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WASHINGTON UNIVERSITY

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SPECIFIC ROLES OF MACAQUE PARIETAL REGIONS IN MAKING

SACCADES AND REACHES

by

Eric Allen Yttri

A dissertation presented to the  
Graduate School of Arts and Sciences  
of Washington University in  
partial fulfillment of the  
requirements for the degree  
of Doctor of Philosophy

May, 2011

Saint Louis, Missouri

# **ABSTRACT OF THE DISSERTATION**

Specific roles of macaque parietal regions in making saccades and reaches

by

Eric A. Yttri

Doctor of Philosophy in Biology and Biomedical Sciences

(Neurosciences)

Washington University in St Louis, 2011

Professor Lawrence H Snyder, Chairperson

A principle task of our brain is to guide movements, including saccade (fast eye movements) and reaches towards things that we see. Regions in the parietal cortex such as LIP and PRR are active during visually-guided movements. Neurons in these areas respond differentially for saccades versus reaches, but in most parietal areas there is some response (in single unit recording as well as in fMRI imaging) with either type of movement. This raises an important question. What is the functional significance of the neuronal activity in parietal areas? Recording and imaging studies can only show correlations; causal roles must be inferred. The activity in any particular area could reflect where the subject's spatial attention is directed, without regard for what behavior the subject will perform. Stronger activity in one task compared to another could reflect differential allocation of attention. For example, we might attend more strongly to a target for an eye movement than to a target for an arm movement, or vice versa. Alternatively, might play a causal role in driving only one type of movement. In this case, the weaker activity evoked during a different type of movement might serve no purpose

at all; it might represent a contingency plan to perform the non-selected movement; or it might be serve some other function unrelated to the specific movement – for example, weak saccade-related activity in an area with strong arm movement related signals might support play no role in driving eye movements, but instead provide timing information to the reaching system to support eye-hand coordination.

To help resolve this mystery, we used an interventional approach. We asked what happens to reaches and saccades when we reversibly lesioned specific areas in the monkey parietal cortex. In order to establish what brain regions were affected in each inactivation experiment, we developed a novel technique to image the location of the lesions *in vivo*. The results of this causal manipulation were clear: LIP lesions delay the initiation of saccades and have no effect on reaches, while PRR lesions delay the initiation of reaches and have no effect on saccades. We obtained further evidence for a more motoric role for parietal areas than previously suspected. PRR was active for reaches of only the contralateral arm, aimed at targets in either hemisphere – similar to the typical profiles of motor but not visual sensory areas. Interestingly, LIP lesions did influence reaches, but only when the animals were allowed to first look at the target before reaching for it. We believe that in this case, the reaching movement "waits" for the saccade system, and so the direct effect of the lesion on the saccades has an indirect effect on the reaches.

These results are important for several reasons. First, they resolve a long-standing debate regarding the functional specificity of parietal areas with regard to particular movements and attention. They provide new information on the circuits guiding eye movements, arm movements and eye-hand coordination. Finally, our results underscore

the fact that measurements of neuronal activity can be misleading, and are only one of several tools that must be used in order to understand brain function.

## Acknowledgements

I came to the lab weary, recently out of funding, and with iffy recommendations – but was welcomed in despite a “middling” yet potentially promising proposal. Larry seems drawn to orphans and oddballs, and offers opportunities and understanding, almost to a fault. His determination and love of science are inspirational. It was a joy to have long discussions with him on everything from what neurons do and the ramifications of tiny changes in experiments, to BurningMan and how much electric fly-swatters hurt.

Yuqing Liu is responsible for the inspiration behind much of this work. She is relentless in her attention to detail and paved the way for our novel muscimol-manganese inactivation imaging. She has an intense passion for whatever she does and like most of the lab, her very own personal flair. I would like to acknowledge Cunguo Wang for contributing inactivation data and instilling in me a greater sense of patience. Steve Chang also contributed physiology data and provided a scaffolding against which pose my own questions about PRR. I would also like to thank Jonathon Tucker, Thomas Malone, and Matthew Denny for technical support and the ability to liven up scans.

Vinod Rao was a member of the lab for many years and was a shining star in the way he thought, felt, but most importantly expressed himself clearly when it came to any issue. I don't have many regrets in life, but I wish to state that I missed out on Marcel Fremont, a lab technician and gifted incoming student who had a phenomenal vision of the world. I would like to thank my committee Richard Abrams, Eric Leuthardt, Daniel Moran, Stephen Petersen for their support and keen ideas; in particular Kurt Thoroughman, for his courage and passion, both in science and beer. I also acknowledge

the financial support of the National Eye Institute for this project. I would also like to thank Tom Thach for pushing me to do better.

I would also like to support my family for their love and support throughout these years. I would not be here without their sacrifices and patience. I am reminded of my concoctions placed randomly in the bathroom, endless curious questions, and many school issues with fondness rather where others might have disdain. Among my family I would like to thank Adarsh Reddy, my brother from another mother, for being there, though predictably running behind, through thick and thin.

Finally, I would like to thank my wife, Jen, and God for bringing us together. Although we met at Washington University, we attended William and Mary together and had some 40 friends in common; it seemed ordained. She is inspiration, direction, beauty and love to me - in science and all things. Our nerdiness and love of biological systems is a great gift we enjoy sharing.

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*"To live a creative life we must lose our fear of being wrong."*

*- Joseph Chilton Pearce*

*"Function without anatomy is pointless. Anatomy without function is boring."*

*- Joseph L. Price*

# Chapter 1: Introduction

## 1.1 Overview

Pick up this thesis. This seemingly simple task requires the movement of the eyes, the movement of the arm, and a brain to organize a complex series of computations. As this example exhibits, we are perpetually taking in sensory cues, pulling out the useful information, and sorting through this information to react to the world around us. Visual stimuli enter the nervous system through the eye, in the form of photons that cause the depolarization of photoreceptors in the retina. and this information is sent up through visual cortical areas, becoming more highly processed and specialized with each step. In the primary visual cortex, neurons are tuned simply to colors, orientations, and locations, while farther downstream, more elaborate properties are extracted. For instance, in area MT, cells respond to objects moving in specific directions (Britten et al., 1993). This information is used to determine what is relevant, where to pay attention, and how to react to the visual world: a visuomotor transformation. The superior colliculus, for example, is a visuomotor area that uses visual information to encode shifts of gaze to an attended target (Sprague and Melkle, 1965).

Straddling the visuomotor stream between “monkey see” and “monkey do” sits the posterior parietal cortex (PPC), where many sensory to motor transformations are thought to occur (Mountcastle et al. 1975; Andersen et al., 1993). Although nearly all PPC neurons respond to visual stimuli, there exists a division of labor between regions; different parts of PPC respond preferentially to different tasks (Colby and Duhamel, 1991). For example, lateral intraparietal area (LIP) on the lateral bank of the intraparietal

sulcus (IPS) responds strongly to a target instructing the performance of a saccade rather than to an arm movement, such as in LIP. The opposite case is true in areas such as parietal reach region (PRR), wherein neuron responses are not only biased for reaches over saccades, but also reaches with the contralateral limb over reaches with the ipsilateral limb (Chang et al., 2008). Putative functional homologues have been identified by MRI studies in humans. These studies have found that human PPC also is incompletely biased, regions within PPC show more activity in connection with either eye and arm movements (Kertzman et al., 1997; DeSouza et al., 2000; Connolly et al., 2003; Medendorp et al., 2003; 2005; Grefkes et al., 2004; Prado et al., 2005; Fernandez-Ruiz et al., 2007, Hagler et al., 2007).

### ***1.2 The functional relevance of activity in parietal regions (The quandary of posterior parietal cortex?)***

A critical question about these data pertains to the functional significance of the incomplete specificity for effector, that is, preferential activity in relation to what is being moved. For example, LIP is very active in the delay period preceding a planned saccadic eye movement, and somewhat less active in the delay period preceding a planned reaching movement. What roles does LIP have in preparing reaches or saccades? Three types of interpretations could be posited for this spectrum of activity. First, LIP could be completely effector specific, playing a role in saccades but not in reaching. In this scenario, the activity recorded prior to a reach would be non-functional or would serve a function unrelated to the actual reach. Second, LIP could be incompletely effector specific, playing a major role in saccades and a minor role in reaches. Third, LIP could be

completely effector non-specific. In this scenario, LIP activity reflects the subject's attentional locus or a salience map of the visual field. The reduced activity prior to a reach may reflect the possibility that subjects pay less attention to a planned reach target than to a planned saccade target.

An equally important issue, the question of how space is represented at different stages of visuomotor transformation, can provide insight to the organization of the brain. Early visual areas receive input only pertaining to the contralateral visual hemifield. Objects are identified in this limited visual space and neural computations address the sensory issues of “where” and “what” in the surrounding world. In later, more motoric regions, this spatial hemifield specificity is lost to an organization that represents both visual fields. At this level, motor commands are generated, encoded relative to the extrinsic space of the effector and its muscles (Georgopoulos et al., 1986; Kalaska et al., 1989, Kalaska et al., 1997; Schwartz and Moran, 2000). Although the input and output ends of this transformation are well studied, we have not clearly identified the roles of the neural populations responsible for visuomotor transformations.

A related question pertains to where motor commands become lateralized to the contralateral side of the body. PRR activity is only weakly biased for reaches with the contralateral limb over the ipsilateral limb, as would be expected in a sensory area. However, the over-representation of the contralateral limb relative to the ipsilateral limb is suggestive of some degree of lateralization. We can postulate similar hypotheses for limb laterality as those identified above for effector specificity. The common thread to all of these issues is the inability to draw conclusions about function from neural responses.

This ambiguity is possible because unit recording and functional MRI can only demonstrate correlations. Unfortunately, when using techniques that record the intensity of biological signals, the scientist becomes merely a passive observer, rather than an active experimenter inducing changes and measuring the subsequent differences in the dependent variables. As a result, unit data and fMRI are not ideal tools for establishing the functional role of cortical regions. This issue is an important one, and its analysis is vital to comprehending how and where the brain interprets stimuli and then formulates an appropriate response.

Interventional methods, unlike observational measurements, provide a straightforward method to establish a causal relationship between PPC regions and behavior. To this end, we used experimenter-induced lesions to study the PPC. Like any technique, the lesion experiments come with their own drawbacks. As we'll address in more detail later, the actual effects of the lesion do not directly indicate the role of the lesioned area, but rather they reveal how the brain functions without the region of interest. This caveat is often made worse due to the non-specific nature of many lesions. Aspiration, resection, many pharmacological techniques and certainly natural lesions are generally difficult to confine to one region, and both the region of interest and fibers of passage traversing through the lesion are removed. This can cause widespread damage to the brain, the combined affects of which are difficult to understand. To counteract this latter issue, we used a more recent technique, injections of the GABA<sub>A</sub> agonist muscimol to temporarily inactivate neurons near the injection site. Just like GABA, muscimol causes chloride channels to open, hyperpolarizing of the cell and preventing action

potentials. Because these GABA<sub>A</sub> channels are only located on the dendrites and soma (Takeuchi and Onodera, 1972), nearby fibers of passage are not affected by muscimol.

Whereas electrophysiology can provide detailed information from individual neurons that can be correlated to behavior, inactivation provides causal connections between the affected area and behavior. By observing the result of a temporary lesion of a particular area on the performance of a battery of tasks, we can characterize the role that area plays in each behavior. This approach is well-suited for addressing my questions – not only is a cause-and-effect link established between the function of a particular area and a particular action, but the results produced are measured in absolute terms of actual behavior. While the significance of small changes in neural activity may be debated or misinterpreted, changes in accuracy or reaction time provide objective and direct indication of what the region of interest is doing.

### ***1.3 The role of LIP in visually-guided movements.***

When a person reaches for an object, many things must happen. First, any sensory cues must be processed in order to determine their identify and location. Next, the “spotlight” of attention focuses in on the object as necessary. Next, movements of the eye and arm to the attended object are planned and executed. If the eyes are involved in another task, for instance, reading the morning paper while you want to grab your coffee, the reach can be dissociated from the eye movement. We perform this progression of activities many times each day, and area LIP in the PPC has been implicated in every step of it.

LIP is a visuomotor area whose role is hotly contested. It has been implicated in

both visual attention (Colby et al., 1996; Gottlieb et al., 1998; Wardak et al., 2002; Bisley and Goldberg, 2003; Wardak et al., 2004) and motor planning (Lynch et al., 1985; Andersen et al., 1990; Barash et al., 1991; Snyder et al., 1997; Their and Andersen, 1998; Li et al., 1999), in addition to numerosity (Roitman et al., 2007), shape (Janssen et al., 2007) and subjective value (Platt and Glimcher, 1999). These claims stem from the activity profile of LIP. LIP consists of neurons that increase their activity in response to a visual cue, particularly in the contralateral visual field, and exhibit prolonged delay period activity prior to movements of the arm or eyes (Gnadt and Andersen, 1988; Goldberg et al., 1990; Snyder et al., 1997; Qian Quiroga et al., 2006).

Although most neurons in LIP respond more strongly to saccades than reaches, one-fifth of LIP cells exhibit greater activity prior to a reach than a saccade (Snyder et al., 1997). The contralateral field selectivity and similar activity in response to movements of different effectors may reflect a role in attention, suggesting that LIP may represent a salience map of potential targets to attend to (Colby et al., 1996; Gottlieb et al., 1998, Bisley and Goldberg, 2003; Constantinidis and Steinmetz, 2005). The small preference for saccades over reaches would be the result of more attention being given to a potential saccade target. The activity could also represent a pluripotent motor intention – an early, intermediate motor plan to move a yet undetermined effector. In either case, downstream regions would be charged with specifying which effector(s) to move.

On the other hand, the bias of activity could be indicative of a motor specific area. Saccades elicit a greater overall response than reaches, and this preferential firing may have a functional significance. LIP could be primarily involved in the planning of saccades, with only some involvement in the planning of reaches. Yet another possibility

is that LIP is saccade specific, with the reach-related activity playing no operative role. A variation on this theme is the hypothesis that LIP plays a role in the coordination of combined movements of the eye and arm. Coordinated eye-arm movements are tightly coupled, such that the latencies for each movement are highly correlated (Prablanc et al., 1979; Fisk and Goodale, 1985, Snyder et al., 2002; but see Abrams et al., 1990). When a behavioral perturbation is introduced, the processing time of the movements increase in a coordinated fashion (Saslow, 1967; Herman et al., 1981; Bekkering et al., 1996; Boulinguez et al., 2001). Neurons that represent both saccades and reaches would be ideally suited to yolk coordinated eye-arm movements (Fischer and Rogal, 1986; Lunenburger et al., 2008). LIP provides an attractive neural substrate for the coordination of saccades and reaches. It is clear that causal evidence is necessary to address the issue of the functional role of LIP.

Beyond observational studies, LIP has been the subject of much interventional research. Microstimulation has been used to inject current into LIP (Thier and Andersen, 1998, Mushiake et al., 1999). These studies found that LIP stimulation evoked saccades while leaving other effectors unaffected. The ability to cause effector-specific movements was interpreted as a sign that LIP is a motor planning area. However, microstimulation effects can be difficult to interpret. The applied current may spread along axons in the vicinity, directly affecting regions that were not intended to be stimulated. Additionally, stimulation may be subthreshold to evoke a movement, but still interfere with the normal processing.

Another interventional approach to studying the brain is to use lesions. By removing or inactivating part of the brain, we can assess what role the missing area

played in behavior. Just as with other techniques, the inactivation studies of LIP have produced mostly contradictory results. A study of rat PPC demonstrated that lesions induce slowed initiating of contralateral limb responses, while leaving attention and covert orienting intact (Ward and Brown, 1997). In LIP inactivation studies in non-human primates, resection (Stein, 1983; Lynch, 1992) or temporary inactivation (Li et al., 1999) of LIP caused pronounced deficits on visually- and memory-guided saccades. However, these saccadic effects could be explained as being resultant of an impairment in attention. In fact, Wardak and colleagues inactivated LIP and found no saccade deficits, but did report significantly increased response times during a visual search task (Wardak et al., 2002). In a later study, this effect on the ability to quickly search for a specific target was dissociated from the saccadic report, fortifying the argument for an attentional role in LIP (Wardak et al., 2004).

Our lab has used temporary inactivation to study LIP previously (Liu et al., 2010). Monkeys were trained in a memory saccade task as well as a search task in which the monkey had to make a single saccade from the fixation point to a designated shape among seven unique distractors of the same color and size. Although the monkeys used saccadic report, we were able to distinguish between an oculomotor and attention effect by inserting trials at random in which no distractors were present. Inactivation solutions were mixed with the manganese, an MR-lucent contrast agent. This novel application of manganese-enhanced MRI (ME-MRI) provided *in vivo* localization of the inactivation site. In a decisive finding, we found a functional division between the dorsal and ventral subdivisions of LIP (LIPd, LIPv). Although there are previous reports identifying the anatomical division (Andersen et al., 1990; Lewis and Van Essen, 2000), most studies

continue to consider LIP a largely homogenous region. When the experimental data were separated into injections that inactivated either the dorsal or ventral subregion, we found that only LIPv inactivation caused deficits in a covert visual search task, indicating that only LIPv may be involved in allocating attention. Inactivation of either subregion caused increased latency in the saccade task, consistent with an oculomotor planning role. The subregions did differ in their effects, as LIPv inactivations caused slowing of saccades only into the contralateral visual hemifield, while LIPd inactivation slowed saccades in both hemifields. These results in part explain the controversy in the field, and establish that oculomotor planning can exist apart from attention.

However, this latest study leaves some important questions unanswered. For either area, the distinction of ‘oculomotor planning region’, rather than “motor region” cannot be made without first dissociating saccades from other movements. LIP strongly modulates its activity for both saccades and reaches, and it is possible that either division may play a role in reaching movements or coordinating eye-arm movements. Similarly, the possibility exists that the saccade effect in LIPv is the result of a loss of attention resources, rather than the loss of the neural substrates for both sensory attention and motor intention. By subtracting out the oculomotor effect from the search task, any additional effect we can attribute to the increased attentional demands of required to search among the distractors (Wardak et al., 2002, Liu et al., 2010). However, this does not rule out that the original effect on saccades was not due to a deficit in attention. Remember, only movements into the contralateral hemifield were affected following LIPv inactivation, while saccades into either hemifield were slowed following LIPd inactivation. This may reflect more sensory-attention and motor-intention roles,

respectively.

The solution to the issues of both oculomotor/motor and attention/motor intention can be achieved if LIP is inactivated during a reach tasks. There have been no lesion studies in which saccades and reaches were directly compared. Not only is this paradigm essential to decipher the purpose of the reach signals found in LIP, but also the above claims about the function of LIPd/v can be tested. LIP's role in saccade, reach, and coordination can be directly assessed using tasks where the animal performs eye movements, arm movements, or coordinated movements of both the eye and arm, respectively. Furthermore, if some degree of effector-specificity is found, the extent to which LIPv contributes to attention can be determined. Deficits in visual attention should affect any cued movement similarly. If whatever effector-specific effect in LIPd is abolished following LIPv inactivation, it can be assumed that the purported motor contribution of LIPv was actually the byproduct of a visual attention deficit. Conversely, if no changes in motor specificity are found, we can conclude that LIPv contains separate motor planning and attention circuits, the latter of which is particularly susceptible to increased task demands.

#### ***1.4 The role of PRR in reaching movements***

Across the sulcus from LIP in the medial and posterior portion of the IPS sits PRR. PRR is a functionally defined region encompassing portions of MIP (Calton et al., 2002) and V6a (Galletti et al., 1999; Lewis and Van Essen 2000b). Neurons in PRR are characterized by visual responses following the appearance of a target within its receptive

field. In addition, PRR is active during delay and movement aspects of a task (Colby and Duhamel 1991; Caminiti et al., 1996; Johnson et al., 1996; Fattori et al., 2001; Buneo et al., 2002). Consistent with its location in association cortex, PRR responds to targets presented in stimulus modalities, including auditory and visual (Cohen and Andersen, 2000; Cohen et al., 2002). Likewise, it encodes information about where in space a movement should be made, as well as non spatial information about what effector to move (Calton et al., 2002). There is an interplay between response modalities, as activity is systematically modulated by the difference between eye and hand position (Buneo et al., 2002; Fattori et al., 2005; Marzocchi et al., 2008; Chang et al., 2009). Like LIP, PRR modulates its activity prior to both saccades and reaches; however, unlike LIP, PRR responds more strongly for reaches than saccades (Snyder et al., 1997; Cohen and Andersen, 2000; Kutz et al., 2003; Calton et al., 2002; Quiñ Quiroga et al., 2006). There is an additional incomplete bias between the limbs. Preceding a movement, roughly 1/3 of PRR cells respond preferentially to movements of the contralateral limb. Half of PRR neurons respond similarly to movements of either limb, while the remaining 1/6 of neurons fire more strongly for ipsilateral limb movements (Chang et al., 2008).

The activity in PRR could be interpreted in one of three ways. First, PRR might encode behaviorally relevant spatial locations, independent of the effector to be moved. In this scenario it is difficult to explain greater activity prior to a reach compared to a saccade. Second, PRR might be partially effector specific, playing a major role in reaches and a minor role in saccades. Finally, PRR might be completely effector specific, contributing to reaches but not saccadic eye movements. In this last case, the activity seen in PRR that is associated with a planned saccade would not be relevant to

function or would serve a reach-related function; e.g., it might help coordinate eye and arm movements (Pesaran et al., 2006).

A related issue concerns the spatial organization of PRR. Does PRR resemble an early visual area, receiving visual input from the contralateral hemifield and contributing equally to movements of ipsilateral and contralateral limbs? Or is the organization more like a cortical motor area, receiving visual input from both hemifields and contributing primarily to movements of the contralateral limb? Recording studies in PRR suggest an intermediate organization. Visual responses reflect targets from both hemifields with a slight contralateral field bias (Fattori et al., 2005, Chang et al., 2008), and movement planning responses are slightly biased for the contralateral forelimb (Chang et al., 2008). The functional significance of these weak biases (reaching over saccades, contralateral limb over ipsilateral limb, contralateral field over ipsilateral field) is not known.

Unlike saccades, reaching movements can be performed with individual effectors. The decision of which limb to move, rather than which effector to move, is a more complex, more specific motor plan. Strong evidence for limb selection currently exists only in downstream visuomotor areas (Donchin et al., 1998; Hoshi and Tanji et al., 2002; Cisek et al., 2003). Based upon the proposed visuomotor hierarchy of Felleman and Van Essen (1991), it is unlikely that limb-specific processing would occur at the level of PRR. However, it is possible that the brain begins to turn the “sensorimotor corner” (Krauzlis and Halfed, 2007) earlier than expected. The activity biases in PRR are suggestive of at least a potential bias in limb representation. Additionally, the level of activity of PRR neurons is inversely proportional to the reaction time of the ensuing movement, but only when the movement is made with the contralateral, not ipsilateral limb (Chang et al.,

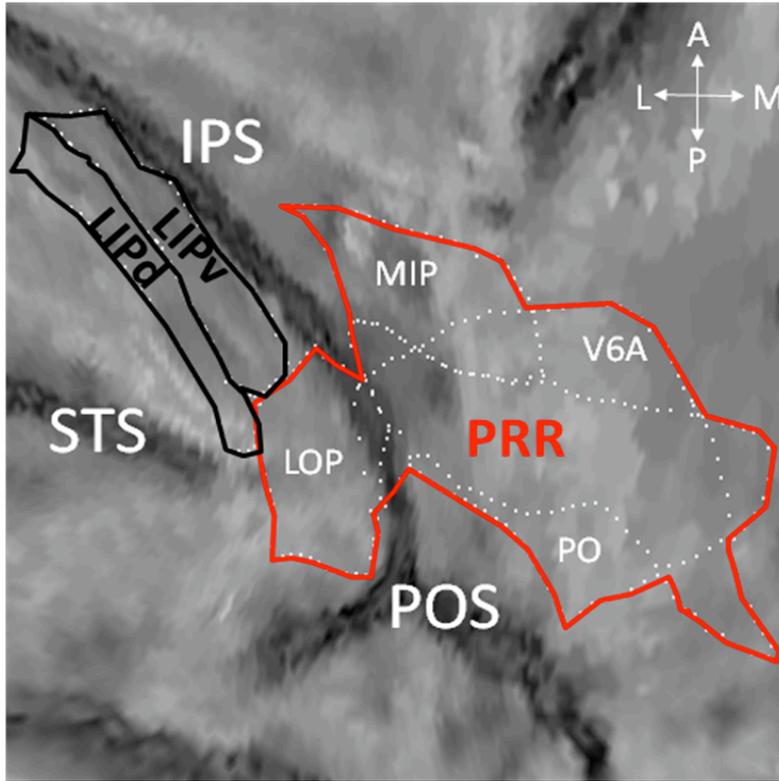
2008). However, it is difficult to determine how these activity correlations shape visuomotor processes.

The functional relevance of neural signals can be tested using interventions. Across primate species there have been interventional studies of the contribution of PRR to behavior. Our lab has previously attempted to use electrical microstimulation to evoke movements (Chang and Snyder, unpublished data), but no clear effect on any effector was found – even when injecting high currents over long durations. Microstimulation effects can be difficult to interpret, and the absence of effect does not signify that the stimulated region plays no role in movements. Lesion studies provide a different interventional technique to determine the functional significance of a region. However, those studies that included the medial bank alone are few.

Lamotte and Acuna (1978) aspirated large tracts of the PPC, but focused their lesions around the medial bank. These unilateral lesions caused contralateral limb-specific deficits in reaching to targets in either visual hemifield. When medial IPS regions MIP, area 5, and dorsal-lateral IPS area 7b were removed, reaches were impaired to remembered targets in the dark (Rushworth et al., 1997). Most recently, V6a, an anatomical region within PRR, was lesioned, causing misreaching and misgrasping with the contralateral limb (Battaglia-Mayer et al., 2002). Only reaching was examined in these studies, so it is impossible to determine if the affected regions contributed to other movements, such as saccades.

To address these issues, we studied the effect of focal lesions in functional area PRR. Monkeys were trained to perform memory-guided saccade and reach tasks. Performance was compared between control and lesion sessions. With this approach, we

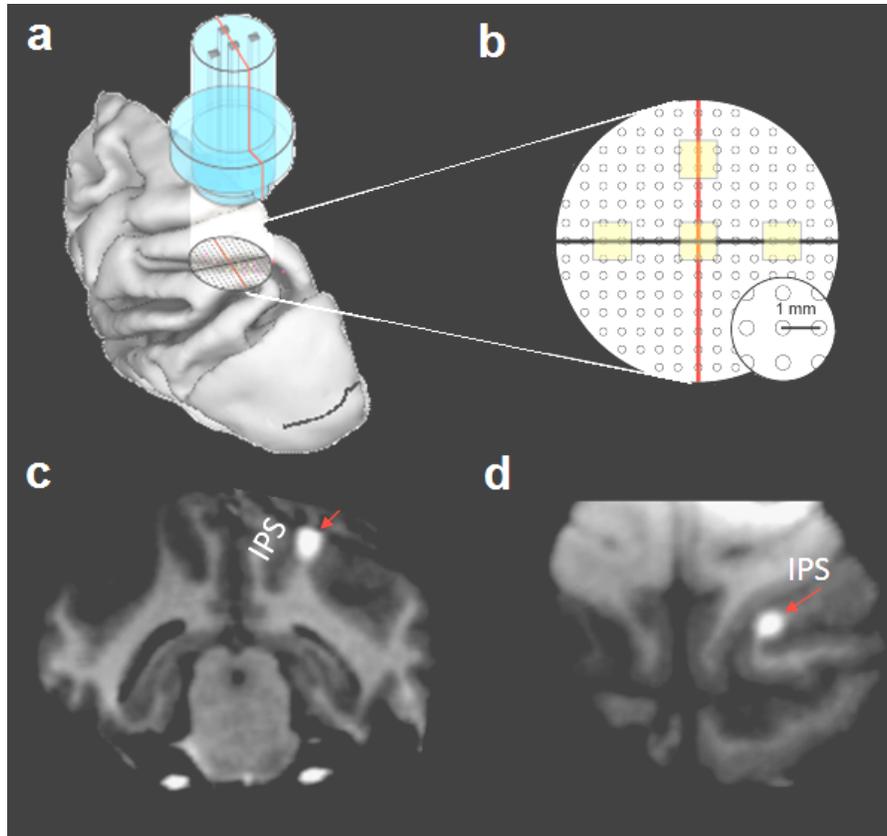
could directly probe the function of PRR. If the neural activity related to saccades or reaches with either limb were functionally utilized, their absence should be expressed in the form of impairment of those respective movements. If more than one effector demonstrates impairment, it is possible that the multiple effector signals reflect a salience map of potential targets. To test for this possibility, the monkeys were also trained in a covert visual attention task in which a unique target had to be chosen from amongst several similar distractors. We assessed the post-lesion performance in this battery of tasks to determine what role PRR plays in visuomotor processing



*Figure 1.1:* Borders of PRR, dorsal LIP and ventral LIP. Anatomical boundaries of PRR, LIPd, and LIPv and are shown on a flat cortical surface. A darkening of the image indicates depth. (generated from Lewis and Van Essen 2000 data, CARET, <http://brainvis.wustl.edu>, sum database: Macaque.F6.BOTH.Std-MESH.73730).

A = anterior; P = posterior; L = lateral; M = medial.

IPS = intraparietal sulcus; STS = superior temporal sulcus; POS = parieto-occipital sulcus; MIP = medial intraparietal area; LOP = lateral occipital parietal area; PO = parietal-occipital area; V6A = area V6a.



*Figure Error! No text of specified style in document..2: Muscimol+Mn-MRI technique. A) Schematic of the chamber coordinate system from a fiducial cylinder projected to the cortical surface. B) The recording grid, separated into one millimeter tracks, while the fiducial cylinder contains axial holes serving as physical landmarks, one in the center and three at offset locations (separated 4.5 mm center-to-center). C, D) Sample muscimol-manganese injections resulting in a bright halo in the dorsal portion of the lateral bank of the IPS, seen here in a coronal slice (left) and horizontal slice (right).*

## **Chapter 2: Reversible inactivation of posterior parietal area**

### **LIP affects reaches only when accompanied by a saccade**

#### ***2.1 Abstract***

Visually guided movements use cues in visual space to create a motor plan for one or more effector. Visual sensory cortex processes spatial information from the contralateral hemifield. At the other end of the visuomotor processing stream, motor output areas demonstrate a contralateral corporal organization for movements towards targets in either visual field. LIP consists of neurons that increase their activity in response to a visual cue and exhibit prolonged delay period activity prior to a movement. The activity profile of LIP neurons is weakly biased such that saccades elicit a slightly stronger response than reaches. To determine the functional relevance of this bias, we compared the effects of LIP lesions in coordinated and dissociated saccade and reach behavior. When comparing dissociated movements, the effects were saccade specific. Additionally, we found evidence that coordinated eye-arm movements are yoked at the neural level, and that reach latency is contingent upon saccade latency.

#### ***2.2 Introduction***

An important function of the brain is to take in visual information, to process that information, and then to react appropriately. For primates like ourselves, reactions are often in the form of either a saccadic eye movement to foveate the target, an arm movement to manipulate the target, or both movements in a coordinated fashion.

Additionally, in order to perceive and plan movements to these targets, we must be able to pay attention to the targets. Neurons in the posterior parietal cortex are active during visual tasks (Mountcastle et al., 1975; Robinson et al., 1978; Bushnell et al., 1981). The lateral intraparietal area (LIP) is located on the lateral bank of the intraparietal sulcus (IPS), responds to visual stimuli (particularly in the contralateral visual field) and exhibits sustained activity in delayed response paradigms (Gnadt and Andersen, 1988; Goldberg et al., 1990). There is substantial activation in saccade, reach and peripheral attention tasks, consistent with a role as a salience map of visual space (Colby et al., 1996; Gottlieb et al., 1998; Wardak et al., 2002; Bisley and Goldberg, 2003; Wardak et al., 2004; Constantinidis and Steinmetz, 2005). However, activation is greater for saccades compared to reaches, and this may indicate a role in saccade planning (motor intention) (Lynch et al., 1985; Andersen et al., 1990; Barash et al., 1991; Snyder et al., 1997; Calton et al., 2002; Quiñero et al., 2006).

The experiments cited so far demonstrate only correlations of neuronal activity with behavior; establishing functional relevance requires a different approach (Wardak et al., 2006; Yttri et al., 2011; see Pierrot-Deseilligny et al., 2004 for review). Interventional approaches can provide direct links between brain and behavior. Electrical microstimulation of LIP can evoke saccades, and reversible inactivation increases saccade latency (Thier and Andersen 1998; Mushiakhe et al., 1999; Constantin et al., 2007; Li et al., 1999; see also Lynch, 1992). However, when Wardak and colleagues repeated the inactivation study, saccades were unaffected but performance in an attention-demanding visual search task was impaired (Wardak et al., 2002, 2004). Liu et al. (2010), using manganese-enhanced MRI imaging to localize each injection site, found

that inactivation of dorsal LIP (LIPd) impairs saccades but not search, while inactivation of ventral LIP (LIPv) impairs both saccades and search.

The results of Liu et al. are consistent with a role for LIPd specifically in saccade planning, and a more general role for LIPv. In the current study, we tested the roles of these areas in reaching, saccades, and the coordination of these two movements. Reaches were affected only when they were accompanied by saccades, but not when they were performed in isolation. Both LIPv and LIPd were saccade-specific in their deficits. Furthermore, there was no change in the coupling of coordinated saccade and reach latencies after inactivation. These results suggest that LIP is saccade-specific: the reach activity in LIP does not contribute directly to behavior and coordination of saccade and reach movements is produced in an area downstream to LIP.

### **2.3 Methods**

Four adult, male macaque monkeys were trained to make eye and/or arm movements to targets on a touch screen 17 cm away. Visual stimuli were back-projected onto the touch screen. Eye movements were monitored with a scleral search implant (CNC Engineering). Animals sat in complete darkness with their heads restrained in custom-made primate chairs (Crist Instruments). The fronts of the chairs were completely open so that the animal had free range of movement of the forelimbs. All procedures were in accordance with the *Guide for the Care and Use of Laboratory Animals* and were approved by the Washington University Institutional Animal Care and Use Committee.

**Behavioral task** – Monkeys were trained to perform a memory-guided center-out reaching or saccade task (Fig. 2.1). For all tasks, trials started with the animal fixating and touching a central fixation cue (5.5° window for the eye, 6° for the hand). Left and right limbs were used in alternating blocks while the other limb was blocked by a Plexiglas panel. All animals were trained to perform a memory movement task either using eye, eye and arm (coordinated), or arm without eye (dissociated, monkeys G, S). After a 350 ms fixation period, a peripheral target was flashed for 150 ms in one of eight equally spaced locations 20° from the fixation point. After a subsequent 1000 - 1600 ms delay, the fixation target was extinguished and the animal had 500 ms to saccade to within 10° of the remembered target location. 150 ms after the eyes acquired the peripheral window, the target reappeared and a corrective saccade to within 5° was required. On coordinated trials, following the completion of a saccade, the animals had 250 ms to reach to within 10° of the target. 150 ms after the initial landing of the hand in the peripheral window, the target reappeared and a corrective saccade to within 6.0° and a corrective reach to within 6.5° was required. Dissociated trials were performed in the same manner but without the non-moving effector leaving the 5.5° fixation window. Accuracy and precision were computed for each target location. Accuracy was defined as the average Euclidian distance between the target location and the endpoint of each movement. Precision was defined as the average Euclidian distance between the mean endpoint and the endpoint of each movement, expressed in degrees of difference.

**Reversible inactivation** – In the four inactivation animals (G,Q,W,S), LIP was identified and localized with single-unit recording assisted by anatomical MR images, before making any intracranial injections. 0.5-2.0ul of the inactivation solution composed of 8

mg/ml muscimol and 0.1 M of the MRI contrast agent manganese (19.8 mg/ml  $\text{MnCl}_2(\text{H}_2\text{O})_4$  mixed in sterile water) were injected through a 33g canula (SmallParts Inc.) attached to a 25ul Hamilton syringe. Ten minutes after lowering the canula to the desired position, a microinjection pump (Harvard Apparatus) was used at a flow rate between 0.5 - 1.5 ul/min. At the conclusion of the injection, the canula remained in place for ten additional minutes before slowly retracting it.

**Lesion localization with MRI** - Following the behavioral session (two to four hours post-injection), T1 weighted anatomical images were collected using a magnetization prepared rapid-acquisition gradient echo (MPRAGE) sequence conducted at  $0.5^3 \text{ mm}^3$  on a 3T head-only system (Siemens Allegra). A single surface coil was used. Animals were lightly sedated with ketamine (3mg/kg) during the procedure. Injections were visible as a bright halo representing the Mn-induced T1 signal increase.

**Data processing-** Behavioral data from injection sessions were compared to data from the two previous control sessions. Control sessions never occurred the day following inactivation. To determine inactivation effects, we parcellated between-control-days and within-control-day variances, then used the within-control and injection means and variances.

## **2.4 Results**

To determine LIP's role in visuomotor processing, we unilaterally inactivated LIP in 42 experimental sessions. Four monkeys performed interleaved saccade and reach trials. The reaches were either accompanied by a coordinated saccade (“coordinated reach”, monkeys G, Q and W) or performed alone while fixation was centrally

maintained (“dissociated reach”, monkeys G and S). There were no significant differences between monkeys and we therefore focused our analysis on the pooled data.

LIP inactivation (Fig. 2.2) slowed reaction times (RT) of both coordinated reaches (8.0 ms,  $p = 0.007$ , two-tailed T test;  $n = 18$  inactivations) as well as the saccades that accompanied those reaches (5.4 ms,  $p = 0.0028$ ). Movements into the contralateral hemifield were slowed more than those into the ipsilateral hemifield for both coordinated reaches (9.4 versus 6.5 ms, contralateral versus ipsilateral hemifield, respectively;  $p$  of difference = 0.02 paired t-test) and saccades (7.6 versus 3.0 ms;  $p = 0.18$ ). However, note that the deficits were significant in each hemifield ( $p < 0.005$  for all four conditions). At the level of each individual inactivation, coordinated reach RTs were slowed in 12 out of 18 sessions ( $p < 0.05$  in 11 of 12 sessions, one-tailed t test). RTs were significantly sped up in only 1 session ( $p < 0.05$ , one-tailed t test). The accompanying saccades were slowed in 15 sessions ( $p < .05$  for 12 of 15 sessions, one-tailed t test). Session by session, the effect of inactivation on coordinated reaches was correlated with the effect on their accompanying saccades (Pearson’s  $r = 0.59$ ,  $p = 0.01$ ).

Previous studies in human and non-human primates have shown that the latencies of coordinated reaches and saccades are tightly coupled (Prablanc et al., 1979; Fischer and Rogal, 1986). Indeed, this was the case in our control data (Fig. 2.2c, black). We found strong correlations between coordinated reach and saccade RTs both at the individual trial level (Pearson’s  $r = 0.637$ ,  $p < 0.000001$ ,  $n = 3441$ ) and across sessions (Pearson’s  $r = 0.869$ ,  $p = 0.000003$ ,  $n = 18$ ). If LIP helps to mediate eye-arm coordination, this coordination should be reduced, if not abolished, by LIP inactivation. This was not the case (Fig. 2.2c, red). Instead, the correlations of control and inactivation

trials were statistically indistinguishable from each other (across all inactivation trials: Pearson's  $r = 0.625$ ,  $p < 0.000001$ ,  $n = 2061$ ;  $p$  of correlation difference = 0.68, Fisher's Z-transformed  $r$  test; across sessions: Pearson's  $r = 0.914$ ,  $p < 0.000001$ ;  $p$  of correlation difference = 0.9, Fisher's Z-transformed  $r$  test). Thus the coupling of eye-arm latencies was unaffected by LIP inactivation.

The similarity between saccade and reach effects could indicate that LIP plays a direct role in mediating both movements, for example, by providing a salience map that encodes spatial locations of special import (Colby et al., 1996; Gottlieb et al., 1998; Kusunoki et al., 2000; Bisley and Goldberg, 2003). Alternatively, LIP may directly affect saccades and only indirectly influence reaches. When either human or non-human primates perform a coordinated eye-arm movement, the reach is typically delayed 50-100 ms relative to the saccade, often not beginning until after the eye has already acquired the target (Angel et al., 1970; Biguer et al., 1982; Helsen et al., 1997; 1998; Snyder et al., 2002; Song and McPeck, 2009). It is conceivable that reach execution is withheld until after an accompanying saccade has begun, so that any delay of the saccade indirectly delays the reach. In order to distinguish between direct and indirect effects on reaching, we tested the effect of LIP inactivation on dissociated reaches, that is, reaches that occur without an accompanying saccade.

The slowing effect of LIP inactivation on reaches was completely abolished when the reach was dissociated from the saccade ( $-0.1$ ms,  $p = 0.93$ ,  $n = 24$  sessions; Fig. 2.3). When considered individually, neither of the two monkeys tested showed an effect (monkey G = 0.1; monkey S =  $-0.7$  ms;  $p = 0.96$  and  $0.75$ ,  $n=17$  and  $7$ , respectively). There was no effect when reaches into either hemifield were considered separately ( $0.2$

and -0.2 ms,  $p = 0.81$  and  $0.84$ , contralateral and ipsilateral fields, respectively; Fig. 2.3b). Finally, there was no effect when reaches made with either limb were considered separately (0.2 and -0.4 ms for the contralateral and ipsilateral limb, respectively;  $p = 0.87$  and  $0.82$ ,  $n = 24$  and  $17$ ). These results rule out a direct contribution of LIP to reaches, and instead suggest that impediments within the saccade planning circuit will affect concomitant motor plans. The reach signal waits on the slowed saccade onset. More generally, these data support previous studies demonstrating that any delay of the saccade will also delay an accompanying reach (Saslow, 1967; Bekkering et al., 1996; Boulinguez et al., 2001).

Unlike reaches, the effect of LIP inactivation on saccades was independent of whether or not the saccade was part of a coordinated eye-arm movement. Saccades were slowed 5.4 ms ( $p = 0.00003$ , two-tailed t-test; Fig. 2.3) when unaccompanied by a reach. As with coordinated saccades, there was significant slowing of saccades to targets in each visual hemifield, although the effect was greater for contralateral targets (7.6 vs 2.8 ms,  $p < 0.002$  for each hemifield;  $p$  of difference =  $0.03$ , paired t test).

Although RT was the most sensitive measure of the effect of LIP inactivation, other parameters were affected in a similar manner (Fig. 2.4). We plotted the inactivation effect under coordinated (abscissa) or dissociated (ordinate) movement conditions, normalized to the maximum level of impairment. Inactivation effects that are independent of movement condition will fall along the unity line, while effects that are specific to either coordinated or dissociated conditions will fall along the X or Y axis, respectively. The data for error rate, accuracy and precision fell along the diagonal for saccades (see also Table 2.1). In contrast, reach impairments either showed a significant

coordinated-specific effect - error rate ( $p = 0.04$ ), accuracy ( $p = 0.05$ ) or no change from controls. We clearly show here that LIP inactivation causes saccade, rather than reach, specific deficits. Furthermore, these data demonstrate that reaching movements and coordinated movements of the eye and limb are dissimilar, distinct motor behaviors that should not be considered equivalent.

Although the anatomical division of LIP into dorsal and ventral subregions has been known for many years (Pandya and Selzer, 1980; Blatt et al., 1990; Lewis and Van Essen, 2001), only recently have clear functional distinctions between the divisions emerged (Ben Hamed et al., 2002; Bakola et al., 2006; Liu et al., 2010, Patel et al., 2010). For example, LIP<sub>v</sub> inactivation causes deficits in visual search while LIP<sub>d</sub> inactivations do not (Liu et al. 2010). From this, one might expect that lesions of LIP<sub>v</sub> (but not LIP<sub>d</sub>) would affect dissociated reaches. In fact, dissociated reach was unaffected by lesions in either area (Fig. 2.4, Table 2.1). We did, however, find differential effects on coordinated movements (Fig. 2.5, Table 2.2). LIP<sub>d</sub> inactivation slowed both saccades and coordinated reaches to targets in either hemifield, while LIP<sub>v</sub> inactivation almost exclusively affected saccades and reaches to targets in the contralateral hemifield.

## ***2.5 Discussion***

The current study demonstrates that both LIP<sub>d</sub> and LIP<sub>v</sub> contribute specifically to saccade planning rather than comprising a general-purpose salience map or reach planning signal. The coordination of eye and arm movements does not occur in LIP, and is likely processed in downstream areas. Finally, LIP<sub>v</sub> contributes only to contralateral saccades, while LIP<sub>d</sub> contributes to saccades into either hemifield.

The complete saccadic specificity revealed by functional inactivation contrasts with the small bias for saccades over reaching observed in LIP recording studies (Snyder et al., 2000). The complete effector-specificity suggests that the effector choice for a forthcoming motor plan is specified in LIP. This specificity could be imposed by an input from FEF, but direct a comparison of the magnitudes and time courses of the effector signals in the two regions suggests otherwise (Lawrence and Snyder, 2006). These inactivation results are in line with previous studies demonstrating that LIP activity reflects an upcoming motor plan-(Platt and Glimcher, 1998; Snyder et al., 1998; Dickinson et al., 2003, Maimon and Assad, 2006).

Although the coordinated reach effects provide insight as to how reaches are coordinated with saccades, we must emphasize that our results imply that LIP were saccade-specific in its motor role.. While it is difficult to train monkeys to perform a dissociated reaching task in an experimental setup, we perform these movements often and accurately in everyday life (i.e. reaching for a cup of coffee while reading the newspaper, playing sports). However, coordinated eye-arm movements and independent reaches are often confused in behavioral studies. The neural mechanisms for executing limb movements are quite segregated from those used to generate saccades. Furthermore, reaches require limb-specific allocation of attention or the divergence of attention between foveated and non-foveated targets (Jonikaitis and Deubel, 2011). As this study demonstrates, “reaching with the arm” and “contaminant eye-arm movements coordinated in time and space” are non-congruous processes in either the psychophysical or neural sense.

In a previous study, we found that LIPd inactivation caused deficits in a simple saccade planning task but not an attention-demanding search task, while LIPv inactivation affected both processes (Liu et al., 2010). The contrafield bias in saccade generation and attention following LIPv inactivation (Wardak 2002, Liu et al., 2010) could be indicative of LIPv playing a stronger sensory role than LIPd. While the overall role of LIP appears to be consistent, the distinct circuits within the dorsal and ventral subregions may subserve different elements of oculomotor planning.

Both dorsal and ventral portions of LIP exhibited saccade selectivity. However, there was a difference in spatial distribution of these effects between the dorsal and ventral subregions. LIPd inactivation exhibited consistent deficits across targets in either hemifield, whereas LIPv inactivation deficits were restricted to the contralateral hemifield. Previously, there have been conflicting lesion and unit activity reports as to whether LIP represented both visual hemifields equally (Platt and Glimcher, 1998) or with a strong contralateral hemifield bias (Blatt et al., 1990; Ben Hamed et al., 2001; Their and Andersen 1996; 1998). However, these studies did not differentiate between dorsal and ventral subregions, nor was accurate localization of each recorded neuron feasible. It is possible that the contradictory findings are the result of recording from different subregions of LIP.

Following LIP inactivation,, Balan and Gottlieb (2009) found deficits only related to targets in the contralateral hemifield, matching the pattern of our LIPv results. However, rather than saccadic report, the monkeys in their task used either limb to respond, and the absence of a limb-specific effect was interpreted to signify that LIP is

principally involved in visuospatial attention. However, we feel that these data actually support our findings. If LIP is motor specific for saccades, there should be no limb effect.

The functional differences between subregions could contribute to other aspects of visuomotor transformations. Both our lesion results and unit recording data (Platt and Glimcher 1998) suggest that LIPd represents both hemifields. Heiser and colleagues (Heiser et al., 2005) predicted that severing the callosal fibers in a macaque would eliminate spatial updating in LIP when the animal made saccades across hemifields. If the spatial processing LIP were specific to the contralateral visual field, cross-hemifield spatial updating would be difficult to accomplish. In fact, neurons ideally would have access to information located anywhere in visual space (Heisner and Colby, 2006), and we propose that the local connections within LIPd could quickly and easily supply this information. . The representation of a both visual hemifields may explain why this characteristic of LIP was intact in the split-brain macaque.

#### *LIP does not contribute to eye-arm coordination*

Our data show that LIP inactivation does not affect the eye-arm coordination, neither at the level of individual injections nor individual trials. Furthermore, reaches executed without a concomitant saccade were unaffected. Removing the influence of the slowed saccade latency eliminated the slowed reach latency. These data suggest that concomitant reaches “wait” for the saccade onset.

Behaviorally, the influence of eye movements on a coordinated arm movement has been well studied (Prablanc et al., 1979; Gielen et al., 1984; Fisk and Goodale, 1985; Johansson et al., 2001). When performing a coordinated eye-arm movement, primates

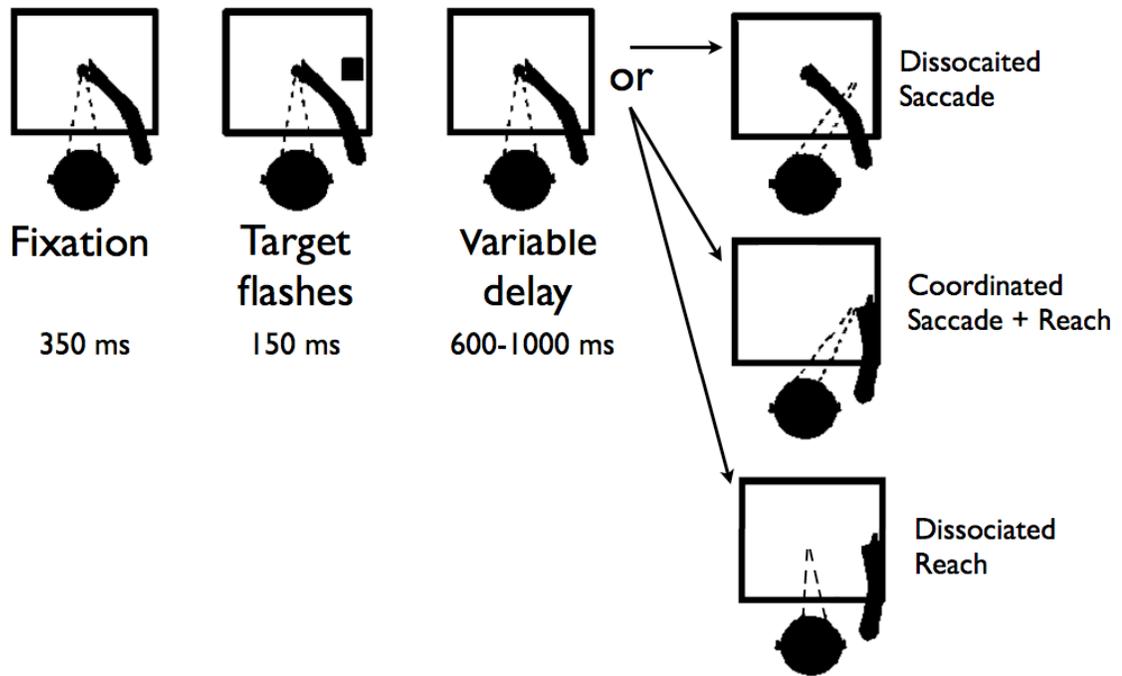
first saccade to a target, often landing at the target prior to reaching for it (Georgeopoulos, 1996; Land and Hayhoe, 2001). There has been much debate as to whether the difference in movement latencies is a result neural mechanism or physical constraints (see Henriques et al., 2002 for review). The coordinated reach effect seen in our study was due to a neural linkage with the slowed saccade plan. The delay between saccade and reach onset remained constant. These data support, though do not confirm, that the delay in coordinated reach onset is the product of neural processes.

The latency coupling could be the result of the reach movement waiting for the saccade, potentially relying upon a corollary discharge from the superior colliculus (SC) to initiate the reaching movement (Sommer and Wurtz, 2002; Reyes-Puerta et al., 2010). The coordinating SC discharge could reach frontal motor areas such as, dorsal premotor cortex, through the mediodorsal nucleus (Goldman-Rakic and Porrino, 1985). Likewise, the integration of the saccadic efference copy into the reach plan could occur elsewhere (i.e. cerebellum) within the skeletomotor circuit (Kennedy, 1972). In either case, the increased saccade latency would directly contribute to the slowing of the coordinated reach onset.

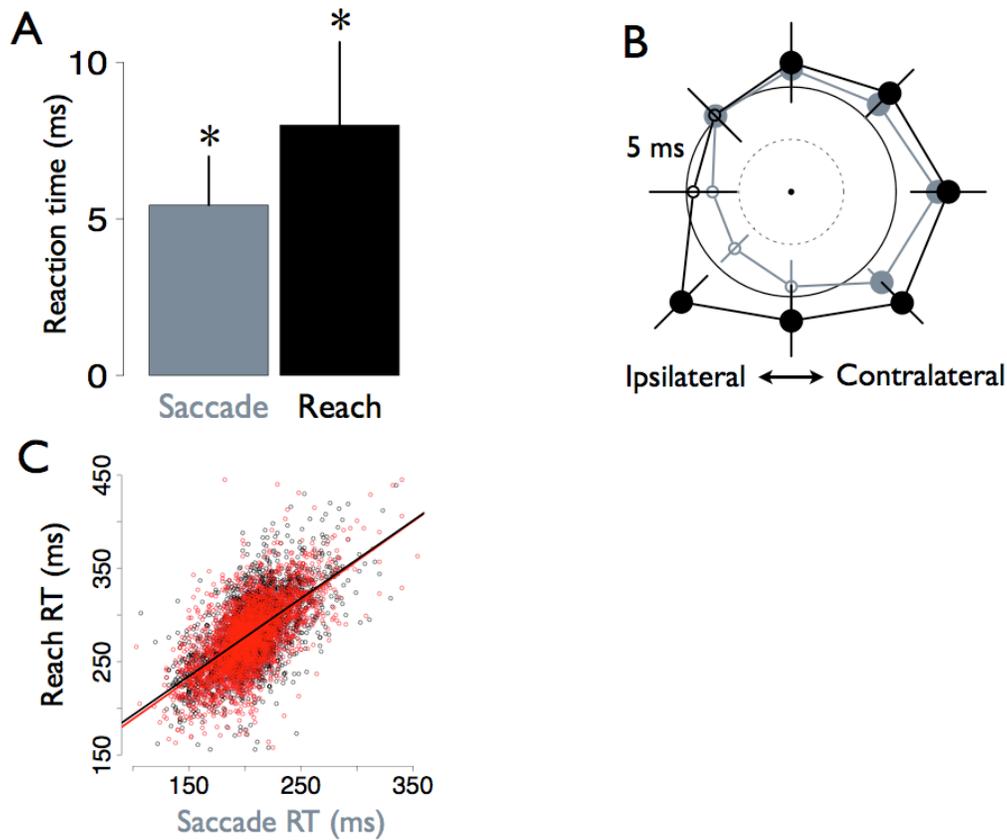
#### *LIP's role in attention*

An apparent inconsistency in our data is the presence of effector specificity and visual attention (Wardak et al., 2002; 2004; Liu et al., 2010) in LIPv. How can a salience map, usually thought to be supramodal (i.e. Posner and Dehaene, 1994) be oculomotor specific? Functional inactivation of other oculomotor planning regions, such as the frontal eye fields (FEF) and superior colliculus (SC), have effects on both behavioral and

neuronal measures of attention (Wardak et al., 2006; Lovekoy and Krauzlis, 2010; Nummela and Krauzlis, 2010). It is possible that activity in these oculomotor areas, including LIPv, reflects attention specific to the potential targets of saccadic movements. In turning the “sensorimotor corner” (Krauzlis and Halfed, 2007), there surely exist intermediate signals that reflect a specific motor plan and the attention dedicated to the target of said movement. A recent study suggests that selective attention for concurrent, dissociated eye and arm targets is independent (Jonikaitis and Deubel, 2011). More generally, the existence of attention that is specific to effectors is consistent with the premotor theory of visual attention (Rizzolatti et al., 1994), which suggests that attention is the driven by motor preparatory activity and not an independent sensory mechanism.

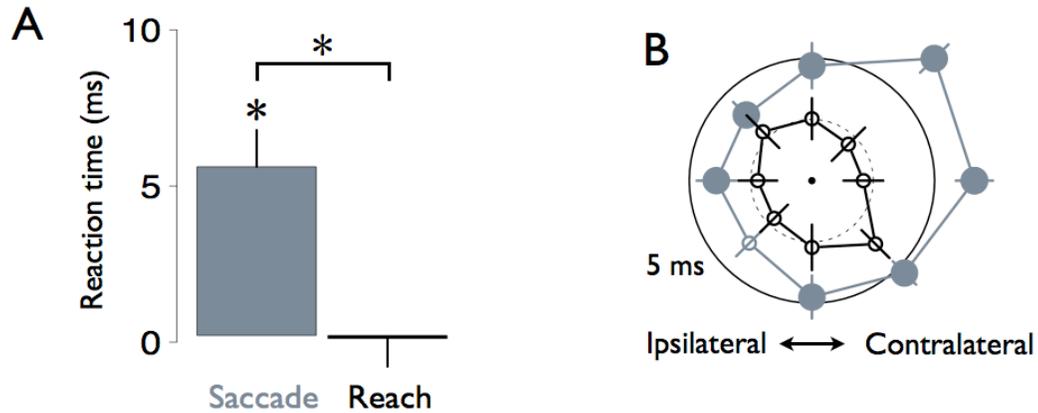


*Figure 3.1:* Behavioral task. After an initial fixation period, target was flashed at one of eight peripheral locations. The target color instructed both movement type and location - green for reach and red for saccade (color not shown in figure). After a variable delay period, the central fixation point disappeared, cueing the animals to make a saccade, dissociated reach, or coordinated reach and saccade to the remembered target. Saccade-alone trials and either dissociated or coordinated reach trials were randomly interleaved.

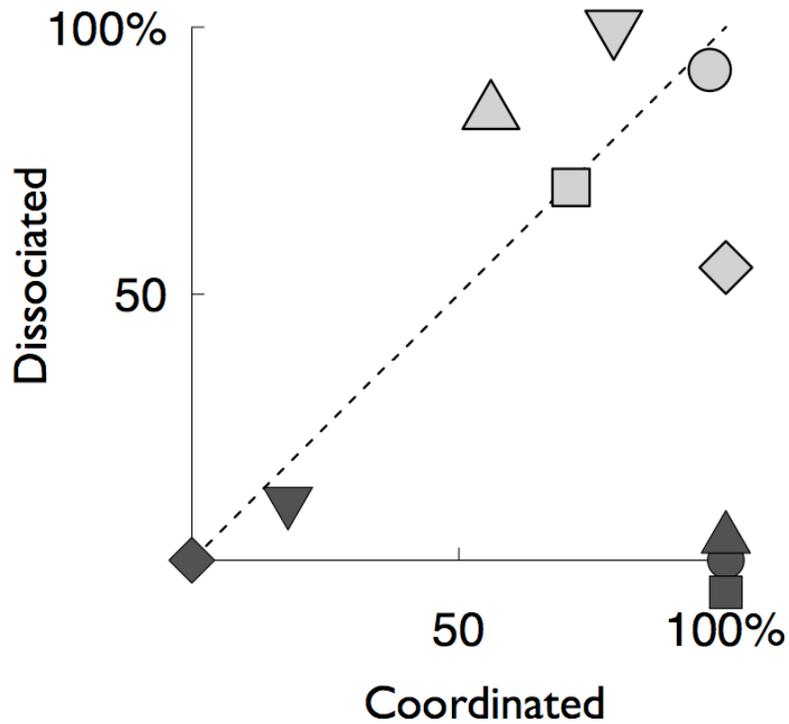


*Figure 2.2:* Effect of LIP inactivation on coordinated saccades and reaches. A) Bar plot of the change in coordinated saccade (gray) and reach (black) reaction time compared to controls. Error bars represent standard error of the mean. B) Polar plot displaying inactivation effect to each of eight targets for saccades (gray) and reaches (black). The dashed inner circle represents no effect. Eccentricity from the no effect circle represents changes in reaction time following inactivation. Significant effects ( $p < .05$ , two-tailed t test) to individual targets are indicated by filled circles. Although the contralateral visual

field for all data is portrayed on the right side of the figure, this was only the case for monkeys Q and W. C) Scatter plot of individual coordinated eye-arm trials in control (black) and inactivation (red) sessions.

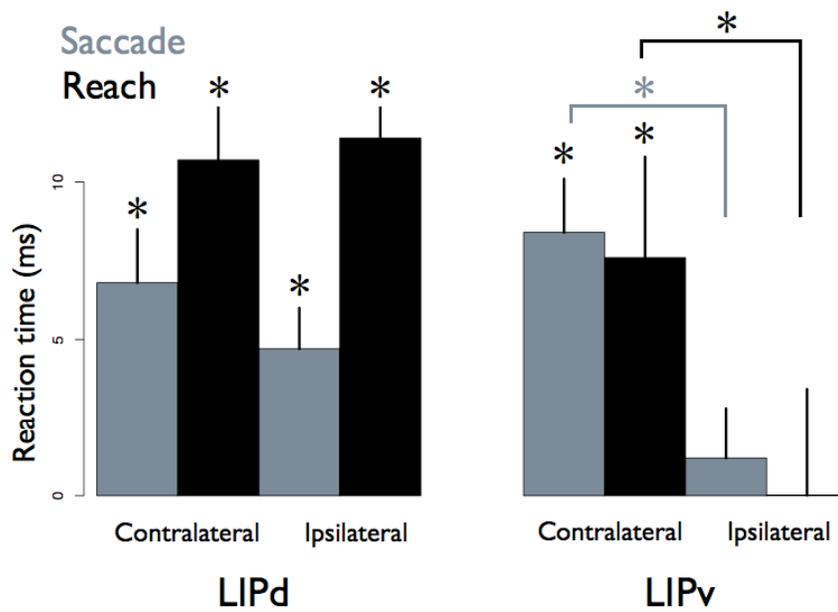


*Figure 2.3: Effect of LIP inactivation on dissociated saccades and reaches. A) Bar plot of the change in dissociated saccade (gray) and reach (black) reaction time compared to controls. Error bars represent standard error of the mean. B) Polar plot displaying inactivation effect to each of eight targets for saccades (gray) and reaches (black). The dashed inner circle represents no effect. Eccentricity from the no effect circle represents changes in reaction time following inactivation. Significant effects ( $p < .05$ , two-tailed t test) to individual targets are indicated by filled circles.*



*Figure 2.4:* Comparison of the effects of LIP inactivation on different aspects of performance. The effect of inactivation is plotted for coordinated (abscissa) and dissociated (ordinate) movements. Saccadic movements are shown in gray, reach movements are shown in black. Dashed line represents equivalent effect in coordinated and dissociated movement task. All values are shown normalized percentage of the maximum absolute inactivation effect. Parameters are error rate (circle), reaction time

(square), duration (diamond), accuracy (triangle up), and precision (triangle down).



*Figure 2.5:* Effects of LIP inactivation in dorsal and ventral LIP on coordinated movements. Bar plot of the effect of inactivation on reaction time for LIPd (left) and LIPv (right). Results are further separated effects for movements into the contralateral (left) and ipsilateral (right) visual hemifields. \* represent significant changes from controls ( $p < 0.05$ ). Bracketed \* represent significant differences between the effects in each hemifield.

	Coordinated		Dissociated	
	Saccade	Reach	Saccade	Reach
Error rate (%)	2.2 (0.9)	2.3 (1.2)	<b>2.1 (0.8)</b>	-2.9 (1.9)
Duration (ms)	1.5 (0.5)	-0.1 (2.4)	0.8 (0.3)	0.0 (1.6)
Accuracy (deg)	0.1 (0.1)	0.2 (0.1)	<b>0.2 (0.0 ??)</b>	0.0 (0.3)
Precision (deg)	0.2 (0.1)	0.1 (.1)	0.3 (0.2)	0.0 (0.1)

*Table 2.1:* Inactivation effects on each movement type of either coordinated or dissociated movements. For each performance parameter, data from the contralateral limb are in the left column, ipsilateral data are in the right column. Italics represent  $p < 0.05$ , bold represents  $p < 0.005$ , two-tailed t test.

		Coordinated		Dissociated	
		Saccade	Reach	Saccade	Reach
<b>LIPd (n=22)</b>	<b>All</b>	<b>6.1 (2.2)</b>	<b>10.8 (2.8)</b>	<b>6.7 (1.5)</b>	-0.3 (1.1)
	<b>Contralateral</b>	<b>6.8 (1.7)</b>	<b>10.7 (2.2)</b>	<b>8.3 (1.2)</b>	-0.7 (1.1)
	<b>Ipsilateral</b>	<b>4.7 (1.3)</b>	<b>11.4 (2.5)</b>	<b>5.1 (1.1)</b>	-1.6 (1.1)
<b>LIPv (n=20)</b>	<b>All</b>	<b>4.7(2.3)</b>	5.4(4.4)	<b>4.6 (1.6)</b>	0.3 (1.1)
	<b>Contralateral</b>	<b>8.4 (1.7)</b>	7.6 (3.2)	<b>7.0 (1.5)</b>	1.3 (1.1)
	<b>Ipsilateral</b>	1.2 (1.6)	0.0 (3.4)	-0.4 (1.3)	1.4 (1.1)

*Table 2.2:* RT effect on each task for inactivations of either LIPd or LIPv.

Contralateral and ipsilateral refer to the visual hemifields. All refers to these hemifields and the targets directly above and below the central fixation point. Italics represent  $p < 0.05$ , bold represents  $p < 0.005$ , two-tailed t test

## **Chapter 3: Resolving ambiguous neural signals in PRR with functional inactivation.**

### ***3.1 Abstract***

Neurons in the posterior parietal cortex are responsible for complex sensorimotor transformations. Parietal reach region (PRR) significantly modulates its activity prior to visually-guided saccades and reaches with either limb. This response profile could be interpreted as encoding attention, motor intention for an unspecified movement, or a selective motor plan for a single effector. Because unit recording cannot provide a causal link to behavior, the functional relevance of these signals is ambiguous. We inactivated PRR with the GABA<sub>A</sub> agonist muscimol and assessed the effects of the temporary lesion. Contrary to the unit data, we found that only movements of the contralateral limb suffered any inactivation deficits. Furthermore, we found that the eye signal in PRR does not contribute to eye-arm coordination. Finally, we found in both our recording and inactivation data that PRR represents each visual hemifield. These results, combined with contralateral limb specificity, suggest that motor-specific planning may exist earlier in the visuomotor pathway than previously thought.

### ***3.2 Introduction***

The posterior parietal cortex is an intermediate region in the dorsal visuomotor network that is thought to be primarily sensorimotor in function (Sakata et al., 1973; Mountcastle et al., 1975; Desmurget et al., 1999). Knowing the role of individual parietal areas is fundamental to understanding how sensory inputs are transformed into

motor outputs. The parietal reach region (PRR) is a visuomotor processing area whose exact role remains controversial. PRR is a functionally defined region (Snyder et al. 1997, Calton et al., 2002) that includes parts of anatomical areas V6A and MIP (Colby et al., 1988, Galletti et al., 1999) in the posterior portion of the medial bank of the intraparietal sulcus (IPS). Single unit recording studies have found visual- and movement-related responses in PRR (Colby and Duhamel 1991; Caminiti et al., 1996; Johnson et al., 1996; Galletti et al., 1999; Fattori et al., 2001; Buneo et al., 2002). PRR neurons increase their activity during the delay period preceding a planned reach, and to a lesser extent, prior to a saccade (Snyder et al., 1997, Cohen and Andersen, 2000; Snyder et al. 2000; Calton et al., 2002; Kutz et al., 2003; Quian Quiroga et al., 2006). This delay activity is systematically modulated by the difference between eye and hand position (Buneo et al., 2002; Fattori et al., 2005; Marzocchi et al., 2008; Chang et al., 2009).

The activity in PRR could be interpreted in one of three ways. First, PRR might encode behaviorally relevant spatial locations, independent of the effector to be moved. In this scenario, the location of potential reach targets may be more salient to PRR neurons than potential saccade targets. Second, PRR might be partially effector specific, playing a major role in reaches and a minor role in saccades. Finally, PRR might be completely effector specific, contributing to reaches but not saccadic eye movements. In this last case, the activity seen in PRR that is associated with a planned saccade would not be relevant to function or would serve a reach-related function; e.g., it might help coordinate eye and arm movements (Pesaran et al., 2006).

A related issue concerns the spatial organization of PRR. Does PRR resemble an early visual area, receiving visual input from the contralateral hemifield and contributing

equally to movements of ipsilateral and contralateral limbs? Or is the organization more like a cortical motor area, receiving visual input from both hemifields and contributing primarily to movements of the contralateral limb? Recording studies in PRR suggest an intermediate organization. Visual responses reflect targets from both hemifields with a slight contralateral field bias (Fattori et al., 2005, Chang et al., 2008), and movement planning responses are slightly biased for the contralateral forelimb (Chang et al., 2008). The functional significance of these weak biases (reaching over saccades, contralateral limb over ipsilateral limb, contralateral field over ipsilateral field) is not known

Functional significance can be tested using specific interventions. For example, lesion studies allow us to observe how the brain functions in the absence of a particular portion of the cortex, and this in turn provides clues as to the function of that tissue. Though few, lesions of the medial bank of the IPS have suggested that this region contributes to reaching with the contralateral limb (LaMotte and Acuna, 1978; Brown et al., 1983; Battaglini et al., 2002). These studies used large surgical lesions, comprising multiple areas and potentially severing unrelated fibers of passage. Additionally, testing typically occurred days after the surgery, allowing ample time for adaptive compensation. None of these studies measured eye movements, and therefore could not address the issue of effector specificity.

We temporarily inactivated PRR with microinjections of the GABA<sub>A</sub> agonist muscimol in three monkeys performing reach and saccade tasks (Fig. 1). We then compared the lesion results with electrophysiological data from a previous study (Chang et al., 2008). The recording study showed modulation when reaches were planned with either the contralateral or ipsilateral forelimb, and reduced but significant modulation

when a saccade was planned. We now report that PRR inactivation impairs only contralateral limb movements, not saccades or ipsilateral limb reaches, and that this effect is not specific to either visual hemifield. Thus our results provide direct evidence for a specialized role of PRR in reaching, and suggest that the organization of PRR has more in common with motor than visual sensory areas. In addition, our findings suggest that the results of correlative studies should be interpreted with caution.

### **3.3 Methods**

Four adult, male macaque monkeys were trained to make eye and/or arm movements to targets on a touch screen 17 cm away. Visual stimuli were back-projected onto the touch screen. Eye movements were monitored with a scleral search implant (CNC Engineering). Animals sat in complete darkness with their heads restrained in custom-made primate chairs (Crist Instruments). The fronts of the chairs were completely open so that the animal had free range of movement of the forelimbs. All procedures were in accordance with the *Guide for the Care and Use of Laboratory Animals* and were approved by the Washington University Institutional Animal Care and Use Committee.

**Behavioral task** – Monkeys were trained to perform a memory-guided center-out reaching or saccade task (Fig. 3.1). For all tasks, trials started with the animal fixating and touching a central fixation cue (5.5° window for the eye, 6° for the hand). Left and right limbs were used in alternating blocks while the other limb was blocked by a Plexiglas panel. All animals were trained to perform a memory movement task either using eye, eye and arm (coordinated), or arm without eye (dissociated, monkeys G).

After a 350 ms fixation period, a peripheral target was flashed for 150 ms in one of eight equally spaced locations 20° from the fixation point. After a subsequent 1000 - 1600 ms delay, the fixation target was extinguished and the animal had 500 ms to saccade to within 10° of the remembered target location. 150 ms after the eyes acquired the peripheral window, the target reappeared and a corrective saccade to within 5° was required. On coordinated trials, following the completion of a saccade, the animals had 250 ms to reach to within 10° of the target. 150 ms after the initial landing of the hand in the peripheral window, the target reappeared and a corrective saccade to within 6.0° and a corrective reach to within 6.5° was required. Dissociated trials were performed in the same manner but without the non-moving effector leaving the 5.5° fixation window.

**Reversible inactivation** – In the three inactivation animals (G,Q,W), PRR was identified and localized with single-unit recording assisted by anatomical MR images, before making any intracranial injections. 0.5-2.0ul of the inactivation solution composed of 8 mg/ml muscimol and 0.1 M of the MRI contrast agent manganese (19.8 mg/ml  $\text{MnCl}_2(\text{H}_2\text{O})_4$  mixed in sterile water) were injected through a 33g canula (SmallParts Inc.) attached to a 25ul Hamilton syringe. Ten minutes after lowering the canula to the desired position, a microinjection pump (Harvard Apparatus) was used at a flow rate between 0.5 - 1.5 ul/min. At the conclusion of the injection, the canula remained in place for ten additional minutes before slowly retracting it.

**Lesion localization with MRI** - Following the behavioral session (two to four hours post-injection), T1 weighted anatomical images were collected using a magnetization prepared rapid-acquisition gradient echo (MPRAGE) sequence conducted at  $0.5^3 \text{ mm}^3$  on a 3T head-only system (Siemens Allegra). A single surface coil was used. Animals were

lightly sedated with ketamine (3mg/kg) during the procedure. Injections were visible as a bright halo representing the Mn-induced T1 signal increase. The data from injections with halos outside our area of interest were excluded (for examples, see Fig. S3.1).

**Recording data** – The unit-recording procedure has been previously described in Chang et al., 2008. Briefly, using a visually-guided center-out task, directional tuning curves were mapped out for each of 90 PRR neurons in two animals, including monkey G (60 neurons). The reported neural activity was measured during the delay period prior to the movement described in the task described above.

**Data processing-** Behavioral data from injection sessions were compared to data from the two previous control sessions. Control sessions never occurred the day following inactivation. To determine inactivation effects, we parcellated between-control-days and within-control-day variances, then used the within-control and injection means and variances.

### ***3.4 Results***

To examine the contribution of PRR to movement planning, we reversibly inactivated PRR in three monkeys in 20 separate injection sessions. Lesion location was confirmed by magnetic resonance imaging of co-injected manganese (see Methods). We measured the inactivation-induced changes in performance, including effects on reaction time (RT), duration and accuracy, in interleaved memory-guided saccade and reach trials. The clearest effect was on the reaction time for reaches with the contralateral limb. Across sessions, the mean effect was a 5.7 ms slowing ( $p=0.0007$ , two-tailed t-test; Fig. 3.2a). Within individual sessions the effect ranged from a 20.3 ms slowing to a 4.1 ms

speeding, with 17 out of 20 sessions slowed. The slowing was statistically significant in 11 sessions, and in no session was there a significant speeding of RT ( $p < .05$ ).

In contrast to the contralateral limb, there was no effect of inactivation on reaches with the ipsilateral limb (mean = 1.1 ms,  $p = 0.5$ , range = -12.0 to 16.0 ms) or saccades (mean = -1.2 ms,  $p = 0.2$ , range = -9.9 to 8.2 ms).

These effects were consistent across individual animals, with significant slowing of reaches with the contralateral limb in one animal and a strong trend in the others, and no effect on ipsilateral reaches or saccades in any individual animal (Table 3.1). Other movement parameters showed similar specificity (Table 3.2). Movement velocity was significantly slowed for reaches with the contralateral limb (3.6 deg/s,  $p = 0.026$ ), but not for ipsilateral limb reaches or saccades (0.8 deg/s and 0.2 deg/s, respectively). Inactivation caused a trend towards decreased precision (0.2 deg,  $p = 0.54$ ). Similarly, the duration of reaches with the contralateral limb showed a trend toward impairment (3.8 ms,  $p = 0.12$ ), Ipsilateral limb reaches and saccades were unaffected for either of these parameters. In sum, the results of PRR inactivation were strongly effector specific, degrading reaches performed with the contralateral limb while leaving ipsilateral limb reaches and saccades intact.

We compared these reversible inactivation results to electrophysiological recordings of delay period activity in an identical interleaved memory saccade and reach task from 90 PRR neurons in a previous study (Chang et al., 2008). In contrast to the effector specific results of inactivation, cell activity was only slightly biased, with significant modulation in association with reaches with either limb and also with saccades (Fig. 3.2b). Prior to a reach made with the contralateral limb towards a target in each

neuron's preferred direction, firing rate increased on average  $12.1 \pm 1.0$  sp/s ( $p < 0.00001$ ). With the ipsilateral limb, firing increased  $10.1 \pm 1.2$  sp/s ( $p < 0.00001$ ). The difference in activity was not significant ( $p = 0.115$ , paired t test). At the individual cell level, the activity increase was significant in 89% of cells for the contralateral limb and 72% of cells for the ipsilateral limb. (Note that cells were only included in this study if they were active during the delay period with movements of at least one limb.) Across the population, 32% of cells had significantly higher activity for a contralateral compared to ipsilateral limb reach, while 21% showed the reverse effect. In contrast to this weak preference for the contralateral over the ipsilateral limb, there was a clear preference for reaches over saccades. Prior to a saccade, firing increased by only 3.8 sp/s. This increase was statistically significant ( $p = 0.00002$ ), but significantly less than the increase prior to a reach ( $p < 0.00002$ ).

A fair comparison of lesion effects to evoked activity requires that the same tissue be sampled in each case. In order to establish the injection location, we co-injected manganese (0.1 M) with muscimol and then visualized the center and approximate extent of each injection in vivo using magnetic resonance imaging (Liu et al. 2010). Only those injections centered in the posterior portion of the medial bank of the intraparietal sulcus, with minimal or no spread across the parietal-occipital sulcus, were included in the study. (Examples of excluded inactivations are shown in supplemental Fig. S3.1.) We then overlaid our PRR recording sites on our injection images to confirm the overlap (Fig. 3.3).

*Both hemifields are represented in PRR*

Lesion effects did not depend on target location. Figure 3.4a depicts the RT effect for each of eight targets. Reaches with the contralateral limb were slowed without regard for target direction ( $p < .05$  for all but one direction, one tailed t test;  $p = 0.52$ , Rayleigh's test for uniformity). In particular, there was no significant difference for reaches made with the contralateral limb to targets in the contralateral versus ipsilateral hemifield (2.0 ms,  $p = 0.21$ , two-tailed paired t-test). Reaches made with the ipsilateral limb, in contrast, were not slowed for any target direction. Figure 3.4b shows the individual injection data. The limb biases (ordinate) are mostly positive ( $p = 0.007$ ,  $\chi^2$  test), indicating greater slowing of reaches with the contralateral compared to ipsilateral limb. The field biases (data from both limbs, abscissa), however, are evenly distributed around 0 ( $p = .82$ ). It was not the case that the limb biases from individual inactivations were correlated with the hemifield biases (Pearson's  $r = -0.06$ ,  $p = 0.82$   $\chi^2$  test).

Like the lesion results, single unit recording indicated that PRR represents both visual hemifields. However, unit recording showed a strong effect of vertical target location. Figure 3.4c illustrates recording data analogous to the lesion data in Figure 3.4A. For each target, we summed the firing rates of cells whose preferred directions were to that particular target. This measurement combines the number of cells with a particular preferred direction with their strength of discharge. The results show that, unlike the lesion effect, evoked activity was similar for the two limbs ( $p = 0.81$ , Rao's test for Homogeneity) and had a strong lower hemifield bias ( $p < 0.000001$  for each limb,  $\chi^2$  test comparing responses to upward versus downward targets). There was also a small but significant bias for contralateral limb reaches into the contraversive compared to the ipsiversive visual field ( $p < 0.002$ ,  $\chi^2$  test;  $p = 0.64$  for the ipsilateral limb).

### *Inactivation effects are not due to impaired attention*

IPS regions, and in particular the lateral intraparietal area, have been suggested to be involved in directing attention to salient targets (Wardak et al., 2002; 2004). We tested PRR for its role in attention using a covert search task. The monkeys were trained to fixate centrally while 1 target and 8 distractors appeared in the periphery (Fig. 3.5a). The target and distractors were the same size and color. The shape (square) indicated which location was the target. The animals were instructed to quickly make one saccade to the target after the stimuli were presented. Trials in which the animal made a saccade to a distractor or double saccade were immediately terminated and counted as errors.

PRR inactivation did not impair performance in this search task (Fig. 3.5b). Deficits in attention most often cause increases in errors, particularly for targets in the contralateral hemifield (Wardak et al., 2002; Liu et al., 2010). Although there was a slight increase in error rate (red) to targets in the contralateral field (1.0% increase in error rate), it did not approach significance ( $p = 0.57$ ). Furthermore, RT (blue) actually improved across targets (speeding of RT to all targets = -1.9, contralateral targets = -2.3, ipsilateral targets = -1.7;  $p = 0.044, 0.16, \text{ and } 0.33$ , respectively). These results provide further evidence that PRR does not contribute generally to the processing of salience maps.

### *PRR inactivation does not affect eye-hand coordination*

Humans and monkeys typically coordinate a saccadic eye movement along with a reach, with gaze arriving on target shortly before the reach is completed (Prablanc et al.,

1979; Biguer et al., 1982, Rogal et al., 1985; Dean et al., 2011; but see Abrams et al., 1990 and Smeets et al., 1996). The onset latencies for these coordinated saccades and reaches are correlated on a trial-by-trial basis (Fisk and Goodale, 1985, Fischer and Rogal, 1986). If PRR plays a role in coordinating eye and limb movement, PRR inactivation should decrease this correlation. Figure 3.4a shows that this was not the case. PRR inactivation had no significant effect on the correlation (contralateral limb,  $r = 0.36$  (control) to  $0.34$  (lesion); ipsilateral limb:  $r = 0.45$  to  $0.46$ ;  $p = 0.68$  and  $p = 0.77$ , Fisher  $r$  to  $Z$  transformation, for contralateral and ipsilateral limbs, respectively. The finding of no change in contralateral limb-eye correlations held even when the data were restricted to just those sessions with significant increases in reach reaction times ( $p > 0.42$ ), as well as when the data were restricted to movements into the contraversive field ( $p = 0.61$ ). These results provide strong evidence that the coordination of saccade and reach timing is not dependent on an intact PRR.

Unlike Fig. 4a, the data presented in Figures 3.2 and 3.4 reflect a mixture of coordinated and isolated movements, that is, reaches made with and without an accompanying saccade to the same target. When the data are separated and compared, we found no differences in the effects of inactivation on either reaches or saccades (Fig 3.6b). For the contralateral limb, coordinated and dissociated reach RTs were slowed by similar amounts (6.4 and 4.5 ms over 11 and 9 sessions, respectively;  $p$  of difference = 0.39). For the ipsilateral limb, neither coordinated nor dissociated reaches were significantly slowed (2.2 and -0.2 ms, respectively;  $p = 0.42$ ). Finally, neither dissociated nor coordinated saccades were significantly slowed by inactivation (-1.0 and -1.4 ms, respectively;  $p = 0.8$ ; also true for saccades made in coordination with movements of

either the contralateral or ipsilateral limb, considered separately). In two experiments, both coordinated and dissociated movements were performed within the same session. In this case, the effect on coordinated and dissociated reach RT differed by only 0.2 ms (4.3 and 4.5 ms, respectively;  $p = 0.9$  paired t test; data not shown).

### ***3.5 Discussion***

Single unit recording is often considered to be the gold standard for understanding how the brain functions at a neuronal level. However, recording cannot directly assess how or even what a particular area contributes to behavior. Reversible lesions can provide evidence in this regard. Our study on the effects of PRR lesions on reaches and saccades revealed three major findings. First, PRR appears to contribute only to contralateral and not ipsilateral limb movements. Second, the spatial organization of PRR is more congruent with motor than with sensory cortical areas. Finally, PRR does not appear to play a direct role in coordinating saccades and reaches. We will consider each of these points in turn.

#### *PRR inactivations affect only the contralateral limb*

Reversible inactivations of PRR impair reaching with the contralateral limb, but have little or no effect on reaches with the ipsilateral limb or on saccades (Figs. 3.2a, 3.4b and 3.6b). Strong deficits were observed in reaction time, along with deficits in mean velocity, duration, and precision. This suggests that PRR may contribute more to the planning than the execution of reaches. Our findings concur with previous studies demonstrating contralateral limb deficits following PPC ablation (LaMotte and Acuna,

1978; Brown et al., 1983, Battaglini et al., 2002). Additionally, Rushworth and colleagues (1997) demonstrated that bilateral removal of areas 5, 7b and MIP resulted in reach performance deficits specific to a memory-guided reaching task, but did not affect visually-guided reaches.

In contrast to inactivations, single unit recordings from PRR reveal substantial activity associated with both contralateral and ipsilateral limb movements (Fig. 3.2b). The striking disparity between the effects of lesions (contralateral limb only) and single unit recording (both limbs) is somewhat mitigated by two factors. First, there is a small contralateral limb bias in the unit recording, and second, activity recorded prior to the movement varies inversely with the RT of the contralateral but not ipsilateral limb (Snyder et al., 2006; Chang et al., 2008). RT-correlated preparatory set activity is a common finding in motor areas ( M1 -Tanji and Evarts, 1976; Lecas et al., 1986; PM – Kurata, 1993; Riehle and Requin, 1993; SC - Basso and Wurtz, 1997; FEF and SEF – Schall, 1991). PRR projects to premotor area PMd (Pandya and Seltzer, 1982). Like PRR, PMd shows modulations prior to both reaches and saccades (Fujii et al., 2000; Pesaran 2010), but preparatory set activity is specifically correlated with reach RT (cite) and disruption of this activity causes a reach-specific increase in RT (Churchland and Shenoy, 2007). Like the current results, these findings suggest that preparatory set activity (defined as a relationship between firing rate and reaction time, Riehle and Requin, 1993), may be a more reliable indicator of function than increases in firing rate that are not correlated with RT.

One important caveat remains. Our lesion study may underestimate the contribution of PRR to reaches performed with the ipsilateral limb. Unit recording

suggests a stronger contribution from contralateral PRR than from ipsilateral PRR. It is conceivable that the intact contralateral PRR is able to fully compensate for the effect of the lost PRR, but that the reverse is not true. This could explain the pattern of deficits we have reported. The substrate for such an effect exists; PRR has cross-collosal connections with itself as well as contralateral PMd (Pandya and Vignolo 1969; Pandya and Seltzer, 1983). Bilateral PRR inactivation could be used to test whether interhemispheric compensation is in fact at play. If compensation is present, the effect of a bilateral inactivation (on both limbs) should be substantially greater than the effect of a unilateral inactivation on the contralateral limb.

*The organization of spatial information in PRR resembles motor rather than sensory areas*

In the cortex, motor regions are generally organized according to the effector to be moved and without regard to where the sensory information giving rise to the movement was located. In contrast, visual sensory areas generally process sensory information from the contralateral hemifield, without regard for which effector will ultimately be engaged in connection with the information. PRR represents visual information from either visual hemifield, and routes this information to the forelimb on the contralateral side of the body. This organization of spatial information is more consistent with that of motor areas than with sensory areas. One might have expected that, as one ascends in the dorsal visual processing stream (Felleman & Van Essen, 1991), one would encounter regions with intermediate characteristics, e.g., responses to visual inputs from either hemifield and involvement in effectors from either side of the

body. Instead, PRR appears to constitute an abrupt change from the sensory-organized areas from which it receives input (e.g., areas PIP, V3a). (for review see Ferraina et al., 2009). Thus it appears that in the monkey the transformation from a general purpose visual signal to an intention signal for a reach occurs abruptly, and within PRR.

#### *Comparisons with human PRR homologues*

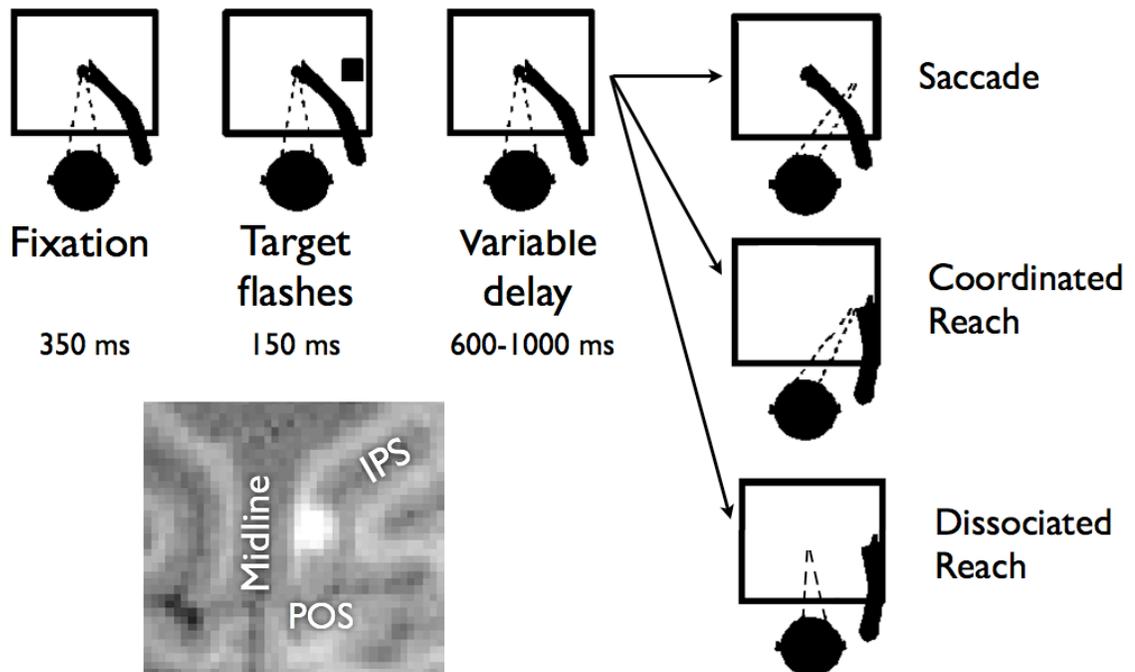
Functional MRI has revealed regions in human parietal cortex (SPOC, AG and mIPS) that appear analogous to PRR in monkeys. These regions exhibit increased blood oxygen levels when subjects plan reaches or a saccades, with greater increases for reaches (Connolly et al., 2003; Medendorp et al., 2003; 2005; Prado et al., 2005; Fernandez-Ruiz et al., 2007, Hagler et al., 2007). When perturbed using TMS, only SPOC stimulation showed performance deficits specific to reaches, while mIPS and AG stimulation caused both reach and saccade deficits (Vesia et al. 2010, but see Trillenberget al., 2007 for reach specific effects following mIPS lesion). To the extent that TMS provides a reliable indicator of function, this suggests that, like single unit recording, imaging results can be misleading with regard to function, unless the results are confirmed by either a demonstration of preparatory set signals (that is, trial-by-trial correlations with reaction time) or an interventional technique such as TMS.

The relationship between parietal regions in monkeys and humans remain unclear. The human reach regions (SPOC, mIPS) are involved primarily in reaching for targets in the contralateral hemifield (Vesia, et al. 2010). Monkey PRR, in contrast, shows almost no hemifield bias (unit recording, lesion studies; Fig. 3.4 a and b). Interestingly, this is the reverse of what is seen for eye movement areas. In humans, the parietal eye fields

show only a weak hemifield bias (fMRI), while in monkeys, area LIP is strongly contralaterally specific (single unit recording: Barash et al; fMRI imaging: Patel et al. 2010; lesion studies: Duhamel et al.; Liu et al.).

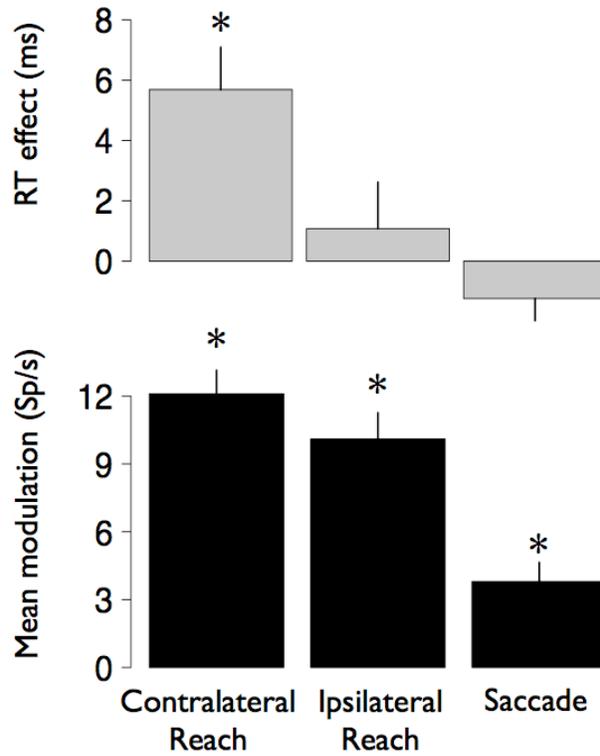
*PRR lesions do not affect eye-hand coordination*

Our animals were trained to make reaching movements either with or without an accompanying saccade. When unconstrained, subjects usually make a saccadic eye movement first and hold fixation until the hand arrives at the target (but see Abrams et al., 1990). Typically, such coordinated reaches and saccades are tightly temporally coupled (Prablanc et al., 1979; Rogal et al., 1985). It has been suggested that, in the monkey, the saccade signals found in PRR may be used to achieve this tight coupling (Boussaoud et al., 1998; Battaglia-Mayer et al., 2001; Pesaran et al., 2006). If this were the case, we would predict that inactivating PRR would result in looser coupling, manifest as a decrease in the correlation coefficient between coordinated saccade and reach reaction times. Alternatively, we might see no change in correlation but a trial-by-trial slowing of saccadic reaction times that matches the slowing of reach reaction times. We saw neither of these two effects, suggesting that PRR does not play a major role in coordinating saccade and reach reaction times, and provides another example of how relying exclusively on patterns of evoked activity to draw conclusions regarding function, without testing those conclusions using an interventional technique, may lead to erroneous conclusions.

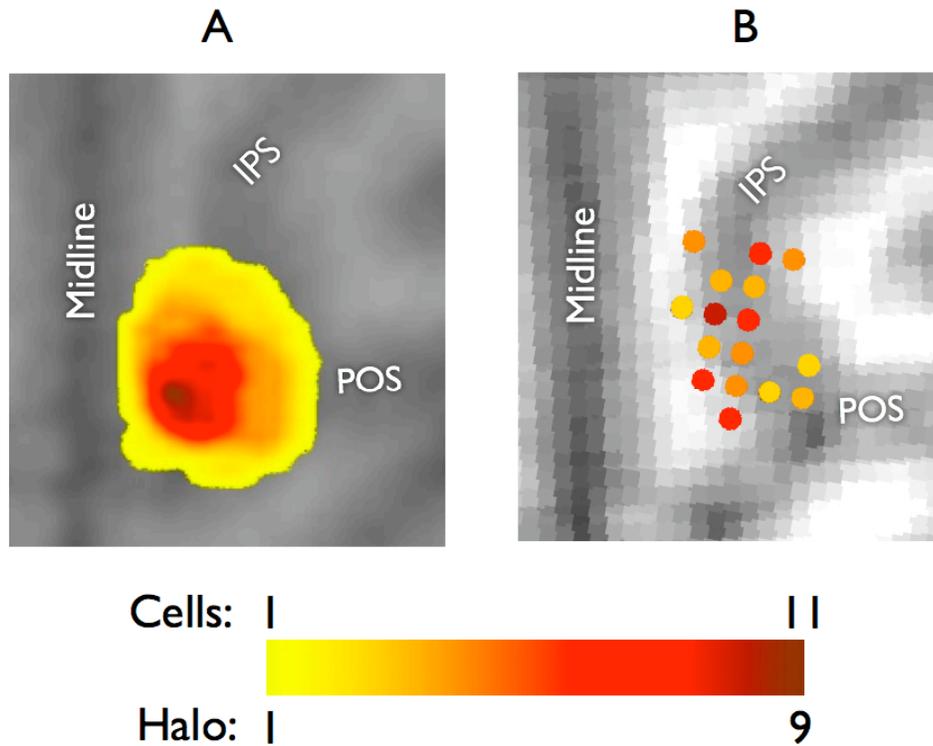


*Figure 3.1:* Behavioral task. After an initial fixation period, target was flashed at one of eight peripheral locations. The target color instructed both movement type and location - green for reach and red for saccade (color not shown in figure). After a variable delay period, the central fixation point disappeared, cueing the animals to make a saccade, dissociated reach, or coordinated reach and saccade to the remembered target. Saccade-alone trials and either dissociated or coordinated reach trials were randomly interleaved.

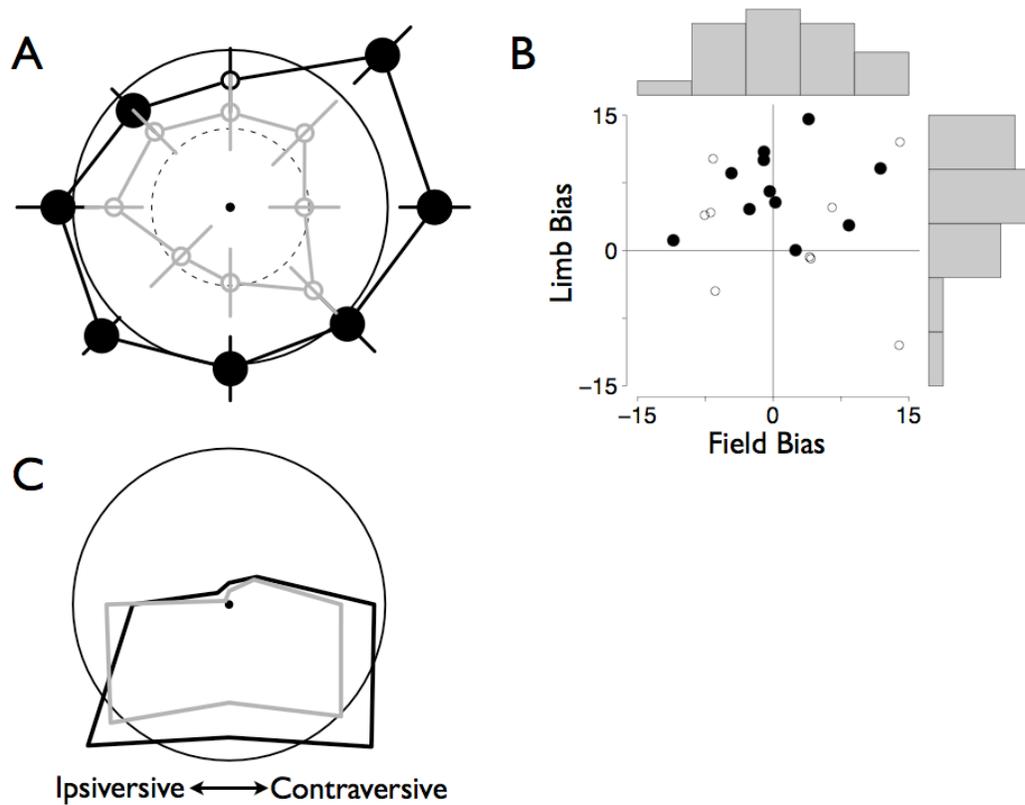
INSERT) Horizontal MR image taken from a representative PRR injection. Bright white sphere indicates the location of the manganese + muscimol injection into the medial bank of the IPS.



*Figure 3.2:* Comparison of inactivation effect on RT (Top) and neural responses (Bottom) in PRR. Mean and standard error are shown for each effector density map of muscimol inactivations.

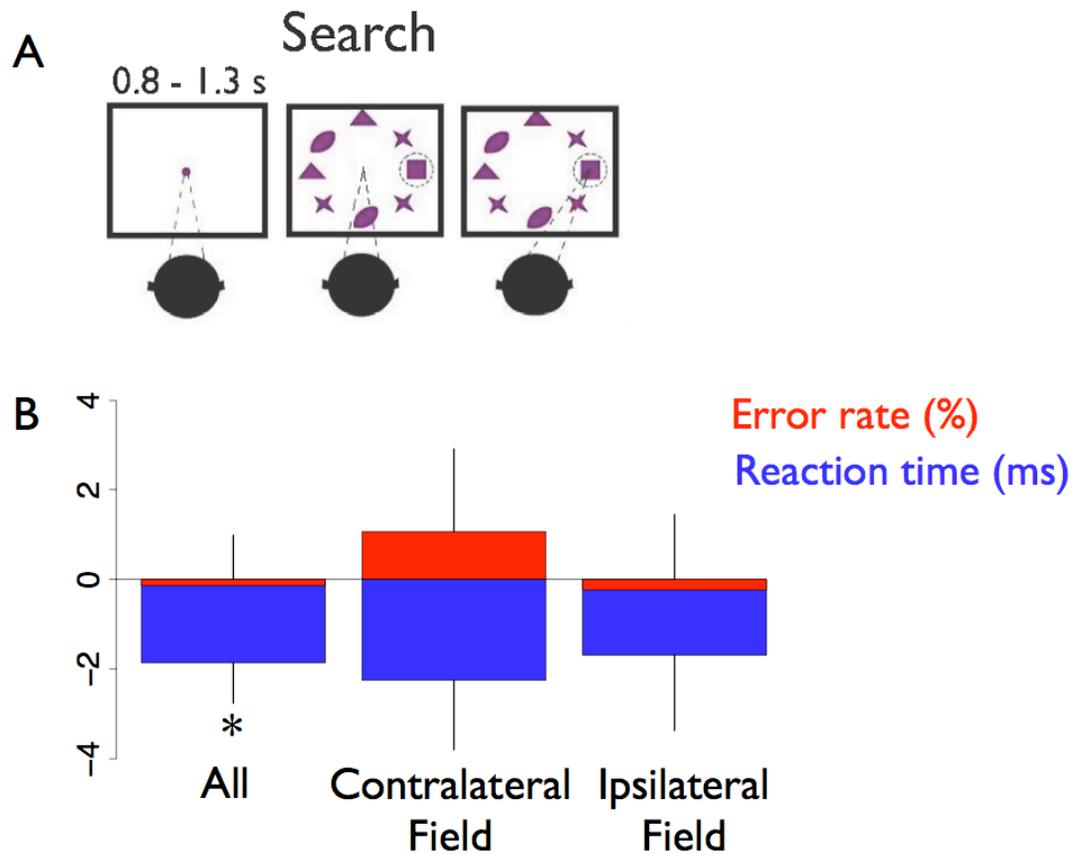


*Figure 3.3: Anatomical comparison of inactivation and recording sites. A) Individual injection halos from one animal were aligned and superimposed on a single anatomical MR image. Darker colors signify tissue that was inactivated in more sessions. B) PRR recording tracks from the same animal are projected onto an MR atlas. Darker colors indicate that more PRR neurons were found along that recording track. Figure only shows tracks in which at least 2 PRR neurons were isolated.*



*Figure 3.4:* Laterality of limb and field in inactivation and neural data. A) Polar plot of the inactivation effect to each of eight targets for contralateral (black) and ipsilateral limb (gray). The inner, dashed circle represents no effect. Eccentricity from the no effect circles represents inactivation-induced changes in RT. Significant effects ( $p < .05$ , one-tailed t test) are indicated by filled circles. Although the contralateral visual field for all data is portrayed on the right side of the figure, this was only the case for monkeys Q and W. B) Laterality of arm and hemifield effects for individual inactivations. For each inactivation, the difference in mean inactivation effect (ms) in the contraversive (positive)

and ipsiversive(negative) visual fields is plotted against the difference in effect for the contralateral (positive) and ipsilateral (negative) arms. Filled circles represent inactivations in which there was a significant contralateral limb effect. C) Polar plot of delay-period activity for the contralateral (black) and ipsilateral (gray) arms. Eccentricity from the center represents change in preferred direction-normalized rate modulation from baseline.



*Figure 3.5: Effect of PRR inactivation on visual search task. A) Behavioral task. Monkeys were trained perform a single saccade as quickly as possible to the target (square) upon presentation of the shapes. Trials in which the animal made a saccade to a distractor or double saccade were immediately terminated and counted as errors. B) Mean changes in error rate (red) and reaction time (blue) are shown for all targets (left), only contralateral field targets (middle) and only ipsilateral field targets (right). Error bars represent SEM. Only the improvement in reaction time across all targets was statistically significant ( $p < 0.05$ ).*

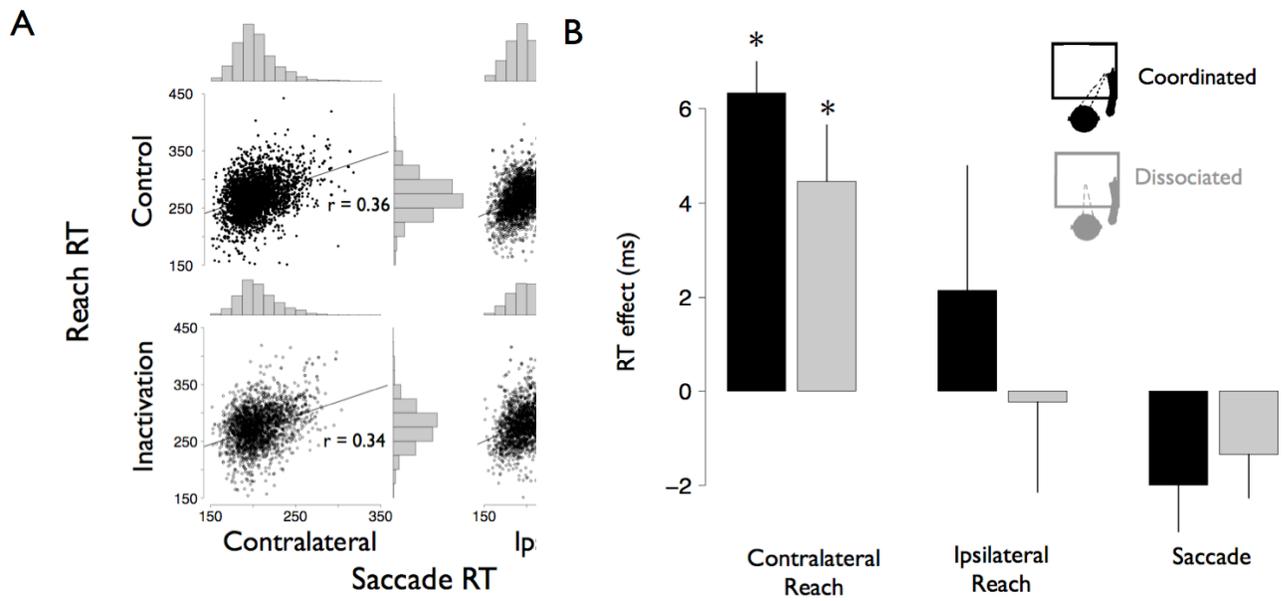


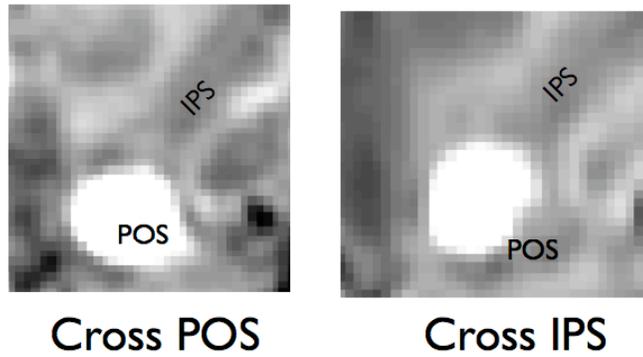
Figure 3.6: Comparison of inactivation effect on coordinated and dissociated reaches. A) Comparison of coordinated saccades and reaches. Saccade (abscissa) and reach (ordinate) latencies are plotted for each trial from control (above) and inactivation (below) sessions. B) Bar plot of inactivation effect on each of effector during the coordinated (black) and dissociated (gray) reach tasks. Coordinated saccades were those saccades made in conjunction with a reach.

*Table 3.1:* The mean control reaction time and the PRR inactivation-induced change are displayed for individual animals. SEM are in parentheses. Bold values indicate significant inactivation effects ( $p < 0.05$ , two-tailed t-test). Italics represent trends ( $p < 0.15$ ).

Monkey (n, side of inactivation)	Contralateral Limb RT		Ipsilateral Limb RT		Saccade RT	
	Control	Change	Control	Change	Control	Change
G (9 right)	<b>212.2 (6.0)</b>	<b>4.5 (1.2)</b>	208.7 (5.2)	- 0.2 (1.2)	192.2 (4.9)	- 1.1 (1.1)
Q (5 left)	<i>264.8 (2.9)</i>	<i>3.9 (1.5)</i>	269.1 (5.3)	1.7 (3.5)	201.5 (3.3)	-0.4 (1.6)
W (6 left)	<i>302.8 (3.0)</i>	<i>9.0 (4.1)</i>	276.9 (3.9)	2.6 (4.2)	229.0 (0.9)	- 2.2 (2.5)
All (20)	<b>249.8(8.6)</b>	<b>5.7 (1.4)</b>	244.3 (7.9)	1.1 (1.5)	205.6 (4.3)	- 1.2 (0.9)

*Table 3.2: Control means and inactivation effects for velocity, duration and precision effects. SEM are displayed in parentheses. Italics indicate non-significant trends ( $p < 0.15$ , two-tailed t-test).*

	Contralateral Limb		Ipsilateral Limb		Saccade	
Mean velocity (deg/s)	<b>118.1</b>	<b>-3.6 (1.5)</b>	122.2	0.8 (2.0)	310.2	0.2 (3.6)
Duration (ms)	<i>123.3</i>	<i>3.8 (2.1)</i>	116.0	-0.2 (2.5)	62.8	-0.1 (0.5)
Precision (deg)	<i>4.8</i>	<i>2.1 (1.3)</i>	5.1	1.0 (1.2)	3.4	-0.6 (0.6)



*Supplemental Figure S1:* Two examples of excluded inactivations. Exclusions were done by a review that was blind to the inactivation results. On the left, the halo extends posteriorly into V3a. This lesion caused impairment to saccades and reaches with either limb, consistent with the visual role ascribed to the region. On the right, the halo extends into cIPs / posterior LIP. There were small increases of saccade RT and no effect on reach RT.

## **Chapter 4: Strong contralateral limb specificity in posterior parietal cortex.**

### ***4.1 Abstract***

Parietal reach region (PRR) is a functional region that is active preceding movements of either limb. However, our lab has found that unilateral inactivation of PRR only causes impairment of movements with the contralateral limb. A possible explanation for discrepancy between neural activity and lesion findings could be that the opposite, intact PRR is able to compensate for the limb contralateral to the inactivation. Another possibility is that the activity related to the ipsilateral limb does not directly contribute to limb movements. To determine the cause of the contralateral limb specific effects following unilateral PRR inactivation, as well as the function of the ipsilateral limb activity, we inactivated PRR bilaterally. Inactivations were performed serially, such that the effect of the first inactivation could be directly compared to the second. We found no change in the effect on the original contralateral limb following bilateral inactivation, consistent with the hypothesis that ipsilateral limb activity does not influence behavior.

### ***4.2 Introduction***

A number of brain areas in the posterior parietal cortex and particularly on the medial bank of the intraparietal sulcus (IPS) are involved in visually-guided reaching (Mountcastle et al., 1975; Lynch et al., 1977; Kalaska et al., 1997; Desmurget et al.,

1999; Johnson et al., 1996; Snyder et al., 1997, Batista et al., 1999). The parietal reach region (PRR), for example, which overlaps anatomical areas MIP and V6a, shows a modulation in single neuron activity when reaches are planned with either arm (Colby and Duhamel 1991; Caminiti et al., 1996; Johnson et al., 1996; Fattori et al., 2001; Buneo et al., 2002; Calton et al., 2002; Snyder et al., 1997; Cohen and Andersen, 2000; Snyder et al. 2000; Calton et al., 2002; Kutz et al., 2003; Quian Quiroga et al., 2006). In either hemisphere, activity is only slightly higher for movements of the contralateral compared to ipsilateral limb, suggesting that limb movements are represented in PRR bilaterally (Fattori et al, 2005; Chang et al., 2008; Yttri et al., 2011). Surprisingly, however, unilateral lesions in and around the IPS medial bank specifically impair movements of the contralateral limb (LaMotte and Acuna, 1978; Brown et al., 1983; Battaglini et al., 2002, Yttri et al., 2011). Thus there is an apparent discrepancy between unit recording and lesion results (Yttri et al. 2011).

Posterior parietal areas may play a causal role in driving only contralateral limb movements. Activity associated with ipsilateral limb movements, like the activity associated with saccadic eye movements that can also be found in other areas, like dorsal premotor cortex (Pesaran et al., 2010) and the frontal eye fields (Mushiake et al., 1996), may be present to help inform the movement of the contralateral limb. For example, information about ipsilateral limb movements may be present in order to help coordinate the contralateral limb with the ipsilateral limb (bimanual coordination) (Kermadi et al., 1998; 2000)). (This explanation is analogous to the idea that saccade-related activity in PRR may drive contralateral arm movements during eye-hand coordination, or may be used to help update eye-centered target locations after an eye movement [Marzocchi et

al., 2008].) If this “contralateral control” model is correct, then a bilateral lesion should produce exactly the same effect in each arm that a unilateral lesion creates in the contralateral arm (Fig. 4.1, top row).

Alternatively, an area may be capable of driving movements of either arm, but the contralateral pathways may be dominant in an intact animal. In this case, losing a (weak) ipsilateral influence after a unilateral lesion is masked by the (strong) influence of the intact contralateral area, so that the limb ipsilateral to the lesion may continue to look normal (Fig. 4.1, middle row). In the opposite limb, however, the normally weak drive from the ipsilateral cortex may take on a larger role and partially compensate for the contralateral lesion. There is evidence from experimental and clinical lesions to support this "compensation" model (Faugier-Grimald et al., 1978; 1985; Calautti and Baron, 2003; Krainik et al., 2004; O'Shea et al., 2007). If this model is correct, then a bilateral lesion should produce a greater effect than the unilateral lesion.

A third model posits that the effect of unilateral lesions reflect hemispheric imbalance. After a unilateral lesion, a second lesion on the opposite, intact side can paradoxically ameliorate the original deficit (Fig. 4.1, bottom row). The Sprague effect was originally shown in cats, but also occurs in humans (Sprague, 1966; Wallace et al., 1990; Oliveri et al., 2001; Hilgetag et al., 2001). There is thought to be balanced inhibition across the two hemispheres and strict contralateral control. When a lesion reduces the inhibition from one side, the resulting disinhibition and loss of inhibitory balance results in the complete suppression of the damaged hemisphere by the intact hemisphere. This suppression, not the original lesion, results in a contralesional deficit. Damage to the intact hemisphere restores the balance and the deficit is abolished. If this

model is correct, then a bilateral lesion should completely abolish the deficit seen with a unilateral lesion.

While recognizing that the three models are not mutually exclusive, we sought the dominant mode by serially lesioning PRR in each hemisphere and testing reaching behavior before and after each lesion. In each experimental session, PRR was lesioned in a staggered fashion, first unilaterally, and then bilaterally. Using this approach, the effect of unilateral lesions could be evaluated with and without the presence on the intact, contralesion PRR. For the purposes of this manuscript, the distinctions of contra- and ipsilesional will be in reference to the first, unilateral lesion, unless otherwise noted. We found that the elimination of the contralesion PRR had no additional affect on reaches with the contralesion limb, strongly supporting the “contralateral” model (Fig. 4.1). More generally, these results suggest that motor planning in parietal cortex may be more lateralized than previously thought.

### ***3.3 Methods***

Two adult, male macaque monkeys were trained to make eye and/or arm movements to targets on a touch screen 17 cm away. Visual stimuli were back-projected onto the touch screen. Eye movements were monitored with a scleral search implant (CNC Engineering). Animals sat in complete darkness with their heads restrained in custom-made primate chairs (Crist Instruments). The fronts of the chairs were completely open so that the animal had free range of movement of the forelimbs. All procedures were in accordance with the *Guide for the Care and Use of Laboratory*

*Animals* and were approved by the Washington University Institutional Animal Care and Use Committee.

**Behavioral task** – Monkeys were trained to perform a memory-guided center-out reaching or saccade task (Fig. 4.1). For all tasks, trials started with the animal fixating and touching a central fixation cue (5.5° window for the eye, 6° for the hand). Left and right limbs were used in alternating blocks while the other limb was blocked by a Plexiglas panel. All animals were trained to perform a memory movement task either using eye, eye and arm (coordinated), or arm without eye (dissociated, monkeys G). After a 350 ms fixation period, a peripheral target was flashed for 150 ms in one of eight equally spaced locations 20° from the fixation point. After a subsequent 1000 - 1600 ms delay, the fixation target was extinguished and the animal had 500 ms to saccade to within 10° of the remembered target location. 150 ms after the eyes acquired the peripheral window, the target reappeared and a corrective saccade to within 5° was required. On coordinated trials, following the completion of a saccade, the animals had 250 ms to reach to within 10° of the target. 150 ms after the initial landing of the hand in the peripheral window, the target reappeared and a corrective saccade to within 6.0° and a corrective reach to within 6.5° was required. Dissociated trials were performed in the same manner but without the non-moving effector leaving the 5.5° fixation window.

**Reversible inactivation** – In the two inactivation animals (G,Q), 0.5-2.0ul of the inactivation solution composed of 8 mg/ml muscimol and 0.1 M of the MRI contrast agent manganese (19.8 mg/ml  $\text{MnCl}_2(\text{H}_2\text{O})_4$  mixed in sterile water) were injected through a 33g canula (SmallParts Inc.) attached to a 25ul Hamilton syringe. Ten minutes after lowering the canula to the desired position, a microinjection pump (Harvard Apparatus)

was used at a flow rate between 0.5 - 1.5 ul/min. At the conclusion of the injection, the canula remained in place for ten additional minutes before slowly retracting it. After the ensuing behavior session, the process (inactivation and behavioral block) was repeated for the opposite PRR.

**Permanent Lesion** – In Monkey G, a 15 mg/ml solution of ibotenic acid mixed with manganese (19.8 mg/ml  $\text{MnCl}_2(\text{H}_2\text{O})_4$  mixed in sterile water) was injected through a 32g Hamilton needle attached to a 25ul Hamilton syringe. The injection procedure was the same as that for temporary muscimol inactivation. At least one week of behavioral session was collected following each permanent lesion. Data from the day of the lesion was excluded.

**Lesion localization with MRI** - Following the behavioral session (two to four hours post-injection), T1 weighted anatomical images were collected using a magnetization prepared rapid-acquisition gradient echo (MPRAGE) sequence conducted at  $0.5^3 \text{ mm}^3$  on a 3T head-only system (Siemens Allegra). A single surface coil was used. Animals were lightly sedated with ketamine (3mg/kg) during the procedure. Injections were visible as a bright halo representing the Mn-induced T1 signal increase. The data from injections with halos outside our area of interest were excluded.

**Data processing-** Behavioral data from injection sessions were compared to data from the two previous control sessions. Control sessions never occurred the day following inactivation. To determine inactivation effects, we parcellated between-control-days and within-control-day variances, then used the within-control and injection means and variances.

#### **4.4 Results**

To evaluate the effect of bilateral PRR lesion, we inactivated PRR first unilaterally, and then bilaterally in 23 separate injection sessions. Following each inactivation, the monkeys ( $n = 2$ ) performed memory-guided saccades and reaches. All data collection was complete within 2.5 hours of the first inactivation, well within the period of maximum efficacy for muscimol (Arikan et al., 2002). In control sessions, the number of trials and the time between behavioral blocks was kept identical, but there was no injection. We measured reaction time (RT), duration, accuracy and precision of movements in control and inactivation sessions. Performance in the behavioral blocks following each inactivation was compared to matched control behavioral blocks (for more details, see Methods).

Following unilateral inactivation, reaches with the contralesion limb were slowed 4.8 ms ( $p=0.073$ , two-tailed t-test; Fig. 4.3a). Neither ipsilesion reaches nor saccades were affected (ipsilateral arm RT effect = 0.3 ms,  $p = 0.9$ , saccade RT effect = 0.8 ms,  $p = 0.48$ ). This specific impairment of reaches with the contralesion limb is consistent with previous studies of unilateral medial IPS lesions (Lamotte and Acuna, Brown, 1983; Yttri et al., 2011).

Following bilateral inactivation, reaches with both arms were slowed 4.8 ms ( $p = 0.011$ ), exactly the same as after unilateral inactivation ( $p = 0.99$ , paired t test). This is consistent with the contralateral model, not the compensation or the Sprague models (Fig. 4.1). The result did not depend on the order of inactivation. After the second lesion, the limb that was contralateral to the first lesion was slowed by 4.9 ms compared to controls,

while the limb that was ipsilateral to the first lesion slowed by 4.7 ms compared to controls (p of the difference = 0.9). Finally, there were also no effects of absolute laterality. The right and left limbs were slowed by equivalent amounts (4.5 and 5.3 ms, respectively; n = 11 and 12 sessions; p of the difference = 0.32).

The two animals performed slightly different tasks. Monkey G performed a dissociated reach in which only the limb moved to the target while the eyes maintained central fixation. Monkey Q performed a coordinated reach and saccade task, moving both the arm and eyes to the target. Inactivation effects were nonetheless similar for unilateral (Monkey G: 6.7 ms, p = 0.37; Monkey Q: 4.0 ms, p = 0.11; p of difference = 0.68) and bilateral inactivations (Monkey G: 7.9 ms, p = 0.14; Monkey Q: 3.6, 0.019, p of difference = 0.63)

When arm and eye movements are coordinated, the latencies of the movements are correlated (Prablanc et al., 1979). We previously tested the effect of unilateral PRR inactivation and found that it does not affect the temporal coupling of eye-arm movements with either limb (Yttri et al., 2011). We now provide further evidence that PRR does not contribute to eye-arm coordination. In control sessions, eye-arm RT correlation was consistent across sessions (r of control trials = 0.16, p < 0.000001). Bilateral inactivation of PRR did not affect the correlation (r of injection trials = 0.17; p < 0.000001; p of difference = 0.82 Fisher r to Z transformation). The degree of correlation was low compared to previous reports (Lunenburger et al., 2000; Dickinson and Snyder, 2002). However, the correlation of eye-arm coordinated movements has been shown to greatly decrease as an animal learns the task (Dean et al., 2011), and our correlation values for both control and injection trials are highly significant.

As a technique, temporary pharmacological inactivation has many advantages. Temporary lesions can be repeated in the same animal multiple times, and their impermanent nature prevents long-term changes in brain (Chowdhury and DeAngelis, 2008). Permanent lesions, in contrast, cannot be repeated within the same animal, but they more closely mimic the effects of naturally occurring lesions and ensure a more complete lesion. We lesioned PRR permanently using the excitotoxin ibotenic acid. Like muscimol, ibotenic acid spares fibers of passage, ensuring that lesion effects reflect the loss of PRR and fibers of passage.

We confirmed the initial spread of the injected lesion solution using MR imaging (Fig. 4.5a). Lesions were largely restricted to the medial bank of the IPS, extending posteriorly into V6a, with only minimal spread across the sulcus into caudal IPS. Using an experimental design similar to that which we employed for the temporary inactivations, we serially lesioned the PRR of monkey G on each side of brain. A unilateral permanent lesion with ibotenic acid (Fig. 4.5b, left) significantly increased contralateral limb RT (5.2 ms,  $p = 0.003$ ). There was also an increase in ipsilateral reach RT, but the increase was not significant (2.4ms,  $p = 0.2$ ). There was no effect on saccades (-1.2 ms,  $p = 0.32$ ; data not shown). After a bilateral permanent lesion, the slowing of the two limbs (5.1 ms,  $p=0.002$ ) was not significantly different from the unilateral lesion effect on the contralesion limb ( $p= 0.98$ ), confirming the results of the temporary inactivations.

#### ***4.5 Discussion***

The visuomotor processing regions of the macaque brain are often thought to be primarily concerned with movements of the contralateral limb. However, the movement of either limb has been shown to increase PRR activity bilaterally. Indeed, in both human and non-human primates, each hemisphere has been suggested to interact with the other and to contribute to motor behaviors of either limb (Brinkman and Kuypers, 1972; Busan et al., 2009). Yet when medial IPS regions are lesioned unilaterally, the effects are generally restricted to reaches with the contralateral limb (LaMotte and Acuna, 1978; Brown et al., 1983; Battaglini et al., 2002, Yttri et al., 2011). In the current paper we asked about the neural architecture underlying these effects. We offered various models that could account for the contralateral-limb specific effect. Each model represents a different functional organization for PRR and the visuomotor pathway.

To examine the contribution of the contralateral PRR to reaching movements, we sequentially lesioned the PRR bilaterally. As previously shown, the first lesion produced contralesion limb specific deficits. A second lesion in the opposite hemisphere did not alter the contralesion effect of the first lesion, and there was no order effect – the lesion effects were the same in both limbs. Finally, permanent lesions made with ibotenic acid produced the same results as temporary inactivations made with muscimol.

These results support the contralateral limb-specific model of PRR (Fig. 4.1, first row). Despite the presence of ipsi- and bi-lateral limb cells and interhemispheric connections (Chang et al. 2008; Fattori et al., 2005; Passarelli et al., 2011), we conclude that PRR contributes solely to the planning of movements with the contralateral limb (but see below). This finding is supported by earlier studies. While preparing for a

movement, the activity of individual PRR neurons predicts RT, but only for contralateral limb movements (Snyder et al., 2006, Chang et al., 2008). More generally, in a series of studies by Gazzagina (1966; 1968), only the contralateral hemisphere was shown to provide visuomotor control of limb movements.

This was a surprising result. During the delay period preceding a movement, half of the cells in PRR respond roughly equally to movements with either limb, and one-sixth fire preferentially for movements of the ipsilateral limb (Chang et al., 2008). Thus a majority of cells are active prior to movements of the ipsilateral limb. From this, we expected that bilateral inactivation would result in a substantial increase in contralateral limb impairment, consistent with a role of PRR in movements of both limbs (compensation model, Fig. 4.1, second row).

An important issue is what role, if any, these bilateral and ipsilateral limb cells play. Our data indicate that PRR contributes only to movements of the contralateral limb. However, PRR has only been studied in the context of reaching with a single limb. The preponderance of bilateral limb cells suggests that PRR may be involved in executing bimanual movements. We often reach towards objects with both limbs or use both limbs together in a single concerted action. In order to be effective, these movements must be coordinated in time and space. Bimanual neurons also exist in dorsal premotor cortex (PMd), supplementary motor area (SMA), and M1, and these neurons of these areas exhibit different activity patterns for coordinated bimanual or unimanual movements (Donchin et al., 1998; 2002; Kermadi et al., 1998; 2000). The modulations related to ipsilateral limb movements in PRR might contribute to planning and execution of contralateral limb movements during a bimanual coordinated action. It is also possible

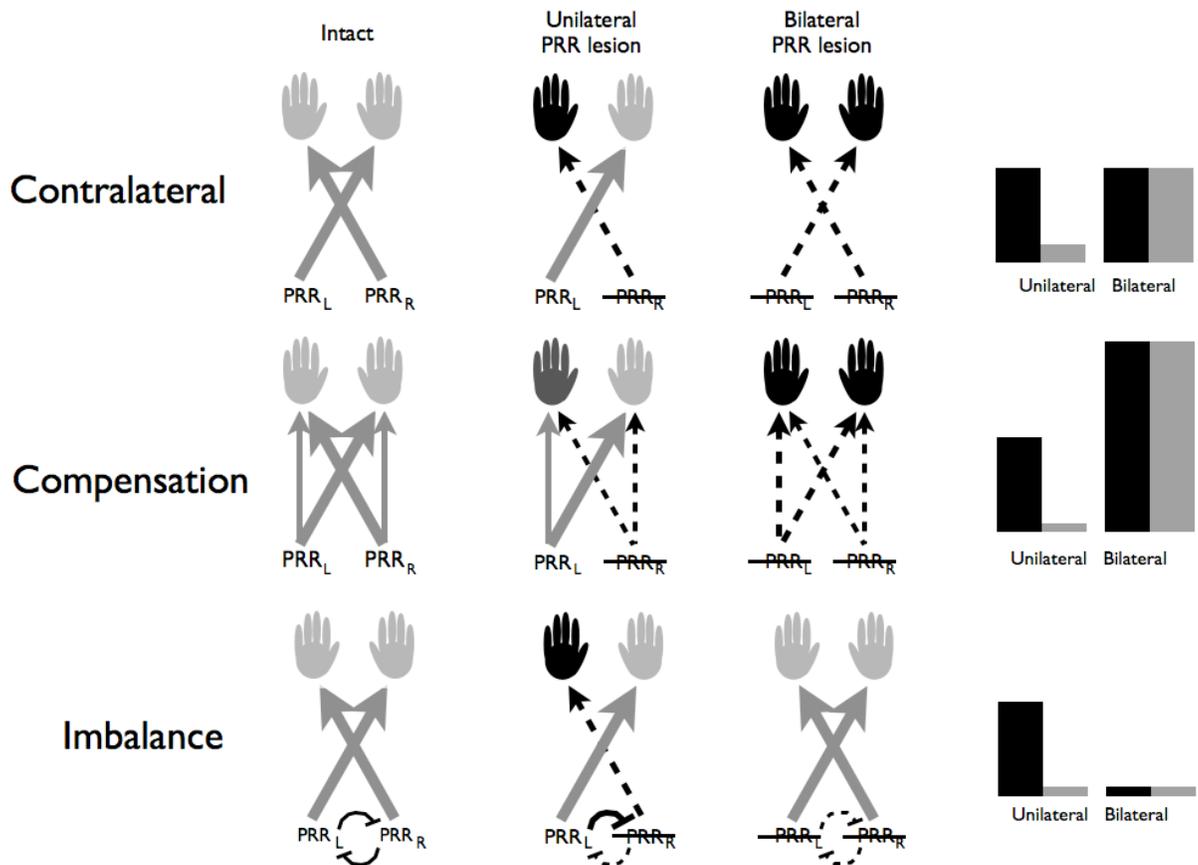
that PRR neurons influence ipsilateral limb movements (only) during bimanual coordinated movements. One final possibility is that PRR contributes to ipsilateral limb movements in a way that we have not tested. For example, PRR might contribute to the on-line response of the ipsilateral limb to a perturbation, or to the trajectory of ipsilateral limb movements. Further experiments will be required to investigate these possibilities.

Our results may be influenced by the overtraining of our subjects. With overtraining, behavior can become automated and stereotyped. This may explain why lesions produced only a slight impairment (5-10 ms slowing). Furthermore, brain plasticity or connectivity changes may occur with extensive practice (Cooke, 1980; Meyer et al., 1988; Tang et al., 2009). However, the cortical representations of movements typically increase with training (Nudo et al., 1996; Kleim et al. 1998). It is possible that our results reflect the effect of PRR inactivation on habitual tasks, rather than individual movements (Roland, 1984; Wise et al., 1996; Graybiel 1998; Pasupathy and Miller, 2005). It would be difficult to perform these experiments in an animal that was not extensively trained. However, studies of human parietal lesions can offer insight on the effects of lesions in the absence of repetitive training.

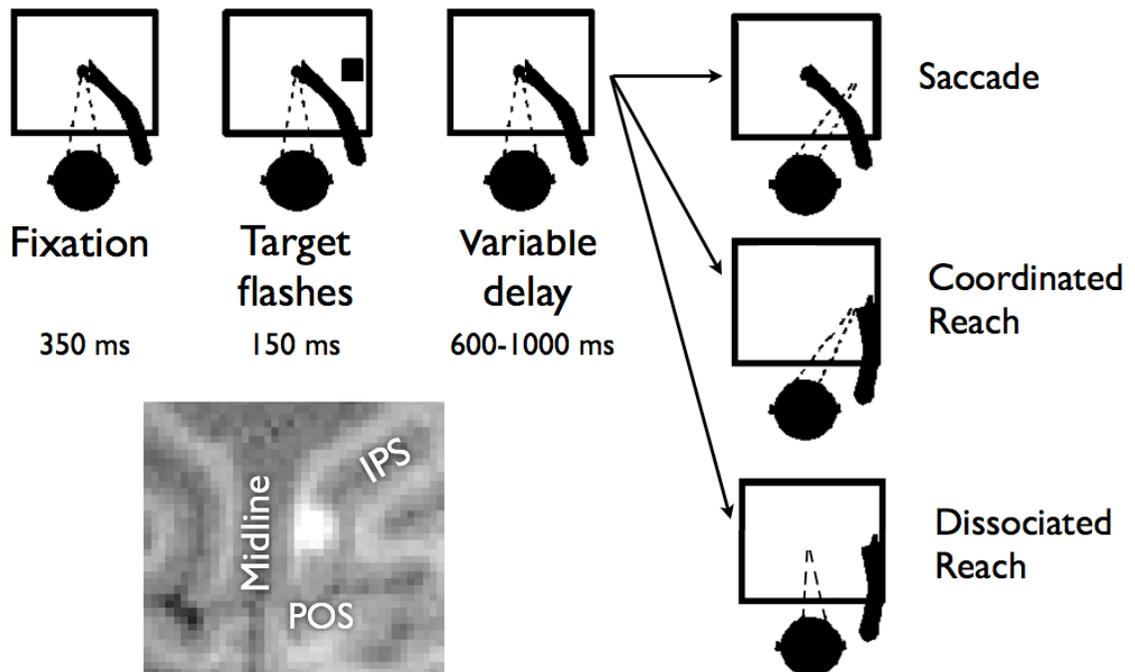
Functional MRI and lesion studies have identified regions of human parietal cortex that might be homologous with PRR in monkeys. These regions exhibit increased blood oxygen level dependent (BOLD) signals when subjects plan reaches or a saccades, with stronger modulation for reaches (Astafiev et al., 2003; Connolly et al., 2003; Medendorp et al., 2003; 2005; Prado et al., 2005; Fernandez-Ruiz et al., 2007). In a patient whose blood supply to the medial IPS was surgically occluded, the resulting bilateral lesion caused only reach deficits (Trillenberget al., 2007). With unilateral

lesions, deficits are primarily contralesional. Two patients with unilateral superior parietal lobule lesions (one left hemisphere, one right hemisphere) were shown to have contralesion limb-specific impairments to targets in either hemifield, while retaining ipsilesion limb and oculomotor abilities (Heilman et al., 1986; Danckert et al., 2009). Because of the individual variances between lesions, and brain, effects of different brain traumas are difficult to compare. However, we show here that a subset of human medial parietal lesions appear to cause contralesion limb impairments.

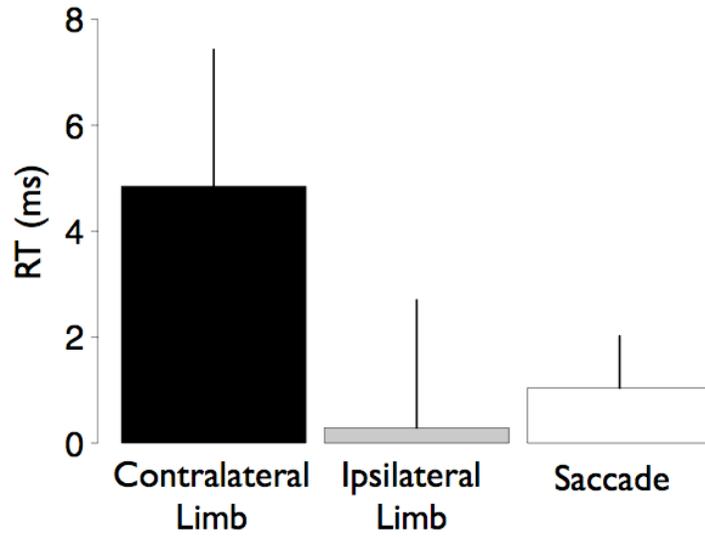
Transcranial magnetic stimulation (TMS) can be used to induce temporary lesions in humans. Unilateral stimulation causes a range of impairments, depending on the stimulation site. Stimulation of a large portion of posterior parietal cortex resulted in deficits in on-line adjustments of reaching with the contralateral limb, and no effects on saccades or ipsilateral limb reaches (Desmurget et al. 1999). More focal perturbation of medial IPS or the angular gyrus caused contralateral limb deficits along with saccade impairment. Superior parieto-occipital cortex stimulation caused reaching deficits in both the contralateral and ipsilateral limbs (Vesia et al., 2010).



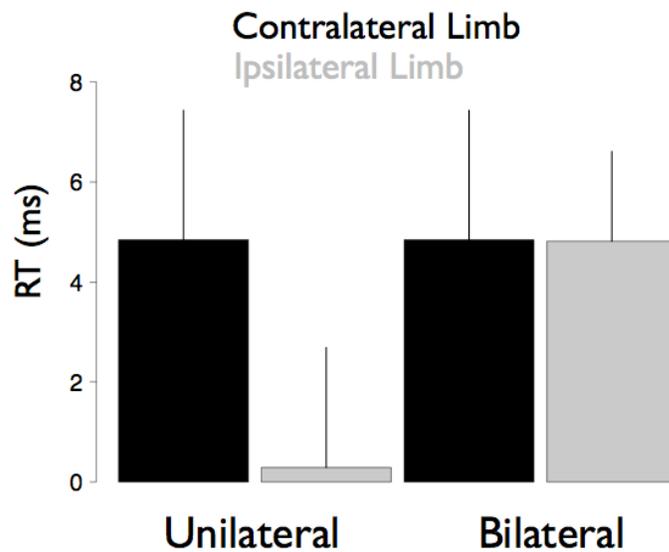
*Figure 4.1:* Simplified schematics for contralateral-specific (top row), hemispheric compensation (middle row), and cortical imbalance (bottom row) models of contralateral limb specificity following unilateral PRR lesion (in this case, the right PRR). Columns represent the visuomotor pathway in its intact, unilaterally and bilaterally lesioned states. Dashed lines represent contributions eliminated following inactivation. Rightmost column represents the degree of impairment for each arm (contralateral to first lesion = black, ipsilateral to first lesion = gray) in each lesion condition.



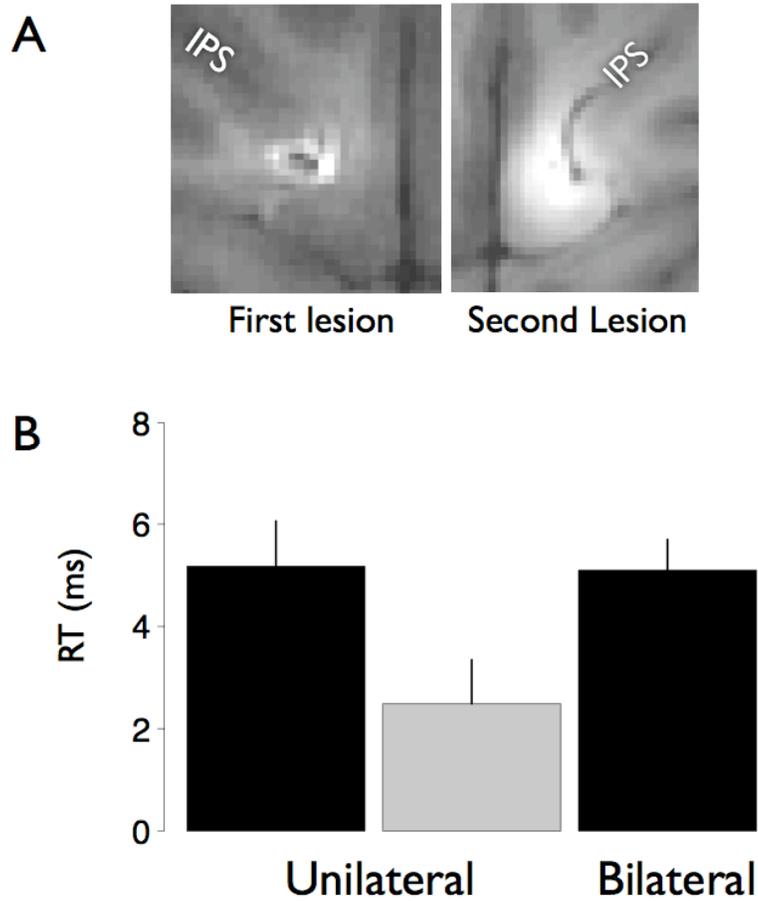
*Figure 4.2:* (A) Behavioral task. After an initial fixation period, target was flashed at one of eight peripheral locations. The target color instructed both movement type and location -- green for reach and red for saccade (color not shown in figure). After a variable delay period, the central fixation point disappeared, cueing the animals to make a saccade, dissociated reach, or coordinated reach and saccade to the remembered target. Saccade-alone trials and either dissociated or coordinated reach trials were randomly interleaved. (B) Horizontal MR image taken from a representative PRR injection. Bright white sphere indicates the location of the manganese + muscimol injection into the medial bank of the IPS.



*Figure 4.3:* Effect on reaction time (RT) following unilateral PRR inactivation. Bar plot of the change of RT for movements of the contralateral limb (black), ipsilateral limb (gray), and saccade (white) compared to controls. Error bars represent standard errors of the mean (SEM).



*Figure 4.4:* Effect of bilateral inactivation on each limb. A) Bar plot of the change in RT relative to control sessions (contralateral to first lesion = black, ipsilateral to first lesion = gray). B) Change in RT relative to the first lesion. Negative values represent a difference in the unilateral and bilateral lesion means such that RT was less strongly affected following the bilateral lesion. For comparison, the effect of unilateral lesion on each of the limbs is shown in the leftmost columns.



*Figure 4.5: Effects of bilateral permanent lesion. A) Location of ibotenic acid lesions used to permanently lesion PRR first unilaterally (left), then bilaterally (right). B) Effect of permanent lesions on reaction time for unilateral (leftmost columns, contralateral to first lesion = black, ipsilateral to first lesion = gray) and bilaterally lesions (rightmost column, limbs combined as the condition of the brain is identical).*

## Chapter 5: Conclusion

*“Are parietal ... neurons sensory or motor? Is the question worth asking?”*

*- John Schlag, MD, 1980*

This dissertation attempts to help answer a question older than its author: What does the parietal cortex do? It is accepted that parietal cortex, in particular the IPS, plays a critical role in visuomotor transformations. Understanding the nature of the contribution of each region is important not only to the internal debate between scholars (Gottlieb and Snyder, 2010), but to all systems and computational neuroscientists who aim to decipher how the brain works. Exploring “sensory or motor?” and the more subtle intricacies within these ideas can provide vital insight as to how we extract salient information and generate plans to interact with what we perceive.

In sum, our work has demonstrated that IPS regions are much more motor than sensory. To say that these regions, LIP and PRR, are more motor than sensory is striking in two ways. First, based upon correlations with neural activity, these regions in sensory association cortex were ascribed sensory roles, such as attention (Colby et al., 1991;). It was thought that motor plans did not arise until later premotor areas. However, our results suggest that a clear motor plan is already taking shape in PPC regions. Later motor areas, like PMd, may process finer aspects of the movement or coordination (Pesaran et al., 2010).

Second, our findings suggest that the change from sensory to motor processing may occur abruptly. Although, the motor contributions of those areas upstream from LIP and PRR have not been extensively studied, there is no evidence that these areas contribute to a motor plan (Lisberger, 2010). That PRR appears to not only be purely motor, but also effector- and limb-specific adds additional weight to these findings. The work presented here underscores the fact that measurements of the activity of neurons may not accurately reflect their functional contribution. We possess several tools that can be combined in order to better understand brain function.

The worth of a question is relative to the value of the potential answers one might receive. At a superficial level, neuroscience as a field disagrees with Dr. Schalg (his vote was “no”), as there have been nearly as many articles published on parietal cortex processing in the first month of this year as there were in the entire year his question was originally posed. More meaningfully, delving into the visuomotor question has produced valuable clinical and basic science results.

Many of the deficits I have reported or cited here have very similar clinical analogs (Grefkes and Fink, 2005). Balint’s syndrome may best embody these psychic deficits. Balint’s syndrome is most often caused by parietal damage resulting from stroke, Alzheimer’s disease, intracranial tumors or traumatic brain injury. Often, both lateral and medial portions of human IPS are affected. It is characterized by optic ataxia (OA) (incoordination of hand and eye movement) and oculomotor apraxia (difficulty initiating task-oriented saccades) (for review, see Rizzo, 1993). Interestingly, most patients also present with simultanagnosia, or the inability to perceive more than one object at a time – particularly those objects which are not foveated. This deficit provides a clear connection

with work done on covert attention (Gottlieb et al., 1998; Wardak et al., 2002; Bisley et al., 2003), and the continued study of LIPv's contribution to this behavior may yield translational benefits.

Lesion studies in monkeys can help inform behavioral therapies. When no visual feedback is available, lesions of medial IPS in the monkey cause deficits in reaching (Chapter 3; 4); however, this effect is mostly abolished when visual feedback is available (Rushworth et al., 1997). Recently, rehabilitation from Balint's syndrome, and OA more generally, has benefited from observations made in non-human primates. OA-related misreaching and misgrabbing to centrally located targets is alleviated when the patients look at their hand (Pisella et al., 2009). Similarly, looking near your hands aid in the formation of movements with the limb (Bekkering and Neggers, 2002; Abrams et al., 2008).

One of the beautiful yet terrible aspects of the human brain is its complexity. Because of this, it is difficult to predict the exact deficits of human lesions. Compared to the macaque monkey, the human PPC is one of the brain areas that has undergone the most evolutionary development (Hill et al., 2010). These changes place some restrictions on the translational value of non-human primate parietal cortex research, but information and techniques gleaned from the non-human primate studies is still useful. Paradoxically, we have identified more parietal subregions in monkeys than we have in man (Caminiti et al., 2010). Our novel inactivation-imaging technique provides further ability to discern functional and anatomical differences between areas of cortex. With the advent of different investigative techniques, both to assess functional deficits and to explore functional anatomy, such as electrocorticographic frequency alteration mapping

(Breshears et al., 2010), we will expand our understanding of the location and types of computations that occur in the human brain.

Among these techniques, transcranial magnetic stimulation (TMS) may be the most powerful. TMS uses magnetic eddy currents to generate electrical currents within the intact human brain, although the exact neurophysiological changes and extent of stimulation are not well-characterized (for review, see Rossini and Rossi, 2007). TMS can be used to focally perturb cortex in healthy subjects, simulating the effects of lesions. There is obvious research value in studying experimentally-induced, localized, temporary lesions in subjects whose performance can be monitored before and after stimulation (for review, see Dimyan and Cohen, 2010). However, the potential for may extend to the direct treatment of brain disorders. Stimulation may assist in motor rehabilitation following a stroke (Nowak et al., 2009; Popovic et al., 2009). Additionally, repetitive TMS has shown promise in treating depression (Gross et al., 2007), autism (Enticott et al., 2010) and Parkinson's disease (Lefaucheur, 2009). TMS as a neurorehabilitation technique is still in its infancy and may provide insight and relief from a variety of neural issues.

To examine the role of LIP in motor planning, we inactivated the LIP of four monkeys while they performed saccade and reach tasks. We found that LIP inactivation only affected saccades, while reaches showed no change. Additionally, we found that when saccades and reaches were coordinated into combined eye-arm movements, both effectors were impaired. The effect on coordinated reaches was proportional to that on saccades within individual trials and across sessions. Finally, we found that the effector

specificity was consistent across LIP subregions, but the spatial specificity of effects differed between dorsal and ventral regions.

These results argue that LIP is a oculomotor-specific planning area. Although coordinated reach RT were slowed following inactivation, we show that this is not due to LIP inactivation directly, but likely the result of other brain areas wait on the delayed saccade onset. Additionally, the onset coupling was not affected by inactivation, suggesting the LIP does not play a role in eye-arm coordination.

We temporarily inactivated PRR with microinjections of muscimol in three monkeys performing reach and saccade tasks and visual search tasks. We then compared the lesion results with electrophysiological data from a previous study of PRR (Chang et al., 2008). The recording study showed modulation when reaches were planned with either the contralateral or ipsilateral forelimb, and reduced but significant modulation when a saccade was planned. We found that PRR inactivation impairs only contralateral limb movements, not saccades, ipsilateral limb reaches, or covert visual attention. There was no specificity of effect to either visual hemifield. Thus our results provide direct evidence for a specialized role of PRR in reaching, and suggest that the organization of PRR has more in common with motor than visual sensory areas. In addition, our findings suggest that the results of correlative studies should be interpreted with caution.

We followed this study with the bilateral PRR inactivation experiments. We lesioned PRR bilaterally in a staggered fashion; one hemisphere at a time, measuring changes in behavior between each injection. These experiments were conducted to determine what influence, if any, the intact PRR of the opposite hemisphere was had on our unilateral lesion effects. The answers provided insight about the ipsilateral signals of

PRR as well as the interhemispheric interplay in visuomotor processing. Following bilateral inactivation, there was no increase in effect compared to that of unilateral inactivations on the contralateral limb. These results are indicative of a lack of interaction between hemispheres following unilateral lesion, neither positive nor negative. Furthermore, the data support our initial assessment that ipsilateral limb activity in PRR does not contribute directly to behavior.

Our effects are modest, but consistent and highly significant. In our examination LIP (Liu et al., 2010, Chapter 2) and PRR (Chapters 3 and 4), the effects were reproduced in specificity and magnitude with different datasets. It is also interesting that, between the two regions, the magnitude of the negative effect is similar.

Some lesion studies of IPS regions have induced relatively larger effects (Li et al., 1999; Faugier-Grimald et al., 1985). Our tasks were not especially difficult, and special emphasis was placed on reaction time. Additionally, unlike these studies we discarded lesions that spread beyond our region of interest. We were able to discern the location of lesions because of our novel muscimol-manganese imaging technique. In the future, we may be able to balance our experiments better, such that performance in control sessions is at a critical point, thereby increasing the sensitivity of our tasks. When compared to the devastating effects of V1 (Stoerig, 2006), M1 (Ward, 2004), or cerebellar lesions (Holmes, 1917), the slowing of initiation even by hundreds of milliseconds is relatively trivial. It is likely that there is redundancy in intermediate visuomotor areas. This redundancy may be at least partially responsible for the differences in effect between parietal and primary cortical lesions.

This body of work has examined the visuomotor processes that occur in IPS regions LIP and PRR. Future work will expand into other IPS regions in an effort to better characterize IPS function. Additionally, I hope to use the inactivation technique to study the contribution of LIP and PRR to other neural processes, such as decision value (Platt and Glimcher, 1999) and bimanual reaching (Donchin et al., 1998).

## References

- Abrams, R.A., Meyer, D.E., and Kornblum, S. (1990). Eye-hand coordination: oculomotor control in rapid aimed limb movements. *J Exp Psychol Hum Percept Perform.* 16, 248-67.
- Abrams, R. A., Davoli, C. C., Du, F., Knapp, W. H., & Paull, D. (2008). Altered vision near the hands. *Cognition*, 107, 1035-1047.
- Andersen, R.A., Asanuma, C., Essick, G., and Siegel R.M. (1990). Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. *J Comp Neurol.* 296, 65-113.
- Andersen, R.A., Bracewell, R.M., Barash, S., Gnadt, J.W., and Fogassi, L. (1990). Eye position effects on visual, memory, and saccade-related activity in areas LIP and 7a of macaque. *J Neurosci.* 10, 1176-96.
- Angel, R.W., Alston W., and Garland, H. (1970). Functional relations between the manual and oculomotor control systems. *Exp Neurol.* 27, 248-57.
- Bakola, S., Gregoriou, G.G., Moschovakis, A.K., and Savaki, H.E. (2006). Functional imaging of the intraparietal cortex during saccades to visual and memorized targets. *Neuroimage.* 31, 1637-49.
- Balan, P.F., and Gottlieb, J., (2009). Functional significance of nonspatial information in monkey lateral intraparietal area. *J Neurosci.* 29, 8166-76.
- Barash, S., Bracewell, R.M., Fogassi, L., Gnadt, J.W., and Andersen, R.A. (1991). Saccade-related activity in the lateral intraparietal area. I. Temporal properties; comparison with area 7a. *J Neurophysiol.* 66, 1095-108.
- Barash, S., Bracewell, R.M., Fogassi, L., Gnadt, J.W., and Andersen, R.A. (1991). Saccade-related activity in the lateral intraparietal area. II. Spatial properties. *J Neurophysiol.* 66, 1109-24.
- Basso, M. A., and R. H. Wurtz. Modulation of Neuronal Activity by Target Uncertainty. *Nature* 389.6646 (1997): 66-69.
- Bekkering, H., Pratt, J., and Abrams, R.A. (1996). The gap effect for eye and hand movements. *Percept Psychophys.* 58, 628-35.
- Bekkering, H., Neggers, S., F. (2002). Visual search is modulated by action intentions. *Psychol Sci.* 13, 370-4.

- Ben Hamed, S., Duhamel, J.R., Bremmer, F., and Graf, W. (2002). Visual receptive field modulation in the lateral intraparietal area during attentive fixation and free gaze. *Cereb Cortex*. 12, 234-45.
- Biguer, B., Jeannerod, M., and Prablanc, C. (1982). The coordination of eye, head, and arm movements during reaching at a single visual target. *Exp Brain Res*. 46, 301-4.
- Bisley JW, and Goldberg ME. (2003). Neuronal activity in the lateral intraparietal area and spatial attention. *Science*. 299, 81-6.
- Bisley, J.W., and Goldberg, M.E. (2003). Neuronal activity in the lateral intraparietal area and spatial attention. *Science*. 299, 81-6.
- Boulinguez, P., Blouin, J., and Nougier, V. (2001). The gap effect for eye and hand movements in double-step pointing. *Exp Brain Res*. 138, 352-8.
- Breshears, J., Sharma, M., Anderson, NR., Rashid, S., and Leuthardt, EC. (2010). Electrographic frequency alteration mapping of speech cortex during an awake craniotomy: case report. *Stereotact Funct Neurosurg*. 88, 11-5.
- Buneo, C.A., Jarvis, M.R., Batista, A.P., and Andersen, R.A. (2002). Direct visuomotor transformations for reaching. *Nature*. 416, 632-6.
- Bushnell, M.C., Goldberg, M.E., and Robinson, D.L. (1981). Behavioral enhancement of visual responses in monkey cerebral cortex. I. Modulation in posterior parietal cortex related to selective visual attention. *J Neurophysiol*. 46, 755-72.
- Calton, J.L., Dickinson, A.R., and Snyder, L.H. (2002). Non-spatial, motor-specific activation in posterior parietal cortex. *Nat Neurosci*. 5, 580-8.
- Caminiti, R., Ferraina, S., and Johnson, P.B. (1996). The sources of visual information to the primate frontal lobe: a novel role for the superior parietal lobule. *Cereb Cortex*. 6, 319-28.
- Chang, S.W., Papadimitriou, C., and Snyder, L.H. (2009). Using a compound gain field to compute a reach plan. *Neuron*. 64, 744-55.
- Churchland, M. M., and K. V. Shenoy. Temporal Complexity and Heterogeneity of Single-Neuron Activity in Premotor and Motor Cortex. *Journal of Neurophysiology* 97.6 (2007): 4235-257.
- Cisek P, Crammond DJ, and Kalaska JF. (2003). Neural activity in primary motor and dorsal premotor cortex in reaching tasks with the contralateral versus ipsilateral arm. *J Neurophysiol*. 89, 922-42.
- Cohen, Y. E., and R. A. Andersen. Reaches to Sounds Encoded in an Eye-centered Reference Frame. *Neuron* 27.3 (2000): 647-52.

Cohen, Y.E., and Andersen, R.A. (2000). Reaches to sounds encoded in an eye-centered reference frame. *Neuron*. 27, 647-52.

Cohen, Y.E., Batista, A.P., and Andersen, R.A. (2002). Comparison of neural activity preceding reaches to auditory and visual stimuli in the parietal reach region. *Neuroreport*. 13, 891-4.

Colby, C.L., and Duhamel, J.R. (1996). Spatial representations for action in parietal cortex. *Brain Res Cogn Brain Res*. 5, 105-15.

Colby, C.L., and Duhamel, J.R.(1991). Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey.*Neuropsychologia*. 29, 517-37.

Colby, C.L., and Goldberg, M.E. (1999). Space and attention in parietal cortex. *Annu Rev Neurosci*. 22, 319-49.

Colby, C.L., Duhamel, J.R., and Goldberg, M.E. (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area.*J Neurophysiol*. 76, 2841-52.

Connolly, J. D., R. A. Andersen, and M. A. Goodale. FMRI Evidence for a 'parietal Reach Region' in the Human Brain. *Experimental Brain Research* 153.2 (2003): 140-45.

Connolly, J.D., Andersen, R.A., Goodale, M.A. (2003). FMRI evidence for a 'parietal reach region' in the human brain. *Exp Brain Res*. 153, 140-5.

Constantin, A.G., Wang, H., Monteon, J.A., Martinez-Trujillo, J.C., and Crawford, J.D. (2009). 3-Dimensional eye-head coordination in gaze shifts evoked during stimulation of the lateral intraparietal cortex. *Neuroscience*. 164, 1284-302.

Constantinidis, C., and Steinmetz, M.A. (2005). Posterior parietal cortex automatically encodes the location of salient stimuli. *J Neurosci*. 25, 233-8.

Cutrell, E.B., and Marrocco, R.T. (2002). Electrical microstimulation of primate posterior parietal cortex initiates orienting and alerting components of covert attention. *Exp Brain Res*. 144, 103-13.

Dean, H. L., D. Marti, E. Tsui, J. Rinzel, and B. Pesaran. Reaction Time Correlations during Eye-hand Coordination: Behavior and Modeling. *Journal of Neuroscience* 31.7 (2011): 2399-412.

DeSouza, J.F., Dukelow, S.P., Gati, J.S., Menon, R.S., Andersen, R.A., Vilis, T. (2000). Eye position signal modulates a human parietal pointing region during memory-guided movements. *J Neurosci*. 20, 5835-40.

Dickinson, A.R., Calton, J.L., and Snyder, L.H. (2003). Nonspatial saccade-specific activation in area LIP of monkey parietal cortex. *J Neurophysiol*. 90, 2460-4.

- Dimyan, M., and Cohen, L.G., (2010). Contribution of transcranial magnetic stimulation to the understanding of mechanisms of functional recovery after stroke. *Neurorehabil Neural Repair*. 24, 125-135.
- Donchin, O., Gribova, A., Steinberg, O., Bergman, H., and Vaadia, E. (1998). Primary motor cortex is involved in bimanual coordination. *Nature*. 395, 274-8.
- Donchin, Y., and Ohry, A. (1998). [A story about the King of Denmark's horse, a mechanical ventilator and a righteous man of nations]. *Harefuah*. 134, 658-9.
- Duhamel, J.R., Colby, C.L., and Goldberg, M.E. (1992). The updating of the representation of visual space in parietal cortex by intended eye movements. *Science*. 255, 90-2.
- Enticott, P.G., Rinehart, N.J., Tonge, B.J., Bradshaw, J.L., and Fitzgerald, P.B. (2010). A preliminary transcranial magnetic stimulation study of cortical inhibition and excitability in high-functioning autism and Asperger disorder. *Dev Med Child Neurol*. 52, 179-83.
- Evarts, E. V., and J. Tanzi. Reflex and Intended Responses in Motor Cortex Pyramidal Tract Neurons of Monkey. *Journal of Neurophysiology* 39.5 (1976): 1069-080.
- Fattori, P., Gamberini, M., Kutz, D.F., and Galletti, C. (2001). 'Arm-reaching' neurons in the parietal area V6A of the macaque monkey. *Eur J Neurosci*. 13, 2309-13.
- Fattori, P., Kutz, D.F., Breveglieri, R., Marzocchi, N., and Galletti, C. (2005). Spatial tuning of reaching activity in the medial parieto-occipital cortex (area V6A) of macaque monkey. *Eur J Neurosci*. 22, 956-72.
- Felleman, D.J., and Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex*. 1, 1-47.
- Fernandez-Ruiz, J., Goltz, H.C., DeSouza, J.F., Vilis, T., and Crawford, J.D. (2007) Human parietal "reach region" primarily encodes intrinsic visual direction, not extrinsic movement direction, in a visual motor dissociation task. *Cereb Cortex*. 17, 2283-92.
- Fischer, B., and Rogal. L. (1986). Eye-hand-coordination in man: a reaction time study. *Biol Cybern*. 55, 253-61.
- Fisk, J.D., and Goodale, M.A. (1985). The organization of eye and limb movements during unrestricted reaching to targets in contralateral and ipsilateral visual space. *Exp Brain Res*. 60,
- Fujii, N., Mushiake, H., and Tanji, J. (2000). Rostrocaudal distinction of the dorsal premotor area based on oculomotor involvement. *J Neurophysiol*. 83, 1764-9.
- Galletti, C., Fattori, P., Gamberini, M., and Kutz, D.F. (1999). The cortical visual area V6: brain location and visual topography. *Eur J Neurosci*. 1999 11, 3922-36.

- Galletti, Claudio, Dieter F. Kutz, Michela Gamberini, Rossella Breveglieri, and Patrizia Fattori. Role of the Medial Parieto-occipital Cortex in the Control of Reaching and Grasping Movements. *Experimental Brain Research* 153.2 (2003): 158-70.
- Georgopoulos, A.P. (1996). On the translation of directional motor cortical commands to activation of muscles via spinal interneuronal systems. *Brain Res Cogn Brain Res.* 3, 151-5.
- Georgopoulos, A.P., and Massey, J.T. (1988). Cognitive spatial-motor processes. 2. Information transmitted by the direction of two-dimensional arm movements and by neuronal populations in primate motor cortex and area 5. *Exp Brain Res.* 69, 315-26.
- Georgopoulos, A.P., Schwartz, A.B., and Kettner, R.E. (1986). Neuronal population coding of movement direction. *Science.* 233, 1416-9.
- Gielen, C.C., van den Heuvel, P.J., and van Gisbergen, J.A. (1984). Coordination of fast eye and arm movements in a tracking task. *Exp Brain Res.* 56, 154-61.
- Gnadt, J.W., and Andersen, R.A. (1988). Memory related motor planning activity in posterior parietal cortex of macaque. *Exp Brain Res.* 70, 216-20.
- Goldberg, M.E., Colby, C.L., and Duhamel, J.R. (1990). Representation of visuomotor space in the parietal lobe of the monkey. *Cold Spring Harb Symp Quant Biol.* 55, 729-39.
- Goldman-Rakic, P.S., and Porrino, L.J. (1985). The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. *J Comp Neurol.* 242, 535-60.
- Gottlieb, J.P., Kusunoki, M., and Goldberg, M.E. (1998). The representation of visual salience in monkey parietal cortex. *Nature.* 391, 481-4.
- Grefkes, C., Ritzl, A., Zilles, K., and Fink, G.R. (2004). Human medial intraparietal cortex subserves visuomotor coordinate transformation. *Neuroimage.* 23, 1494-506.
- Gross, M., Nakamura, L., Pascual-Leone, A., and Fregni, F. (2007). Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatrica Scandinavica.* 116, 165-173.
- Hagler, D.J., Jr., Riecke, L., Sereno, M.I. (2007). Parietal and superior frontal visuospatial maps activated by pointing and saccades. *Neuroimage.* 35, 1562-77.
- Hamed, Ben S., Duhamel, J.R., Bremmer F., and Graf, W. (2001). Representation of the visual field in the lateral intraparietal area of macaque monkeys: a quantitative receptive field analysis. *Exp Brain Res.* 140, 127-44.
- Heiser, L.M., and Colby, C.L. (2006). Spatial updating in area LIP is independent of saccade direction. *J Neurophysiol.* 95, 2751-67.

- Heiser, L.M., Berman, R.A., Saunders, R.C., and Colby, C.L. (2005). Dynamic circuitry for updating spatial representations. II. Physiological evidence for interhemispheric transfer in area LIP of the split-brain macaque. *J Neurophysiol.* 94, 3249-58.
- Helsen, W.F., Elliott, D., Starkes, J.L., and Ricker, K.L. (1998). Temporal and spatial coupling of point of gaze and hand movements in aiming. *J Mot Behav.* 30, 249-59.
- Hill, J., Inder, T., Neil, J., Dierker, D., Harwell, J., and Van Essen, D. (2010). Similar patterns of cortical expansion during human development and evolution. *Proc Natl Acad Sci.* 107, 135-40.
- Holmes, G. (1917). The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain*, 40: 463–535.
- Hoshi, E., and Tanji, J. (2002). Contrasting neuronal activity in the dorsal and ventral premotor areas during preparation to reach. *J Neurophysiol.* 87, 1123-8.
- Isa, T., and M. Yoshida. Saccade Control after V1 Lesion Revisited. *Current Opinion in Neurobiology* 19.6 (2009): 608-14.
- Johansson, R.S., Westling, G., Bäckström, A., and Flanagan, J.R. (2001). Eye-hand coordination in object manipulation. *J Neurosci.* 21, 6917-32.
- Johnson, P.B., Ferraina, S., Bianchi, L., and Caminiti, R. (1996). Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb Cortex.* 6,102-19.
- Jonikaitis, D., and Deubel, H. (2011). Independent allocation of attention to eye and hand targets in coordinated eye-hand movements. *Psychol Sci.* 22, 339-47.
- Kalaska, J.F., Cohen, D.A., Hyde, M.L., and Prud'homme, M. (1989). A comparison of movement direction-related versus load direction-related activity in primate motor cortex, using a two-dimensional reaching task. *J Neurosci.* 9, 2080-102.
- Kalaska, J.F., Scott, S.H., Cisek, P., and Sergio, L.E. (1997). Cortical control of reaching movements. *Curr Opin Neurobiol.* 7, 849-59. Review.
- Kerkhoff, G., Heldmann, B., Struppler, A., Havel, P., and Jahn, T. (2001). The effects of magnetic stimulation and attentional cueing on tactile extinction. *Cortex.* 37, 719-23.
- Krauzlis, R.J., and Hagedorn, Z.M. (2007). Finding our way around the sensory-motor corner. *Neuron.* 54, 852-4.
- Kurata, K. Premotor Cortex of Monkeys: Set- and Movement-related Activity Reflecting Amplitude and Direction of Wrist Movements. *Journal of Neurophysiology* 69.1 (1993): 187-200.

- Kutz, D.F., Fattori, P., Gamberini, M., Breveglieri, R., and Galletti, C. (2003). Early- and late-responding cells to saccadic eye movements in the cortical area V6A of macaque monkey. *Exp Brain Res.* 149, 83-95.
- Lamotte, R.H., and Acuna, C. (1978). Defects in accuracy of reaching after removal of posterior parietal cortex in monkeys. *Brain Res.* 139, 309-26.
- Land, M.F., and Hahoe, M. (2001). In what ways do eye movements contribute to everyday activities? *Vision Res.* 41, 3559-65.
- Lawrence, B.M., and Snyder, L.H. (2006). Comparison of effector-specific signals in frontal and parietal cortices. *J Neurophysiol.* 96, 1393-400.
- Lecas, J. C., J. Requin, C. Anger, and N. Vitton. Changes in Neuronal Activity of the Monkey Precentral Cortex during Preparation for Movement. *Journal of Neurophysiology* 56.6 (1986): 1680-702.
- Lefaucheur, J. P. (2009). Treatment of Parkinson's disease by cortical stimulation. *Expert Review of Neurotherapeutics* 9, 1755–1771.
- Lewis, J.W., and Van Essen, D.C. (2000). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *J Comp Neurol.* 428, 112-37.
- Lewis, J.W., and Van Essen, D.C. (2000b). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *J Comp Neurol.* 428, 112-37.
- Li, C.S., Mazzoni, P., and Andersen, R.A. (1999). Effect of reversible inactivation of macaque lateral intraparietal area on visual and memory saccades. *J Neurophysiol.* 81, 1827-38.
- Lisberger, S.,G. (2010). Visual guidance of smooth-pursuit eye movements: sensation, action, and what happens in between. *Neuron.* 27, 477-91.
- Lünenburger, L., and Hoffmann, KP. (2003). Arm movement and gap as factors influencing the reaction time of the second saccade in a double-step task. *Eur J Neurosci.* 17, 2481-91.
- Lovejoy, L.P., and Krauzlis, R.J. (2010). Inactivation of primate superior colliculus impairs covert selection of signals for perceptual judgments. *Nat Neurosci.* 13, 261-6.
- Lynch, J.C., Graybiel, A.M., and Lobeck, L.J. (1985). The differential projection of two cytoarchitectonic subregions of the inferior parietal lobule of macaque upon the deep layers of the superior colliculus. *J Comp Neurol.* 1985 235, 241-54.

- Maimon, G., and Assad, J.A. (2006). A cognitive signal for the proactive timing of action in macaque LIP. *Nat Neurosci.* 9, 948-55.
- Marzocchi, N., Breveglieri, R., Galletti, C., and Fattori, P. (2008). Reaching activity in parietal area V6A of macaque: eye influence on arm activity or retinocentric coding of reaching movements? *Eur J Neurosci.* 27, 775-89.
- Medendorp, W. P., H. C. Goltz, T. Vilis, and J. D. Crawford. Gaze-centered Updating of Visual Space in Human Parietal Cortex. *Journal of Neuroscience* 23.15 (2003): 6209-214.
- Medendorp, W.P., Goltz, H.C., Crawford, J.D., and Vilis, T. (2005). Integration of target and effector information in human posterior parietal cortex for the planning of action. *J Neurophysiol.* 93, 954-62.
- Medendorp, W.P., Goltz, H.C., Vilis, T., and Crawford, J.D. (2003). Gaze-centered updating of visual space in human parietal cortex. *J Neurosci.* 23, 6209-14.
- Mountcastle, V.B., Lynch, J.C., Georgopoulos, A., Sakata, H., and Acuna, C. (1975). Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J Neurophysiol.* 38, 871-908.
- Mushiake, H., Fujii, N., and Tanji, J. (1999). Microstimulation of the lateral wall of the intraparietal sulcus compared with the frontal eye field during oculomotor tasks. *J Neurophysiol.* 81, 1443-8.
- Nowak, D.A., Grefkes, C., Ameli, M., and Fink, G.R. (2009). Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabil Neural Repair.* 23, 641-56.
- Nummela, S.U., and Krauzlis, R.J. (2010). Inactivation of primate superior colliculus biases target choice for smooth pursuit, saccades, and button press responses. *J neurophysiol.* 104, 1538-48.
- Oristaglio, J., Schneider, D.M., Balan, P.F., and Gottlieb, J. (2006). Integration of visuospatial and effector information during symbolically cued limb movements in monkey lateral intraparietal area. *J Neurosci.* 26, 8310-9.
- Pandya, D., and L. Vignolo. Interhemispheric Projections of the Parietal Lobe in the Rhesus Monkey. *Brain Research* 15.1 (1969): 49-65.
- Pandya, D.N., and Seltzer, B. (1982). Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *J Comp Neurol.* 204, 196-210.
- Patel, G.H., Shulman, G.L., Baker, J.T., Akbudak, E., Snyder, A.Z., Snyder, L.H., and Corbetta, M. (2010). Topographic organization of macaque area LIP. *Proc Natl Acad Sci U S A.* 107, 4728-33.

- Pesaran, B., Nelson, M.J., and Andersen, R.A. (2010). A relative position code for saccades in dorsal premotor cortex. *J Neurosci.* 30, 6527-37.
- Pesaran, B., Nelson, M.J., and Andersen, R.A. Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. *Neuron.* 51, 125-34.
- Pierrot-Deseilligny, C., Milea, D., and Müri, R.M. (2004). Eye movement control by the cerebral cortex. *Curr Opin Neurol.* 17, 17-25.
- Pisella, L., Sergio, L., Blangero, A., Torchin, H., Vighetto, A., Rossetti, Y. (2009). Optic ataxia and the function of the dorsal stream: contributions to perception and action. *Neuropsychologia.* 47, 3033-44.
- Platt, M.L, and Glimcher, P.W. (1998). Response fields of intraparietal neurons quantified with multiple saccadic targets. *Exp Brain Res.* 121, 65-75.
- Popović, D.B., Sinkaer, T., and Popović, M.B. (2009). Electrical stimulation as a means for achieving recovery of function in stroke patients. *NeuroRehabilitation.* 25, 45-58.
- Prado, J., Clavagnier, S., Otzenberger, H., Scheiber, C., Kennedy, H., and Perenin, M.T. (2005). Two cortical systems for reaching in central and peripheral vision. *Neuron.* 48, 849-58.
- Quiñan Quiroga, R., Snyder, L.H., Batista, A.P., Cui, H., and Andersen, R.A. (2006). Movement intention is better predicted than attention in the posterior parietal cortex. *J Neurosci.* 26, 3615-20.
- Rizzolatti, G., Riggio, L. and Sheliga, B.M. (1994). Space and selective attention. In C. Umiltà & M. Moscovitch, *Attention and Performance XV*, 231-265.
- Rizzo M. (1993). 'Bálint's syndrome' and associated visuospatial disorders. *Baillieres Clin Neurol.* 2, 415-37.
- Robinson, D.L., Goldberg, M.E., and Stanton, G.B. (1978). Parietal association cortex in the primate: sensory mechanisms and behavioral modulations. *J Neurophysiol.* 41, 910-32.
- Rossini, P., and Rossi, S. (2007). Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. *Neurology.* 68, 484-488.
- Rushworth, M.F., Nixon, P.D., Passingham, R.E. (1997). Parietal cortex and movement. I. Movement selection and reaching. *Exp Brain Res.* 117, 292-310.
- Saslow, M.G. (1967). Latency for saccadic eye movement. *J Opt Soc Am.* 57, 1030-3.

- Schall, J. D. Neuronal Activity Related to Visually Guided Saccades in the Frontal Eye Fields of Rhesus Monkeys: Comparison with Supplementary Eye Fields. *Journal of Neurophysiology* 66.2 (1991): 559-79.
- Schwartz, A.B., and Moran, D.W. (2000). Arm trajectory and representation of movement processing in motor cortical activity. *Eur J Neurosci.* 12, 1851-6.
- Seltzer, B., and D.N. Pandya. The Distribution of Posterior Parietal Fibers in the Corpus Callosum of the Rhesus Monkey. *Experimental Brain Research* 49.1 (1983).
- Snyder, L.H., Batista, A.P., and Andersen, R.A. (1997). Coding of intention in the posterior parietal cortex. *Nature.* 386, 167-70.
- Snyder, L.H., Calton, J.L., Dickinson, A.R., and Lawrence, B.M. (2002). Eye-hand coordination: saccades are faster when accompanied by a coordinated arm movement. *J Neurophysiol.* 87, 2279-86.
- Song, J.H., and McPeck, R.M. (2009). Eye-hand coordination during target selection in a pop-out visual search. *J Neurophysiol.* 102, 2681-92.
- Sprague, J.M., and Meikle, T.H., Jr. (1965) The role of the superior colliculus in visually guided behavior. *Exp Neurol.* 11, 115-46.
- Stoerig, P. (2006) Blindsight, conscious vision, and the role of primary visual cortex.
- Takeuchi, A., and Onodera, K. (1972). Effect of bicuculline on the GABA receptor of the crayfish neuromuscular junction. *Nat New Biol.* 236, 55-6.
- Ward, N.S. (2004). Functional reorganization of the cerebral motor system after stroke. *Curr Opin Neurol.* 17, 725-30.
- Wardak, C., Olivier, E., and Duhamel, J.R. (2004). A deficit in covert attention after parietal cortex inactivation in the monkey. *Neuron.* 42, 501-8.
- Yttri, E.A., Chang, S.W.C., Liu, Y., Wang, C., Snyder, L.H. (2011). Mixed signals: Resolving ambiguous biases in parietal reach region with functional inactivation. In preparation