is consistent across animals, though monkey D showed the greatest percent of neurons using eye coordinates. It could be that slightly different regions of PRR were sampled from the three animals. Structural MRI and histological reconstruction of tracks offer methods to relate recording sites to anatomic patterns. Future explorations of PRR will benefit from these techniques. In general trends, however, the results from the three animals are comparable.

4.3.3 Limb-centered coding in PRR

Two pieces of evidence make it surprising that there is not a clear limb-centered representation of the target in PRR. First, PRR is likely to be reciprocally connected with areas that have limb proprioceptive information, such as area 5. Second, psychophysics studies show that initial hand position influences reach planning. The observation of eye-centered coding of the reach plans was surprising, so we looked more closely for limb position information in the coordinate frame data.

As is evident in figure 4.3, not all neurons represent the reach goal in an unambiguous eye-centered coordinate frame. Two exceptions to retinocentric representations of reach plans were noted in PRR. One, limb-centered coding, will be discussed first. The other, gain influences on

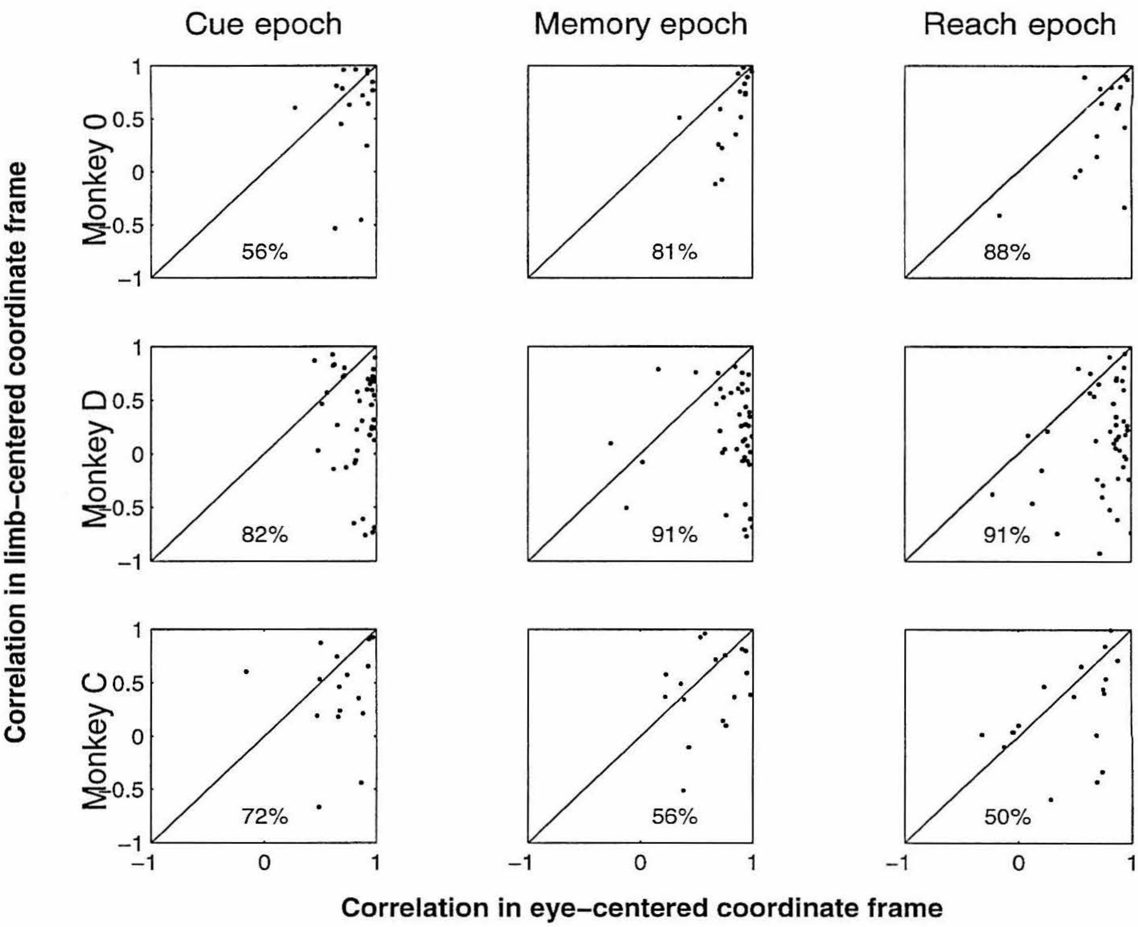


Figure 4.6: Population coordinate frames for different epochs, for each animal. All neurons selective for reaches are shown. Each column depicts correlations during three epochs: *cue epoch* is the 300 ms for monkeys D and O and 150 ms for monkey C starting 100 ms after cue onset; *memory epoch* is from 100 ms after cue offset until the "go" signal (earliest "go" signal for monkey C); *reach epoch* is 0 to 400 ms after the "go" signal. It includes the reach reaction time, and at least part of the movement. Each row illustrates data for a different animal.

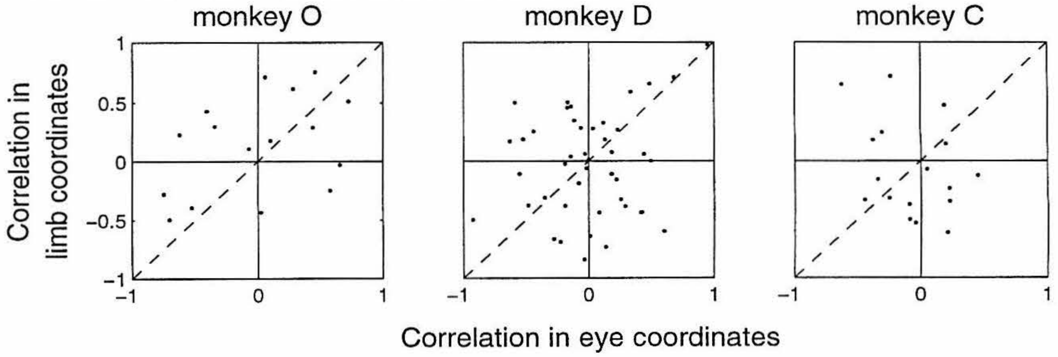


Figure 4.7: Correlations in the pre-cue interval for three monkeys. These values provide a measure of the baseline of the correlation metric.

eye-centered response fields, are discussed in the next section.

Strikingly, no neurons had response fields that moved with the limb when the initial hand position was altered, and were uninfluenced by the retinal position of the target. This is unlike area PMv, where 70 % of cells (that exhibited somatosensory responses on the arm and visual responses) have visual receptive fields that move with the limb (Graziano, Hu, and Gross 1997). The best example of a neuron coding in limb coordinates in PRR is shown in figure 4.8. Notice that the tuning curve peak moves with the hand, in configurations A and B. Altering the eye position (figure 4.8, C and D) had a different effect on the cell. This cell's tuning curve seems best described as a sum of an excitatory hand-centered response field and an inhibitory and more narrowly-tuned eye-centered response field. This neuron marks an interesting comparison with the cell shown in figure 4.1.

A few other examples of limb-centered responses were observed. Occasionally, cells would have a cue response that seemed dependent on the position of the hand, while the memory response did not show this dependence. These cells were not common, as can be seen in the left-hand column of figure 4.6, where no such trend across the population is evident.

In the coordinate frame data for many neurons, there was a high degree of similarity between the tuning curves measured with the eye and hand in the same position relative to one another; often these two tuning curves even more closely resembled one another than the two tuning curves measured with the eyes in the center, and the hand changed from one side to the other of the point of fixation. Figure 4.1 exhibits this: notice the similarity between the tuning curves in configurations A and D (shifted one position to the left), and between configurations B and C (shifted one position to the right). This suggests two things: first, that the position of the hand relative to the eyes is an important modulatory influence on PRR neurons, and second, that the position of the eyes and hand relative to the head does not affect neurons very much, at least over the 16° range we tested.

Chris Buneo developed a sensitive analysis to quantify the improved correlation when initial hand position is accounted for. Consider the left-hand panel in figure 4.9. It compares the behavior of the population of PRR neurons in the two hand-centered configurations. Each point represents the mean firing rate of one cell during the memory epoch for reaches made to one target. The point's position along the abscissa represents the cell's firing rate when the eyes fixate to the left, and the point's position along the ordinate is determined by the cell's mean firing rate for reaches made to the same target, when the eyes are to the right. Thus, each neuron contributes 8-11 points, depending on the number of reaches that were tested for that cell. If most points lined up along the diagonal line $y = x$, that would show the firing rates were similar for reaches to the same hand-

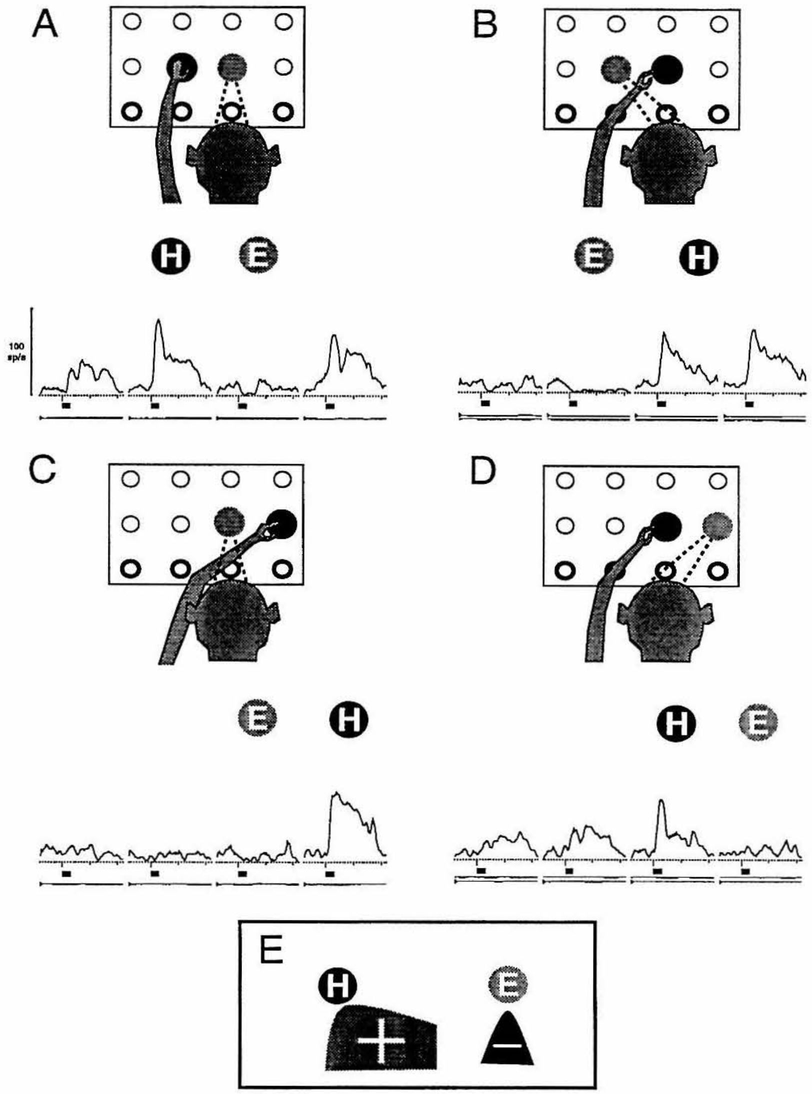


Figure 4.8: A PRR neuron with a hand-centered response field. **A**-**D**, Reaches performed from four different configurations of eye and initial hand position. Only responses for reaches to targets in the lower row (thicker circles at target locations) are pictured. Bar below each PSTH illustrates the timing of the cue. Lines below each PSTH show the horizontal and vertical components of eye position for all trials. **E**, Excitatory hand-centered (gray) and inhibitory eye-centered (black) response fields can explain the cell's response.

centered target, regardless of eye position, meaning the cells coded in hand-centered coordinates. There is a lot of scatter around the diagonal line (the correlation coefficient is 0.44), showing that the population does not code in hand-centered coordinates.

The center panel of figure 4.9 compares the firing rates for each cell in eye-centered coordinates. The cells show a greater correlation ($r = 0.84$), showing that the population of PRR neurons is better characterized as using eye-centered representations than hand-centered representations.

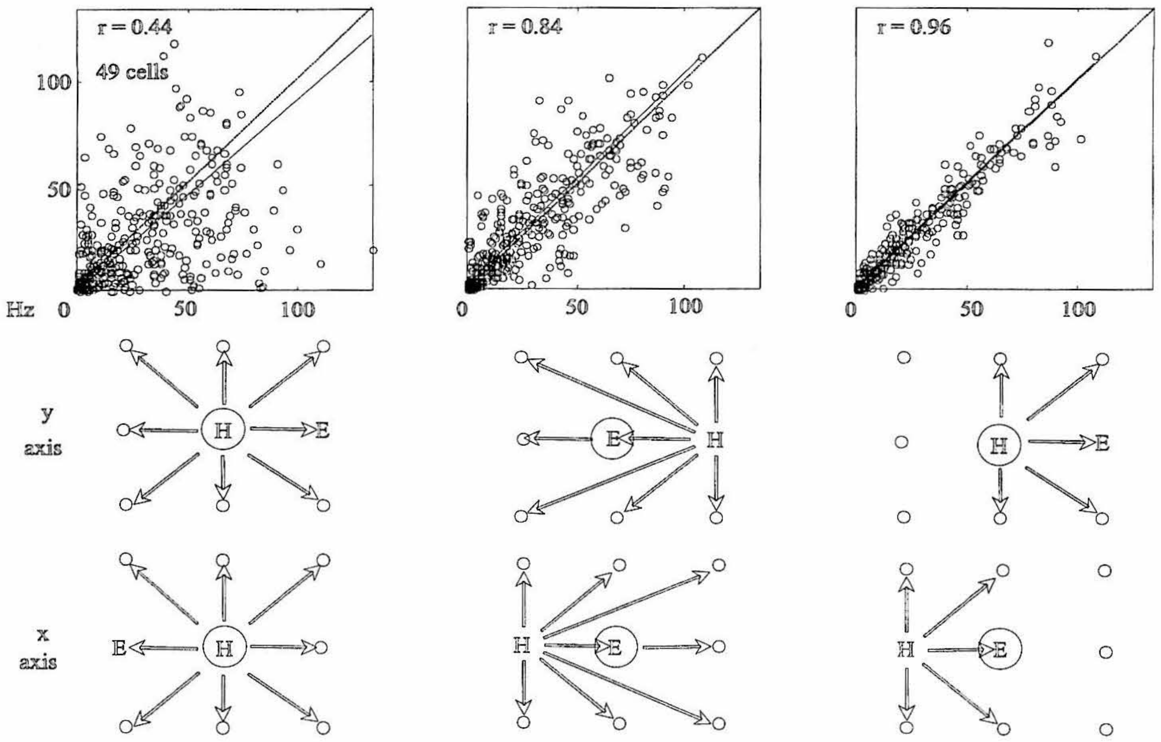
These analyses corroborate the results shown in figure 4.3. The rightmost panel presents a new observation: the highest correlation is seen in the comparison in that panel. It compares the firing rates when both eye and initial hand position are accounted for. That is, the two configurations of the coordinate frame experiment where the hand position relative to the direction of gaze is the same are compared. The correlation coefficient is 0.96 in this case, showing the most variability can be accounted for when the position of the hand with respect to the eyes, as well as the position of the reach endpoint with respect to the eyes, is considered. In other words, PRR represents the reach *vector* (from initial to final hand position), and not just the reach endpoint, in eye coordinates.

Thus, initial hand position is an important modulatory influence on many PRR neurons. This suggests that initial hand position and target position are both encoded in the same area in eye coordinates. Therefore, PRR may contain the signals necessary to act as a comparator between final hand position and target position. This would provide the necessary signals for adapting reach plans to perturbations of visual space or of the arm, such as during prismatic adaptation or tool use.

Also, the observation of an influence of initial hand position means PRR may be involved in path planning. As discussed in section 1.5, evidence from human psychophysics suggests that the path of the arm movement is planned in eye coordinates (Wolpert, Ghahramani, and Jordan 1995; Flanagan and Rao 1995). Further experiments are planned by Chris Buneo and Richard Andersen to explore in more depth the influences of initial hand position and the planned hand path on PRR responses.

4.3.4 Gain influences

We examined PRR data from monkeys C and D for gain field effects of eye and hand position. A gain field in this case is a scaling factor applied to an eye-centered response field due to the position of the eyes in the head, or the hand position with respect to the point of fixation. The observation of gain fields is important, for the presence of such effects indicates that a distributed population of cells can convey information in a different reference frame (Zipser and Andersen 1988; Pouget and



Mean Firing Rate is Best Correlated with Reach Vector in Eye Coordinates in PRR

Figure 4.9: PRR responses are best correlated with the reach vector in eye coordinates. From left to right, the scatter plots indicate the correlation in limb-centered coordinates, the correlation in eye-centered coordinates, and the correlation in a combined eye and hand coordinate frame. Each point represents the mean firing rate for reaches to a particular target for one neuron. The diagonal line represents equal firing rates in the two configurations. The off-diagonal line is a line of best fit to the data. Analysis performed and figure created by Christopher Buneo.

Sejnowski 1992).

We occasionally observed such gain effects on neural responses. For neurons that are not strongly aligned in one reference frame, it is difficult to disambiguate between the reference frame employed by that neuron and the gain influences affecting it. Some PRR neurons do not code in strict eye-centered coordinates; these cells appear to be affected by the target's position both on the retina and relative to the hand, and in addition by the eye position and the initial hand position. Thus, these cells carry a signal of the hand-centered position of the target.

For the 50% of neurons from monkeys C and D that were strongly eye-centered (i.e., they showed a correlation between 0.9 and 1.0 in an eye coordinate frame), gain effects could be tested. To test for a gain effect of eye position, we used the two tuning curves measured with the initial hand position at the center button and the eye position deviated. We shifted these curves so that the retinal positions of the targets were brought into register. Then, the neuron's maximal delay-period response was compared to its response at the same retinal location in the other tuning curve, if data had been collected there. For 23% of the cells where we could make this comparison, we found a significant modulation with eye position (Mann-Whitney test, $p<0.05$). The average modulation was 2.3%/degree.

To test for a gain effect of initial hand position in this subpopulation of neurons with clear eye-centered response fields, we compared the delay-period responses at the target location that maximally excited the neuron, in the tuning curves measured with two different initial hand positions. None of these neurons were significantly different in this test (Mann-Whitney test, $p<0.05$). However, as discussed in section 4.3.3 and shown in figure 4.8, some PRR neurons that are less well correlated in eye coordinates do convey information about the initial position of the hand. Thus, the possibility exists that populations of PRR neurons could act together to specify target positions in head-centered and limb-centered coordinates.

4.3.5 Head-centered coding in PRR?

The fact that there is modulation with changes in eye and/or limb position rules out head-centered coordinates. A neuron that used head-centered coding would occupy the upper right hand corner of the population plot in figure 4.3; that is, it would show no change when the target moved in retinal or hand-centered space. This region of the plot contains only a few cells, suggesting that head-centered response fields are not common in PRR. For a few neurons that seemed only weakly modulated by changing eye and hand position, we explicitly tested for head-centered responses by shifting the eye and hand together to one side or another. In this way, correlations could be compared between head-centered and "eye-and-hand-centered" alignments. All neurons tested in this way showed response fields that stayed fixed to the position of the eyes and hand, and not the head. This was true even for neurons where the response fields could not be shown to stay fixed to either the eyes or hand alone.

Another explanation why neurons might show a high correlation in both eye and hand coordinate frames is because the response fields are large, relative to the shifts we introduced. For example, consider a response field that is anchored to the eyes, and occupies a large region of visual space. If the eyes are moved a small amount relative to the size of the response field, the response field will seem to not move at all. By visually inspecting the data, it appears that some cells have response fields too large to ascertain what coordinate frame they are using.

4.3.6 Coordinate frames for reaches to auditory targets in PRR

What does it mean that reaches are coded in eye coordinates in PRR? One possibility is that the area reflects the spatial format of the sensory stimulus. Another possibility is that eye coordinates are a general format for representing space, perhaps to allow communication between different brain areas. To test between these explanations, Yale Cohen and Richard Andersen (1998) explored the coordinate frames used by PRR in representing auditory targets for reaching. Auditory stimuli enter the brain in head-centered coordinates. A head-centered representation of the reach plan would be expected if PRR merely reflected the format of the sensory stimulus. On the other hand, if auditory stimuli are coded in eye coordinates in PRR, that would suggest that PRR uses an eye-centered reference frame as its standard format for representing reach targets.

Cohen and Andersen found that responses in PRR for reaches to auditory targets are coded in eye-centered coordinates. Monkeys were trained to reach to the remembered location where a broad-band sound had been presented. Coordinate frames were measured by comparing responses for reaches made in the four different configurations of eye and initial hand position. Figure 4.10 shows the response of one neuron tested in this task. Panels A and B show that the cell is largely unaffected by the target's position with respect to the hand. Panels C and D show that the preferred reach endpoint is highly modulated by the direction of gaze.

Although the coordinate transformation for reaches to auditory targets could, in principle, go directly from head-centered to limb-centered coordinates, plans are in fact represented in eye coordinates. This supports the hypothesis that eye coordinates represent a universal scheme for representing space in the primate brain, for a variety of functions, and across a variety of stimuli.

Furthermore, this result suggests that individual neurons use a particular coordinate frame, regardless of the task situation. This corroborates and extends the result discussed in section 4.3.1 that PRR neurons do not change their coordinate frame as a function of time in the task, even as the task demands do change. This usage of a consistent coordinate frame across tasks and across time is a sensible encoding strategy, since in this way, downstream neurons need receive no information about the modality of the input or the behavioral state of the animal, to know what spatial location is represented by the PRR signal.

PRR resembles LIP in its representation of space. Some neurons in area LIP also encode auditory stimuli in eye-centered coordinates (Stricanne, Andersen, and Mazzoni 1996). Thus, it may be that parietal cortex represents space in a standard manner, eye-centered coordinates, regardless

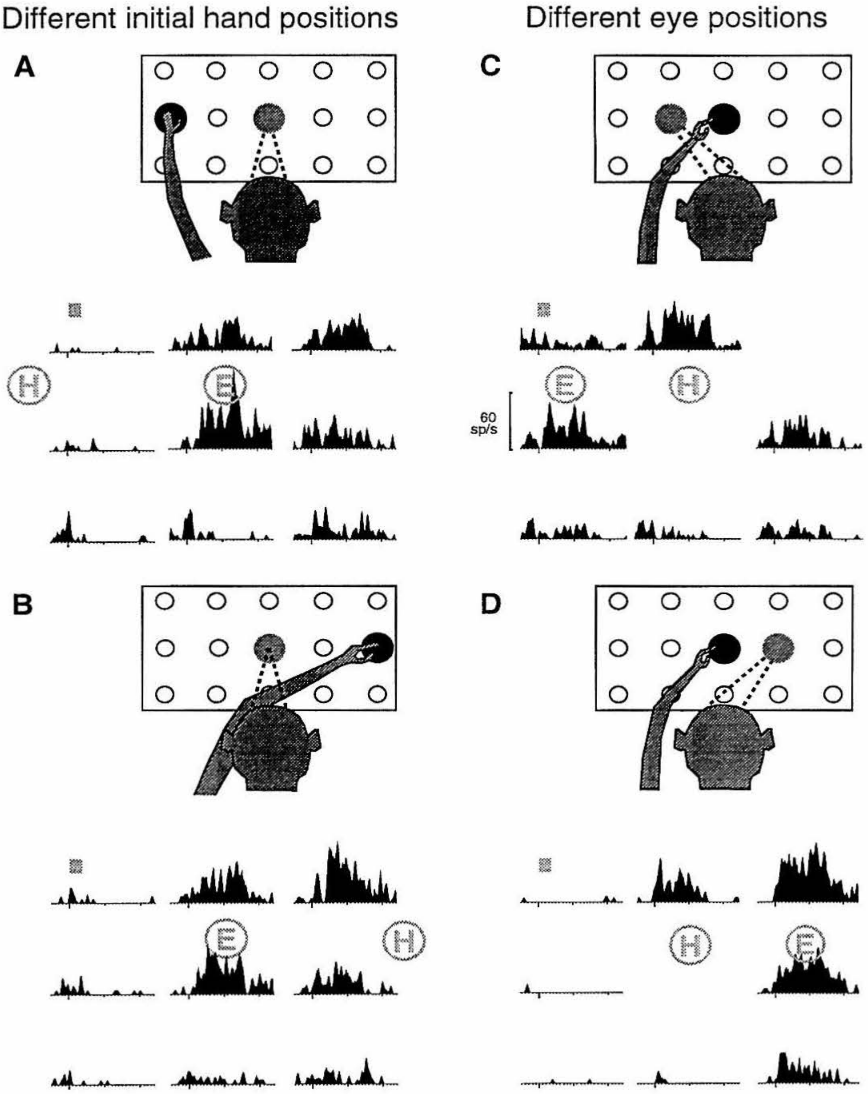


Figure 4.10: A PRR neuron using eye coordinates for planning a reach to an auditory target. Same format as figure 4.1. Gray bars above histograms indicate timing of sound burst. Data were collected by Yale Cohen.

of both the function served by the area, and the form of the input (Andersen, Snyder, Bradley, and Xing 1997).

4.3.7 Could eye coordinate frames in PRR be for moving the eyes?

There is a range in the degree of reach selectivity exhibited by PRR neurons. During saccade planning, many PRR neurons respond at a level near baseline, while others respond at higher levels (see section 2.2.1). It is possible that the PRR neurons which use eye coordinates do so because they are also involved in moving the eyes (or the eyes and arm together). To test this, we explored whether it would be possible to predict the coordinate frame based on the degree of movement selectivity. If there is a correlation between movement selectivity and coordinate frame (cells more active before saccades are more likely to use eye coordinates), that could suggest these cells are involved in saccades. Or, it might indicate that they occupy a stage early in processing for both movement choice and coordinate transformation. A lack of correlation would indicate that coordinate transformation and movement selectivity are different processes, which vary independently in the population of PRR neurons.

As seen in figure 4.11, the degree of movement selectivity and the coordinate frame are not correlated. If the cells that were more active during saccades were also more retinotopic, the upper right corner of the plot would be disproportionately filled. This discredits the idea that the use of eye coordinates is for eye movements, and supports the hypothesis that the eye coordinates in PRR indeed code reach plans.

4.3.8 Spatial tiling in PRR

While recording, it seemed that many PRR neurons spared the fovea. Also, the area appeared to have an over-representation of lower visual space. We quantified the representation of space in PRR by examining the spatial extent of response fields for the population of neurons. It was important that this be visualized separately for each monkey, for several reasons. First, an unequal number of cells was collected from each, so a bias in one animal might swamp the population. Second, different regions of PRR might have been explored in each animal, a different tiling of space would be an indicator of that. Third, the representation of space in PRR could differ between the animals.

Figures 4.12 through 4.14 show the data for monkeys D, O, and C. Responses during the delay period were considered. Each neuron contributed to each bin an amount proportional to the firing

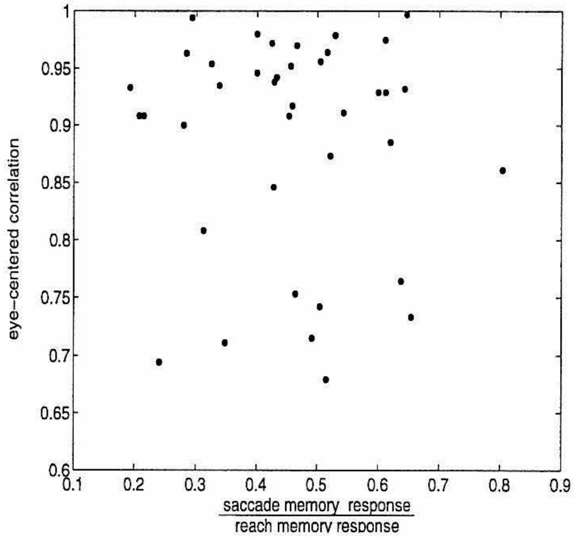


Figure 4.11: Relationship between reach selectivity and coordinate frame. The eye-centered correlation is plotted against the degree of reach selectivity, for all reach-selective neurons from monkey D. Five neurons with correlations below 0.6 have been excluded.

rate for reaches there, expressed as a fraction of the maximum firing rate for the neuron. Then, the value at each bin was divided by the number of neurons tested for reaches there. In monkey D, there is an over-representation of lower visual space. Also, there is a comparatively lower response for reaches to the foveated target. Monkey O exhibited amplitude tuning, a contralateral bias, and a somewhat enhanced response to the lower midline target. The lowest average response is for a reach to the fovea. Monkey C exhibited a slight under-representation of upper visual space. General trends in the representation of space in PRR seem to be an enhanced representation of lower visual space, a decreased representation of the fovea, and an increased response for movements of larger amplitude.

It is clear that the fovea is not over-represented in PRR. This is in contrast to other visually-responsive areas. Although we typically look at the objects we pick up, a close investigation of human movement behavior revealed that when reaching toward a peripheral target, the arm begins to move while the eyes are still in flight (Jeannerod, 1988). Thus, the reach had to have been programmed toward a target then in the visual periphery. Areas separate from PRR may be involved in the foveal component of the reach. These areas could be the same ones that are involved in grasping, such as AIP and PMv. That is to say, shaping the hand to the object, and precisely localizing the object in relation to the hand position could be processes with shared neural substrates. It also makes sense that PRR should over-represent lower visual space, since the arms and hands

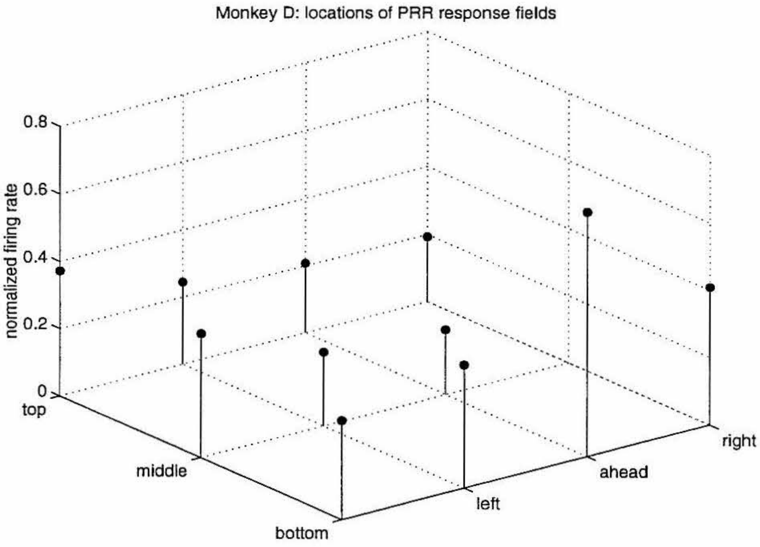


Figure 4.12: Tiling of space in PRR of monkey D. The initial hand position was in the middle row, one button to the right of the straight-ahead button. Thus, the animal did not reach there, and the normalized firing rate is zero. At each location, between 37 and 45 neurons were tested.

are typically below the point of fixation. PRR seems to offer some support for the distinction made in psychophysics between transport and grasp components of reaching; PRR may be principally involved in the transport component of the reach.

Both the bias away from the fovea and the bias toward lower visual space could be due to incomplete sampling of PRR. Evidence from other laboratories bears on this issue: other researchers (Galletti, Fattori, Kutz, and Gamberini 1998; Colby, Gattass, Olson, and Gross 1988) have reported that PO/V6A represent the visual periphery. Thus, our observations bolster the conclusion the fovea receives weaker representation than is typical for visual areas. On the other hand, Colby et al. (1988) reported that the medial wall of area PO represents upper visual space, while the lateral region of PO represents lower visual space. Thus, it could be that the lower visual field bias we observed is due to the placement of our recording chambers.

The complex of areas at the medial edge of the parietal cortex possesses anatomic connections indicative of contributions to visually-guided reaching. Other authors have reported reach responses in these areas. Our chamber placement is near these areas. The representation of peripheral and lower visual space is consistent with other reports in areas V6A and PO. Our observation of a similar trend for the representations of space in PRR are further evidence that PRR overlaps with the known areas V6A and MIP.

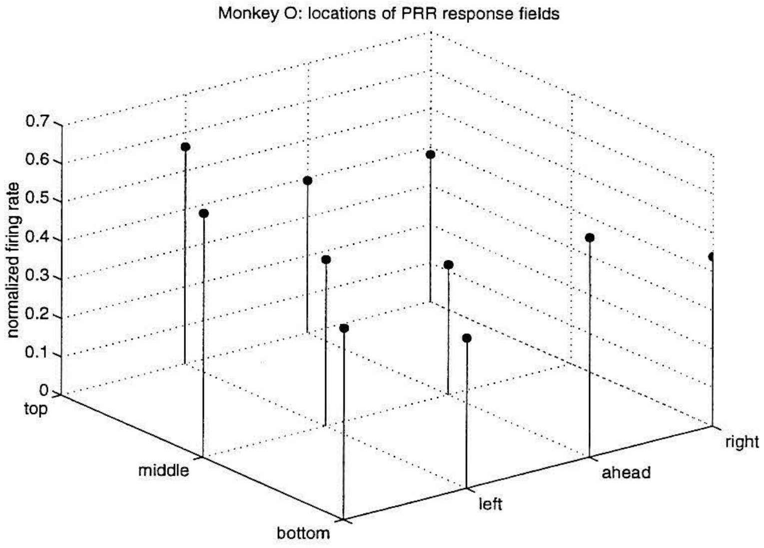


Figure 4.13: Tiling of space in PRR of monkey O. Between 10 and 16 neurons were tested at each location. Again, no value is plotted at the location just right of center, because the initial hand position was at this button.

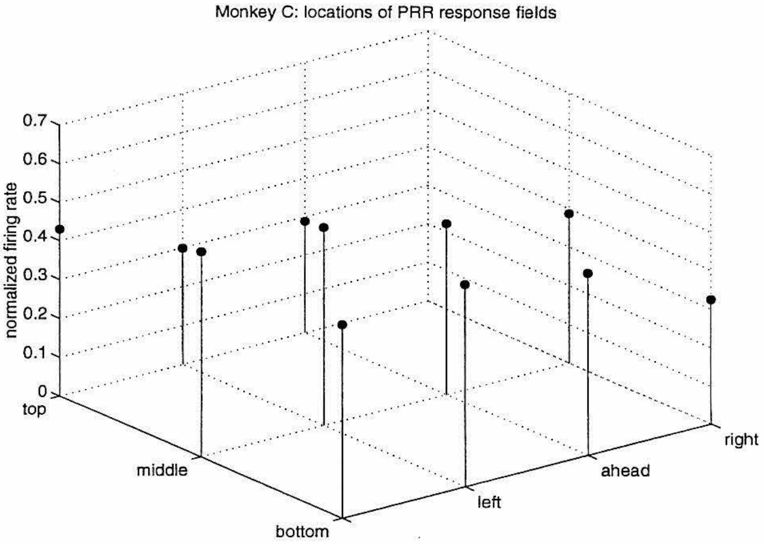


Figure 4.14: Tiling of space in PRR of monkey C. Between 12 and 15 neurons were studied at each location. Because the initial hand position for this animal was two positions to the right of straight ahead, data are available at the bin one position to the right of straight ahead.

4.3.9 Prospects for a neural prosthetic for arm movements in PRR

Perhaps reach plans might be decoded from PRR, if a population of neurons could be monitored at once? Since reach plans are represented in a comparatively simple and high-level manner in PRR, the area is much better suited for decoding than are other areas related to reaching, such as M1, where the neural representation of the reach is affected by many more factors. The ability to decode reach planning signals in PRR could have tremendous scientific and medical benefits. We would learn about the organization of an arm movement command across a population of neurons. Also, from a medical perspective, the ability to decode signals for an arm movement could lead to a prosthetic device to control a robot arm for human beings with stroke, ALS, or other neural disorders.

Krishna Shenoy and Richard Andersen are leading a project to develop a system for recording from a population of PRR neurons, and using those signals to guide the movement of a robot arm. An important first step has been performed in the lab. Krishna has been able to reconstruct the reach endpoint by applying a Bayesian reconstruction algorithm (Zhang, Ginzburg, McNaughton, and Sejnowski 1998) to data from the population of PRR neurons collected in the coordinate frame experiment.

The reconstruction was performed using the mean firing rates during the delay period for 49 neurons recorded from monkey O. Reconstructions were computed for simulated reaches to different targets. A range of sizes of neural ensemble were used, and reconstruction error was studied as a function of the number of neurons in the ensemble, for each direction. An error occurred if the reconstructed reach was more than one push button from the actual planned reach direction. Monte Carlo simulations were performed for each neural ensemble size by selecting a reach direction, drawing a probabilistically representative set of spike counts, and reconstructing from them the estimated planned reach direction using a Bayesian algorithm (Zhang et al. 1998). An ensemble of neurons of a particular size was selected from the total population of 49 neurons at random and with replacement. Figure 4.15 shows values measured from 2500 reconstructions per data point.

As can be seen from figure 4.15, as few as 10 cells yield a reconstruction of the reach endpoint that is accurate 90% of the time, in the best direction. Shenoy and Andersen will soon implant a chronic array of electrodes in PRR, which ought to allow recording from 20-30 neurons. With the chronic electrode array, the reconstructions are likely to be even better than that performed on our coordinate frame data. Shenoy and Andersen will be able to map out response fields more

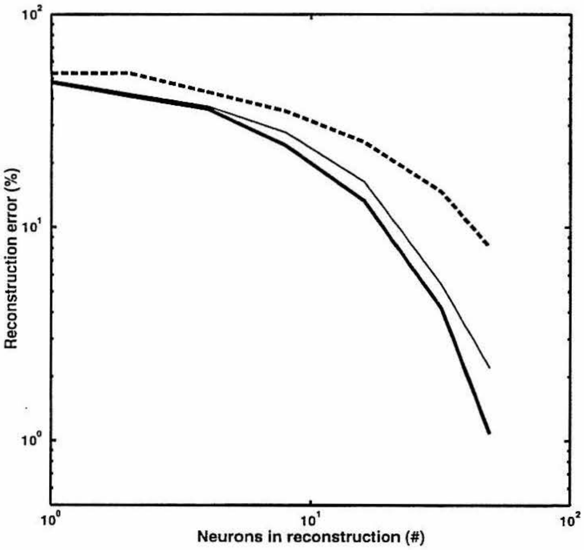


Figure 4.15: Reconstruction of the reach from a population of PRR neurons. Reconstruction error is plotted versus the number of neurons in the ensemble. Performance for up-left reaches (thick line), left reaches (thin), and for down-left reaches (dashed) are shown. These directions are contralateral from the recording site. Reconstructions for ipsilateral reaches were similar, though not as good. Analysis and figure courteousy of Krishna Shenoy

accurately, since cells can be held across days. And, simultaneously recorded neurons are likely to yield more information than cells collected individually.

Our discovery of eye-centered reach coding in parietal cortex has opened the door to an important new possibility for neural prosthesis: high-level control signals like we discovered in PRR could be readily amenable to decoding with arrays of electrodes.

4.3.10 Evidence for bimanuality in PRR

Unlike the eyes, both hands can move independently. What is the neural correlate of bimanual movements? Jun Tanji (Tanji, Okano, and Sato 1987) explored the supplementary motor area, and discovered that neurons respond differently during bimanual tasks. Since PRR conveys movement planning signals that are largely independent of the mechanics of the arm movement, might neurons even be insensitive to the arm used to make a reach?

As discussed in section 3.5, whether PRR was probed while reaches were made with the ipsilateral or contralateral hand did not affect the proportion of reach-responsive neurons encountered. However, in that data set, we never studied individual neurons while animals reached with either hand.

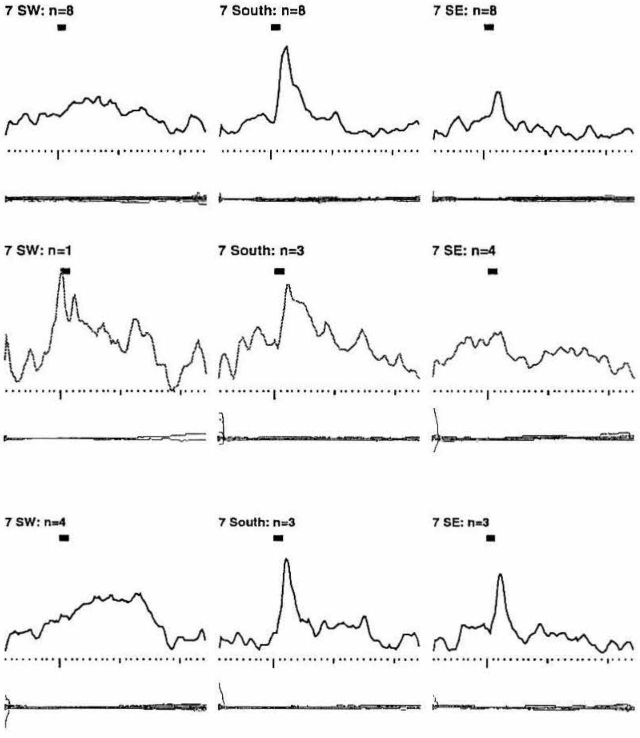


Figure 4.16: A PRR neuron tested for reaches with either hand. In each row, delayed reaches to three targets centered below the fixation point are shown. The top and bottom row show the response for reaches with the contralateral arm, before and after a block of reaches with the ipsilateral arm. The animal was not as good at reaching with the ipsilateral arm, so fewer trials were collected. Responses are more similar in the top and bottom rows than either is to the middle row, suggesting that the hand used to reach does affect this neuron.

While recording one neuron from monkey C, we loosely restrained his contralateral arm, so that he had to reach with the ipsilateral arm. The neuron that we studied in this manner did exhibit some changes in response, according to the arm that was used (figure 4.16). More importantly, the neuron was active for reaches made with either arm, suggesting that PRR is involved in bilateral control of reaching.

Experiments are planned in the Andersen laboratory to study more extensively the hand preference of PRR neurons, and the changes in tuning dependent on the hand used (see section 6.7). This study will also include tasks where reaches are planned with both hands, to the same target, or to different targets.

Mountcastle et al. (1975) reported that four times as many area 7 neurons were bimanual or ipsimanual than in area 5. This suggests a trend from more goal-related to more movement-related signals for the reach as processing progresses from area 7 to area 5.

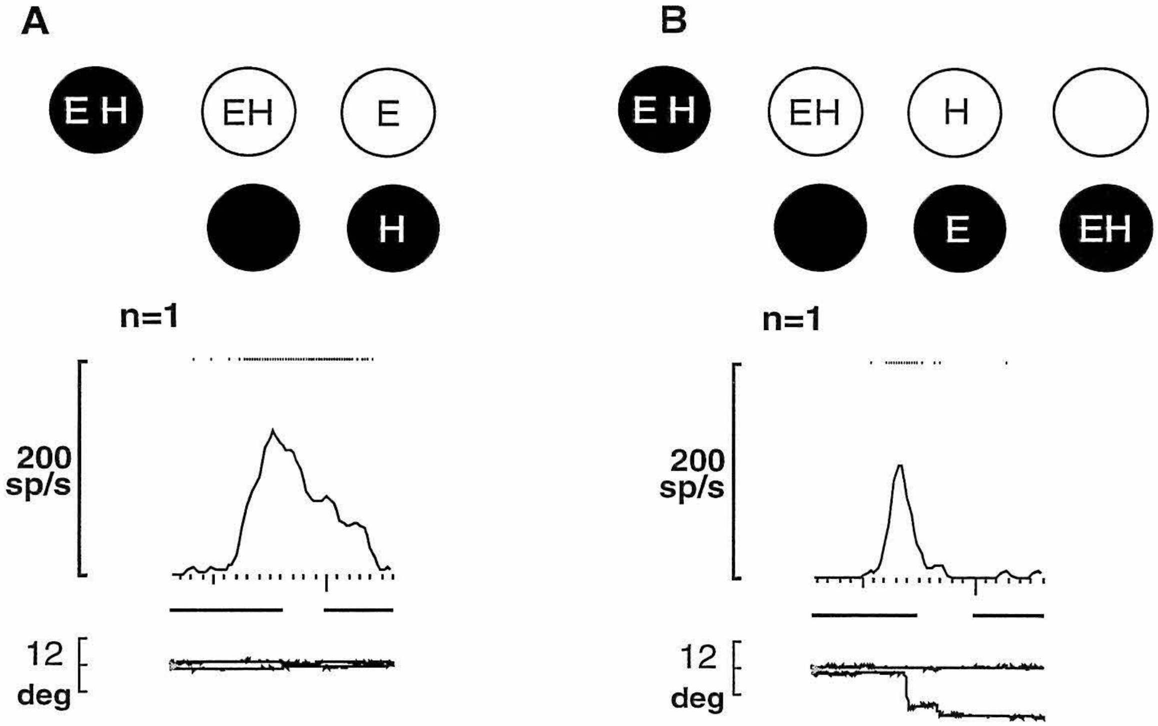


Figure 4.17: A PRR neuron during unconstrained reaches. This neuron is the one shown in figure 4.2. Two trials were collected for reaches to eight locations in this direct reach task with unconstrained eye position. (**A**) The monkey chose to fixate the center location throughout the trial. Icons above data depict the events in the task. Black circle, button with green LED; open circle, unlit button; E, eye position; H, hand position. Data from top to bottom, raster and PSTH for one trial, time course of button presses, horizontal and vertical components of eye position. (**B**) The monkey looks to the green reach target before reaching. Activity in A and B is consistent with an eye-centered response field located below the point of fixation, as mapped out in delayed reaches.

4.3.11 Responses in PRR during more natural behaviors

A few cells were tested in a free reach task, where the monkey was permitted to reach directly to green lights as they appeared, with no constraint on the eye position. These trials would begin with a green light illuminated at the center. Six hundred milliseconds later, the green light would jump to a different location on the board, and the monkey would reach to it. The neuron pictured in figure 4.17 exhibits an eye-centered response field in this unconstrained reach task. When the response field was mapped using the delayed reach task, this cell exhibited a preferred reach endpoint located below the point of fixation. Figure 4.17 shows responses for two reaches made to the target straight down. In one trial (A) the animal maintained fixation at the center button throughout the trial. The neuron's response is high through the reaction time and the reach, as this target is in the eye-centered response field. Activity declines soon after the reach is completed. In another trial (B) the animal first saccaded to the target, then reached to it. The cell's response drops precipitously after the saccade, as the response field no longer overlaps the target.

So, the finding of eye-centered response fields seems not to be a task-dependent phenomenon; it can be observed during more natural movements. However, this observation does not speak to the possibility that neurons may have developed eye-centered response fields as a result of their extensive training. It would be interesting to study neurons in PRR as an untrained animal performed a task similar to this one.

Eye-centered responses could be a trained-in property of PRR. The brain's internal representation of eye position is more stable than its representation of limb position. Thus, since the experiment requires maintaining a memory of reach targets for a long time, the brain may adopt the strategy of holding the target in the more stable eye-centered reference frame[2]. In addition, since the head is braced in these experiments, there may be little advantage to converting targets to a head-centered representation, since the eye-centered representation is often equivalent, and may be arrived at with fewer neural transformations.

The finding of an eye-centered representation of reaches instructed by auditory cues (section 4.3.6) provides a strong suggestion PRR is likely to code in eye coordinates, regardless of training history.

Another method to study whether eye-centered response fields have been trained in would be to train animals to reach to targets that are indicated by touch[3]. For example, monkeys could be trained to touch a location on their bodies that the experimenter indicates by touching first. In this case, would cells use eye-centered coordinates? Since there would be no reason to code somatosensorily-instructed reaches in eye coordinates, this would be a powerful test of whether the eye-centered coding in PRR is the inherent coding scheme for the areas, or a trained-in task contingency.

4.3.12 Coordinate frames for reaching in other parietal areas

Christopher Buneo has studied area 5 neurons in the coordinate frame paradigm. Figure 4.18 shows one such neuron. This cell shows a clearer hand-centered response field than do any neurons found in PRR. The hand-centered response field is gain modulated by eye position and hand position. These gain fields are oppositely directed, with the result that the cell is most active for a specific triple of eye, hand, and target position.

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[2] Thanks to Mel Goodale for pointing out this possibility.

[3] Thanks to Shin Shimojo for suggesting this experiment.

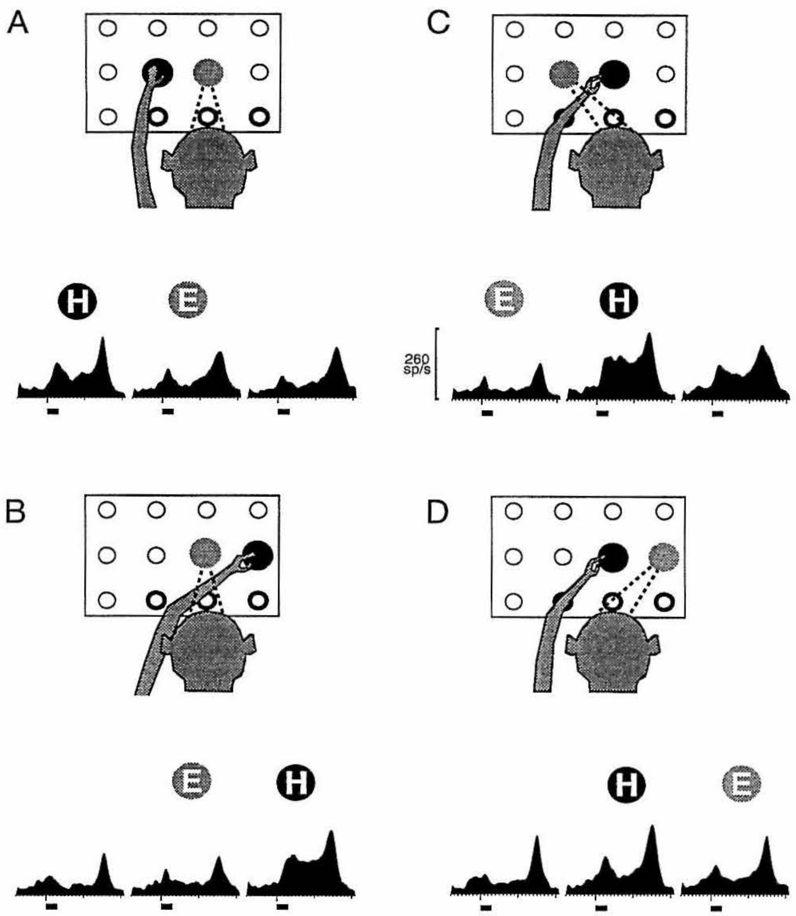

Figure 4.18: An area 5 cell with a hand-centered response field. Responses are shown for reaches to the three targets indicated by thick circles. (Collected by Chris Buneo.)

This neuron was located 7 mm from the border of PRR. The cell seems characteristic of the area 5 neurons whose coordinate frame Chris has studied, although he reports that few area 5 neurons have as strong a memory response as this cell. It seems that area 5 may represent a stage in coordinate transformation that is closer to the command to move the limb. Parietal cortex may contain a spatially distributed network that performs the coordinate transformation for reaching. Evidence exists that PRR and area 5 are connected. It would be intriguing to monitor activity simultaneously in connected areas during a reach. Such an investigation could allow us to observe the coordinate transformation as it occurs.

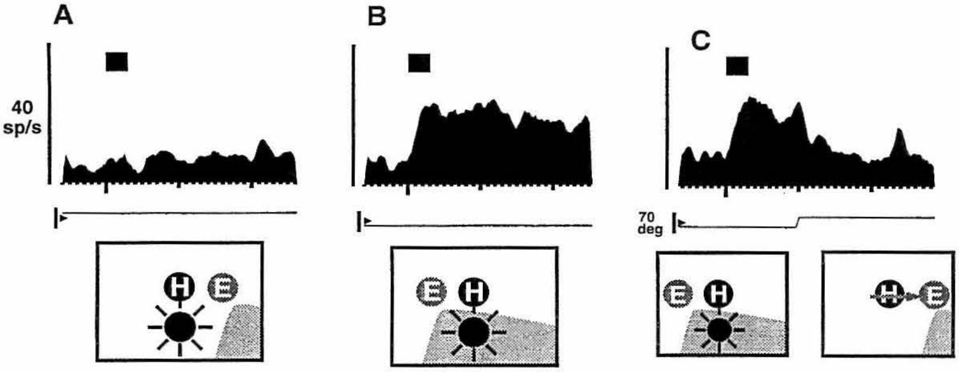

Figure 4.19: A PRR neuron which compensates for a target exiting the response field. Same neuron and same format as in figure 4.4A-C. Panels A and B are the same as in that figure, but now, panel C shows the response when the saccade is directed so that the memorized target goes from inside to outside the response field.

4.4 Further considerations on compensation for eye movements

4.4.1 Offset of response as target exits response field

As discussed in section 4.2, all PRR neurons that we tested exhibited an increase in response when a saccade brought a reach goal into the response field. Some neurons were tested in the inverse configuration: the reach target would be presented in the response field, then a saccade would be instructed which would bring the target out of the response field. Figure 4.19 shows the neuron of figure 4.4A-C tested in this configuration. Activity drops after the saccade, indicating that the neuron compensates for changes in the retinal position of the target, whether it moves into or out of the response field.

Sixteen cells were tested in this manner; 11 of them showed a statistically significant drop in activity (Mann-Whitney test, $p < 0.05$) after the saccade, consistent with compensation. However, the offset of response is not as powerful an effect as the onset of response when the remembered target enters the response field (which was seen in 100% of neurons). Figure 4.20 compares effects across the population of 16 neurons, using the index:

$$\frac{after\ saccade - target\ out}{after\ saccade + target\ out}$$

where *after saccade* is the mean firing rate in the IS trials during the 500 ms epoch from 100 ms after the saccade to the "go" signal (configuration C in figure 4.19, and *target out* is the mean firing rate during the 500 ms before the "go" signal for trials where the target is out of the response field,

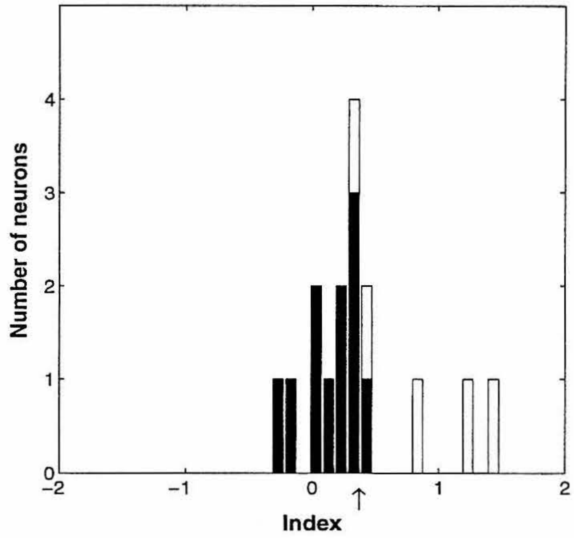

Figure 4.20: Population analysis for drop in response when a saccade takes reach goal out of the response field. An index of 0 represents full offset; an index of 1 represents no offset. Filled bars represent neurons that show a significant decrease in response, hollow bars are for cells that do not update significantly. Index value for the cell in figure 4.19 is indicated by the arrow.

and no saccade is performed (configuration A in figure 4.19).

Although the effect of a target exiting the response field was strong, it was not as reliable as the effect of a target entering the response field. Is this difference meaningful? It seems that when an eye movement intervenes, there are two loci of activity in PRR: a large level of activity at the location that represents the new retinal position of the target, and a smaller response at the location that represents the original position of the target. Does that residual activity serve a function, or is it only an imperfection in the compensation system? In our experiment, it seemed not to compromise monkeys' ability to perform the task.

An important further exploration of this phenomenon will be to instruct an intervening saccade in a situation where the target remains lit. In this case, the onset of activity would be trivially due to the presence of the illuminated target. But, the offset of activity might be more robust, meaning that the presence of a visual stimulus is capable of suppressing the response at the original location of the target.

4.4.2 Predictive updating?

Duhamel et al. (1992) found predictive updating across saccades in area LIP. Cells would become active 100 ms or so before the eyes even began to move. These authors concluded that LIP re-

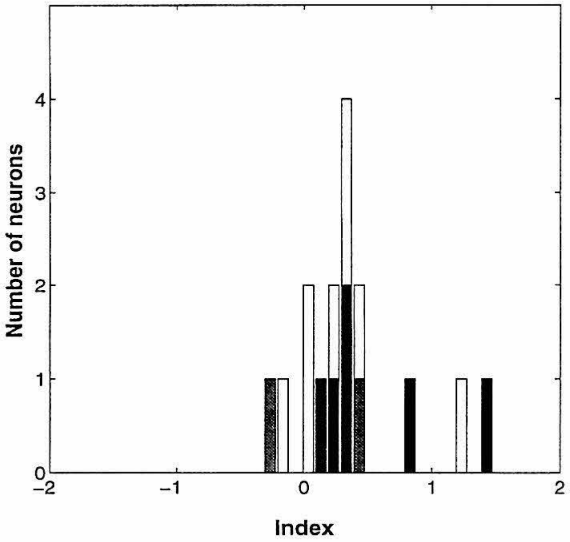

Figure 4.21: Population analysis for the offset of activity in response to an eye movement that brings the reach goal out of the response field. Neurons are coded by monkey: black bars are data from monkey O, grey bars are for monkey G, and white bars are for monkey D.

sponse fields move in advance of the saccade to the location where they will be once the saccade is completed. We did not observe such an effect in PRR.

We considered one possible explanation for this discrepancy. Duhamel and colleagues used a continuously lit target, while in our experiment, monkeys reached to memorized locations. Perhaps the difference in latencies in the two studies is due to the presence of an illuminated target? To test this, we trained one monkey to perform a simple variant of the IS task, where the target remained illuminated throughout the trial.

Both neurons we tested with continuously illuminated reach targets did not show a decrease in latency. Thus, the reason why Duhamel et al. observed predictive updating and we did not could be due to some other difference in the training or task. Or, this discrepancy could represent a real difference between the manners in which LIP and PRR compensate for eye movements.

An interesting unintended observation arose from these studies. In addition to no effect on the latency, we found that holding the target lit continuously increased the response of neurons only slightly, or not at all. This is further evidence that cells do not convey sensory signals, but instead represent reach intentions.

4.4.3 Eye movement and position signals in PRR

Where is the saccade compensation performed? One possibility is that the computation occurs directly in PRR. To make this hypothesis conceivable, there must be eye position and eye movement signals in PRR. Cortical areas that may overlap with PRR are known to be connected with the deep layers of the superior colliculus (Zeki 1986), and with LIP; thus there is anatomical evidence for the possibility of eye movement and position signals in PRR.

PRR neurons do indeed show responses during saccades (Snyder, Batista, and Andersen 1999). Roughly one quarter of PRR neurons show saccadic activity. For most cells, this activity is postsaccadic, it begins after the completion of the eye movement. This indicates PRR does not control the eye movement itself, but keeps track of it for other purposes. This signal could be used to provide the needed input for compensation for eye movements.

Interestingly, the postsaccadic responses and the reach planning responses are generally well-aligned. This rules out a simple model for saccadic compensation. One might have expected that compensation occurred by subtracting the eye movement. That model predicts that reach planning and eye movement responses are oppositely directed.

An important control analysis demonstrates that cells with saccadic activity are not involved in eye movements. These cells do not have stronger saccade planning activity than the ones without saccadic activity.

Future research will be important to study the mechanism for the compensation, and to explore whether the inaccuracies in reach behavior (as observed by Henriques et al. (1998)) can be accounted for by the behavior of PRR in intervening saccades.

This proposal that eye movement signals are used to update spatial representations across saccades can be applied to other studies. Eye movement and position signals that have been reported in other brain areas could also be used by those areas to compensate for eye movements: the presence of eye movement signals in a population of neurons does not guarantee the area is involved in moving the eyes.

Chapter 5 Target Selection in Parietal Cortex: The Role of the Parietal Reach Region in Movement Sequencing[1]

5.1 Introduction

Three brain processes must occur in the planning of a goal-directed movement. A type of action must be chosen, a target must be selected, and the sensory representation of the selected target must be converted into a format usable for guiding the action. Regarding the first of these processes, it is now known that different regions of the parietal cortex of monkeys are involved in planning different types of movements. Area LIP is selectively active when an animal must saccade, and the nearby parietal reach region (PRR) is active when the animal plans to reach (Snyder, Batista, and Andersen 1997; Snyder, Batista, and Andersen 1998). Thus, the process of movement choice is reflected in the activity of parietal neurons. Regarding the third process, saccades are represented in oculomotor coordinates in area LIP (Gnadt and Andersen 1988; Colby 1998), thus LIP occupies a stage of sensory-motor processing that is consequent to the process of sensory-to-motor coordinate transformation. In contrast, reaches are coded in eye-centered coordinates in PRR (Batista, Buneo, Snyder, and Andersen 1999): thus PRR occupies a stage of reach planning that is antecedent to the process of coordinate transformation. Eye-centered coordinate frames may represent a universal representation for movement plans in parietal cortex. Regarding target selection, the second process listed above, in a double saccade task, LIP neurons in majority represent the motor plan, and not the sensory memory of the stimuli (Mazzoni, Bracewell, Barash, and Andersen 1996). We now explore the behavior of PRR neurons when two reach targets are presented: does PRR store the memory of reach targets, or does the area represent the plan for the next movement?

5.2 Methods

5.2.1 Animals

Three adult male monkeys (*Macaca mulatta*; designated D, G, and O) were studied in this experiment. Surgery and recording methods have been described elsewhere. During recording sessions,

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[1] This chapter is intended for submission as Batista and Andersen (1999).

the animal's head was fixed, and an electrode was lowered into PRR. All three animals are still involved in experiments, so our definition of PRR is based on the functional criteria of significantly greater reach planning activity than saccade planning activity, and the fact the area occupies a region of the brain just medial and caudal to LIP (see Snyder, Batista, and Andersen (1997) and Batista, Buneo, Snyder, and Andersen (1999)). Eye position was monitored using the scleral search coil method of Judge, Richmond, and Chu (1980). Animals sat in a dark room facing a vertically-oriented array of touch-sensitive buttons, 24 cm away. Each button was 3.7 cm in diameter and contained a red and a green LED behind a translucent window 1.2 cm in diameter.

The neurons reported here are from the same data set considered in Batista, Buneo, Snyder, and Andersen (1999).

5.2.2 Behavioral task

Neurons were first tested for reach selectivity and response fields were mapped while animals performed delayed reach and delayed saccade tasks, as described in Batista, Buneo, Snyder, and Andersen (1999) and Snyder, Batista, and Andersen (1997). Briefly, red and green LEDs were illuminated at the center button, signaling the animal to look at and press that button. Five hundred milliseconds later, either a red or a green cue would appear at a random location. An 800 ms delay period (termed *d epoch*) ensued, which was terminated by extinguishing both central LEDs as a "go" signal. Then, if the cue had been red, the animal would saccade (without moving its hand) to its location; if the cue had been green, the animal would reach to its location (without making a saccade). After holding the final position for 600 ms, a juice reward was delivered. A neuron was deemed reach selective if its maximal response during the delay epoch of the delayed reach task was significantly greater (Mann-Whitney test, $p < 0.05$) than its maximal delay-period response in the delayed saccade task. Only neurons reach selective by this criterion were analyzed in the current experiment.

In the target selection experiment, the monkey performed interleaved trials of a delayed reach (DR) task and an intervening reach (IR) task. The task types and target configurations are depicted in figure 5.1. The DR task was as described above, except the delay period was lengthened, typically to 1100-1500 ms[1]. On each trial, a cue could appear at one of two locations: either in the response

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[1] Delay periods for the DR task were 1100 ms for monkey O, 1500 ms for monkey G, 1250 ms for 8 cells in monkey D, and 800 ms for 6 cells in monkey D. The delay periods for the DR task were set close to the length of the interval between c_{in} and the first "go" signal in the IR task. This was to help ensure that differences in neural responses in the two tasks would be due to the stimuli being presented, and not to differences in the duration of the delay period. However, when the delay epoch was too long, monkeys' performance would drop. The delay period lengths chosen generally reflect this tradeoff.

field of the neuron currently under consideration (c_{in}) or out of the response field (c_{out}).

The IR task was a variant of the DR task where, 600 ms into the delay period, a second cue (c_{out}) was presented, out of the response field. Another 600 ms of delay period ensued before the "go" signal. The delay period following the first cue is termed *d1*, and *d2* is the delay following the second cue. The animal reached (without moving its eyes) to the location where c_{out} had been presented (r_{out}). Upon completion of that reach, the central red LED and the green LED at the button the monkey was pressing (c_{out}) were reilluminated, and a third delay period (*d3*) occurred for 500 ms. Both LEDs were extinguished as the "go" signal, and the animal reached to the location where the first cue had been presented (r_{in}), again without breaking fixation of the central button. Conceptually, in this task, c_{in} instructs a reach which is eventually executed, but a delayed reach to c_{out} intervenes between the appearance of c_{in} and the reach to it.

Typically, ten trials of each of the three types (DR task to c_{in} and c_{out}, and IR task) were performed. The positions of c_{in} and c_{out} were fixed throughout the test of an individual neuron. Animals generally performed over 90% correct; animals almost never mistakenly executed the first reach to c_{in}.

An additional target configuration was included for some neurons: the order of cues in the IR task, and thus the order of reaches, was reversed. The target outside of the response field, c_{out}, was presented first, and the target in the response field, c_{in}, was cued second.

5.2.3 Experiment design

In the target selection experiment, the neuron would become active when c_{in} appeared in the response field. In half the trials when it appeared, the monkey would reach to it at the end of the delay period (DR task). In the other half of trials (the IR task), c_{out} would appear. The monkey would shift its reach plan to that location. The experimental question was whether the presentation of c_{out} would affect the cell's activity. If the firing rate did not change, that would show that PRR continues to hold the reach plan to c_{in}, even though it is no longer the impending reach. On the other hand, if the cell's activity were to drop when c_{out} was presented, that would indicate that PRR stores only the representation of the target that has been selected for the impending reach.

For some neurons, the order of cues in the IR task was reversed, with the second target placed in the response field. Reversing the order of cues in the IR task would show whether the intervening reach plan was indeed represented in PRR. If the outcome of the target selection experiment was that the neuron continued to be active, that could be because PRR does not represent the reach to

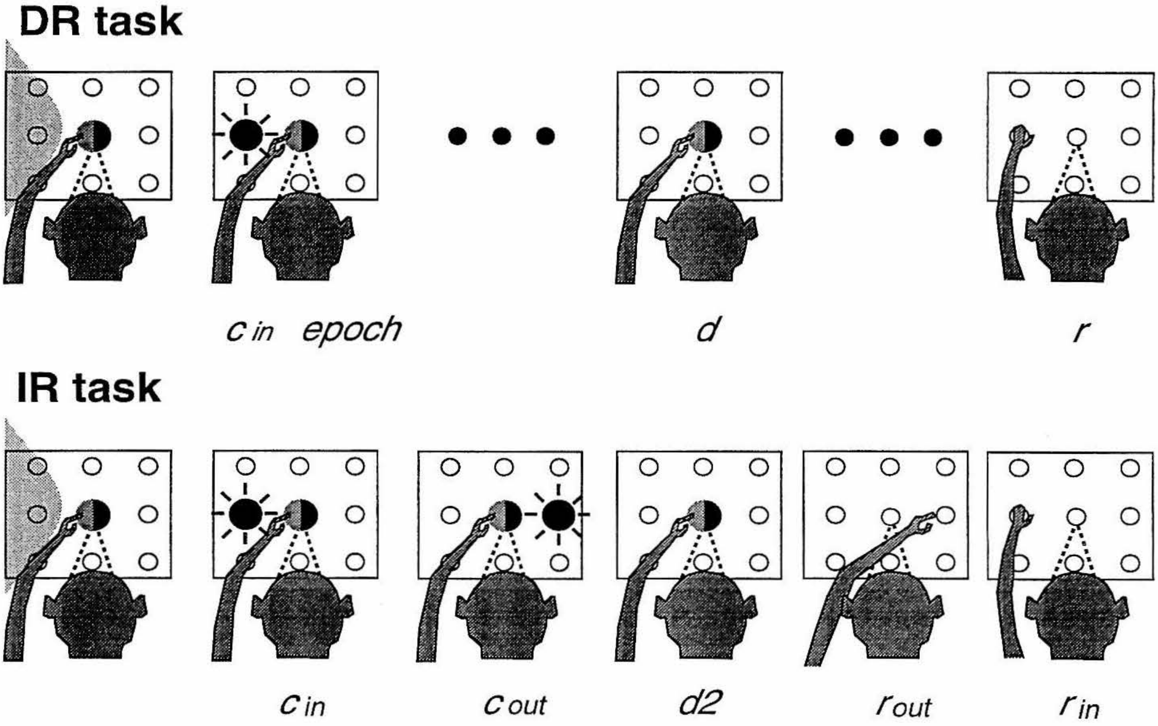

Figure 5.1: The delayed reach (*DR*) task (first row) and intervening reach (*IR*) task (second row). Each panel shows a behind-the-head view of the monkey and the button array. An example response field location is shown in the first panel. The monkey begins the trial by fixating and pressing the central button, where a red LED (shown as gray) and green LED (shown as black) have been illuminated. In the DR task, a cue is presented in the response field (c_{in}). A delay period (*d*) ensues before the center LEDs are extinguished to trigger the reach (*r*). In the IR task, c_{in} is followed by a delay period (*d1*, not shown), then a cue is presented out of the response field (c_{out}). After the "go" signal, the animal reaches to the location of c_{out} (r_{out}). A third delay period ensues (*d3*, not shown) before reaching to the location of c_{in} (r_{two}, shown in the final panel). Tic marks, 100 ms. Two other trial types are not shown: the DR task where c_{out} is presented, and the IR task with the order of c_{in} and c_{out} reversed.

c_{out} at all. On the other hand, if the cell's activity dropped, that could indicate either that PRR falls silent during *d2*, or that other neurons tuned to the location of c_{out} begin to respond to that reach plan. Thus, we examined how some neurons would respond when the first target was presented out of the response field, and the second target was presented in it.

5.2.4 Analysis

A one-tailed Mann-Whitney test (nonparametric t-test) at the $p < 0.05$ level was used for all comparisons of neural activity. The epochs used were generally as follows. In the IR task, *d1* was measured as the 500 ms between the 100 ms after c_{in} was extinguished until the appearance of c_{out} , *d2* was the 500 ms between the 100 ms after the offset of c_{out} until the first "go" signal, and *d3* was the 400 ms interval between 100 ms after the monkey touched the location of c_{out} until the second "go" signal. In the DR task, the final 500 ms of the *d* epoch (preceding the "go" signal) was used. In all comparisons, the same duration is used for both epochs in the comparison. Thus, for the comparisons to *d3*, the *d*, *d1*, and *d2* epochs were shortened to 400 ms.

Neurons were screened to ensure that c_{in} and c_{out} were indeed in and out of the response field, respectively. The firing rates during the delay epoch of the DR task was compared for reaches to each target. Only if the response for reach plans to c_{in} was significantly greater than the response for reach plans to c_{out} were data from the IR task considered.

To quantify the behavior of the population of cells, an index was measured for each neuron:

$$\frac{DR_{out} - IR}{DR_{out} - DR_{in}}$$

where DR_{out} is the mean firing rate during the final 500 ms of the DR task, for the condition where the target is out of the response field, DR_{in} is the firing rate for the DR task when the target is presented in the response field, and *IR* is the firing rate for the *d2* period of the IR task. An index near 1 indicates that the cell is unaffected by c_{out} , while an index of 0 indicates that the cell's response after c_{out} is equal to its response on trials of the DR task where the target is presented out of the response field. To establish a baseline, this index was also computed for the first delay interval in the IR task and the early portion of the delay interval (from 100 to 600 ms after cue offset) in the DR task. The index is expected to be near 1 during this epoch, indicating no drop in activity in the IR task.

5.3 Results

5.3.1 Coding of the impending reach

In the intervening reach task, the first cue (c_{in}) activated the neuron, since it was positioned in the response field. The presentation of the second cue (c_{out}) shifted the reach plan to a location outside the response field. The neuron in figure 5.2 dropped in activity when c_{out} was presented. Thus, the neuron did not continue to signal the location of the first target, once it was no longer the target for the impending reach. The animal must continue to remember that target location, since he will eventually reach there; however, this neuron is not involved in that process. This neuron's behavior is consistent with the hypothesis that PRR represents the impending reach only, and is not involved in storing plans for reaches that will be performed subsequently.

Most neurons (100% of 14 tested in monkey D, 100% of 13 tested in monkey O, and 3 of 7 tested in monkey G) dropped significantly in mean firing rate when the second cue was presented (*d2* activity significantly less than late *d* activity, Mann-Whitney test, $p < 0.05$). Figure 5.3 histograms the population of neurons, according to an index of the strength of offset (described in Methods). Although the monkey must remember the location of c_{in} until the second reach is performed, PRR seems to contribute only weakly to storing that plan. Figure 5.4 shows one of the four counterexample neurons: it continued to signal c_{in} after the presentation of c_{out} .

As a comparison, this analysis was repeated on the *d1* interval of the IR task, and the first 500 ms of the delay interval in the DR task. The index in this case is expected to be near 1, since there should not yet be any drop in activity as c_{out} has not yet appeared. The index computed during this interval had a mean of 1.12, with a range of 0.47 to 2.78. Only one neuron showed a significantly different response between the IR and DR$_{in}$ task during this epoch. The distribution is shown in figure 5.6.

Once the first reach is executed, the animal resumes planning a reach into the response field. Accordingly, activity returns to neurons during *d3*, as seen in the neuron in figure 5.2. This was true for most cells: 26 of the 34 neurons showed a significantly greater response during *d3* than during *d2* (Mann-Whitney test, $p < 0.05$). The average response during *d3* was 3.03 times the response during *d2* (with a range of 0.18 to 13.72).

Responses during *d3* were often indistinguishable from responses in *d1*. 18 of 34 cells show no significant difference (Mann-Whitney test, $p < 0.05$) during the *d3* and *d1* epochs. The mean ratio of *d3* to *d1* activity was 0.97, with a range of 0.02 to 1.90.

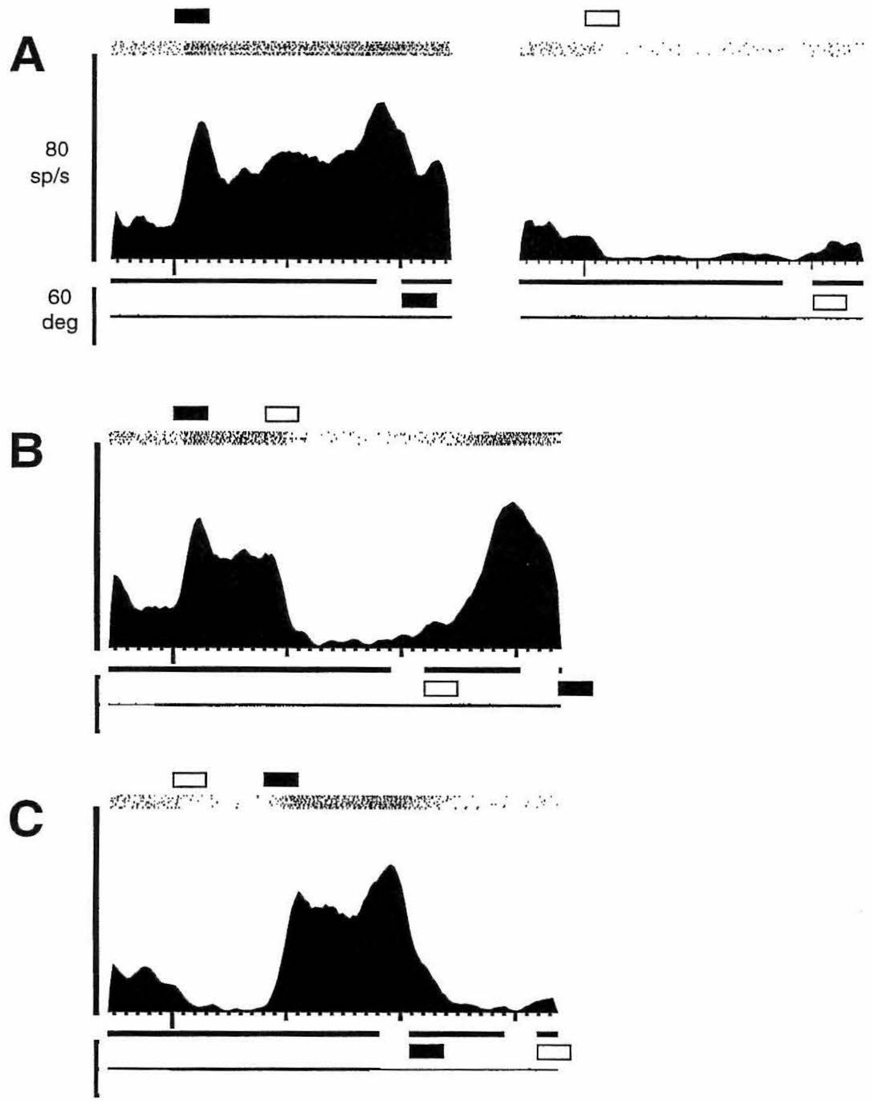

Figure 5.2: Behavior of one PRR neuron tested in the target selection experiment. (**A**-**C**) Each subplot shows, from top to bottom: timing and location of cue presentation, where a filled symbol represents a cue in response field, and an open symbol represents a cue out of the response field; rasters for ten repetitions of the movement; PSTH constructed from those rasters, using a triangular kernel (Scott 1985); the timing of button presses for one representative trial; the symbols below this trace show which target was acquired; horizontal and vertical components of eye position for all ten trials. (**A**) The DR task performed to a target in the response field (left) and out of the response field (right). (**B**) The IR task where the first cue is presented in the response field, and the second is presented outside. The first reach is to the second target, the one outside of the response field. (**C**) The IR task where the first cue is presented out of the response field, and the second is in the response field. Tic marks, 100 ms in all plots.

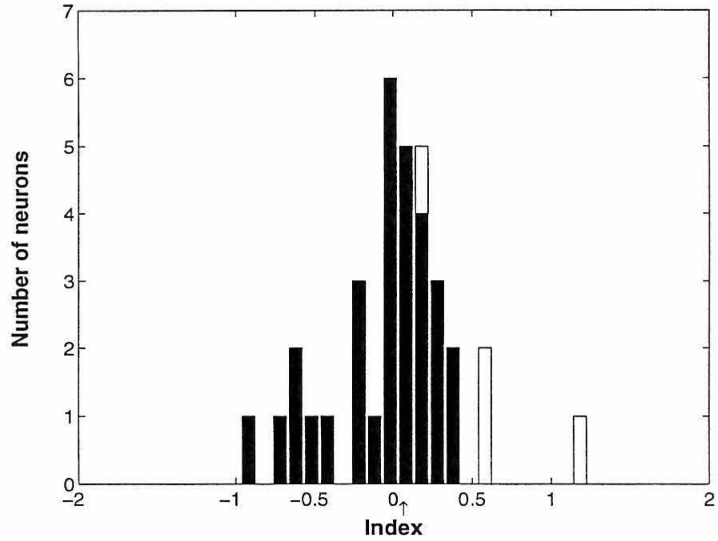

Figure 5.3: Population plot for the intervening reach task. See methods for formula. Black bars show significant neurons (see methods), and white bars show nonsignificant neurons. The arrow shows the index of the cell in figure 5.2. The neuron shown in figure 5.4 is the one with the index of 1.2.

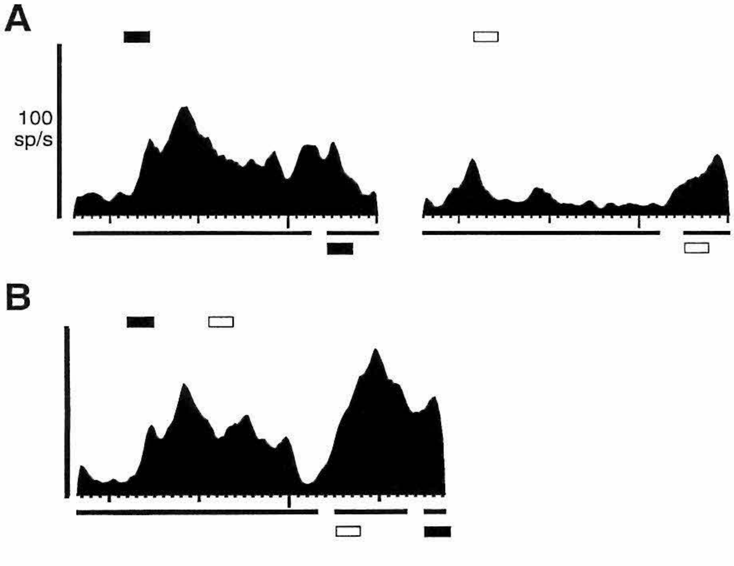

Figure 5.4: A PRR neuron that may contribute to target memorization. Subplots are as described in figure 5.2 caption, except rasters and eye position traces are not shown, and data are aligned on the first "go" signal (long tic on time axis). (**A**) Behavior of the neuron during DR task to a target in the response field (left), and out of the response field (right). (**B**) Behavior of the neuron during IR task.

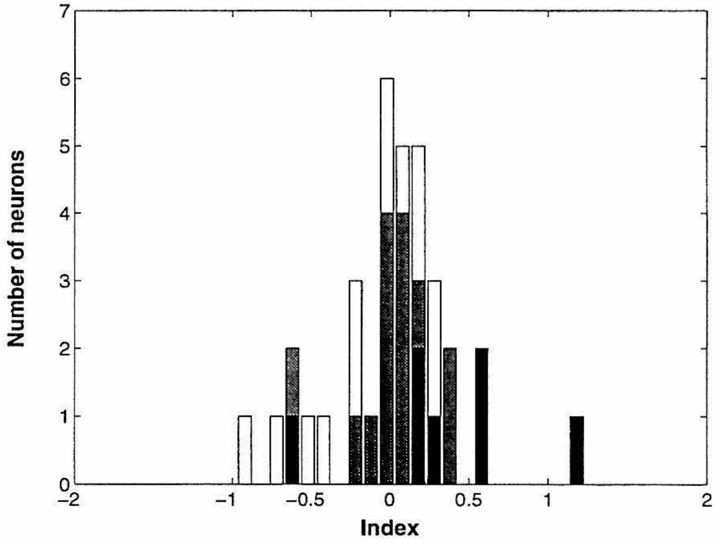

Figure 5.5: Population plot for the intervening reach task, by monkey. White bars show all neurons from monkey O, gray bars for monkey D, and black bars for monkey G.

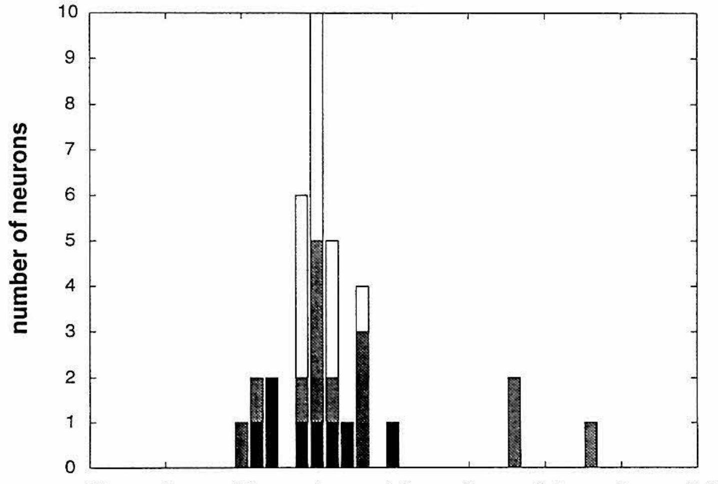

Figure 5.6: Population plot for the intervening reach task, during the first delay interval, by monkey. White bars show all neurons from monkey O, gray bars for monkey D, and black bars for monkey G.

In the delayed reach task, PRR neurons are active when reaches are planned into their response fields. We would expect that when the target order is reversed so that the second target, and thus the first reach plan, is in the response field, neurons will represent that reach plan. To ensure that PRR behaves similarly in the IR and DR tasks, we tested 5 neurons from monkey D by reversing the order of target presentation. The first target was presented out of the response field, and the second cue was in the response field. In this case, the appearance of the second cue, but not the first cue, should activate the neuron. All 5 cells tested showed a significant increase in activity when the second cue was presented in the response field, compared to the cell's response during the equivalent time period in the DR task when the sole target was out of the response field. All five neurons also dropped in activity during *d3*, once the first reach was completed and the monkey resumed planning a reach to a target out of the response field (response during *d3* significantly less than response during *d2*, Mann-Whitney test, $p < 0.05$). Thus, most PRR neurons were active when and only when the impending reach was planned into the response field. Interestingly, activity during *d1* and *d3* was distinguishable, with *d3* responses 4.3 times greater than *d1* responses, on average (range from 2.1 to 9.0).

5.4 Discussion

Animals performed a task where two targets had to be remembered, but only one was selected for action. We explored whether neural responses in PRR would correlate with the memory of targets, or with the movement plan. Eighty-eight percent of the 34 PRR neurons studied represented the next planned reach, and not reaches planned subsequently. In other words, stimuli that are of behavioral relevance to the animal do not activate PRR neurons, unless they are the target for the impending reach. Thus, PRR occupies a stage in sensory-motor processing that is consequent to target selection.

Four neurons were exceptions to this rule. All four cells that continued to represent the first target even after the second appeared were found in monkey G. We think it is unlikely that the difference between the result in this animal and in the other two can be explained as the outcome of drawing three different samples from similar populations of neurons. Rather, we believe the most likely explanation for this discrepancy is the fact that the hemisphere had been recorded from extensively in a separate experiment. Neurons were occasional, and difficult to isolate when encountered. It could be that damage to the area resulting from extensive recording changed its response properties. Another possibility for the discrepancy is that the animals may have adopted different strategies to perform the task. Monkey G was trained quite differently from the other two (it had been trained to perform delayed reaches to auditory targets before being used in this experiment), which may have led to a different behavioral strategy. Finally, it is possible that we recorded from a different subregion of PRR in this animal, one that is involved in storing the memory of reach targets. This would be an intriguing functional segregation.

Two parietal regions, LIP and PRR, share many of the properties that have been tested so far. Each is active only when a specific movement is planned: the intention to make a saccadic eye movement activates LIP, and the intention to reach activates PRR (Snyder, Batista, and Andersen 1997; Snyder, Batista, and Andersen 1998). Both areas represent movement plans in an eye-centered reference frame (Batista, Buneo, Snyder, and Andersen 1999; Gnadt and Andersen 1988; Colby, Duhamel, and Goldberg 1995), although in LIP this is a motor reference frame, and in PRR it is a sensory or cognitive reference frame (Cohen and Andersen 1998). And, with these results, it is known that both areas represent the impending movement predominantly, and movements planned subsequently to a much lesser extent, if at all. The similarities in the way these two areas function in sensory-motor processing make them well suited to exchange information, perhaps in order to subserve coordinated movements of eyes and hand.

This experiment reinforces an evolving view that parietal cortex is involved in movement planning (Mountcastle, Lynch, Georgeopoulos, Sakata, and Acuna 1975; Goodale and Milner 1992). It also extends this view, by suggesting that target selection also occurs in parietal cortex. Traditionally, motor areas in the frontal cortex have been thought to be involved in the process of target selection. It could be that those neurons reflect the outcome of performed in parietal areas. Alternatively, target selection may be implemented by a network of frontal and parietal areas.

Evidence suggests that movement planning areas in parietal cortex carry potential movement plans: in cases where a movement target is not explicitly given, parietal regions seem to form a movement plan to a likely target in the environment, which downstream neurons may cancel. Kalaska and Crammond (Kalaska and Crammond 1995) observed activity of this sort using a GO/NO-GO task: parietal neurons in area 5 were equally active when a target was presented, whether or not the animal would be required to reach to it, while frontal neurons were only active in the GO task. Platt and Glimcher (1997) found that neurons in LIP were somewhat active to stimuli that could become targets for saccades. In LIP and PRR, Snyder et al. (1997) observed some neurons in PRR that were active for saccades into the response field, unless a reach plan in the opposite direction was explicitly instructed. (Similarly, weak effects in LIP before reaches went away when an oppositely-directed saccade was planned simultaneously.) However, in frontal cortex, this kind of default motor planning is generally not observed (Kalaska and Crammond 1995). This seems to be a major difference between parietal and frontal cortical contributions to these tasks: frontal cortex may reflect only movement plans that will be executed, whereas parietal areas may represent potential motor actions. The current findings refine and extend this conception of parietal function: whenever a movement is explicitly instructed, PRR represents only that movement, and suppresses the representation of subsequent or potential movements.

The mechanism for this suppression may be lateral inhibition within PRR between neurons tuned to different directions. Injection of a GABA antagonist in PRR might affect the suppression of activity in response to c_{in} we have observed; and could consequently affect animals' ability to suppress the reach to the first target.

It is intriguing that PRR codes the impending reach, but does so using an eye-centered coordinate frame. This is evidence that much arm movement planning is performed in visual coordinates, with the transformation to limb coordinates occurring quite late in sensory-motor processing.

In a series of psychophysical studies (Baylis, Tipper, and Houghton 1997; Tipper, Brehaut, and Driver 1990), subjects were required to suppress one stimulus, and respond to another. Negative priming, seen as behavioral traces of the suppression, such as reaction time increases and error rate increases in the subsequent trial were evident at the location of the suppressed target. The suppression of the neural representation of the c_{in} target we have observed in PRR may offer a neural mechanism for the sorts of effects of distractor suppression seen psychophysically.

5.4.1 Where is the first reach plan?

What happens to the first reach plan when the second cue is presented? It must still be stored centrally, since the animal is given no further indication of the endpoint of the second reach, although signals in PRR do not seem sufficient for that storage. There are certainly many distinct possibilities; two will be proposed here. Perhaps there is an area that stores both plans. The appropriate one could be gated into PRR, according to task demands. An extrastriate visual area, perhaps V6, or a working memory area, perhaps the prefrontal cortex, are candidate areas where a representation of the memory of both targets might be found. Alternatively, there may be a motor area, perhaps in premotor cortex or the supplementary motor areas (Tanji and Shima 1994) that is responsible for storing the plan for the second reach. That area could also code in eye-centered coordinates, and represent the retinal position of the first cue. Or, it may code in limb-centered coordinates, and signal the second reach as a vector relative to the endpoint of the first reach. It will be important to record from neurons in other areas involved in short-term memory or reach planning while monkeys perform this task, to decide between these possibilities.

Chapter 6 Conclusion

The experiments presented in chapters 2 and 3 illustrate that parietal cortex is primarily involved in motor intention, and not sensory attention. This goes a long way toward resolving an old debate about the function of the parietal cortex. During these studies, we serendipitously discovered a region of posterior parietal cortex that is dedicated to planning reach movements. We have named this area the parietal reach region (*PRR*) based on its function and location. In chapter 4 we explored the strategies used by PRR to represent space. A large majority of neurons use an eye-centered reference frame for representing goals of reaches. Far fewer use limb-centered or head-centered coordinate frames. Furthermore, we saw that these neurons are capable of compensating for intervening eye movements, in order to maintain a correct representation of the eye-centered position of the target. In chapter 5 it was shown that PRR is involved in specifying the target for the next reach and is not involved in planning movements that will be made later on. These findings lend support to the view, originally proposed in 1975 by Mountcastle et al., that parietal cortex is involved in commanding movements, in representing space for the purpose of action, and in keeping track of the changes in the body's position and the world's position relative to the body that result from those changes.

In the introduction, I proposed that there are three critical components to a sensory-motor transformation. These components offer a framework that can characterize the experiments described in this thesis. First, a movement must be chosen. Parietal cortex reflects the outcome of the process of movement choice, and could even be a critical locus for that process.

Second, a target must be selected. The study in chapter 3 showed that parietal cortex indicates the target for the next reach and does not signal the presence of other targets toward which reaches are planned. Thus, PRR represents the outcome of a process of target selection. Indeed, this process could also be performed directly in PRR.

The third component of a sensory-motor transformation is to convert the sensory representation of the target into a motor representation. We saw that, instead of representing reach targets in a reference frame appropriate for arm movements, PRR stores targets in eye-centered coordinates. Importantly, this does not mean that the parietal signal for the reach is an unprocessed sensory representation. Rather, we believe that eye-centered coordinates are used because this is a useful framework for planning reaches. This hypothesis is supported by the observation that even auditory targets for reaches are stored in eye coordinates (Cohen and Andersen 1998). Nevertheless, PRR occupies a stage in sensory-motor processing that is antecedent to the process of coordinate transformation. Indeed, in light of observations made by other groups studying areas to which PRR projects, we believe PRR may represent the final stage in reach planning before the transformation to limb coordinates begins. Studying other areas using the experimental paradigm we designed will be needed to piece together the complete coordinate transformation process. Those studies are already underway in the Andersen lab.

Guided by the framework of the three components of movement planning, we have learned quite a lot about what parietal cortex contributes to planning reaches. Interestingly, in the cortical processing of a reach plan, coordinate transformation seems to take place only after target selection has been performed. This is consistent with psychophysics that indicates a large portion of endpoint selection and trajectory planning is done in visual coordinates, before transforming to limb coordinates.

What was learned in these studies about the parietal reach region approaches the level of knowledge gained about area LIP. The two areas are very similar in all the properties for which both have been tested. Figure 4.5 characterizes these similarities, uniting them with our view as to how movement selection and coordinate transformation are implemented in cortex. The figure highlights that there are distinct areas in parietal cortex active for different movements. Both of these areas use an eye-centered scheme to represent movement targets, even though quite different processing must happen subsequently in the two streams. Each area can compensate for saccades that disrupt the alignment between the retinal position of the target and its real position in order to preserve eye coordinates. Neurons in LIP, and perhaps in PRR, are modulated by the position of the body parts. These signals could provide the information needed for subsequent coordinate transformations. Another similarity (which is not noted in figure 4.5) is that both areas signal the movement about to be performed, and are much less involved in the processes of holding the memory for later movements and detecting candidate movement targets. This process of target selection is perhaps mediated by lateral inhibitory connections local to each area. In all, the strong similarities between PRR and LIP in the ways they process different movements suggests the areas are well-suited to exchange information; possibly functioning to plan coordinated hand-eye movements.

6.1 Why are reach plans coded in eye coordinates?

Why should there be a representation of a reach in eye-centered coordinates? From several perspectives, it is an odd fact. It had been hypothesized that brain areas involved in actions encode plans in a manner useful for generating the appropriate movement (Rizzolatti, Riggio, and Sheliga 1994; Colby 1998). We were surprised to find there is at least one exception to this hypothesis. Given that most cortical connections are reciprocal (Felleman and Essen 1991), and that PRR is likely connected to premotor cortices involved in arm movements, which do have arm position signals, we might wonder why such signals are not more prevalent in PRR.

The most straightforward interpretation of these findings is quickly ruled out. One might suppose that the signal in PRR is simply a raw, unprocessed representation of the sensory stimulus, with the exception that stimuli that are not reach targets have been filtered out. There are three pieces of evidence to rebut this claim. First, as we saw in section 4.3.6, reaches to auditory targets are often coded in eye-centered coordinates in PRR. Thus, extra computation is performed to ensure that different sensory signals are brought into register. An eye-centered representation, and not residual sensory coordinate frames, is the parsimonious explanation for these observations. Second, as seen in section 4.2.3, when an eye movement occurs, PRR updates to account for the change in the retinal position of the target. If retinal encoding were not important to the processing performed in PRR, special mechanisms like this would not need to be present to ensure that eye-centered coding is preserved. The existence of saccade compensation suggests eye-centered encoding is of functional importance in the area. Third, the fact that the area encodes only the next planned reach and not subsequent reaches (chapter 5) suggests the area does not contain unprocessed sensory signals, but is indeed representing the plan for the impending reach. These lines of evidence converge to suggest that an eye-centered representation of the reach plan is indeed functional and not an artifact of the spatial representation of the input.

What, then, might be the importance of maintaining a representation of the reach plan in eye-centered coordinates? One possibility is that eye-centered coordinates form a common language for spatial representations in the brain. If different regions represent spatial locations in the same way, signals are easily exchanged between them; hard-wired connections between neurons that respond to the same region of the retina would be sufficient. Area LIP, for example, uses eye-centered coding (Gnadt and Andersen 1988; Barash, Bracewell, Fogassi, Gnadt, and Andersen 1991; Colby, Duhamel, and Goldberg 1995). Given that eye and hand movements often occur in close concert, it may be helpful to encode reaches in the same coordinate frame as eye movements. The use of a common eye-centered coordinate frame may also be observed in other brain areas, which serve different functions. Indeed, eye-centered coding may be the cortical lingua franca.

The reach system is flexible: reaches can be modified rapidly if the target moves while the arm is in mid-flight (Georgopoulos, Kalaska, Caminiti, and Massey 1983). In prismatic adaptation experiments (Held and Hein 1958; Clower, Hoffman, Votaw, Faber, Woods, and Alexander 1996), subjects learn to modify their subsequent reaches to restore accuracy. In both of these scenarios, errors are detected in visual coordinates; thus visual coordinates seem the optimal coordinate frame for adjusting for the errors.

Obstacle avoidance is best done in visual coordinates (Sabes and Jordan 1997). Often, to move the hand to a target other features in the environment must be avoided. Planning a path around objects is straightforward in visual coordinates, but to form a plan in the intrinsic coordinates of the arm, the entire visual scene would need to be converted into the intrinsic coordinate frame.

Moving objects would be naturally represented in eye coordinates. If a reach were planned to a moving object, its position could be estimated and predicted straightforwardly by PRR.

Another possible explanation is that the brain might more accurately track the position of the eyes than the hands. If so, eye-centered coding of the environment would provide a more robust representation than limb-centered coding. While the efference copy of a cortical eye movement command is a reliable estimate of the post-movement position of the eyes, the efference copy of a reach command is probably not as accurate an estimate of the final position of the hand. Since the eye muscles face a constant load, and since there are fewer underdetermined degrees of freedom in eye movements than in arm movements, cortical movement commands are likely to offer very accurate estimates of the final position of the eyes but not of the arm. Thus, to store a memory, an eye-referred representation may be more stable with time than a hand-referred representation.

A final possibility is that it may be neurally most efficient to perform coordinate transformation as the final stage in the sensory-motor transformation. In simulations, coordinate transformation seems to necessitate a neural network with a hidden layer (Zipser and Andersen 1988). In contrast, target selection is potentially implemented by broad lateral inhibition in a single-layered network, and may be a less intensive computation. Thus, the most demanding transformation may be performed last, when absolutely necessary, to ensure it is never performed extraneously.

Although it might have been expected that arm movement plans would be coded exclusively in limb coordinates, these considerations may explain why early reach plans are coded in eye coordinates. These possible reasons are neither exhaustive, nor are the explanations disjoint. Several of them, or some different reasons, could be the functional significance of reach plans coded in eye-centered coordinates.

6.2 Anatomic substrate of PRR

We have performed histology on one of the four monkeys studied in these experiments. Figure 2.3 shows the positions of LIP and PRR in that animal's brain. The reach-selective neurons occupied a diffuse area around the medial portion of area 7 and the caudal aspect of area 5. The other three animals are being used in other experiments. The positions of PRR were very similar in stereotactic coordinates in the brains of the other animals, so the locations of recording sites relative to anatomic features is likely to be similar.

These recordings are likely to cover several distinct anatomic areas, including areas V6A and MIP (described in section 1.3.2 and 1.4.5). Furthermore, some of the existing physiological studies of these areas fit well with the observations we have made.

PRR is unlike most other visual areas in that it does not over-represent the fovea (figures 4.12 through 4.14). This phenomenon has been observed several times in area V6A and PO/V6, in both physiological and anatomical studies. Physiological studies have shown that most neurons have response fields that are large and do not overlap the fovea (Galletti, Fattori, Kutz, and Gamberini 1998; Galletti, Fattori, Battaglini, Shipp, and Zeki 1996). Anatomical studies have shown connections from the peripheral representations of visual space in extrastriate visual areas to PO and V6A (Colby, Gattass, Olson, and Gross 1988; Shipp, Blanton, and Zeki 1998).

Also, reach responses have been reported in areas V6A (Galletti, Fattori, Kutz, and Battaglini 1997) and MIP (Colby and Duhamel 1991; Johnson, Ferraina, Bianchi, and Caminiti 1996). In the study of V6A, Galletti et al. sought to determine the function of the non-visual neurons in the area. They found that some of them were active for reaches. Presumably, some of the cells with visual responses would also be active for reaches. Those cells are likely to be precisely the ones we have studied.

A final piece of evidence suggesting that PRR overlaps with PO/V6 and V6A comes from a coordinate frame experiment performed by Galletti, Battaglini, and Fattori (1993). These authors mapped out receptive fields with moving bars of light while monkeys fixated. They observed that 10% of neurons were not in retinotopic coordinates. This number is strikingly similar to the percentage of cells observed that did not use retinotopic coordinates in our reaching task.

These correspondences suggest that PRR is likely to overlap with MIP, V6A, and other areas near the caudalmost aspect of area 5. Since a monkey is a valuable animal, and because so much time is invested in training each animal before recordings can begin (over a year for each animal), they are studied as extensively as possible before the terminal anatomy studies are performed. Eventually, studies will be performed to localize these recording sites more precisely. And in the future, structural MRI methods will allow recording sites to be localized in living monkeys.

6.3 Relations to other physiology studies

The experiments presented in chapter 4 illustrate how essential it is that scientists who study the neural coding of reach behaviors monitor and control eye position, since the retinal position of the reach target has a profound effect on responses in PRR, and is likely to strongly affect other reach planning areas. Earlier studies of the cortical control of reaching have been severely hindered by not accounting for this source of neural variability.

Mushiake et al. 1997 performed a study very similar to our coordinate frame experiment in area PMv, and found that 41% of 200 neurons were modulated by eye position during a reach. At least some of these cells coded in retinotopic coordinates; their example neuron was one such cell. In contrast, they report that perhaps as little as 4% of MI neurons are modulated by eye position. In another study of PMv where eye position was monitored, Graziano and colleagues (1994) discovered that many neurons have visual receptive fields centered on the limb. These neurons could be active during arm movements, although these authors did not test them for reach responses.

It is intriguing to think that the transformation from eye-centered to limb-centered coding of the reach is gradual, going from almost exclusively eye-centered coding of reach plans in PRR to a mixture of eye and limb coordinate frames in PMv, to exclusively limb-centered representations in M1. To thoroughly explore this issue, it will be important to test the coordinate frames used by neurons in premotor cortex and other reach areas using our coordinate frame paradigm, since it is the only one developed so far that allows the relative influences of eye and arm coordinate frames to be compared directly.

6.4 Relations to psychophysics studies

In the introduction (section 1.5), we explored a number of studies of the psychophysics of reaching. Several of these provide evidence that reaches are planned in eye-centered (Henriques, Klier, Smith, Lowy, and Crawford 1998; Vetter, Goodbody, and Wolpert 1999) or visual (Wolpert, Ghahramani, and Jordan 1995; Flanagan and Rao 1995) coordinate frames. Based on these studies, it might be expected that there is a cortical area encoding reaches in eye coordinates. The reach coordinate frame study presented in chapter 4 directly demonstrates the existence of such an area. Considering the relation between the psychophysics and the physiology from another perspective, the fact that PRR uses eye coordinates suggests it is well-poised to be the critical locus for the reach behaviors that these psychophysics studies involve.

A psychophysics study of particular relevance is that of Henriques et al. (1998). These authors independently developed an intervening saccade task that was nearly identical to ours (chapter 4). They concluded from the pattern of subjects' reach errors that humans use an eye-centered encoding of reach targets that compensates (imperfectly) for saccades. This is just what we have observed in PRR.

Some scientists have proposed that a reach consists of two distinct components: transporting the arm, and shaping the hand. The fact that most PRR neurons respond most strongly for reach targets in the visual periphery suggests that the area is involved in the transport component of the reach. Other areas, such as AIP, are presumably involved in the grasp component of the reach. Another way to view the observation of an over-representation of peripheral space in a reach planning area is that it supports this psychophysical division of reaching.

Another feature of the representation of space in PRR resonates well with the area's involvement in reaching. PRR may preferentially represent lower visual space (see figures 4.12 through fig:cyptile). This is sensible for an arm movement area, since the hands are generally below the eyes.

In all, there is much mutual reinforcement between the psychophysics of reaching and the physiology of PRR.

6.5 Other interpretations

We believe that signals in PRR and LIP represent plans for movements. Other interpretations of the effects we have observed are possible. It has been proposed that parietal cortex is responsible for maintaining a representation of the positions of the body and objects in the environment. It could be that the signals we observe before movements occur are actually signals for anticipated changes in body position. This seems unlikely to us, because almost all neurons in PRR have much weaker static hand posture signals than movement intention signals.

The experiments of chapter 4 demonstrated that PRR uses eye coordinates for representing reach targets. We believe that this is the natural coordinate frame for the area. However, it could be objected that the effects we observed would not be present in naive animals, or in human beings. We believe that given the strong similarities (noted above) between psychophysical studies and these results, we think that this is probably also the natural coordinate frame for the human homologue of PRR. Recording studies in naive animals performing natural behaviors would be important to establish that eye coordinates are the natural coordinate frame. Those studies may now be possible, since we now know what to look for. Another useful approach would be to train a somatosensory-reach task (discussed in section 4.3.11), and explore whether neurons used eye coordinates in a situation where such a coding scheme is very remote from the demands of the task.

6.6 Where are the head-centered receptive fields?

Efforts to discover a head-centered encoding of space in individual neurons have been surprisingly unsuccessful. Some areas, such as VIP, contain some head-centered neurons, but no area contains predominantly head-centered cells, and most areas have no head-centered cells. Instead, it seems most areas use eye-centered representations of space. These could be sufficient to represent space, since the brain seems to be very good at keeping track of where the eyes are, and where they are going to be. This accuracy is probably afforded by the simplicity of eye movements, and the large amount of neural tissue devoted to moving the eyes; the internal copy of the eye movement command seems sufficient enough to specify precisely where the eyes will end up. Our observation of saccade compensation in PRR is liable to be a general property of areas that use eye-centered representations.

Indeed, the proposal offered by Andersen and Mountcastle (1983) and Andersen and Zipser (1988), that head-centered information can be stored in a distributed population of retinocentric neurons with modulatory influences of eye position, is likely to be the dominant mode of representing head-centered space in the brain.

It seems assumed by many researchers that eye coordinates are a raw, unprocessed coordinate frame, waiting to be converted to more useful coordinate frames: head-centered or effector-centered. We suggest that eye coordinates are cortex's predominant reference frame, for a variety of processes. Additional spatial information is handled by modulations on signals in eye coordinate frames.

6.7 Further studies

The parietal reach region is an exciting new brain area, with many questions unique to it. Also, PRR provides another window of opportunity to ask general questions about the brain processes of sensory-motor transformation. The avenues for future research are very exciting. Here, I will discuss some further studies into PRR that are ongoing in the Andersen lab, and suggest some other possible avenues for further research.

Reach prosthetics

Can PRR signals be used to guide a robot arm? Since PRR neurons seem largely unconcerned with the position of the hand or the specifics of the movement path, signals from PRR can yield an unambiguous specification of the reach endpoint. Krishna Shenoy, Daniella Meeker, and others in the Andersen lab are exploring whether an array of electrodes implanted in PRR can be used to manipulate a robot arm to a position that the monkey specifies. These studies could lead to prosthetics for patients with paralysis.

Coordinate frames in other reach areas

Our coordinate frame paradigm is the most thorough that has been used for studying coordinate frames for reaching. Paradigms employed by other labs have either varied eye position but not initial hand position (Mushiake, Tanatsugu, and Tanji 1997) or varied initial hand position without monitoring eye position (Johnson, Ferraina, Bianchi, and Caminiti 1996). Our methodology allows a direct comparison of the influence of target position with respect to eye and limb, while the other paradigms do not permit these influences to be compared in individual neurons. It will be important to repeat the coordinate frame experiments in different reach areas. A fuller insight into the process of coordinate transformation will emerge from comparisons between different areas of the relative importance of eye and hand position of the target.

Christopher Buneo has performed the coordinate frame experiment in area 5. There, he finds much more influence of the hand position than in PRR. This suggests that mapped across parietal cortex are several stages in a gradual transformation from eye to hand coordinates.

By simultaneously recording from neurons in two different areas involved in visually-guided reaching, much could potentially be learned about the way information is transformed between connected neurons. Experiments similar to this are planned in the Andersen lab by Jyl Boline, Bijan Pesaran, and John Pezaris, who will study interactions between LIP and the frontal eye fields during saccades.

Path planning in PRR?

Does PRR convey information about the path the hand will take, or only about the endpoint of the reach? There is evidence (Sabes and Jordan 1997; Wolpert, Ghahramani, and Jordan 1995) that path planning (not just endpoint planning) takes place in visual coordinates. Such a finding is sensible, for if path planning were to occur in limb or joint coordinates, then much of the visual scene would need to be transformed into that coordinate frame. It is reasonable to expect, then, that PRR conveys information about the path the hand will take.

To test this, obstacles can be placed in the hand path. If a clear Plexiglas partition is placed between the target and the endpoint, so that the visual position of the target was unaffected but the hand path to reach it was forced to change, would PRR responses reflect the altered hand path? One suggestion, made by Philip Sabes, is that a few key intermediate positions along the path (such as the edge of the partition) are coded in PRR, along with the target.

Contributions of PRR to reach calibration

Clower et al. (1996) showed parietal cortex is the critical locus for prism adaptation. Their study may have revealed the human homolog of PRR. Could PRR act as a comparator between actual and desired hand position? Chris Buneo's observation of initial hand position information in PRR (section 4.3.3) indicates this might be so.

Giving distorted feedback about reaching, as is done in human psychophysics, could allow the target position and the hand movement to be dissociated. Would PRR represent the visual position of the endpoint, or would it change as the reach needed to acquire the target was distorted?

Coordinate frames for grasping

What coordinate frame is used by area AIP for representing targets for grasping? The conception of a common coordinate frame used by different cortical areas implies that AIP is also eye-centered. On the other hand, since the demands of grasping and reaching are quite different, a different coordinate frame could be used. Investigations of the coordinate frame used by AIP are being performed by Bjorn Christianson and Chris Buneo in the Andersen lab, in collaboration with Melvyn Goodale at the University of Western Ontario.

Reversible inactivation

An important prediction of the experiments described in chapters 2 and 3, which show that plans for different movements are reflected in separate parietal regions, is that inactivation of PRR should affect reaches but not saccades, while inactivation of LIP should affect eye movements but not arm movements. To test this idea, Hans Scherberger and Richard Andersen plan to inject muscimol, a GABA agonist that acts for 2-3 hours, into PRR and LIP. Based on inactivation studies in LIP (where only eye movements but not reaches were tested), effects of inactivation are most likely to be seen in an extinction paradigm. When an animal is given free choice between orienting toward two targets, it will tend to favor the ipsilesional target (Li, Mazzoni, and Andersen 1995). Hans will explore whether there are differential effects on eye and hand movements depending on whether LIP or PRR is inactivated.

A dual experiment is to inject current into PRR, and observe whether reach endpoint can be affected. Their and Andersen (1998) found that injecting current into LIP can elicit saccades.

Bimanual reaching

As shown in figure 4.16, some PRR neurons are active before reaches with either hand. Whether this is true for most neurons needs to be explored. If most neurons are insensitive to which hand actually performs the reach, that would strengthen the coordinate frame observation. PRR would be seen to be even less concerned with the details of the reach. If cells are mostly unimanual, then there is at least some information about the reach encoded in PRR. Hans Scherberger plans to study issues of bimanuality.

In a study of arm movement-related activity in area V6A, Galletti et al. (1997) found that half of the neurons were activated by movements of the contralateral arm, one quarter responded to movements of the ipsilateral arm, and one quarter were bimanual. Since it is possible that PRR contains V6A or is similar to it, we might expect similar effects in PRR.

As seen in chapter 5, PRR represents only the impending reach, even when two reaches are planned. An interesting question is whether PRR can represent two reaches, if they are to be made with different hands.

The dual to these experiments, bihemispheric studies of PRR, could also be informative. In the intervening saccade task, the location of the stimulus is often coded in the other hemisphere. Inactivating one hemisphere might prevent the updating from occurring. If so, that would suggest that the updating is performed by mechanisms local to PRR.

A further test for intention in PRR

The intervening reach task of chapter 5 offers another opportunity to compare sensory and intention responses in PRR. The result of that experiment was that PRR neurons represented only the impending reach: a target location that the monkey was memorizing did not drive neurons, unless the animal intended the next reach to that location. What would happen if the target was actually illuminated, instead of only being remembered? In this circumstance, there is a competition in PRR between a visual stimulus (not merely a remembered stimulus) and a movement plan. Would neurons continue to fire, due to the presence of the visual stimulation? Or would they behave as they have in the tests we have done, and signal the monkey's intention?

3D space in PRR

We restricted our reach studies to movements in a two-dimensional space near the animal. Since PRR is involved in forming arm movement intentions, it is likely to represent space only within arm's reach. This would be in contrst to area LIP, which can represent stimuli far from the animal (Gnadt and Mays 1995; Platt and Glimcher 1998). It will be interesting in the future to study responses of PRR neurons to stimuli that are out of arm's reach. The experiments here predict that cells would not respond to such targets. Perhaps, even the short-latency brisk responses that often prelude the delay period activity would vanish.

Origin of motor specificity?

Can we find the cortical stage at which movement selectivity first appears? Can the highest visual area that does not reflect movement specificity be identified? Area V6/PO is a likely candidate, as *it* projects both to LIP, and to V6A and MIP (Blatt, Andersen, and Stoner 1990), the areas where PRR is likely to be situated. Other candidates are MT and V3A.

Perhaps a mixture of movement selective and nonselective neurons will be found in these areas? Perhaps, through training, the "red" selective neurons in extrastriate visual areas have come to project preferentially to LIP, while the "green" selective neurons in the same areas project to PRR? If so, these areas could be miscategorized as "movement selective." An identical visual stimulus triggering the different movements would be needed. Perhaps a color cue at the fixation point or an auditory cue could instruct the type of movement. On the other hand, if an enhanced connection between visual "red" cells and LIP could be demonstrated, that could go a long way toward revealing the neural mechanism of movement choice.

Predicting target selection based on PRR activity[1]

In a situation where the animal is free to choose between two stimuli, can we predict which he will select, based on PRR responses? If so, we might be able to demonstrate a neural corrlate of the animal's decision to move. Conceptually, the experiment could work by training an animal to saccade to the brighter of two visual stimuli. By presenting a variety of brightness differences, we might be able to alter the animal's accuracy in discriminating the brighter. When the stimuli are equiluminant, the animal makes the choice based on internal factors. If one of two equiluminant stimuli were placed in the response field of a PRR neuron, would responses be greater when the animal chose that one as the reach target? How would the neuron's firing rate compare to a situation where the target was clearly brighter? The paradigm is similar to ones introduced by Shadlen and Newsome (1996) and Glimcher and Sparks (1992), and could yield valuable information about the role of PRR in decision-making.

Eye and hand interactions

How about more complicated movements of eye and hand? The dissociation task of chapter 2 suggests PRR is unaffected by saccades planned simultaneously with reach plans. What might

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[1] Thanks to Pietro Perona for proposing this experiment.

simultaneous recordings from PRR and LIP reveal about the nature of the interaction between the two subserving hand-eye coordination?

Attention-centered coordinate frames?

What would happen in PRR if a monkey were instructed to detect a faint dimming in a peripheral target during the reach planning epoch? Would the reach plan be coded relative to the location of *attention*? In this way, we might dissociate eye-centered and attention-centered coordinate frames. In our coordinate frame paradigm, the locus of visual attention is not controlled, although presumably the animal attends the point of fixation, then the position of the target. Perhaps if attention were deviated to a different location, we might observe that some neurons represent the reach relative to the attended location, and not the point of fixation.

Mechanism of target selection in PRR

Is the process of target selection observed in the intervening reach task of chapter 5 implemented within PRR, perhaps by lateral inhibition? Or does another area suppress activity in PRR when the second target is presented out of the response field? A method to test these hypotheses would be to inject a GABA antagonist into PRR, and record neural responses in the intervening reach task. Potentially, neurons would continue to respond to the first target after the second appeared. How would the animal behave? Perhaps he would erroneously perform the reach to the first target?

Fast reorganization of PRR

In the intervening reach experiment of chapter 5, we found that PRR encodes the second cue, because the monkey has learned that it represents the target for the first reach. If the animal were trained so that, according to an instruction given at the start of the trial, the first reach would either be made to the first or second cue, then the area would likely represent only the first or second target, depending on the initial instruction.

If the area does indeed switch its behavior depending on the rule in effect for that trial, it could be that PRR rapidly reconfigures in response to the rule. This could be handled, for example, by altering the strength or timing of inhibitory connections within the area. If PRR is capable of undergoing fast reorganization according to task demands, this would be an exciting process to study. This kind of fast reorganization is quite different from the forms of brain plasticity that are usually studied.

A less interesting possibility would be that PRR reflects the outcome of a decision performed in another area, and merely reflects the impending reach plan broadcast by that area. In that case, this proposed rapid reorganization would not be as easily localized.

Topography of connections between LIP and PRR

How might LIP and PRR be connected? If the areas function together to control coordinated movements of eye and hand, there might be a direct, topographic projection between the areas, so that cells representing the same retinal location are connected. On the other hand, if LIP supplies PRR with signals for updating across saccades, this might be implemented in neural circuits that connect oppositely tuned sites in LIP and PRR. By recording simultaneously from LIP and PRR, and exploring the correlation as a function of the degree of overlap of movement fields, we might be able to discover the nature of the connection between the areas, and the behaviors those connections serve.

6.8 Coordinate frames: A fact of brain organization or only a useful description?

Neurons certainly represent space. And, typically a number of factors influence a cell's firing rate. However, is it fair to say that a neuron or brain area represents space in a particular reference frame? Or are coordinate frames merely a description of the manner in which we *measure* neural responses? If reference frames just provide a description of cellular responses, without accurately capturing the truth about neurons, might a more accurate model be more fruitful?

A use of the concept of coordinate frames is that it is easy to imagine transforming information from one coordinate frame to another. How much sense does this make as a description of brain processing? Neural network theory provides useful intuitions about coordinate transformations. In their influential modeling study, Zipser and Andersen (1988) showed that hidden units in a neural network that is trained to perform coordinate transformations resemble parietal cortex neurons. This seems to give a positive answer to the question of whether neurons can be viewed as transforming from one reference frame to another. On the other hand, if a variety of influences affect the activity individual neurons, it becomes difficult to ascribe a particular coordinate frame to that cell.

An intuitive picture of coordinate frames and transformations is one of discrete stages where information is represented in a particular manner. The brain seems little like that. Instead, signals are fed back intricately, and individual areas represent many different influences. Coordinate transformations in the brain are likely to occur gradually, not through discrete, complete stages. How might the anatomic pathways and feedback between brain areas allow for the transformation from one reference frame to another? How can this transformation change in a task-dependent manner, or with time as a motor skill is improved?

Even if coordinate frame studies are eventually supplanted by a more powerful view of how the brain represents space and transforms those representations for different purposes, these studies have provided a powerful tool to dissect the sensory-motor processing circuits of the brain.

Where in the neural processing of movement does our sensation of free will reside? Introspectively, we formulate intentions at a high level: we think more of where we want to go than of how to get there. Neural activity in the parietal reach region seems to resemble closely our sensations of forming intentions. It could be that parietal cortex is the critical area where movement plans are first formulated. How might neural activity in parietal cortex differ just before and just after the moment when we make a decision to move? As our understanding of the brain processing of movement advances, we may gain insights into questions like these. Or, future progress in behavioral neuroscience may lead to an evolution or even a replacement of these concepts.

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