NEURAL SIGNALS UNDERLYING COORDINATE FRAME OF ATTENTION IN
AREA 7a OF PRIMATE POSTERIOR PARIETAL CORTEX

By

Justin Rawley

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Approved By:

Christos Constantinidis, Ph.D., Advisor ___________________________

Examinining Committee:

Dale A. Dagenbach, Ph.D., Chairman ___________________________

Dwayne W. Godwin, PhD. ___________________________

Terrence Stanford, Ph.D. ___________________________

Emilio Salinas, Ph.D. ___________________________
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LIST OF ABBREVIATIONS

AIP  Anterior Intraparietal Sulcus
BA   Brodmann's Area
CIP  Caudal Intraparietal Area
DAP  Dual Attention Process
dIPFC dorsolateral Prefrontal Cortex
DP   Dorsal Prelunate
EEG  Electroencephalography
fMRI Functional Magnetic Resonance Imaging
FS   Fast-Spiking
IPS  Intraparietal Sulcus
IS   Intermediate-Spiking
LIP  Lateral Intraparietal Area
LS   Lateral Sulcus
LS   Lunate Sulcus
MIP  Medial Intraparietal Area
MST  Medial Superior Temporal
MT   Medial Temporal
PET  Positron Emission Tomography
PFC  Prefrontal Cortex
PPC  Posterior Parietal Cortex
PRR  Parietal Reach Region
PSTH Peri-Stimulus Time Histogram
RF   Receptive Field
RS   Regular-Spiking
STS  Superior Temporal Sulcus
TPJ  Temperoparietal Junction
VIP  Ventral Intraparietal Area
WHH  Width at Half Height
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ABSTRACT

Justin Rawley

CONTEXT DEPENDENT REPRESENTATION OF COORDINATE REFERENCE FRAME IN PRIMATE POSTEDIOR PARIETAL CORTEX

Dissertation under the direction of
Christos Constantinidis, Ph.D., Assistant Professor of Neurobiology and Anatomy

The posterior parietal cortex is recognized as an association area that amalgamates sensory information and transforms it into signals enabling the coordination of motor actions. The allocation of visual attention is a necessary part of this process and posterior parietal area 7a is one of the main areas thought to mediate it. When 7a is compromised, disruptions such as visual neglect and apraxia can result. While evidence exists that 7a encodes sensory signals in world centered coordinates, the reference frame of visual attention was previously unknown. We observed that while some elements of 7a encoding are malleable dependent upon behavioral context, the reference frame of attention is also predominantly encoded in a world-referenced system. We also find that the electrophysiologically defined pyramidal and interneuron subtypes participate in approximately equal proportions in the 7a networks that mediate both visual attention and working memory.
CHAPTER I

INTRODUCTION: FUNCTION OF POSTERIOR PARIETAL CORTEX AND ITS ROLE WITHIN DISTRIBUTED NEURAL NETWORKS

Justin B. Rawley

The following chapter is an expansion of an article first published in Neurobiology of Learning and Memory, Jan. 15, 2009 titled “Neural correlates of learning and working memory in primate posterior parietal cortex.” Justin Rawley prepared the manuscript. Christos Constantinidis acted in an advisory and editorial capacity.
Abstract

The posterior parietal cortex has been traditionally associated with coordinate transformation necessary for interaction with the environment and visual spatial attention. More recently, neural correlates of other cognitive functions such as working memory and task learning have been identified in the posterior parietal cortex and the neural circuits mediating these functions have been studied in greater detail. Experiments in non-human primates have revealed a great deal about the neural correlates of memory and learning at the single neuron level while human imaging has offered a broader view of posterior parietal contribution at the brain network level. During working memory, a population of posterior parietal neurons continues to discharge after stimuli are no longer present. This activation resembles the activity of the prefrontal cortex during working memory, although important differences between these areas have been identified in terms of the ability to resist stimulation by distracting stimuli. Various areas of the parietal cortex also become active during tasks that require the organization of information into larger structured elements and this activity is modulated according to learned context-dependent rules. The mean discharge rate and spectral power of neuronal spike trains are modulated by training in behavioral paradigms that involve learning of new task sets or rules. These findings demonstrate the importance of posterior parietal cortex in brain networks mediating working memory and learning.

Keywords
Monkey, area 7a, intraparietal sulcus, attention, neurophysiology
Introduction

Experiencing the world is dependent upon an observer’s ability to amalgamate disjunct waves of sensation into a cohesive internalized model that depicts the surrounding environment. From this internalized representation, the viewer can extrapolate the necessary information to effect meaningful interaction with the environment and its component objects. The brains of higher animals adapted to handle the increasing sensory load by diversifying and distributing processing. In the primate visual system, segregated streams emerged to convey different aspects of each stimulus to be processed in parallel. The ventral visual pathway encodes physical attributes of a stimulus important for recognition and identification such as its color and shape, whereas the dorsal pathway tracks its location and movement (Ungerleider and Mishkin, 1982). The posterior parietal cortex (PPC) sits at the apex of the dorsal visual pathway. It has also long been recognized as an important association area that acts as an interface between the external world and the actions of an animal. Functions of the PPC can be grouped in four domains: sensorimotor transformations, selective attention, working memory, and learning. We will provide a brief overview of these functions next, and focus on the latter two for the remainder of this review.

An important role of the PPC, recognized very early, is its function in receiving and integrating information across multiple sensory areas, and transforming it into a common reference system from which goal-directed motor movements can be computed (Seal, 1989; Stricanne et al., 1996; Batista et al., 1999). To do this, it must take into account the changing alignment of body parts during movement. Eyes, head, trunk, and limbs move independently, each with its own intrinsic coordinate reference system that
places items relative to itself. For example, an object tracked on a region of the observer’s retina will be in a different location with respect to the head when the eyes are deviated within the orbits than when the eyes are oriented straight ahead. A turn of the head will produce a different frame of reference with respect to the trunk, limbs and so on. An ongoing series of computations must continuously update the body’s internal model in order to maintain the fluid dynamic of interaction with the environment. These coordinate subsystems are encompassed by two larger points of view within the world schema: that of the egocentric observer, who understands the disposition of surrounding space and its contents in relationship to itself, and that of the allocentric point of view which construct relative spatial maps based upon landmarks or relationships of objects relative to one another; the latter has emerged only recently in the phylogenetic lineage and also develops fairly late in adolescence in humans (Mathews, 1992; Pine et al., 2002). Posterior parietal cortex has been implicated in mediating sensory motor behavior with reference to both viewpoints.

In spite of the level of development of the primate brain, it still cannot process all sensory stimuli simultaneously. Instead, it must allocate resources to some localized region in space in which a relevant event is occurring, or expected to occur. A second important function of the posterior parietal cortex is to act as a mediator of this process, known as selective attention. PPC has been shown under different experimental paradigms to be activated when an organism directs its attention towards or away from a specific location, as well as when the organism is actively maintaining attention on a locale (Constantinidis, 2006a).

Closely tied with the function of selective attention is working memory, or the
ability to keep pieces of pertinent information temporarily available during ongoing execution of a mental operation. Working memory has traditionally been ascribed to the prefrontal cortex, but a wealth of recent research demonstrates that posterior parietal cortex is not only activated during working memory, but that inactivation of, or damage to posterior parietal regions can cause specific working memory deficits. This newfound role of PPC is not entirely surprising in view of the fact that this region has dense reciprocal connections with frontal cortex and limbic areas, thus placing it within a distributed network with other areas known to participate in the working memory circuit (Constantinidis and Procyk, 2004).

Selective attention and working memory are subservient to learning and long-term memory. Some prior experience must govern where an animal attends, what stimulus is to be remembered, and ultimately how to act with respect to that stimulus in order to achieve a result. Learning imparts the ability to react to a stimulus differently depending on the behavioral context and according to a desired goal. The effects of learning on PPC have received relatively less attention until recently, and will be discussed in the final section of this chapter.

**Clinical Relevance and Pathology**

An understanding of the importance of posterior parietal cortex was initially derived from the deficits observed in human lesion patients. Perhaps the signature effect of PPC damage is the neglect syndrome, typically occurring after a lesion in the right hemisphere. Disturbances include the inability to detect an object in the contralateral (left) visual hemifield (egocentric neglect) or to perceive the left side of objects,
regardless of where they appear within the visual field (allocentric neglect). Related conditions involve constructional apraxia and extinction, which can occur after lesions on either side of PPC. These conditions are characterized by inability to reconstruct a visual scene (constructional apraxia) (Benton, 1967; Critchley, 1969; Grossi, 1999) and to attend to stimulus in the hemisphere contralateral to the lesion when a stimulus in the ipsilateral hemifield appears at the same time (extinction) (Oppenheim, 1885). The most severe effects of bilateral parietal lesions produce Balint’s syndrome, characterized by the inability to perceive more than one visual stimulus at a time, to direct visual attention outside the fovea, to scan visual space, and to coordinate hand movements to visual targets (Balint, 1909).

Although the study of parietal lesions has emphasized the attentional character of the deficits, spatial working memory performance and capacity can also be affected (Maguire and Ogden, 2002; Malhotra, 2005). It has been proposed that an interaction between working memory deficits and neglect may exacerbate the effect of neglect, possibly by interfering with the ability to keep track of what spatial locations have already been searched (Husain et al., 2001; Wojciulik et al., 2001). Additionally, damage to the right Temporal-Parietal Junction (TPJ), which has been implicated in neglect (Heilman KM, 1983; Vallar and Perani, 1986; Leibovitch FS, 1998; Vallar, 2001) has also been shown to produce spatial working memory deficits (Malhotra, 2005). In the latter study, modified versions of the Corsi blocks task were used to dissociate the working memory aspect of the pathology from the neglect. Viewers had to remember the order of a series of highlighted discs whose locations were restricted to the vertical midline, thus eliminating the attentional bias towards the ipsilesional visual field.
Damage to the Temporal-Parietal Junction was associated with poor performance in the task. Interestingly, poor performance was also observed in two patients with right lateral frontal lesions who showed no neglect (Malhotra, 2005), confirming that a dissociation can exist between spatial working memory and neglect in some cases. While the symptoms of neglect often attenuate over time, sustained attention and visual memory problems have been found in long-term neglect patients as well (Maguire and Ogden, 2002). These studies support the idea that disrupting or disconnecting important nodes within the spatial working memory network may induce an inability to keep track of previously searched locations in the ipsilaterial hemifield that contributes to the failure to attend to the contralateral one (Driver, 2002; Malhotra, 2005).

Recent neuropsychological research provides more details about the nature of memory deficits produced by parietal damage (Pisella, 2004; Finke, 2006; Berryhill et al., 2007; Berryhill, 2008a, b; Davidson, 2008; Haramati, 2008). For a comprehensive review, see Olson and Berryhill in this issue (Olson, 2008). Visual working memory impairment in both location and object working memory has been shown in patients with right and bilateral parietal lesions (Berryhill, 2008a); (Berryhill, 2008b), though these deficits may depend on the particular demands of the task (Pisella, 2004; Finke, 2006). Work by Berryhill and Olson has pointed specifically to a deficit in retrieval of information from Working Memory (Berryhill, 2008b, a). Quite unexpectedly, recent work has also pointed to a deficit in long-term, episodic memory after parietal lesions. For example, one study reported that bilateral damage decreases the amount of detail with which patients describe autobiographical events during free recall, but not when prompted by specific questions (Berryhill et al, 2007). In another study employing a
source memory task, recalling the correct answer when cued was unimpeded, whereas “recognition” that an item was encountered before was impaired and “remembering” subjective details was found to be significantly diminished (Davidson et al, 2008).

**Anatomical Organization**

A gross overview of anatomical connections reveals that PPC receives inputs from primary and secondary sensory modalities and has extensive reciprocal connections with prefrontal association areas, frontal regions, limbic structures, as well as superior colliculus and basal ganglia. The triad of network modules comprised by the parietal association, the prefrontal association cortices and limbic regions defines one of the mainstays of higher cognitive behavior. Within PPC, there exists differential connectivity within these larger networks and diverse interconnectivity among distinct sub-regions, each with its own specialization.

The human posterior parietal region occupies the largest percentage of cortical area than in any primate (Hyvarinen, 1982). It lies within and along either side of the intraparietal sulcus (IPS), bounded anteriorly by the postcentral sulcus. It is comprised of Brodmann’s areas (BA) 5, 7, 40 and 39 (Figure 1). Functional and anatomical studies that map posterior parietal function from the macaque onto human cortical analogues confirm that the PPC is relatively well aligned across species (Astafiev, 2003; Grefkes, 2005). Grefkes and Fink identify two general functional gradients, one running anterior to posterior and the other medial to lateral (Grefkes, 2005). These authors note that anterior structures, closest to somatosensory and motor brain regions, are involved in sensorimotor processing, whereas posterior structures in PPC, located next to extrastriate
Figure 1. Outline of the human posterior parietal cortex. Abbreviations: IPS, intraparietal sulcus; BA, Brodmann’s area.
visual areas, are visually related. Areas situated within the medial bank of intraparietal sulcus are more closely associated with arm movement whereas regions along the lateral bank are mostly eye-movement related (Grefkes, 2005).

Though the human PPC is considerably more specialized than that of other primates, the monkey PPC is phylogenetically similar and can account for a wide range of functions observed in the human. As in the human brain, macaque PPC centers around the IPS and occupies areas 5 and 7 on either side of it (Figure 2). One can loosely define the boundary delineated by the Sylvian Sulcus (SS), the Superior Temporal Sulcus (STS) and the bend in the Lunate Sulcus, as the posterior-lateral edge of the PPC (Brodmann, 1909). Various subregions of PPC have been proposed (Vogt and Vogt, 1919; von Economo and Koskinas, 1925; von Bonin and Bailey, 1947; Pandya, 1982). Areas 5 and 7 have been further subdivided based on cytoarchitectonics and functional specialization. Within IPS, anterior, ventral, lateral, medial, and caudal intraparietal divisions have been identified, each also handling a different aspect of neural processing (Cavada and Goldman-Rakic, 1989b, a; Colby, 1999; Grefkes, 2005).

A source of confusion regarding PPC organization and function involves the correspondence between human and monkey PPC subdivisions. The first part of this dilemma arises from the discrepancy of area assignments from one species to another and the various naming schemes that have been applied by the pioneering anatomists. The gross level differences in area placements between species are immediately obvious in the anatomical atlases. In the human, Brodmann’s areas 5 and 7 reside within the superior
Figure 2. Outline of the macaque monkey posterior parietal cortex. Abbreviations: AIP, anterior intraparietal area; CIP, caudal intraparietal area; DP, dorsal premunate area; IPS, intraparietal sulcus; LIP, lateral intraparietal area; LS, lunate sulcus; MIP, medial intraparietal area; STS, superior temporal sulcus; VIP, ventral intraparietal area. Inset shows the intraparietal sulcus unfolded to view areas along the banks. Area 7m lines the medial surface of the parietal lobe (not visible in lateral view).
Figure 2.
temporal lobule while areas 40 and 39 occupy most of the inferior parietal lobule. In
monkeys, area 5 is found in the superior temporal lobule whereas areas 7a and 7b fall in
the inferior parietal lobule. Brodmann’s Areas 39 and 40 have not been identified in the
monkey. An equivalent arrangement has been proposed by Von Economo and Koskinas
for the human brain. In this nomenclature human area PG is roughly equivalent to
Brodmann’s human area 39, PF is in register with area 40, PE corresponds to area 7, and
PA to area 5. Von Bonin and Baily adapted Von Economo’s and Koskinas’ terminology
to the macaque brain. In their scheme, monkey area PG is best aligned with (monkey)
area 7a, PF with 7b, and PE with area 5.

Another source of ambiguity exists regarding the functional correspondence
between human and monkey parietal areas. Activation of the human superior parietal
gyrus has been observed during spatial attention shifts and visually guided saccades
(Vandenberghe et al., 2001). Based on observations of activation to selectivity for
saccade direction, others have ascribed macaque LIP as homolog to this area, (Sereno and
Maunsell, 1998; Koyama et al., 2004; Nakahara et al., 2007). Corbetta and colleagues
have characterized activation of the temporoparietal junction (TPJ) in redirecting
attention to behaviorally relevant stimuli in novel or unexpected locations (Corbetta et al.,
2000; Corbetta and Shulman, 2002), in analogy to area 7a activation in the monkey
(Steinmetz and Constantinidis, 1995; Constantinidis and Steinmetz, 2001a). However,
few monkey neurophysiological studies have directly compared neuronal responses in
multiple cortical areas in order to establish clear functional differences between them.
Therefore, the functional correspondence between monkey and human posterior parietal areas remains unclear.

Despite this uncertainty, cytoarchitectonic and physiological studies in the macaque brain have determined a number of well-defined cortical areas. A brief overview of these areas is presented next, along with their major cortical patterns of connectivity and physiological properties that offer insights on their main functions.

**Area 5 and MIP (PRR)**

Area 5, lies anterior to the intraparietal cortex and is interconnected with the primary and secondary somatosensory cortex other parietal areas, as well as motor, premotor and supplemental motor cortices (Jones, 1969, 1970, 1978; Kunzle, 1978; Strick and Kim, 1978; Lynch, 1980; Petrides M, 1984). It additionally sends efferents to the corticospinal tract (Peele, 1942; Weisendanger, 1979; Toyoshima K, 1982). Adjacent to area 5, lining the medial bank of the Intra-parietal suclus is the medial intraparietal area (MIP). This anatomical area corresponds to the functionally-defined Parietal Reach Region (PRR), although the latter may extend into area V6a as well (Cohen and Andersen, 2002). Both area 5 and PRR have been identified as part of a fronto-parietal network involved in generating reaching movements (Wise et al., 1997; Caminiti et al., 1998). The parietal reach region coordinates hand movements to visual targets within reaching distance, encoding impending arm movements in eye-centered coordinates (Batista et al., 1999; Snyder et al., 2000) and is activated during delay periods before memory guided arm movements (Snyder et al., 1997, 2000). A gradient of neurons with strictly visual to strictly sensorimotor response properties runs from the fundus of the intraparietal sulcus to the outer edge within MIP, with bimodal neurons bridging the two pools (Colby and
Duhamel, 1991). Activity during saccades is proposed to facilitate hand-eye coordination or maintain eye-centered object representation during reaching movements as eye movements are being made (Snyder, 2000). Neurons in the area 5 encode target location before and during a movement in both hand and the eye-centered reference frame (Andersen and Buneo, 2002). Within the network, the transformation from eye to hand coordinates arises simultaneously without intermediary steps relative to the head or body (Buneo et al., 2008).

VIP

The Ventral Intra-Parietal area has been implicated in motion detection across sensory modalities including tactile, visual and vestibular (Colby et al., 1993; Duhamel et al., 1998; Bremmer et al., 2002). Neurons in this area are sensitive to stimulus speed and direction, as can be hinted by their anatomical connection with areas MT and MST (Ungerleider and Desimone, 1986; Boussaoud et al., 1990; Rosa et al., 1993). Multisensory neurons that respond to both visual and tactile stimuli are head-centered and demonstrate alignment of the receptive fields such that a correspondence exits between regions of space with analogously placed body parts; a neuron that is activated by a visual stimulus presented in the upper left quadrant of a screen will also react to a tactile stimulus on the upper left part of the head (Duhamel et al., 1998). Another distinguishing feature of VIP is sensitivity for the distance of stimuli, with “ultraneam” neurons encoding visual stimuli only when they come within 5 cm of the face (Colby et al., 1993). This area is interconnected with parietal areas including LIP, MIP and 7b, somatosensory areas including 5 and S2, and projects to premotor area F4, which has been implicated in the
encoding of head and mouth movements (Gentilucci M, 1988; Rizzolatti G, 1988; Luppino, 1999; Lewis, 2000).

*Area 7b*

Area 7b is mainly connected with the primary and secondary somatosensory cortex, parietal area 5, dorsal premotor, and orbital prefrontal cortex (Cavada and Goldman-Rakic, 1989b; Andersen et al., 1990a; Neal et al., 1990). Area 7b has a rough motor somatotopic organization, and neurons are activated both by a motor act and during observation of the act performed by a different individual, in analogy to “mirror neurons” first described in the premotor cortex (Fogassi et al., 2005).

*AIP and CIP*

The Anterior Intraparietal (AIP) and Caudal Intraparietal (CIP) areas, both in the lateral bank of the IPS, are involved in the transformation of visual 3D information into appropriate hand movement for grasping objects (Jeannerod et al., 1995; Rizzolatti, 1998; Murata et al., 2000; Fogassi et al., 2001; Sakata, 2003). Different populations of neurons in area AIP respond to either object manipulation alone, simultaneous visual and tactile stimulation, or 3-D visual stimulation (Sakata et al., 1995). Some neurons also demonstrate sustained discharges to 3-D objects after viewing before handling, interpreted to encode memory for shape or motor preparation to grasp (Murata et al., 1996). The anterior intraparietal area (AIP) has connections with the inferior parietal lobule, LIP, and secondary somatosensory area, as well as the lower bank of STS, ventral premotor area F5, and prefrontal areas 12 and 46 (Matelli et al., 1986; Rizzolatti,
Like area AIP, CIP is involved with processing 3D attributes. It responds in the visual modality to 3D cues and surface orientation and is involved in stereopsis, or the computation 3D surfaces from binocular disparity (Tsutsui et al., 2001). It is thought to combine feature and location information relevant to guiding hand movement (Tsutsui et al., 2003). Neurons here also show sustained discharges after stimulus presentation when a surface orientation feature must be remembered in order to complete a task (Tsutsui et al., 2003). The Caudal Intraparietal area receives afferents from visual areas V3, V3A and projects to AIP (Adams, 1997; Nakamura et al., 2001).

**LIP**

Area LIP is located between AIP and CIP within the lateral bank of the intraparietal sulcus and has been shown to guide saccades to both visual and auditory targets (Barash et al., 1991; Linden et al., 1999). An extensive literature has implicated area LIP in visual attention (reviewed by Gottlieb in this issue). LIP neurons continue firing after the offset of a behaviorally relevant stimulus, implying a function in working memory (Gnadt and Andersen, 1988). LIP is connected with visual extrastriate regions, parietal areas AIP, VIP, 7a, and the Frontal Eye Fields (Andersen et al., 1990a; Blatt et al., 1990; Stanton et al., 1995; Nakamura et al., 2001).

**Area 7a and DP**

Area 7a shares connections with visual cortical areas including area MST and PO, other parietal areas, including areas LIP and 7m, and extensive connections the dorsolateral
prefrontal cortex, most heavily concentrated in the posterior part of the principal sulcus (Cavada and Goldman-Rakic, 1989b, a). Its limbic connections encompass the parahippocampal gyrus, the presubiculum, ventral posterior cingulate cortex, agranular retrosplenic cortex, and the caudomedial lobule, while it sends direct connections to CA1 of hippocampus (Rockland, 1999). Neurons in area 7a have large and often bilateral visual receptive fields (Lynch et al., 1977; Motter and Mountcastle, 1981). A large literature also exists regarding the modulation of area 7a responses by attention (Constantinidis, 2006a). The dorsal prelunate (DP) is continuous with area 7a, and has similar visual properties (Andersen et al., 1990a; Siegel et al., 2003). Both areas exhibit gain fields such that the amplitude of the neural response is modulated as a function of eye position of the orbit. Furthermore neurons in both areas are responsive to optic flow, which provide motion cues for navigation (Motter and Mountcastle, 1981; Read and Siegel, 1997; Siegel and Read, 1997).

Area 7m

Area 7m lies in the medial surface of the parietal lobe; the human homologue is often referred to as the precuneus area (Liu et al., 2003; Serences et al., 2004). Area 7m is interconnected mainly with visual cortical areas PO and MST, parietal area 7a, dorsal prefrontal cortex, and the Frontal Eye Fields (Cavada and Goldman-Rakic, 1989b; Leichnetz, 2001). Cingulate sulcus and granular retrosplenic cortex comprise the major limbic constituents of the network connected with area 7m (Cavada and Goldman-Rakic, 1989b).
Neural correlates of higher cognition in PPC

Neurophysiological recordings in monkeys have been instrumental for investigating cognitive functions. Monkeys are widely used in neurophysiology and imaging experiments because of their close structural homology to humans and the fact that they are capable of performing behavioral tasks that allow researchers to test cognitive processing within well defined parameters. We have introduced the functions of posterior parietal cortex in performing coordinate transformation, mediating visual attention, as well as in contributing to working memory, and we have touched on what can happen when one or more of these processes is disrupted. In some sense, these higher functions are difficult to dissociate fully because of their interdependence on one another. To illustrate this point, consider working memory; it is utilized during goal-directed visual attention in that a location or feature to be attended is maintained in the viewer’s internal representation. As we have discussed in relation to pathology, a malfunction in working memory may contribute to, or exacerbate deficits in spatial attention (Husain et al., 2001; Wojciulik et al., 2001).

Navigation is dependent upon the ability to make accurate coordinate transformations but spatial attention and working memory can be essential parts of this process as well. A common problem encountered by people with spatial neglect is running into objects on their neglected side. In the context of foraging and exploring, the spatial cues such as the relationships between landmarks must to be accounted for to keep from recursively searching the same area (Posner and Cohen, 1984; Klein, 1988). In getting from point A to point B, one must also keep the destination in mind so as not to wander off course. Lawrence Peter “Yogi” Berra put forth the keen observation that: “If
you don’t know where you’re going, you’ll end up someplace else (Lawrence Peter Berra).” In a combination of all these processes, navigation requires the recollection of route information along a known path and the learning of new information when traversing an unfamiliar one. As we shall see, working memory is invoked during the initial stages of learning, and in some instances, spatially defined mnemonic structures assembled in working memory can facilitate learning. In the following sections, we will review research in both monkeys and humans and address these specific roles of posterior parietal cortex in higher processing.

Sensory-motor transformations

One of the elementary problems encountered by medical practitioners and basic science researchers alike is sorting out which coordinate reference frames are being used to encode visual-spatial stimuli in PPC and how sensory-motor transformations are made. This becomes particularly important in designing treatment methodologies to address neglect syndromes and optic ataxia experienced by those with lesions to PPC.

Serial vs. parallel processing

For a long time, the established view was that visual information is encoded in retinal coordinates during the early stages of processing in the visual motor pathway, and then, through a series of progressively hierarchical transformations, is remapped into the appropriate coordinate reference frame for the motor system to be activated. Posterior parietal cortex was purported to be at the center of these transformation, acting as the intermediary structure through which visual information is first converted from retinal,
through head-centric to body-centric coordinates (Jeannerod, 1991; Flanders, 1992; Boussaoud and Bremmer, 1999).

Neurons across the various regions in PPC have already been found to encode stimuli in head, hand, and eye-centered coordinates, as noted in the section on anatomy. Furthermore, neurons in parietal areas VIP, LIP, 7a and DP have all been shown to be responsive to position of the eyes in the orbit (Bushnell et al., 1981; Andersen et al., 1985; Andersen et al., 1990b; Read and Siegel, 1997; Bremmer, 1998, 1999) and populations of parietal cells can combine eye position signals with retinal signals to compute head-position (Zipser and Andersen, 1988). Several modeling studies have demonstrated networks that can output the location of a visual stimulus in head-centered coordinates given retinal and eye position information. Neuron responses in the hidden layers of these artificial networks approximated activity of area 7a neurons (Zipser and Andersen, 1988). As a prerequisite for unequivocally establishing PPC’s role in this sensory transformation, Bremmer, Pouget and Hoffman developed an algorithm that allows them to extract eye position from counterbalanced activity of subpopulations of cells which they recorded in area 7a from monkeys fixating targets of different eccentricities (Bremmer, 1998).

Though the simplicity of this idea is attractive and seems to be born out by several experiments, other studies demonstrate that eye position signals are available all along the visuo-motor pathway, including both early and late stages. Bremmer and Boussaoud suggest that the coordinate transformation may not be entirely a serial one, but to a certain extent, distributed along a gradient of parallel processing with the eye position signal being the common element across structures. Indeed neurons located in regions as
early in the pathway as V1 (Trotter et al., 1992, 1996; Guo, 1997), V3A (Galletti and Battaglini, 1989), V4 (Bremmer and Hoffman, 1995), V6; (Galletti and Battaglini, 1989; Galletti et al., 1995; Bremmer, 1998), MT, MST (Bremmer et al., 1997; Pouget, and Hoffman, 1998), and as late as the dorsal premotor cortex are sensitive, to varying degrees, to eye position (Bremmer, 1998; Boussaoud and Bremmer, 1999). At the same time, some PPC neurons appear to encode target locations in more than one reference frame simultaneously (Andersen and Buneo, 2002) so that transformations from one to another can occur without intermediary steps (Buneo et al., 2008). Even before this discovery, the theoretical possibility had already been demonstrated using computational methods.

**Simultaneous representation of multiple reference frames**

Throughout the visual pathway, retinal receptive fields are well-approximated by Gaussian distributions such that a stimulus appearing in the optimal retinal location elicits maximal firing. As a target is moved further away in either direction from the optimal location, firing falls off on either side of the peak. Within PPC, these Gaussian curves are modulated by eye position in the orbit so that the same retinal location still exhibits the maximal peak, but the height of the curve changes. The family of Gaussian curves associated with the eye position in the head for a given retinal location can be constructed along a sigmoid distribution and the result is known as a gain field. Computational studies have successfully modeled single neuron responses in the posterior parietal cortex using the product of such a Gaussian function of retinal position, and a sigmoid function of eye position. The resulting non-linear transformation can serve as a reference frame.
independent basis function, the set of which represented by all the neurons in PPC can be used to calculate appropriate sensory-motor transformation over the entire visual space. Such a transformation allows visual objects to be represented in several coordinate systems simultaneously (Pouget, 1997). Furthermore, network simulations built on the basis function model of neurons can be made to approximate the same behavior demonstrated by patients with posterior parietal lesions (Pouget and Sejnowski, 2001). Perhaps when networks are damaged, the coordinate reference frames become dissociated in such a way that patients can no longer relate their internal representations to the external world.

_Egocentric vs. allocentric viewpoint_

Another complication in unraveling the coordinate transformation problem is how the egocentric vs. allocentric point of view might be represented. Snyder and his colleagues addressed whether head position signals within the PPC are referenced with respect to the body or to the external world. By employing a paradigm in which the animal’s body could be passively rotated under the head, the head and body could be passively rotated together, or the animal could actively move its head, these investigators determined that head position information in the lateral interparietal (LIP) region is largely body-referenced, while in area 7a, it is mainly word-referenced (Snyder et al., 1998). However, neural responses were recorded while animals performed the relatively simple task of acquiring fixation, then saccading to a peripheral target. It is possible that the neural activity would be markedly different depending upon the type of task being executed.
Context dependence

As we have already alluded to, and as we will discuss in greater detail later, visual responses in PPC can be modulated differentially in a context dependent manner. If responses of individual neurons change according to behavioral requirements, or how groups of neurons in PPC might switch between context representations, has not been thoroughly investigated. The possibility that different coordinate reference frames could be represented under different behavioral paradigms by the same neurons or networks constitutes one of the aims of our research. It stands to reason that if posterior parietal networks represent multiple reference frames simultaneously, then somewhere along the way, the readout is extracted according to an animal’s behavioral needs into the appropriate coordinate system. Theoretically, a population of readout neurons residing in PPC that receives information in multiple reference frames could act as a selector switch, relaying its output signal in a specific coordinate frame to effector neurons in motor and higher cortical areas. The rule governing the selector switch position could be dictated by networks in PPC, or from a top down signal.

Navigation

The issue of managing movement across multiple coordinate reference frames and making the appropriate transformations plays a key role in navigation, which requires understanding of the body in relationship to the world. Posterior parietal cortex is heavily interconnected with limbic structures (Cavada and Goldman-Rakic, 1989b) and is thus in a position to transmit information about body position in space to regions primarily involved in navigation. Neurons in parietal area 7a is sensitive to visual motion cues
conveyed by optic flow including speed, center of motion, and radial expansion and contraction (Read and Siegel, 1997; Phinney and Siegel, 2000; Merchant et al., 2001). In humans, evidence suggests that the posterior parietal cortex is involved in calculating a heading to the goal from the observer’s point of view (Spiers, 2007).

In some instances, visual cues may not be referenced to the body at all but may be entirely allocentric. Researchers have recently identified separate networks subserving allocentric vs. egocentric representations of space in humans. Task involving navigation through mazes or other complex scenes can invoke both of these points of reference. One EEG study conducted on humans navigating virtual tunnels identified two different groups of people that report the use of strategies employing the one or the other of two viewpoints to achieve the same objective. During the straight segments of the tunnels, activation was the same in the two groups, but once subjects started their turns, two separate underlying networks distinguished the strategies employed. Participants employing an egocentric (path integration) strategy activated posterior parietal and premotor regions, whereas those adopting an allocentric frame of reference (pilotage) activated primarily occipito-temporal structures (Gramann, 2006). The results of a functional MRI study revealed differential activation of similar networks when subjects switched backing and fourth between tasks that required locating an object in reference to themselves or to other objects. The core network recruited by both tasks included superior occipital gyrus, precuneus, and bilateral prefrontal cortex. When reporting object position in relation to oneself, in addition to the core network, medial superior posterior parietal lobe areas were preferentially activated. When an allocentric abstraction was required, the additional network modules that were recruited included right parietal
cortex, bilateral ventrolateral occipitotemporal cortex and bilateral hippocampus (Zaehle, 2007).

In another fMRI study investigating navigation ability in human subjects, task demands recruited parietal areas, but stronger activation in MT and precuneus was found in good navigators than in those who did not perform as well. Interestingly stronger activation in right superior parietal lobule was negatively correlated with task performance (Ohnishi et al., 2006).

**Visual Attention**

Visual attention can be thought of as the increased sensitivity of a neural system to specific visual features or locations. This bias is often related to expectation, as demonstrated by reaction time studies in which subjects detect a stimulus much faster when they are validly cued, meaning informed in advance where the stimulus will appear. Likewise, reaction times are markedly slower when subjects are invalidly cued, or told to direct their attention somewhere else (Posner et al., 1980). Interestingly, in humans this effect reverses from ~0.5 to 3 seconds, so that it actually takes longer to detect a stimulus in a cued location. This observation, termed inhibition of return (IOR), (Posner and Cohen, 1984; Posner et al., 1985) has been suggested as an inhibitory mechanism to prevent return to previously searched space (Posner MI, 1984; Klein, 1988) and for facilitating the search for novel stimuli in locations that have not recently been attended (Klein, 1988; Klein, 2000).
**Overt vs. covert attention**

Visual spatial attention is manifest in several forms. The term overt attention describes what, under typical interactions with the environment, is an unrestricted orientation to a location of interest. In some psychophysical studies, subjects may move their eyes or head to foveate an object in obvious manner. Covert attention, on the other hand, refers to the process of keeping eyes fixed on one location while actively monitoring another. Many behavioral tasks in which a physiological signal is being measured as in fMRI or single electrode recordings, are constructed around the latter because it removes the confound of neural activity related to motor movement.

**Exogenous and endogenous attention**

Attention can arise exogenously as a consequence of an external event that has immediate relevance, for example, the sudden appearance of a dangerous tiger. Exogenous attention can be thought of in terms of a bottom-up process, which involves a prevalent stimulus invoking a strong neural signal because of its salience, or the fact that it “pops out” from the background. Bottom-up processing in the visual system starts at the earliest stages, and it is now accepted that stimuli compete for neural resources through each successive level of the hierarchy, with the progression from small center-surround receptive fields in striate and early extrastriate cortices feeding forward to increasingly larger RFs in late visual and association areas (Luck et al., 1997; Chelazzi et al., 1998; Reynolds et al., 1999; Beck, 2007). Experimentally, exogenous attention is captured by a cue stimulus that appears in the same location of a probable upcoming target.
Attention may also arise endogenously as the result of an internally defined goal. If one is specifically hunting tigers, then being on the lookout for orange and black striped things will make items fitting that description get noticed first, possibly at the expense of more pressing stimuli such as the presence of an elephant about to charge. If it is known that tigers congregate in a certain area, then the hunter’s attention is directed there rather than to the nearby swamp where the elephant is. This is a top-down process, meaning that it requires an internally generated signal specifying what is being sought, or where it might be found. In the most basic sense, this signal allows the visual system to filter out features or locations that do not match those of the target (Treisman and Gelade, 1980; Treisman, 1988). To summon the endogenous attention of research subjects performing covert spatial attention tasks, a directional indicator collocated with the fixation point is often used. Areas within the same networks may be activated differentially as a function of exogenous vs. endogenous attention.

Most behavior in the natural environment is mediated by an interaction of both processes. Single electrode recordings in monkeys, as well as fMRI studies in humans show that allocation of attention to a particular location increases baseline activity of neurons representing the corresponding topographical region as early as areas V1-V4 (Kastner et al., 1999; Ogawa, 2004; Silver, 2007; Li et al., 2008). Furthermore, saliency relayed by purely bottom up mechanisms can be overridden by task demands (Einhauser, 2008) as in our tiger and elephant example. An interesting question then arises: at what point in the transversal through the visual processing to the higher cognition pathway does willful object selection emerge? Though the specific answer to that question is not yet known, Corbetta and Shulman have outlined what they call the two attention, latter
dual attention process (DAP) model in which there is an interaction between top-down attention mediated by dorsal fronto-parietal networks with bottom-up attention mediated by ventral frontal-temporoparietal network (Corbetta and Shulman, 2002).

Behavioral relevance of stimuli

While neurons in posterior parietal area 7a do respond to the appearance of salient objects purely because of their salience in monkeys passively viewing stimulus displays, (Constantinidis and Steinmetz, 2005), the same objects can elicit stronger responses when monkeys are trained to use them in a behavioral context. Constantinidis and Steinmetz conducted a set of experiments where monkeys were exogenously cued at the beginning of a trial to remember a particular location by the appearance of a visual stimulus there. To complete the trial successfully, subjects had to respond to the reappearance of the stimulus at the cued location and ignore physically identical intervening stimuli presented elsewhere (Constantinidis and Steinmetz, 2001a). These investigators showed that individual objects presented in a neuron’s receptive field elicit similar responses in both trained and naïve animals. The same objects viewed as pop-out targets within a stimulus array are less effective at driving neural responses in untrained monkeys, and do so following a slower time course. A non-salient array stimulus appearing in the receptive field has little effect in either case (Constantinidis and Steinmetz, 2001a, 2005). This consequence of training also has important implications in learning, as we shall note in a later section.

The different aspects of allocation, maintenance, disengagement and reorientation of visual attention may be encoded by separate neural sub-systems and activate different
areas within PPC. Recordings in monkey suggest that regions in the intraparietal sulcus are important for the allocation of attention, while 7a might be important in disengaging attention at one location and re-establishing it at another, (Constantinidis and Steinmetz, 2005). In support of this view, one fMRI study revealed that interparietal sulcus becomes active when attention is engaged, and that that the temporal parietal junction (TPJ), which is proposed to contain the analogue of area 7a in monkeys, is involved in reorienting attention when a novel stimulus appears somewhere other than the attended location (Corbetta et al., 2000). Analogous to the results described in monkey experiments for trained vs. untrained animals, human imaging studies have also demonstrate that stimuli inducing shifts in attention must be behaviorally relevant to activate TPJ (Kincade et al., 2005).

**Neural correlates of working memory**

The role of the PPC in working memory was first described utilizing electrophysiological recording techniques in monkeys. The bulk of these studies related to working memory have been conducted in areas LIP and 7a and these areas will be the basis of our discussion. The next sections briefly review the physiological and psychological literature on working memory and its correlates in posterior parietal neuronal activity.

**Characteristics of working memory**

Short-term memory, lasting for a period of a few seconds, was first addressed in primates by testing them in delayed response tasks. These types of tasks require subjects to remember a cued location or object in the absence of its continued physical presence for
short periods of time in order to receive a reward. Lesions to the prefrontal cortex produced deficits in performance (Jacobsen, 1936). Failure to perform the task in lesioned animals was attributed to a disruption in the ability to maintain an internalized representation of the cue and early investigators deduced that the anatomical correlate of this internalized representation must be localized in prefrontal cortex. Early neurophysiological studies provided neural correlates for such an internalized representation in the form of sustained discharges for neurons in the macaque prefrontal cortex and mediodorsal nucleus of the thalamus (Fuster and Alexander, 1971; Kubota and Niki, 1971). Fuster further described the attributes of this sustained activity as being dependent on goal-directed need to hold information in memory, not induced simply by reward expectancy, being correlated with ability to remember the information, and being susceptible to distracting influences (Fuster, 1973, 2003). Cells exhibiting working memory characteristics have subsequently been found distributed throughout many other areas including, inferotemporal cortex, somatosensory and posterior parietal cortices (Fuster and Jervey, 1981; Andersen et al., 1990b; Miller and Desimone, 1993; Constantinidis and Steinmetz, 1996).

The concept of working memory also emerged in the psychological literature (Pascual-Leone, 1970; Baddeley, 1974; Baddeley, 1986; Baddeley and Hitch, 2000). Working memory does not refer to a memory system that differs from that of short-term memory; the term rather emphasized that this type of memory does not function simply as a passive storage of information but it allows integration of remembered information with current contingencies and future goals. Recent models propose four subsystems of working memory, a “central executive,” responsible for controlling and coordinating
information through “slave” systems called the visual-spatial sketchpad for manipulation
of visual objects, the phonological loop for verbal rehearsal, and the latest addition, an
episodic buffer, that allows for temporal storage and binding of information within the
other subsidiary subsystems (Baddeley and Hitch, 2000). It should be made clear
however that these working memory subsystems refer to functional rather than
anatomical units. On the one hand, PFC has emerged in the literature as a logical
functional neural analogue to the central executive. Smith and Jonides identify selective
attention and task management as two of the main components of executive control and
cite examples of related activity in both prefrontal and anterior cingulated cortices
(Smith, 1999). Physiological evidence exits that subdivisions of PFC receiving
connections from differing cortical regions along the “what” and “where” pathway are
also specialized for these modalities in working memory processing (Goldman-Rakic,
1988). In another review of the neuroimaging literature, Smith and Jonides pinpoint left
posterior parietal, Broca’s, premotor and supplementary motor areas subserving verbal
aspects of working memory, and right posterior parietal, occipital and prefrontal regions
specific for spatial working memory; they further delineate these regions into storage and
rehearsal components (Smith, 1998). However, while it may be tempting to assign
specific executive, visuospatial, phonological, or episodic functions to exclusive cortical
areas, current physiological archetypes are drifting away from the idea that working
memory is mediated by a collection of independent buffers towards a more distributed
model of processing (Mesulam, 1990; Postle, 2006; Repovs, 2006; D'Esposito, 2007).
For example, Miller and Cohen assert that activity sustained in PFC may represent a
goal along with an associated plan of action, rather than a memory trace for a particular
item (Miller and Cohen, 2001). Cowan suggests that instead of being maintained in dedicated modality-specific buffers, information held in working memory is represented by the activity of those processes within the current focus of attention (Cowan, 1988, 1999). Along similar lines, it has been posited that working memory is an emergent property of cognition and the network of brain regions that mediate it (Hazy, 2006; Postle, 2006; D'Esposito, 2007).

**Neural mechanisms mediating working memory**

One obvious question is how might the neural activity seen in working memory networks be maintained during the representation of the memoranda. Computational models have been instructive in that respect and spiking neural network with recurrent connections have been shown to achieve a remarkably close approximation to actual neurons recorded in monkey cortex (Zipser, 1993). Reverberating activity within recurrent circuits is a characteristic of this type of architecture: pyramidal neurons form reciprocal, excitatory connections between them and transmit action potentials to each other, so that even when the original stimulus is no longer present, discharges continue to reverberate in the network. A critical property revealed by models is that discharges can be sustained if the postsynaptic neuron continues to be in an excited state at the time presynaptic inputs accumulate. Given the fairly low firing rate of cortical pyramidal neurons, postsynaptic receptors with fairly slow time constants are essential for this function. The NMDA receptor has therefore been proposed as a critical element of cortical circuits involved in working memory (Lisman et al., 1998). Reverberatory networks, when left unperturbed, will settle into an attractor state defined by a stereotyped pattern of activity within the
network (Hopfield, 1982). Attractor models may undergo spontaneous oscillations, although network instantiations have also been shown to be capable of mediating sustained responses without oscillatory discharges (Compte et al., 2000). These models emphasize the importance of spiking mechanisms as a means for the maintenance of working memory, however it is possible that intracellular and synaptic mechanisms may also play a role (Egorov et al., 2002; Mongillo et al., 2008).

*Posterior parietal contributions to working memory*

Although working memory has been traditionally associated with the prefrontal cortex and neural correlates of working memory where first described there, the posterior parietal cortex is closely associated with the prefrontal cortex via reciprocal connections and shares many of its functional properties. In fact, prefrontal and parietal regions are almost invariably activated simultaneously in human imaging studies of working memory (Jonides et al., 1993; Courtney et al., 1997; Owen et al., 1998; Ungerleider et al., 1998; Marshuetz et al., 2000; Bunge et al., 2001; Stern et al., 2001; Munk et al., 2002; Raye et al., 2002). A meta-analysis of imaging studies involving working memory tasks revealed that area 7 was reliably activated by all aspects of executive function examined (ordering, updating, and manipulating items held in working memory), as well as the spatial content of working memory (Wager and Smith, 2003).

Initial reports of working memory activity in the posterior parietal cortex described discharges in monkey area LIP that followed the offset of a visual stimulus which was to be a target for a planned eye movement (Gnadt and Andersen, 1988). Later studies in area 7a demonstrated that posterior parietal neurons represent the remembered
locations of visual stimuli, independent of a planned motor response (Constantinidis and Steinmetz, 1996). Activity of area 7a neurons was directionally tuned but independent of a directional motor movement, suggesting that the activity is indicative of a memory signal rather than a motor preparation signal. Two types of neural activity were revealed: The first was a sustained response during the delay period following a stimulus presentation that evoked a strong response. This activity remained elevated or gradually decreased until a stimulus at a new location was presented. The second type was an anticipatory response that was observed in some neurons as a ramping up of activity before a following stimulus, a type of activity also observed during the planning of a motor response (Quintana and Fuster, 1992).

The similarity in patterns of activity between prefrontal and parietal neurons was also confirmed by neurophysiological studies in monkeys. Virtually identical percentages of neurons exhibiting working memory responses were observed in parietal areas 7a and LIP and prefrontal areas 46 and FEF (Chafee and Goldman-Rakic, 1998). The importance in the interaction between the two areas was revealed by deactivation of either PPC or PFC by cortical cooling which was shown to produce a profound effect on the output of neurons in the other area (Chafee and Goldman-Rakic, 2000).

Despite these similarities between PPC and PFC, important differences have also emerged (Constantinidis and Procyk, 2004). Memory-related activity in the parietal cortex differs from the memory trace held in frontal cortical neurons in that it is disrupted by intervening, distracting stimuli (Constantinidis and Steinmetz, 1996). In contrast, frontal neurons continue to discharge even after the presentation of intervening stimuli, and continue to do so until the behaviorally relevant stimulus appears (di Pellegrino and
Wise, 1993; Miller et al., 1996). These results suggest that posterior parietal cortex encodes the memory of the last stimulus location. Prefrontal areas are critical for mental operations that span multiple items of a sequence of stimuli. This idea has been supported by human fMRI studies which revealed that prefrontal activation is critical for memory of sequences of items (Sakai et al., 2002). Similarly, right Transcranial Magnetic Stimulation (TMS) applied over both prefrontal and posterior parietal cortex during the delay phase of a spatial working memory task increased reaction times whereas TMS applied during the decision phase of the task disrupted performance only when applied over the prefrontal, but not PPC (Koch et al., 2005).

A series of recent imaging studies have indicated posterior parietal activation during recall of information from long-term memory Cabeza 2008, Cabeza et al, 2008, Wagner, 2005). Wagner and his coworkers put forward three hypotheses about episodic memory retrieval (Wagner et al, 2005): first, the parietal cortex may subserve attention to an internal representation, shifting, or maintaining attention on internally derived mnemonic representations; second, parietal cortex may function as a mnemonic accumulator such that memory strength signals are accrued until they reach a decision criterion; or third, the parietal cortex may provide a working memory buffer, holding a readily-accessible transient memory trace available to decision making processes analogous to the working memory buffers of Baddeley’s model (Baddeley, 1998). The first of these theories directly links attention to the memory retrieval process. An earlier model of attention processing, the dual attention process (DAP) hypothesis, proposes that there is an interaction in top-down attention mediated by dorsal fronto-parietal networks with bottom-up attention mediated by ventral frontal-temperoparietal networks (Corbetta
and Shulman, 2002). This idea has been expanded by Cabeza and to suggest that similar processes occur, not just for attention to external events, but also to internally derived memory of events (Cabeza, 2008, Cabeza et al, 2008). In this model, episodic memory deficits described in free recall tasks can be attributed to a failure of bottom up processes to capture attention, a phenomenon Carbeza calls memory neglect. Specific probe questions may provide top-down cues that induce patients to recall details that they would otherwise miss. He offers another possible explanation stemming from disruption in internal attention called “memory simultanagnosia” suggesting that the deficits observed in free episodic recall arise from an inability to pay attention to more than one memory at once (Cabeza 2008, Cabeza et al, 2008).

**Neural correlates of learning**

Learning encompasses cognitive phenomena that traditionally have also not been associated with the posterior parietal cortex. However, recent evidence suggests parietal involvement in a number of cognitive tasks that require or depend on learning. Even if it is not the sole brain area mediating these effects, the activity of prefrontal cortical neurons reflects learned tasks and associations.

**Human imaging studies**

As already discussed, working memory does not involve simple buffering of prior information, but relies on executive processes to organize, monitor, and use it. Information can be re-coded in a structured way to make it easier to remember and utilize in the course of ongoing operations – or for retrieval and use at any given time later on. A
strategy known as “chunking” (Miller, 1956) takes small pieces of information and combines them into meaningful groups that constitute larger, single units of information. This type of manipulation is used in reading, language acquisition and many types of expert learning e.g. chess (Gobet et al., 2001). In humans, the use of structured grouping strategies in working memory can help reduce the working memory load and allow far greater amounts of information to be retained simultaneously (Bor et al., 2003; Bor, 2004). When structured grouping is utilized during learning, both short- and long-term memory systems are engaged to add new information along previous learned patterns or paradigms. Organizational strategies that encode information, including chunking as well as more generalized grouping of information into organizational and spatial relational structures revealed involvement of both the prefrontal and posterior parietal cortex (Bor et al., 2003; Bor, 2004; Bor and Owen, 2007; Wendelken et al., 2008).

In addition to mediating some of the more complex forms of working memory utilized during generalized learning, posterior parietal cortex is also recognized for its role in motor learning and retrieval of acquired motor skills including highly developed, complex motor skills (Goodale and Milner, 1992; Gallese V, 1994; Rushworth et al., 1998; Haaland et al., 2000). Vingerhoets provided a compelling demonstration of the latter in an fMRI experiment where he presented human subjects with pictures of hand tools. Common or familiar tools, in comparison to ones with which the observer was unfamiliar or had little experience, elicited supramarginal and superior parietal lobule activation, consistent with the recall of motor programs for the use of the tool (Vingerhoets, 2008). A recent study demonstrated that training and execution of a visual motor task in humans engaged separate areas of posterior parietal areas for different
components of motor learning (Grafton et al., 2008). These investigators showed that acquisition of the ability to produce predictive feedforward commands in response to external input activated areas within the left supramarginal gyrus and intraparietal sulcus while response and modification of feedback control elements of the task produced bilateral activation in the superior parietal lobule and anterior intraparietal sulcus (Grafton et al., 2008).

Expert learning and the development of specific motor and tool-use skills rely upon building on knowledge gained from previous experience. These are not simply the result of transient organization of neural activity for the completion of a short-term goal nor are they limited to sequences of learned procedures to be applied in a stereotypic manner. Skills and knowledge can be built on over the course of a lifetime, and new approaches to old problems can emerge by the integration of previous experience into new behaviors.

Neurophysiological studies of learning in posterior parietal cortex

In recent years, neuronal activity in the monkey posterior parietal cortex has also been shown to depend on prior experience and training in a behavioral task. These studies provide insights on the neural correlates underlying learning. PPC neurons typically have low selectivity for color; only a small percentage of area 7a neurons demonstrate significantly different responses to green and red stimuli of equal luminance (Constantinidis and Steinmetz, 2001a). However when animals execute a behavioral task for which color is important because it signifies eye movements, a larger percentage of PPC neurons exhibit selectivity for the color of the stimuli (Toth and Assad, 2002).
Similarly, responses to visual stimuli can differ based on the sensorimotor association or rule that the monkey is trained to perform (Stoet and Snyder, 2004). In its simplest form, a rule can be explicitly stated about how a task is to be executed by a cue at the beginning of the trial or it can be implicitly deduced by the presence or lack of reinforcement in consequence to a given action. Behavior involving rule updating under changing task demands is known as set shifting and probably one of the most famous deficits observed is in frontal lobe patients is the inability to do this successfully. Human studies confirm that set shifting involves posterior parietal regions (Asari, 2005; Lie, 2006; Ng, 2007). These results suggest that learning the contingencies of a behavioral task can modify the responses of PPC neurons to identical stimuli.

A more fundamental effect of learning was revealed by comparing responses of PPC neurons in animals trained to perform a behavioral task (Constantinidis and Steinmetz, 2001a) with responses in animals naïve to behavioral training (Constantinidis and Steinmetz, 2005). These studies revealed that although the overall pattern of responses was similar, neuronal activity in monkeys trained to detect a salient stimulus in a visual display reflected the target faster, and produced a more discriminable level of activation. In an attempt to understand the underlying neural mechanisms mediating learning, a later study investigated the patterns of responses of neurons in the naïve and trained monkeys (Joelving et al., 2007). The results demonstrated that active attention and maintenance of a stimulus in working memory was characterized by distinct firing patterns, most notably a decrease in spectral power in the 5-10 Hz frequency range. These studies suggest that learning to perform a behavioral task has profound and enduring changes in neuronal processing.
Conclusions

The research reviewed here demonstrates that the primate PPC plays a central role in the mediation of cognitive functions, in agreement with the profound cognitive deficits following PPC lesions. More specifically, the activity of PPC neurons plays a role in the maintenance of working memory, at least for the most recent stimulus. Posterior parietal activity could provide a physiological correlate to the “visual-spatial sketchpad” in Allan Baddeley’s model of working memory by allowing for the manipulation of items held in working memory into larger organized structures. At the same time, PPC activity is modulated by experience and learning, contributing to the acquisition of new skills and rules. Neural correlates of learning are reflected in the activity of parietal neurons and performance of different tasks is critically dependant on PPC.

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CHAPTER II

COORDINATE FRAME OF ATTENTION IN PRIMATE POSTERIOR PARietAL CORTEX

Justin Rawley

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Justin Rawley performed the experiments and prepared the manuscript. Christos Constantinidis acted in an advisory and editorial capacity.
Abstract

The activity of neurons in the primate posterior parietal cortex (PPC) reflects the location of stimuli relative to the eye, body, and world, and is modulated by selective attention. It is not known however in what coordinate frame attention is represented itself. To address this question, we recorded neuronal activity from area 7a of monkeys trained to perform two variants of a delayed match-to-sample task. The monkeys attended to a spatial location defined in either spatiotopic (world-centered) or retinotopic (eye-centered) coordinates. Neural responses in the task were typically enhanced for a match stimulus, allowing us to determine the coordinate frame of the attentional enhancement. Our results revealed that representation of attention in spatiotopic coordinates was dominant overall, although the task also influenced the coordinate frame. Our results offer insights on the nature of deficits following damage to a posterior parietal area homologous to human areas implicated in neglect.
Introduction

The posterior parietal cortex of humans and other primates plays a critical role in representing visual-spatial relationships and mediating spatial attention (Constantinidis, 2006b; Goldberg et al., 2006). One of the most striking conditions that follows posterior parietal damage, typically of the right hemisphere in humans, is known as neglect (Mesulam, 1999). Neglect patients are unable to perceive sensory stimuli on the side contralateral to the lesion, (egocentric neglect) and/or to process the contralateral side of objects even if they appear in their ipsilateral field of view (allocentric neglect).

Neurophysiological studies in primates have revealed that posterior parietal neurons are modulated powerfully by selective attention, including bottom-up and top-down attention (Gottlieb et al., 1998; Constantinidis and Steinmetz, 2001a; Bisley and Goldberg, 2003; Buschman and Miller, 2007). They are also modulated by the angle of gaze (position of the eyes in the orbit or rotation of the head), which allows the neural population to represent information about the position of the stimulus in multiple coordinate frames, e.g. relative to the eyes, head, or body (Andersen et al., 1985; Snyder et al., 1998; Pouget and Snyder, 2000).

Despite these research findings, the coordinate frame of attention itself has not been determined until now. In particular, it is not known whether posterior parietal neurons represent the locus of attention in retinal coordinates, or relative to an object, which may appear at different positions on the retina. In order to investigate this question, we recorded activity in monkey posterior parietal area 7a. Area 7a comprises the end-stage of the dorsal visual pathway, which puts it in a key position to process information about location and spatial relationships of stimuli in the visual field (Felleman and Van
Essen, 1991). Although the homology of human and monkey parietal areas is not entirely clear, area 7a appears to be most similar to human areas 39/40 which include the temporal-parietal junction (TPJ) in humans (Vincent et al., 2007; Buckner et al., 2008). This region of the human parietal cortex is often referred to as the “ventral attention system”, and has specifically been implicated in allocentric neglect (Karnath et al., 2001; Hillis et al., 2005; Corbetta et al., 2008; Medina et al., 2008). Understanding how neurons represent the locus of attention in this area is essential for uncovering the nature of perceptual deficits in neglect.

Previous neurophysiological studies in area 7a have demonstrated robust effects of directed attention (Steinmetz et al., 1994; Steinmetz and Constantinidis, 1995; Constantinidis and Steinmetz, 2001a, b, 2005; Raffi and Siegel, 2005). In the present experiment, we relied on a paradigm that has been used extensively in the study of attentional effects in area 7a: a spatial version of a delayed-match-to sample task. In order to perform the task, monkeys are required to attend to and remember the location of a visual cue appearing on a screen, ignore stimuli appearing elsewhere, and release a lever to indicate appearance of a stimulus at the attended location. In this task, individual neurons respond with significantly different responses to the same stimulus depending on whether it appears in or out of the locus of attention. We exploited this property in order to test how neuronal responses are represented when visual stimuli appear in either the same retinal coordinates (retinotopic frame), or the same coordinates on the screen (spatiotopic frame).
Results

Data from a total of 210 neurons in posterior parietal cortical area 7a were collected from two monkeys trained to perform the delayed match to sample task. In the basic task, the monkeys were required to maintain fixation on the center of the screen, observe and remember the position of a cue stimulus, ignore intervening stimuli appearing at different locations, and release a lever after a stimulus that appeared at the same location as the cue (Fig. 1A). We used two additional variants of this task to probe the influence of coordinate frame of attention on the responses of parietal neurons. In the first variant, subjects had to respond when a stimulus appeared at a location that matched the position of the cue on the screen, while the fixation angle might change during the trial (Fig. 1B). In the second task, animals had to report when a stimulus matched the cue in terms of its position on the retina, which might now correspond to a different location on the screen (Fig. 1C). We refer to these tasks as “Screen Match” and “Retinal Match,” respectively (Supplementary Fig. 1). Data from these latter 2 tasks are reported in this study.

Recordings were performed in posterior parietal area 7a, on the crown of the gyrus bounded by the intraparietal and superior temporal sulci (Supplementary Fig. 2). A total of 72 visually responsive neurons were tested in their receptive field with the Screen Match task and 138 with the Retinal Match task. Monkeys were initially trained to execute the Screen Match task and neurophysiological data were collected. The same animals were subsequently retrained on the Retinal Match task and a second round of recording was conducted.

Our analysis of neural responses first sought to determine whether neurons in area 7a responded differently to identical stimulus presentations, depending on the locus and
Figure 1. The behavioral tasks

(A) Example trial in the spatial delayed-match-to-sample task (basic task). Frames represent successive stimulus presentations. The monkeys were required to pull back a lever in order to initiate a trial, to ignore a pseudo-random number of nonmatch stimulus presentations appearing at different locations and to release the lever after the offset of a match stimulus.

(B) Possible positions where the fixation target (black dot) and stimuli (gray squares) could appear on the screen, in the basic task.

(C) Example trial from the Screen Match task. The fixation point could now move after the presentation of the cue and the monkey was required to remember the location of the cue in screen coordinates and to release a lever when a subsequent stimulus appeared at the same screen location.

(D) Example trial from the Retinal Match task. The monkey was required to remember the location of the cue in retinal coordinates (relative to the fixation point) and to release a lever after a match stimulus appeared at the same retinal location.

(E) Possible locations of the fixation target (black dots) and stimuli (gray squares) in the Screen and Retinal Match tasks.
Figure 1.

A. Spatial Delayed Match to Sample Task

B. Screen Match Task

C. Retinal Match Task

D.  

E.  

1.5°
coordinate frame of the match. Modulation of mean firing rate to a stimulus presentation depending on the locus of attention has been described in previous studies, most prominently showing a reduced responsiveness to a stimulus when it constitutes a match compared to the same stimulus appearing as a nonmatch (Steinmetz et al., 1994). We similarly identified neurons with significantly different mean firing rates to presentation of the stimulus in the receptive field, when it represented a match or nonmatch stimulus, and when it appeared in the same screen or retinal coordinates as the preceding cue (Supplementary Fig. 1). A total of 35 neurons displayed significant modulation to these stimulus conditions (ANOVA, p< 0.05). We refer to these neurons as “Attention Selective”. We were surprised to discover that the majority of Attention Selective neurons (21/35) exhibited a stronger response to a stimulus appearing as a fixed match (with no movement of the fixation point) than the same stimulus appearing as a fixed nonmatch. Responses from a representative neuron are shown in Fig. 2. This neuron responded more strongly to a match stimulus (Fig. 2A) than to the identical stimulus appearing as a nonmatch (Fig. 2B). When we examined this neuron’s responses to a stimulus appearing at the same screen position as the cue (Fig. 2C) we determined that the neuron responded better to this screen match compared to a stimulus appearing at the same retinal coordinates as the cue (Fig. 2D). This response was specifically related to the stimulus presentation rather than nonspecific factors like the release of the lever or the anticipation of reward that followed a match presentation; no responses were elicited after presentation of a match stimulus out of the receptive field (Fig. 2E). This result was representative of our sample (Supplementary Fig. 2 left). Specifically, 17/21 (81%) of Attention Selective neurons with higher responses for a fixed match stimulus also
Figure 2. Example neuron in Screen Match Task

Histograms and rasters are shown of one area 7a neuron recorded while the subject performed the Screen Match task. The cue and 2nd Stimulus (test stimulus) are shown in each condition. Note that the test stimulus is identical in panels A-D and appears inside the neuron’s receptive field and under gaze directed to the center of the screen. Trials from all stimulus types were randomly interleaved, including trials where the second stimulus appeared out of the receptive field (not shown – see supplementary Figure 1 for complete description).

(A) Fixed Match stimulus. This neuron responded well to the test stimulus appearing in the same location as the cue, when the fixation point remained stationary in the center of the screen.

(B) Fixed Nonmatch stimulus elicited virtually no response. Additional stimuli followed in these trials (not shown).

(C) Strong response to the Screen Match stimulus which was a behavioral match in this task.

(D) A retinal match stimulus (which was a behavioral nonmatch in this task) elicited a poor response. Additional stimuli followed in these trials (not shown).

(E) No response was observed for presentation of a match stimulus out of the receptive field, providing evidence that the preference of the neuron for a behavioral match was not due to non-specific factors such as the preparation for a level release or anticipation of reward.
Figure 2.
responded best for a Screen Match (which was a behavioral match stimulus requiring a lever release in this task) over a Retinal Match stimulus.

The preference for a screen match over a retinal match among neurons with higher responses to a fixed match stimulus over a fixed nonmatch was also evident in the population peri-stimulus time histogram (Fig. 3A-B). The mean firing rate during the presentation of the screen match stimulus was significantly higher than the response to the retinal match for this population of neurons (t-test, p<0.05). This analysis also revealed that activity following cue presentation in the receptive field was sustained during the delay period, while the monkey presumably remembered and attended the cued location (Fig 3A-B). Subsequent appearance of a fixed match or screen match produced an elevated response over a fixed nonmatch or retinal match stimulus.

To determine if a neuron’s preference for a screen match vs. retinal match could be determined from its preference for a fixed match vs. fixed nonmatch, we plotted the difference in responses for these two pairs of conditions (Fig. 4). A regression analysis revealed that there was a significant relationship between the two measures (p<0.005). In other words, the difference in firing rate between a match and nonmatch stimulus could predict the difference in responses to a screen match vs. a non-screen match on a neuron by neuron basis. Most of the points in Fig. 4 fell in the lower right quadrant, confirming that responses were higher for both the fixed match stimulus and the screen match stimulus, which in this task constituted the behaviorally relevant match.

Similarly, neuronal preference for a match over a nonmatch stimulus remained unchanged when additional stimuli appeared between the cue and match (Fig. 5). Mean discharge rates to a match stimulus appearing immediately after the cue, and after two
Figure 3. Population responses of Match-preferring neurons

Peri-Stimulus Time Histograms (PSTHs) for the population of neurons with higher mean responses for a Fixed Match over a Fixed Nonmatch stimulus. Insets to the right of each panel represent condition averaged by each trace. The location of the stimulus (black square) relative to the receptive field (arc) is depicted schematically; these differed for each neuron included in the PSTH average. Left column (A, B) represents responses from the Screen Match Task, Right column (C, D) from the Retinal Match Task. Top row (A, C) represents neuronal responses under no fixation movement (fixed match and fixed nonmatch presentation). Bottom row represents neuronal responses with a moving fixation (screen match and retinal match).
Figure 3.
**Figure 4.** Relationship between Match and Nonmatch responses

Scatter plots of the difference in firing rate between the Fixed Match – Fixed Nonmatch responses plotted against the difference between the Screen Match – Retinal Match responses. Each dot represents one Attention Selective neuron. Points falling along the diagonal indicate neurons with identical difference of responses to the two conditions. Top panel depicts the set of all Attention Selective neurons in both tasks while the bottom panel illustrates a subset of neurons recorded during sessions that are matched across tasks for accuracy of behavioral performance (see text).
Figure 4. Relationship between Match and Nonmatch responses
Figure 5. Responses to Immediate and Late Match stimuli

Scatter plots of mean responses to a Match stimulus appearing after two intervening nonmatch stimuli (Late Match) vs. a Match stimulus appearing immediately after the cue (Immediate Match). Each dot represents one Attention Selective neuron. Points falling on the diagonal represent neurons with identical responses to the two conditions.
intervening stimuli were significantly correlated ($r=0.85$, $p<0.005$). A significant relationship between the difference between a match and nonmatch response was also present ($r=0.69$, $p<0.005$), when the stimulus appeared immediately after the cue and after two intervening stimuli (Supplemental Fig. 5). Overall, our findings from experiments in the Screen Match task indicate that individual neurons had a set magnitude of response for stimuli that signified a behavioral match vs. a nonmatch and this relationship was reliable across task conditions.

These results could mean that neurons in area 7a of the posterior parietal cortex represent attentional effects in screen coordinates. However, they could also be a consequence of the behavioral paradigm that required the monkey to respond to a stimulus matching the cue in screen coordinates. In order to distinguish between these two possibilities, we tested the same two monkeys in a task that required them now to respond to a stimulus that constituted a match in retinal coordinates (Figure 2B). We also sought to determine whether increased responsiveness to the match was specifically dependant on the screen-match paradigm, in contrast to the decreased responses to the match stimulus observed in previous studies (Steinmetz and Constantinidis, 1995; Constantinidis and Steinmetz, 2001b).

After retraining the same animals, we recorded from a total of 138 neurons in the Retinal Match task. Of those, 46 neurons responded differentially to an identical stimulus in their receptive field, depending on the preceding cue (ANOVA, $p<0.05$). Figure 6 depicts the responses of a neuron tested with the Retinal Match task. As in the two previous examples recorded during the Screen Match Task, we saw enhanced responses to the behavioral match (Fig. 6A). Across the population of neurons, 28/46 (61%)
**Figure 6.** Example neuron in Retinal Match Task

Histograms and rasters for an example neuron recorded while the subject was engaged in the Retinal Match task. Conventions are the same as in Figure 2.

(A) Match stimulus presentation in the receptive field elicited a strong response.

(B) Nonmatch stimulus presentation in the receptive field elicited a weaker response.

(C) The neuron responded well to a screen match, although this was no longer a behavioral match in this task (did not require a lever release).

(D) The neuron responded poorly to a retinal match, although this was a behavioral match.

(E) The neuron did not respond to a match stimulus out of the receptive field.
Figure 6.
exhibited a stronger response to a match than a nonmatch stimulus in the non-moving fixation condition. This result essentially replicated our findings from the Screen Match task, and stood in contrast with the previous studies mentioned earlier, where the typical effect was overwhelming suppression of match responses. An overall preference for the match stimulus was observed in both of our monkeys; 63% and 52% of attention selective neurons responded better to the match over the nonmatch stimulus, respectively (pooled across both tasks). As we have done for the previous data set, we compared responses to the match stimulus when it appeared immediately after the cue and when it appeared after two intervening stimuli during trials in which the fixation did not move. The graph at the right of Fig. 5 shows that responses were again strongly correlated (r=0.82, p<0.005). The difference in firing rate between match and nonmatch stimuli was also significantly correlated (Supplementary Fig. 5), for stimuli appearing immediately after the cue vs. stimuli appearing after two intervening stimuli (r=0.76, p<0.005). These results confirmed that after training in the Retinal Match task, area 7a neurons still had an overall preference for a match over a nonmatch stimulus, and that this preference was reliable, regardless of intervening stimulation.

When we compared the retinal match vs. screen match conditions, we now saw mixed responses in the Retinal Match task (Supplementary Fig. 3). Among neurons that responded best to the fixed match, approximately equal numbers of neurons also responded best to the screen match (now a behavioral nonmatch) or the retinal match (12 vs. 16 neurons, respectively). An example of the first type of neuron is shown in Fig. 6D; of the second type, in Supplementary Fig. 4. This result stood in contrast with the behavior of neurons in the Screen Match, which was skewed towards the screen match.
The difference between the two distributions was statistically significant ($\chi^2$-test, $p<0.05$). By examining results on a neuron-by-neuron basis, we found that the difference between the match and nonmatch stimulus was still significantly correlated ($r=0.32$, $p<0.05$) with the difference between the retinal- and screen-match stimulus (Figure 4), although the slope of the regression was now less steep. This result indicates that the preference of area 7a neurons for a fixed match over a nonmatch remained predictive of the difference in firing rate for a screen match stimulus over a retinal match stimulus, even though the behavioral significance of the latter two stimuli was now reversed. However, neurons were now more evenly distributed in their overall preference for a screen or retinal match (around the horizontal axis). This mixed response to the two conditions was also evident in the population PSTH (Fig. 3D); There was no overall significant difference between the retinal match and the screen match.

Behavioral performance was slightly lower in the Retinal Task (see Supplementary Data), therefore we wanted to ensure that this attentional modulation of responses by the screen stimulus was not the result of the monkeys’ confusion in the task and habitual responses towards the screen match stimulus, as if it still were a behavioral match. In order to exclude this possibility, we selected a subset of sessions from the Screen and Retinal Match tasks that were closest in behavioral performance; we excluded the sessions with the highest performance rate from the Screen Match task and lowest performance rate from the Retinal Match task, and then paired each Screen Match session with the Retinal Match session that was closest in performance with it. Average performance was 81.1% in the Screen Match and 81.2% in the Retinal Match for this set of sessions. We then repeated the regression analysis of Figure 4 for the 23 neurons
recorded in the Screen Task and 20 neurons recorded in the Retinal Task in the performance-matched sessions. This analysis confirmed that the difference between fixed match and nonmatch was positively correlated with the difference between retinal and screen match, in both the Screen Match and Retinal Match tasks ($p<0.05$ in both cases). Furthermore, the slope of the regression was still steeper for the Screen Match ($\alpha=0.76$) than the Retinal Match task ($\alpha=0.58$). This result revealed that attentional modulation was still encoded in screen coordinates in the Retinal Match task and that this effect was not an artifact of difference in performance. Overall, our findings show that the representation of attention in neural activity was somewhat plastic depending on the task requirements; however, the frame of attention in screen coordinates remained dominant in area 7a.

Discussion

We have recorded neuronal activity in area 7a of the Posterior Parietal Cortex while monkeys performed two variants of a spatial delayed match to sample task. Previous studies have shown that neural responses to a visual stimulus are modulated depending on whether it appears at an attended or unattended location and we confirmed this in our study, with most neurons responding best to a stimulus appearing at an attended location. We exploited this phenomenon to determine whether attentional modulation is represented in retinal or screen coordinates. Our results revealed that attentional modulation in screen coordinates is dominant, although the relative proportion of neurons modulated by attention is affected by training and task demands.
*Match vs. Nonmatch responses*

A preference for the match stimulus was observed among the neurons in our sample, across both tasks (60% in the Screen Match task, 61% in the Retinal Match) and in both monkeys (63% and 52%, respectively). Responses to match and nonmatch stimuli were reliable in our task, with consistent preference for the match regardless of whether additional stimuli intervened between cue and match (Fig. 5 and Supplementary Fig. 4). These results stand in stark contrast with previous studies that indicated an overwhelming reduction of match over nonmatch responses in area 7a. Steinmetz et al. (1994) reported that among the 60% of neurons in three monkeys that were significantly modulated by attention, 92% showed a decreased response to the match, and only 8% of neurons showing an increased response. A second study in two different monkeys with a task that involved multiple-stimulus displays indicated that among the 55% of neurons significantly modulated by attention, 95% exhibited decreased and 5% increased match responses (Constantinidis and Steinmetz, 2001b). Similarly, overall decreased responses to a stimulus appearing at an attended location were observed in posterior parietal area LIP and in the context of other behavioral tasks (Robinson et al., 1995; Powell and Goldberg, 2000).

A possible explanation for this discrepancy comes from analogous experiments in the inferior temporal (IT) cortex. Neuronal responses in a delayed match-to-sample task that required monkeys to remember the features of stimuli revealed decreased responses to match over nonmatch stimuli (Miller et al., 1991, 1993). When animals were tested with stimulus sequences which included repeated nonmatch stimuli (A-B-B-A sequences), IT responses for the repeated nonmatch were also diminished (Miller and
Desimone, 1994). Furthermore, monkeys tested in this paradigm initially responded incorrectly to the second nonmatch presentation (they treated it as a match), and required extensive re-training in order to perform the task. At the end of this retraining period, preference to a match over a nonmatch stimulus had reversed, with enhanced responses observed in most IT neurons (Miller and Desimone, 1994). Our results appear to be similar to that effect. Our monkeys were first trained in the Screen Match task, in which they were required to perform an eye movement and ignore a stimulus that appeared at the same retinal location as the cue. This requirement to ignore stimuli appearing at a repeated location on the retina seems as a likely cause of enhanced match responses.

Coordinate Reference Frames

Regardless of the sign of the difference between match and nonmatch responses, the preference for one or the other allowed us to determine whether neurons are modulated by stimuli appearing at the same screen or retinal location. During execution of the Screen Match task, a large majority of neurons with preference for the fixed match stimulus (81%) also responded best for a stimulus that appeared at the same screen coordinates as the cue. A significant correlation was present between the difference of fixed match vs. nonmatch responses and the difference of screen vs. retinal match responses (Fig. 4). Hence, neurons that responded differentially to a stimulus depending on whether it appeared within the locus of attention or not exhibited the same modulation for stimuli appearing at a matching location in a screen-centered reference frame. To test whether this attentional modulation in screen coordinates was simply a consequence of the task that required a response to the screen match stimulus, we retrained the same
animals in the Retinal Match task. A significant correlation was still present between
match-nonmatch and screen-retinal match responses (Fig. 4B). This finding indicates that
overall, neuronal responses continued to be modulated by the locus of attention in screen
coordinates.

An important caveat for the interpretation of the frame of attention is that the
monkey’s head was fixed during the experiments. In that sense, attentional modulation
might be in head- or body-centered coordinates rather than allocentric (world)
coordinates. Previous experiments have shown that stimulus location in area 7a is at least
partially encoded in world-centered coordinates, unlike responses in neighboring area
LIP, where position signals are represented predominantly in body-centered coordinates
(Snyder et al., 1998). It remains to be seen whether attentional modulation shows a
similar dichotomy as well.

Eye Movements

Our paradigm relied on an eye movement to shift the locus of attention in each trial. The
observed responses might in principle be related to the eye movement. This is unlikely
for several reasons. Unlike area LIP, neurons in area 7a are weakly modulated by eye
movements (Blatt et al., 1990). In any case, eye movements in our experiment were
directed from outside the receptive field, so as to bring a stimulus into the receptive field
after the saccade (see Fig. 2, 6). Finally, all responses examined were obtained from a
time interval at least 50 ms after the offset of the saccade.

A related caveat is that receptive fields of Posterior Parietal neurons (at least in
area LIP) appear to move prior to the actual eye movement, so that neurons respond to
visual stimuli appearing at retinal locations that will fall in the receptive field after the saccade (Duhamel et al., 1992). This is not an issue in our experiment, either. No stimuli were displayed until the monkeys had already completed their saccade and maintained fixation at the new target for at least 50 ms (typically ~200 ms).

**Implications for Neglect**

Our results shed light on the consequences of parietal lesions and the nature of neglect. We show that area 7a neurons represent an attended location primarily in screen-centered coordinates. Such a signal may be necessary for directing attention to a part of an object, regardless of its position on the retina. Conversely, loss of such a signal due to parietal injury may be responsible for the inability to shift attention to a part of an object, even when the entire object appears in the same side as the lesion (Pouget and Sejnowski, 2001). This is the hallmark of allocentric neglect, a condition that has been specifically associated with injury of the Temporal-Parietal Junction (Karnath et al., 2001; Hillis et al., 2005; Medina et al., 2008). This area is part of the “ventral” attention system in the human (Corbetta and Shulman, 2002; Corbetta et al., 2008). Recent anatomical work investigating the default network in humans and monkeys has suggested that monkey area 7a is homologous to this region, in agreement with previously known anatomical and physiological homologies (Vincent et al., 2007; Buckner et al., 2008). As discussed above, our experimental design did not distinguish between an object-centered coordinate frame and a coordinate frame that remains anchored to the body. However, symptoms attributed to allocentric neglect are not typically contrasted with a body-centered coordinate frame either.
We do not wish to suggest that the representation of the locus of attention in screen-centered coordinates is a generalized property across all areas of the visual system. As alluded to earlier, damage to other parts of the right parietal lobe can produce egocentric neglect, with loss of sensitivity to stimuli appearing in the left hemifield of vision (Hillis et al., 2005). In fact, a recent psychophysical study concluded that reaction times of humans after an eye movement are fastest when attention is directed to a location matching a cue in retinotopic rather than spatiotopic coordinates (Golomb et al., 2008). Our results only speak to area 7a, which represents the end-stage of the dorsal visual stream and exhibits long response latencies; it is entirely consistent with our findings that behavior is initially guided by retinotopic attentional effects, and effects in spatiotopic coordinates emerge later in time.

**Task effects**

Although we have emphasized the overall dominance of screen-centered attentional modulation in both versions of our behavioral paradigm, it is important to point out that significant changes were also evident between tasks. Overall, a significantly smaller percentage of neurons displayed attentional modulation in the Retinal Match than the Screen Match task ($\chi^2$-test, $p<0.05$), and a larger percentage of neurons responded best to the retinal match stimulus when that was the behavioral match ($\chi^2$-test, $p<0.05$). Previous studies have shown the responses of area 7a neurons to visual stimuli that capture attention differ depending on what task the animals have been trained to perform (Constantinidis and Steinmetz, 2005). Additionally, modulation of responses of the same neurons has been previously reported in area LIP depending on task rule and type of
motor response required (Snyder et al., 1997; Stoet and Snyder, 2004). Our current experiments extend these findings by showing that the modulation of neuronal responses by the locus of attention is plastic, and does depend on the nature of the task performed.

**Experimental Procedures**

Two male macaque monkeys (*Macaca mulatta*) weighing between 5 – 7 kilograms were trained in the behavioral tasks described below. Neurophysiological recordings were made in area 7a of the posterior parietal cortex. All experiments were performed in accordance with guidelines set forth by the National Institutes of Health, reviewed and approved by the Institutional Animal Care and Use Committee of the Wake Forest University.

**Behavioral Task**

Subjects were seated in a purpose-built primate chair with their heads fixed while they viewed stimuli displayed on a monitor 60 cm in front of them. They performed a variant of a spatial delayed match to sample task: During each trial they were required to remember the location of the first stimulus presented briefly on the screen as a cue, then report when they saw the stimulus reappear at the same location as a match while ignoring any intervening nonmatch stimuli that appeared at different locations (Figure 1). A pseudo-random number of zero, one, or two nonmatch stimuli could be presented before the match. The monkeys were required to perform this task while maintaining fixation of a 0.2° fixation point throughout the trial which appeared prior to the presentation of the cue. Eye position was monitored on line and trials were terminated if
eye position deviated from a 2° window. The animals had to pull a behavioral control lever to start each trial and release this lever to signal a match stimulus. In some trial types, the fixation point appeared at an eccentric location (10 degrees peripheral to the center in one of the cardinal directions). In these trials, 500 ms after the cue presentation, the fixation point moved to the center of the screen. Subjects were required to shift their gaze within 450 milliseconds to acquire the new, central fixation point. The interval between the cue and the second stimulus was always one second, even when the fixation did not move. All other stimuli were separated by 500 ms delay periods. Subjects were required to wait during the presentation of the match, then had 500 milliseconds to react to its disappearance by releasing the lever to receive a drop of liquid reward and hear a tone confirming correct execution. Early lever release constituted an error and aborted the trial. An infrared eye tracking system (model RK-716, ISCAN, Burlington, MA) monitored eye position to within a 0.3 degree resolution around the center of vision. All eye data were sampled, digitized and recorded at 240 Hz. Subjects did not receive a reward on error trials, but instead heard one of two feedback tones indicating the type or error (incorrectly timed lever release, or gaze deviation from the fixation window).

Stimuli consisted of 1.5° red or green squares. Stimuli of the same color were always used to test each neuron. Stimulus locations were constrained to a 5 x 5 grid centered in the monitor of equally spaced 10 degree increments (corner locations were not used). Software developed in the laboratory using Matlab (Mathworks, Natick, MA) and psychophysics toolbox (Brainard, 1997) controlled visual stimulus display, synchronized behavioral with physiological data, and verified the lever and eye position online during trial execution (Meyer and Constantinidis, 2005).
Two variants of the task were used to collect the experimental data described here. Initially subjects were trained to report appearance of a match stimulus at the same location on the screen as the cue. A set of neurophysiological recordings was performed in each monkey. The animals were subsequently re-trained over a period of several months in a second task in which they had to report appearance of a match stimulus at the same retinal coordinates as the cue. For example, if the fixation moved by 10 degrees in any direction, the match moved relative to the cue by 10 degrees in the same direction (retinocentric coordinates). A second set of neurophysiological recordings was then obtained from each monkey. We refer to these paradigms as the Screen Match and Retinal Match task, respectively.

During recording sessions, we first determined the location of neuronal receptive fields by performing a match-to-sample task with a stationary fixation point (Figure 1A). In this paradigm, the fixation point stayed in the center throughout each trial and stimulus locations were constrained within 10° of the center of the screen (Figure 1D; same as inner 3 x 3 grid in Figure 1E). Nine randomly interleaved trial types showed the cue/match stimulus in each of the nine grid positions to determine the locations in which neurons responded optimally to stimulus appearance. The number of intervening nonmatch stimuli between the cue and match varied pseudo-randomly to prevent monkeys from associating a particular location with a specific number of nonmatch stimuli. Once the receptive field of the neuron was determined, we tested neurons with the screen or retinal match paradigm, placing the stimuli of interest at the neuron’s receptive field and its diametric location. In the case of simultaneous recordings from
more than one visually-responsive neuron, the test stimulus was placed in the receptive field of the most responsive neuron.

The Screen Match and Retinal Match sets consisted of trials representing 10 conditions, the first five of which always displayed the second stimulus (first stimulus after the cue) in the neuron’s receptive field. Conditions tested were broken down into the following five trial types in which the second stimulus could be: 1) absolute match to the cue with stationary fixation (fixed match), 2) match in retinal coordinates (retinal match), 3) match in screen coordinates (screen match), 4) nonmatch with stationary fixation (fixed nonmatch), 5) nonmatch with moving fixation. The difference between the Screen Match and Retinal Match versions of the task is that in the Screen Match task, the test stimulus in trial type 3 is the behavioral match to which the animal responds, whereas in trial type 2, the second stimulus is a behavioral nonmatch and the animal must wait for an additional stimulus to appear in the original screen location of the cue (Figures 1 and 2). Trial types 6-10 are the mirror opposites of 1-5 and were included so that the subject would not be able to anticipate the location of the stimuli. Because the fixation point is always in the center of the screen before the onset of the second stimulus, the latter always falls within the central 3 x 3 grid. In this manner, the neuron’s response to a stimulus in the receptive field could be measured under different operant conditions in which the stimulus dictated action or was to be ignored. Trials were randomly interleaved in blocks such that, within each block, each trial type was represented and appeared only once. Typically ten repetitions of each trial type were shown to the subject during neurophysiological recordings.
**Surgery and Recording**

Once the subjects could perform the Screen Match task proficiently, an anatomical MRI was done to determine the stereotaxic coordinates of posterior parietal area 7a (Supplementary Figure 2). A 20 mm diameter craniotomy was then made over the region and a recording cylinder implanted over it. Extracellular recordings were made using up to 4 electrodes spaced 0.2-1.5 mm apart. Electrodes could be advanced independently through the dura and into the cortex using an electronic microdrive system (EPS micodrive, Alpha-Omega Engineering, Nazareth, Israel). Signals isolated by each electrode were amplified, band pass filtered between 500 Hz and 10 KHz, then sampled at 40 kHz, and digitized. A 1.75 ms sample was captured around each action potential and recorded for off-line analysis.

**Data Analysis**

We implemented the automated clustering algorithm KlustaKwik (Harris et al., 2000) in Matlab to separate recorded waveforms into signals from individual neurons. Groupings were made on the basis of pre-defined user features such as the peak, valley, and first principle component of each waveform. Spike trains were constructed for each neuron using the timestamps of the peak of each waveform associated with the neuron, and then average firing rates were computed for each task epoch. First, visually responsive neurons were identified by comparing discharge rate during visual stimulation in any task to the baseline firing rate recorded within the 500 milliseconds preceding the cue. Those neurons that showed significant rate elevation during the presentation of any stimulus (paired t-test, p <0.05) were included in the analysis. Since recording sessions were
performed from multiple electrodes monitoring several neurons at once we excluded recordings in which a significant effect of trial presentation sequence was evident in the baseline firing rate (ANOVA, p<0.05), e.g. due to a neuron disappearing or appearing during recording. Data from these sessions were truncated so that analysis was performed on a range of trials with stable firing rate. A spike density function was then obtained by convolving the spike trains with a Gaussian kernel function of 10 ms standard deviation, producing a smoothed and continuous function. All further analysis was performed on firing rates computed based on these spike density functions.

To test if a neuron’s response to visual stimulation in the receptive field varied depending on task condition, a 1-way ANOVA test was performed comparing firing rates during the presentation of the second stimulus in the receptive field. Neurons with significant effects ($p < 0.05$) were considered to be modulated by the locus of attention. We refer to these neurons as “Attention Selective”. Population responses in both tasks were evaluated using Peri-Stimulus Time Histograms (PSTHs) constructed from the mean firing rates of multiple neurons. PSTHs span the epochs before the presentation of the fixation through the delay after the second stimulus. We compared responses to match and nonmatch stimuli in trials where the fixation point did not move, and retinal- and screen-match responses. A linear regression analysis was performed to test the relationship between firing rates of each neuron in the match and nonmatch conditions.
Acknowledgments

This work was supported in part by NIH grant EY16773 and the Whitehall Foundation.

We wish to thank Rob West and Keith Roberts for technical contributions to the experiments, Travis Meyer for essential help in implementing the behavioral control system, and Emilio Salinas for his comments on the manuscript.
References


**Supplemental Data**

**Recording Apparatus**

Extracellular recordings were made using up to 4 electrodes spaced 0.2-1.5 mm apart. Electrodes could be advanced independently through the dura and into the cortex using an electronic microdrive system (EPS microdrive, Alpha-Omega Engineering, Nazareth, Israel). Electrodes moved within stainless steel guide tubes that were placed onto the dura with a mechanically driven microdrive (FHC, Bowdoin, ME). The electrode/guide tube position was fixed laterally by a grid system (Crist Instruments, Hagerstown, MD). A second grid with holes offset from center by .5 millimeters was also used to increase the number of available areas to sample. In the case where electrode distances were less than a millimeter, all electrodes were epoxylite-coated tungsten with a diameter of 125 μm, had an impedance of 4 MΩ at 1 KHz, and housed within single guide tube. They were segregated by spacers that kept them electrically insulated from one another and insured independent movement (2 or 4 electrode, single guide-tube manifold, FHC, Bowdoin, ME). For recordings with electrode separations greater than 300 microns, only two electrodes were used and each electrode was housed within it own guide tube (2 electrode-, 2 guide-tube manifold, FHC, Bowdoin, ME). For these experiments, either glass-coated tungsten electrodes were used, with a diameter of 250 μm and an impedance of 1 MΩ at 1 KHz (Alpha-Omega Engineering, Nazareth, Israel) or epoxylite-coated tungsten electrodes with a diameter of 250 μm and impedance of 4 MΩ at 1 KHz (FHC, Bowdoin, ME).
**Training**

Monkeys were trained to perform the task in the following sequence. They were initially shown a 0.5 degree square in the center of the screen, on which they had to fixate while they held back the behavioral control lever. Once the fixation target was extinguished, subjects had to release the lever within a predetermined reaction time to receive a reward. Both the fixation target illumination time and the reaction time could be set by the operator. Target illumination time was gradually increased while reaction time incrementally decreased to 500 milliseconds. Upon mastering the fundamental components of fixating, using the lever to start the trial, and releasing the lever for reward, the additional element of behavioral stimuli added. The animal was presented with trials involving immediate match presentations, in which the cue and match stimulus was repeated after a 1 second interval. The subject was initially shown the match in only one location and was rewarded for releasing the lever after the second stimulus disappeared. Gradually, more locations, and intervening nonmatch stimuli were included until the animal could perform the basic version of the match to sample task (Figure 1). Subjects were then trained to do the Screen Match variant of the task and all physiological data for this part of the study were recorded over a period of several months. Animals were finally retrained on the Retinal Match version of the task. When they reached criterion performance on the latter, recording recommenced and the second dataset was collected.

**Behavioral Performance**

Both tasks were extremely challenging for the monkeys and required several months of
training. We computed the monkeys’ performance in the task by calculating the percentage of correct responses, after excluding eye errors due to breaks in fixation. During the sessions in which area 7a neurons were recorded in the Screen Match task, the monkeys performed 83% correct trials (90% and 74% for our two animals, respectively). The error rate of our second monkey was inflated by timing errors involving premature lever releases before the offset of the match stimulus; such errors were observed in all tasks and types of trials, including those where the fixation point did not move. After retaining in the Retinal Task, the average performance in sessions where area 7a neurons were recorded was 78% (84% and 70%) respectively. The slightly increased error rate in the Retinal Task was stable during the time period of recordings and represented asymptotic performance: no significant effect of session number on performance was seen in this task (regression analysis, p>0.2 for both monkeys), and performance in the first half sessions was essentially identical to last half (84% vs. 83% correct for the first monkey and 71% vs. 69% for the second one).
Supplemental Figure 1. Set of trials types

Left panel: Schematic illustration of a block of trial types used in the Screen Match Task. The second frame in the sequence involves presentation of the stimulus either in the upper left or the lower right location. During recordings, we displayed blocks of trials where the second stimulus would appear inside the neuron’s receptive field and its diametric location. All trial types were randomly interleaved. Additionally, multiple sets of trial blocks involving the same second stimulus location but different locations of nonmatch stimuli were used during experiments.

Right panel: All trial types in a block of trials of the Retinal Match Task.
**Supplemental Figure 2.** Recording location

(A) Schematic diagram illustrating location of area 7a in the monkey brain. IPS: Intraparietal Sulcus, STS: Superior Temporal Sulcus.

(B) Anatomical MRI from one subject. Recordings were performed from the crown of the gyrus posterior to the intraparietal sulcus.
Supplemental Figure 3. Neuron preferences in the tasks.

Top: Number and percentage of neurons showed significant difference in terms of the firing rate in the task (Attention Selective), judged by an ANOVA test (p<0.05).

Middle: Percentage of neurons from the previous group that responded best to a Fixed Match over a Fixed Nonmatch stimulus.

Bottom: Percentage of neurons from the previous group that responded best to a Screen over a Retinal Match stimulus.
Supplemental Figure 3.

Screen Match Task
- Attention Selective: 35/72 (49%)
- Fixed Match > Fixed NonMatch: 21/35 (60%)

Retinal Match Task
- Retinal Match: 46/138 (33%)
- Screen Match > Retinal Match: 17/21 (81%)

- Fixed Match > Fixed NonMatch: 28/46 (61%)
- Screen Match > Retinal Match: 16/28 (43%)
Supplemental Figure 4. Neuron in Retinal Match Task with Retinal stimulus preference

Histograms and rasters for an example neuron recorded while the subject was engaged in
the Retinal Match task. Conventions are the same as in Figure 3 of the main text.

(A) Match stimulus presentation in the receptive field elicited a strong response.

(B) Nonmatch stimulus presentation in the receptive field elicited a weaker response.

(C) The neuron responded well to a retinal match, which was a behavioral match in this
task (required a lever release).

(D) The neuron responded poorly to a screen match.
Supplemental Figure 5. Differences between Match and Nonmatch responses

Scatter plots of the difference in firing rate between a Match and nonmatch stimulus appearing after intervening nonmatch stimuli, plotted against the difference in firing rate between a match and nonmatch stimulus appearing immediately after the cue. Neurons appearing on the diagonal represent neurons with identical response differences to the two conditions. Top panel: all Attention Selective neurons in both tasks. Bottom panel: neurons recorded in sessions matched for similar performance across both tasks.
Supplemental Figure 5. Differences between Match and Nonmatch responses
CHAPTER III

PYRAMIDAL NEURON AND INTERNEURON CONTRIBUTIONS WITHIN VISUAL ATTENTION AND WORKING MEMORY NETWORKS IN PRIMATE POSTERIOR PARIETAL CORTEX

Justin Rawley

Justin Rawley performed the experiments and prepared the manuscript. Christos Constantinidis acted in an advisory and editorial capacity.
Introduction:

Mediation of behavior within the cortex is dependent on the properties and interactions of individual interconnected neurons, often working in networks that are activated by the same behavioral demands. The neural composition of cortical networks can be divided into two main categories, excitatory pyramidal and inhibitory interneurons, each with specific morphological and physiological characteristics. While various cell morphologies have been meticulously documented since Ramon y Cajal’s work, the correlation between action potential widths and neural firing rates more than half a century later provided the first in vivo observations that pointed to the existence of distinct physiological subtypes. Not surprisingly, two broad categories emerged: high frequency firing rates associated with narrow spike widths characterize fast-spiking (FS) neurons while neurons that fire with lower frequency, or regular-spiking (RS) neurons, generally exhibited wider action potentials (Mountcastle et al., 1969; Simons, 1978). Early in vitro investigations into these differences, carried out in non-primate models, suggested that pyramidal and interneuron subtypes could be identified on the basis of RS-FS characteristics, respectively (McCormick et al., 1985; Connors and Gutnick, 1990).

In vivo neurophysiological recordings in animals performing tasks offer insight into the mechanism of behavior, but they have traditionally been limited by the fact that the morphological properties of the neurons under study are not known. For this reason, methods to identify neurons based on the physiological parameters of spike width and baseline firing rate have been used to classify neurons into “putative” pyramidal and interneuron categories post hoc (Swadlow, 1995; Csicsvari et al., 1998; Jung et al., 1998;
Rao et al., 1999; Frank et al., 2001; Constantinidis and Goldman-Rakic, 2002; Diester and Nieder, 2008). Though by no means are these classification systems comprehensive, they offer a window into a medium where it is untenable to probe neural distinction by visual examination.

Because non-human primates are often used in behavioral neurophysiology and represent perhaps one of the closest models of human brain function, recent in vitro research in primate prefrontal cortex sought to verify to what extent the physiological and morphological properties of primate cortical neurons coincide and found a general agreement with that previously assumed in the literature (Krimer et al., 2005). This work replicated in the monkey, findings of cell types originally described in rodent cortex (Kawaguchi and Kubota 1997; McCormick et al. 1985). The neurons in this study were grouped into two larger categories, fast-spiking (FS), corresponding to several morphologically defined categories of inhibitory interneurons, and non fast-spiking (NFS), that contain excitatory pyramidal cells and some non-fast spiking interneuron types. The latter group was further subdivided into regular-spiking (RS) and intermediate-spiking (IS) neurons. Armed with reliable techniques for making physiology-based classifications, investigators have sought to elucidate the functional specializations that exist between the two populations and validate the biological reality of neuron interactions hypothesized through theoretical models.

Computational simulations of prefrontal architecture demonstrated that stable working memory in this region is dependent upon interneurons possessing wider tuning curves than their excitatory counterparts (Compte et al., 2000). This finding has since been confirmed through neurophysiological recording (Constantinidis and Goldman-
Rakic, 2002) in one of several studies exploring the functional differences between excitatory and interneuron types in primate dLPFC (Rao et al., 1999; Constantinidis and Goldman-Rakic, 2002; Mitchell et al., 2007; Diester and Nieder, 2008).

A renewed interest in physiologically defined neuron characteristics has sparked a number of studies investigating functional differences between excitatory and interneuron types. Recent research spans several brain regions from early to late stages of processing and studies neurons under a variety of behavioral contexts. In V1 for example, difficulty of a spatial attention task modulates attentional gain differentially within distinctly identifiable neuron populations. Response enhancement was observed for neurons with narrow waveforms while response suppression, greater directional selectivity, more tightly distributed interspike intervals, and higher contrast sensitivity were observed in neurons with broad waveforms (Chen et al., 2008). In macaque V4, attention dependent modulations of absolute firing rate, as well as reduction of response variability, have been observed, with the effects being more prominent in fast-spiking units with narrow waveforms (Mitchell et al., 2007). Further work in dlPFC demonstrates non-spatial tuning profile differences between putative interneurons and pyramidal cells for abstract numerical categorization. Prefrontal interneurons showed better discrimination across categories while pyramidal neurons were more selective for a particular category (Diester and Nieder, 2008).

Neural activity observed in posterior parietal and prefrontal regions is similar for processes requiring similar mental operations, indicating a partial overlap in function (Chafee and Goldman-Rakic, 1998). Furthermore PPC cortex receives input from many of the aforementioned visual areas studied. Our research extends the use of
physiologically defined properties to classify neurons recorded in posterior parietal cortex. We investigate possible operative differences between pyramidal and interneuron classes during processing of spatial and attention selective aspects of visual information as well as the role of each neuron type in working memory. Our objectives were first, to describe spatial tuning curves for both neuron types, as well as any differences that may exist between them; second, to differentiate the contribution that each neuron type makes to spatial working memory by examining sustained activity during the delay period following the cue; and third, to elucidate possible context dependence of excitatory vs. inhibitory neuron participation in networks that mediate visual spatial and attention selectivity.

Methods:

Neurophysiological recordings

Data presented in this study were obtained from two male macaque monkeys (Macaca mulatta) weighing between 5-8 kg. Surgery and training was conducted in accordance with the guidelines set forth by the National Institute of Health and approved by the Animal Care and Use Committee of Wake Forest University. Surgical procedures, behavioral task, training and multi-electrode recording have been described in detail in Chapter two. Stereotactic coordinates of the posterior parietal cortex were determined using MRI and a craniotomy was performed to expose a 20mm-diameter area that included area 7a. Monkeys were trained to perform a visual-spatial delay match to sample task. They had to pull back and hold a behavioral control lever while maintaining gaze within a 2 degree window on a .2 degree central fixation point throughout each trial. A
1.5 degree cue stimulus appeared for 500 milliseconds in one of 9 locations spaced 10 degrees apart on a square grid centered on the fixation. Cue presentation was followed by a delay period of 1 second before a subsequent test stimulus appeared. The test stimulus could be a match to the cue in terms of spatial location, or a non-match. Monkeys responded to a match by releasing the lever within 500 milliseconds of the offset of the stimulus and ignored any intervening non-match stimuli. Zero to two non-match stimuli could appear between the cue and match presentation, each with a 500 millisecond delay preceding the next stimulus. Nine classes represented each of the grid locations in which a cue/match could occur (Figure 1). Subjects generally ran 10 blocks of trials consisting of one correct execution of each of the nine trial types, which were pseudorandomly interleaved. All stimuli were either red or green throughout the trial. This paradigm was designed to test the spatial selectivity of a neuron and determine its visual receptive field (RF).

The second paradigm was similar to the first except that the fixation could move during some trials from the periphery to the center (see chapter 2, figure 1; B, C and E). It consisted of ten trial types in which the second stimulus was always in one of two locations representing one diametric pair of stimuli, in and out of the neuron’s receptive field; neural responses to the second stimulus in each trial were assessed to see how they varied under differing behavioral conditions and coordinate reference frames. As in the previous task, subjects generally executed 10 blocks consisting of one correct example of each trial type. Premature lever release or gaze deviation resulted in termination of the trial without reward. Eye position was monitored with an infrared tracking system (model
Figure 1. Spatial Delay Match to Sample Task

Panels represent each of the successive task epochs; initial fixation, cue, delay, a non-match stimulus (0-2 possible), delay, match stimulus to which the animal responds. The inset represents the nine locations in which a cue could appear. Subjects waited until the reappearance of the cue as a match, then released a lever within 500 milliseconds of its offset to obtain a reward.
RK-716, ISCAN, Burlington, MA) to within a .3 degree resolution around the center of vision. Eye position data were continuously sampled, digitized and recorded at 240 Hz.

Extracellular recordings were made using up to 4 electrodes spaced 0.2-1.5 mm apart, advanced independently through the dura and into the cortex using an electronic microdrive system (EPS microdrive, Alpha-Omega Engineering, Nazareth, Israel). Electrodes were glass-coated tungsten with a diameter of 250 μm and an impedance of 1 MΩ at 1 KHz (Alpha-Omega Engineering, Nazareth, Israel) or epoxylite-coated tungsten electrodes with a diameter of 250 μm and 4 MΩ at 1 KHz (FHC, Bowdoin, ME). Isolated signals were amplified, band pass filtered between 500 Hz and 10 KHz, then sampled at 40 kHz, and digitized. A 1.75 ms sample was captured around each action potential and recorded for off-line analysis.

Spike classification

All signals used in this analysis were recorded from 354 neurons in area 7a of the posterior parietal cortex with significant visual responses (see Chapter 2). Spikes were classified on the basis of 2 properties, their waveform width and their baseline firing rate as recorded during the initial fixation period before the onset of the cue. Spike widths were calculated to be the microsecond distance between the two transient depolarizations preceding and following the action potential waveform (Figure 2). The frequency distribution of neuron spike widths, shown in figure 3A, appeared to be bimodal with a natural delineation between the two modalities occurring at approximately 575 microseconds. This delineation corresponds well to the 570 μm threshold identified in a previous study (Constantinidis and Goldman-Rakic, 2002) and we use it as the threshold
Figure 2. Waveforms and Rasters of Fast-Spiking and Regular-Spiking Neurons

Top left panel represents the 100 sample waveforms and their average for a typical fast-spiking neuron in our sample. Right panel illustrates the rasters recorded from the neuron at the right in all trials of one class in the NoJump task. Bottom panel shows representative waveforms and rasters for a typical regular-spiking neuron.
spike width in one method for classifying neurons into fast or regular spiking as
described below.

Two classification schemes were used; the first method assigned neurons to fast-
spiking (FS) or regular-spiking (RS) groups based on the narrow criteria of spike width
and firing rate thresholds. According to this method, neurons with a waveform width less
than the 575 microsecond threshold and a firing rate that exceeded that of the overall
population average of 6.08 spikes per second were considered FS neurons. Neurons
demonstrating waveforms of 575 μs or wider and firing rates below the overall average
were grouped into the RS category. Two hundred and thirty seven units from the total
354 neuron population (67%) were classified on the basis of these criteria. Of those,
27/237 (11%) were FS neurons and 210/237 (89%) were RS neurons. Figure 3B
demonstrates percentage of neurons in each bin from the distribution in 3A with firing
rates above the population average.

To ensure that the results of this method were not prejudiced by the choice of our
criterion spike width and firing rate, we repeated the classification using an automated,
unbiased statistical procedure known as k-means clustering. This algorithm is an iterative
process that groups data into a predetermined number of clusters that are defined by a
given set of attributes. Briefly, a centroid for each cluster is initially chosen and every
data point is assigned to the cluster with the nearest centroid. A new centroid is then
computed for each cluster from the average of the current members of that cluster; then
the data points are reassigned accordingly. This procedure continues until the distance
from each data point in the group to the centroid is minimized, the distance between
centroids is maximized, and no further reassignments occur. The output of this analysis
Figure 3. 2-means and narrow classification of visual responsive neurons

A. Histogram of waveform width distributions in our sample of visually responsive neurons. B. Percent of neurons in each bin of the histogram in A that demonstrated baseline activity that exceeded that of the sample average (6.08 sp/s). Horizontal lines represent the average of all Type I and Type II neurons that exceeded the overall average. Vertical dashed line in A and B represents the waveform width that divides the data into 2 bimodal distributions. C and D represent the 2-means clusters obtained for each animal. Each point represents one neuron: Type I neurons are denoted by blue circles while Type II neurons are shown as red triangles. Action potential width for each neuron is plotted on the abscissa against the neuron’s firing rate (sp/s) on the ordinate axis. Horizontal dotted lines in each plot denote the overall average baseline firing rate of the sample. Vertical dotted lines in each plot represent the same waveform width threshold as in A and B.
Figure 3.
resulted in the differentiation of neurons into type I and type II, respectively. MATLAB and its Statistics Toolbox module (Mathworks, Natick, MA) were utilized to implement this analysis using the default squared Euclidian distances as the measure between data points and centroids. The location of the final centroids in k-means clustering depends on what starting points are chosen; therefore the final clusters may not be optimal for any given run. To optimize the process, we repeated the clustering algorithm up to 100 times using random initial starting points for each run. The distances for each data point to its defining cluster centroid were summed to get an overall measure of the within cluster variance. The clusters were taken from the run that generated the smallest summed distance. The final solution by this method was always returned within 100 runs.

One hundred and five neurons (105/354, 30%) were designated as type I neurons and the remaining 249/354 (70%) were assigned to the type II category. The differences between the narrow and k-means classifications stem from the fact that not all cells could be categorized according to the narrow criteria (figure 3 C&D), and that the k-means algorithm makes no a priori assumptions about biologically derived divisions in the data. All neurons defined as FS based on our narrow classification criteria were categorized as type I neurons by k-means clustering. Additionally, 91% (191/210) of neurons identified as RS were also classified as type II. Interestingly, work by Krimer’s group exploring in vitro primate physiology demonstrated that while a small minority of morphologically identified interneurons displayed regular spiking characteristics, no pyramidal neurons had fast or intermediate spiking attributes (Krimer et al., 2005). The scatter plots of figure 3 C and D show the respective groupings for all neurons recorded in each of the two animals.
Data Analysis

We tabulated the firing rates for all neurons in each of the task epochs, fixation (500 ms), cue presentation (500 ms), delay following the cue (1 sec, further subdivided onto 500 ms halves), and for each visual stimulus after the cue, including the match and any intervening non-match stimuli (500 ms). Neurons in either task that demonstrated significant response modulation during the presentation of any visual stimulus, as compared to baseline firing measured during the first fixation, are considered task responsive (paired t-test, $P < .05$). Our dataset contained 213 neurons responsive to the stationary fixation task and 210 to the moving fixation task (72 in the Screen Match, 138 in the Retinal Match paradigm). Many neurons were recorded during the performance of both tasks and demonstrated responsiveness in each, bringing the total number of neurons in this study to 354.

Neurons were considered visually responsive in the stationary fixation task if cue presentation in at least one of the nine locations elicited a significant change in firing rate from baseline (paired t-test, $P < .05$). A one way ANOVA of the cue stimuli in each of the nine classes further revealed if neurons preferred one cue location over another ($P < .05$). Those that demonstrate response modulation for at least one of the locations are considered spatially selective. Interneurons in dIPFC exhibit wider tuning curves than regular spiking neurons (Constantinidis and Goldman-Rakic, 2002) so we investigated whether the same was true of posterior parietal neurons. Spatial tuning curves for each neuron were constructed by computing the width at half height: First, the range of response was determined by subtracting the minimum firing rate (the location where the neuron was least responsive) from the maximum (at the neuron’s best location). This
number was divided by two to obtain the absolute half height of the response, which was then corrected for DC offset by adding back the minimum response. The width at half height is reported as the number of locations that induced the neuron to fire above the half height value (Figure 4).

It is already established that some neurons in posterior parietal cortex exhibit elevated firing after the offset of a stimulus, consistent with working memory function (Gnadt and Andersen, 1988; Constantinidis and Steinmetz, 1996). We examined the responses of neurons recorded during the second half of the delay interval after the cue to determine if activity during this epoch differed significantly from the baseline recorded during fixation (paired t-test, p < .05). Neurons that exhibited spatial selectivity and significantly elevated delay period activity are considered spatial working memory neurons.

The total number of type I and type II neurons recorded in each task was tallied, as well as the within-type proportion responsive to each of the tasks or conditions. These were assessed using a Chi-square or Fisher’s exact t-test as appropriate. Tuning curves for spatially selective neurons were averaged within each type. The overall averages were compared (t-test) as well as the distribution of tuning curve widths to determine if a between-type difference exists (Mann-Whitney U test). The following results will be presented in terms of the type I/ type II classifications obtained from the MATLAB cluster analysis. The same analyses were performed on the subset of FS/RS units, considering as the total population only those neurons that were classified under the
**Figure 4.** Representative tuning curves for Type I (FS) and Type II (RS) neurons

Tuning curve data for the same neurons shown in figure 2. Dashed line represents the half height of the response. The number of points above this line is the width at half height. Best response location for each neuron is shown in the inset. Task directions are represented on the abscissa and the firing rate in spikes per second on the ordinate.
Figure 4.

Tuning Curves

Type 1 (FS) Neuron

Type 2 (RS) Neuron
narrow criteria, although the sample of FS neurons was small and some statistical tests lacked sufficient power. The analyses of the two data sets yielded similar results.

**Results:**

Out of a total of 354 area 7a neurons demonstrating task responsiveness, 105 (30%) neurons were classified as type I (which included the FS, putative inhibitory neurons) and 249 (70%) neurons were classified as type II. The percentage of Type I neurons is higher than the percentage of interneurons based on anatomical studies, although it is consistent with previous physiological results using the same classification method (Constantinidis and Goldman-Rakic, 2002). This classification scheme is conservative in that it is likely to dilute the real physiological differences between putative interneurons and pyramidal neurons. These proportions remained fairly consistent for each of the task types, and within the subpopulations of neurons sensitive to any task aspect (see table 1).

*Stationary fixation task: neural activity*

**Spatial Selectivity**

One hundred forty-eight visually responsive neurons were recorded in the NoJump task. This population is comprised of Forty-four (30%) type I units and 104 (70%) type II units. The NoJump (stationary fixation) paradigm was designed to measure the spatial selectivity of a neuron under study by examining response differences across all nine locations arranged in a 3x3 square grid centered on the fixation point. We assessed neural activity associated with the first stimulus (cue) which had to be remembered in order to make a correct response.
Table 1. Neuron Types Enumerated by Task and Condition

This table demonstrates the consistency with which each of the neurons types was encountered during recording of each task and demonstrates to what extent roughly the same percentages of the significant populations in each of the conditions we tested are maintained. One notable exception is the fact that all neurons classified as FS by the narrow criteria were nonmatch preferring.
<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Total</th>
<th>FS</th>
<th>RS</th>
<th>Total</th>
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<td>105</td>
<td>249</td>
<td>354</td>
<td>27</td>
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<td>(29%)</td>
<td>(70%)</td>
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**Table 1. Neuron Types Enumerated by Task and Condition**

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<td>(visually responsive)</td>
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<td>104</td>
<td>148</td>
<td>12</td>
<td>80</td>
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<tr>
<td>Spatially Selective</td>
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<td>76</td>
<td>4 (8%)</td>
<td>45 (92%)</td>
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<td>(30%)</td>
<td>(70%)</td>
<td>210</td>
<td>(11%)</td>
<td>(89%)</td>
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<td>Attention Selective</td>
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<td>4 (7%)</td>
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<td>2 (6%)</td>
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<td>20 (28%)</td>
<td>52 (72%)</td>
<td>72</td>
<td>6 (11%)</td>
<td>50 (89%)</td>
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<td>Attention Selective</td>
<td>11 (31%)</td>
<td>24 (69%)</td>
<td>35</td>
<td>2 (7%)</td>
<td>25 (93%)</td>
<td>27</td>
</tr>
<tr>
<td>Match Preferring</td>
<td>4 (19%)</td>
<td>17 (81%)</td>
<td>21</td>
<td>0</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Task</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Total</th>
<th>FS</th>
<th>RS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal Match Protocol</td>
<td></td>
<td></td>
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<tr>
<td>42 (30%)</td>
<td>96 (70%)</td>
<td>138</td>
<td>9 (12 %)</td>
<td>67 (88%)</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Attention Selective</td>
<td>16 (35%)</td>
<td>30 (65%)</td>
<td>46</td>
<td>2 (7%)</td>
<td>25 (93%)</td>
<td>27</td>
</tr>
<tr>
<td>Match Preferring</td>
<td>11(39%)</td>
<td>17 (61%)</td>
<td>28</td>
<td>2 (13%)</td>
<td>14 (87%)</td>
<td>16</td>
</tr>
</tbody>
</table>
From the visually responsive dataset, 76 (51%) units demonstrated significant selectivity for spatial location (ANOVA, p < .05) including twenty-one (28%) type I and 55 (72%) type II. The percentage of type I neurons that were spatially selective was 21/44 (48%) while 55/104 (53%) of type II units showed spatial selectivity. A Chi-square test confirms that the proportion of spatially selective type I neurons (48%) is in fact, statistically equivalent to that of spatially selective type II neurons (53%) ($P = 0.57$). We therefore cannot reject the null hypothesis that the attribute of spatial selectivity is equally distributed among the constituent groups of neurons. This is graphically summarized in figure 5; each bar graph shows the proportion of spatially selective neurons by type.

We then considered in the analysis, only those visually responsive neurons identified under the narrow criteria to determine if classification by that method yielded different results. Ninety-two neurons were categorized as according to these criteria, consisting of 12 FS (13%) and 80 RS (87%). Spatially selective neurons accounted for 49/92 (53%) of the total. The proportion of FS neurons that was spatially selective was 4/12, 33% while the proportion of RS neurons was 45/80, 56%. A Fisher’s exact t-test reveals that these percents also conform to those expected if the FS and RS populations equally express the attribute of spatial selectivity ($P = 0.21$).

Since posterior parietal cortex is one of the primary cortical areas where visual spatial processing takes place, we calculated spatial tuning curves for all visually responsive neurons recorded in this task. First we compared the average widths at half
Figure 5. Visually Responsive neurons with Spatial Selectivity

The bar graph summarizes the proportion of spatially selective neurons within the visually responsive population for each type for both the 2-means and narrow classification systems. Neurons with spatial selectivity are denoted by filled bars while non-spatially selective neurons are represented by open bars.
height (WHH) for each of the neuron types identified by both the two-means cluster algorithm (type I, type II), and by the narrow classification method (FS and RS), then we considered the widths at half height for each neuron type from the subset of only those neurons with spatial selectivity.

In the visually responsive population, the average width at half height for the 44 type I neurons was 2.95 while the average for the 104 type II neurons was not much different at 3.09 (t-test, $P = 0.64$). We tested to see if the distributions of widths at half heights for each neuron type differed significantly, a possibility that cannot be discounted solely by comparing the overall averages, and we found them to be equivalent (Mann-Whitney U test, $P = 0.87$). Many non-spatially selective neurons were included in the sample, and not surprisingly, the distributions of neurons displaying each of the widths at half height ranged over almost the full breadth of possibilities from one to seven for Type I neurons and one to eight locations for type II.

Under the narrow criteria seven Type I neurons switched their affiliation to RS, making the overall average width at half height slightly wider for FS neurons. The observed averages were nevertheless similar at 3.08 for the 12 FS neurons and 2.89 for the 80 RS neurons (t-test, $P = 0.65$). Widths at half height ranged from one to five for FS units and one to seven in RS but the percentage were weighted a little more heavily toward the lower end of the distribution in the RS subset, thus producing the lower overall average. The distributions differences however, were minor and did not produce a significant finding (Mann-Whitney U test, $P = 0.57$).

The seventy-six spatially selective neurons demonstrated tighter tuning curves than those of the overall population; Type I and II had widths at half height ranging from
1 to 5 locations and type II had one additional outlier that displayed 7 locations above half height. Here again, the average values for the widths at half height were nearly identical (t-test, \( P = 0.95 \)) at 2.48 locations for type I neurons and 2.45 for type II. The histograms in figure 6 show the distribution of percentages of neurons displaying each of the widths at half height for each neuron type. A Mann-Whitney U test (\( P = 0.91 \)) confirms that they were statistically equivalent, a result that is underscored by the nearly overlapping cumulative distribution function (cdf) plots for each distribution (Figure 6, inset).

The delineation between the average widths at half height for the 49 spatially selective FS/RS neurons was slightly sharper than it was for the type I/type II neurons; spatially selective FS neurons averaged 2.75 locations above half height compared to 2.4 for RS neurons. This observation is due in part to the fact that five type I neurons migrated into the RS category under the narrow criteria. These five neurons represent a substantial part of the type I constituency that, under the narrow criteria, weight the RS category even more heavily. Nevertheless, the difference between the averages for FS and RS neurons that expressed spatial selectivity did not reach statistical significance (t-test, \( P = 0.57 \)). The distributions of widths at half height for FS and RS types were also similar (Mann-Whitney U test, \( P = 0.34 \)).

**Delay period activity**

The physiological correlates of working memory have been described as a continuation of elevated firing after the offset of a stimulus that must later be used to make a decision (Fuster, 1973, 2003). Because neurons in posterior parietal cortex have
Figure 6. Distribution of Widths at Half Height for All Spatially Selective Neurons

Histograms represent the distribution of widths at half height for each group of neurons. The number of locations above half height is represented on the abscissa. Percentage of neurons in type is plotted on the ordinate. Blue histogram corresponds to Type I, and red to Type II. Empirical cumulative distribution function plots in the inset represent probability distributions for the data in the histograms. Their near overlap indicates the similarity of the distributions.
been shown to exhibit features associated with working memory, we investigated the
subset of neurons in our sample with increased activity during the delay period. We
identified neurons whose activity remained elevated after the offset of the cue during the
delay, consistent with the working memory trace (figure 7C-D). We also observed some
neurons that demonstrated a ramping up of firing before the cue (figure 7A-B), similar to
the anticipatory signal described by Quintana and Fuster (Quintana and Fuster, 1992).

From the sample of visually responsive neurons recorded in the NoJump task,
51/148 (34%) demonstrated sustained elevated activity during the second half of the
delay period following the cue. These included 15/44 type I neurons (34%) and 36/104
(35%) type II neurons; the proportions of neurons expressing delay activity within each
of the 2 groups is quite similar (Chi-square test, $P = 0.95$). Twenty-eight (30%) of the
total 92 FS/RS neurons displayed delay activity. The percentages of FS and RS types that
were modulated during the delay were almost identical at 4/12 (33%) FS and 24/80 RS
(30%) neurons (Fisher’s exact t-test, $P = 1.0$).

Tuning curves for the group of neurons with delay activity were similar to those
of the overall visually responsive population. The differences between neuron types in
this sample were also not statistically different from each other. The average width at half
height was 2.87 for Type I neurons, and 3.11 for type II (t-test, $P = 0.67$). The
distributions of widths at half height was similar between the two groups as well (Mann-
Whitney U test, $P = 0.80$). The averages for neurons with cue delay activity were
practically identical under the narrow criteria at 2.75 for FS and 2.79 for RS (t-test, $P =
0.96$). The distributions of neuron types under both classification systems, likewise
showed no significant underlying differences (Mann-Whitney U test, $P = 1.0$).
Figure 7. Two example neurons with Delay activity

Both neurons, panels A-B and C-D respectively, exhibit elevated firing during the delay period after the cue when the cue appeared inside the receptive field but not when it was outside the RF. The neuron presented in panels A and B show a ramping up of activity before the match, characteristic of an anticipatory signal where the neuron in pannels C and D demonstrates continuous sustained activity during the delay in the absence of any visual stimulus.
Figure 7.
Spatial working memory: spatial selectivity with delay activity

Neurons in posterior parietal cortex that demonstrate both a preference for location and sustained firing after the cue are good candidates for mediators of spatial working memory. See example neuron in figure 7C. For this reason, we investigated the possibility that the subgroup of neurons that exhibited both spatial selectivity and activity in the delay period following the cue might display tuning curve differences between neuron groups in line with what has previously been reported in dIPFC.

Thirty out of the 76 (39%) spatially selective units showed significant activity during the second half of the delay period after the cue (paired t-test, \( P < .05 \)). The proportion of spatially selective type I neurons that demonstrated delay activity, 9/21 (43%), was not significantly different from that of the type II units (21/55, 38% (Fisher Exact t-test, \( P = 0.80 \)). Comparing these same percentages between FS (1/4, 25%) and RS neurons (15/45, 33%) also did not change the significance (Fisher’s exact t-test, \( P = 1.0 \)). These results are presented in the graphs of figure 8.

Somewhat surprisingly, however, was the fact that neither the overall averages of the width at half height, (2.22 locations for type I, and 2.10 for type II, t-test, \( P = .75 \)), nor their underlying distributions were statistically different (Mann-Whitney U test, \( P = .78 \)). Figure 9 demonstrates that the tuning properties of spatially selective type I and type II neurons with delay activity are similar to those of the overall population of spatially selective neurons. The only FS unit present in this subset of neurons had a width at half height of 2 locations, which by visual inspection, we see is consistent with the 2.13 average of the 15 RS cells.
**Figure 8.** Spatially Selective neurons with Cue Delay Activity

Same conventions as in figure 5.
**Figure 9.** Distributions of Widths at Half Height for neurons with Delay Activity

Same conventions as in figure 6.
Moving fixation task

Two hundred and ten neurons were collected while the subjects performed the JumpFix Task. Activity during the second (test) stimulus was assessed for each unit using a one way ANOVA to determine if any of the classes differentially modulated response ($P < .05$). To gage the general contributions of type I and type II neurons to attention selectivity, data from both coordinate reference reporting paradigms were pooled.

Eighty-one units (39%) from this population from the 210 total were selective for attention. Attention selective type I neurons constituted (27/62, 44%) of all type I neurons recorded in the JumpFix task. The corresponding proportion of type II neurons was 54/148, or 36%. These proportions do not reflect a large enough difference to reject the null hypothesis that I and type II neurons are equally selective for attention (Chi-square, $P = .34$). The top panel of figure 10 illustrates these data in the same format as figures 5 and 8.

One hundred and thirty-two neurons recorded in this part of the study were classified under the FS-RS designation; 54 (41%) were differentially modulated by the attentional aspects of the JumpFix task. The difference in the proportions of attention selective FS neurons (4/15, 27% ) and attention selective RS neurons (50/117, 43%) is quite a bit wider than in the type I – type II classification system, but a Fisher’s exact t-test reveals that it still does not reach significance ($P = .28$). As we have seen before in the spatially selective population, the division between the FS and RS types is sharper than for the 2-means classification.
Figure 10. Task responsive neurons with attention selectivity.

Top panel: cell types within the overall population, bottom panel: comparison of Match vs. NonMatch preference within the population of attention selective neurons. Filled bars correspond to proportion of neurons with enhanced activity for Match stimulus and open bars represent the proportion of neurons that preferred a NonMatch stimulus.
Figure 10.

Task Responsive Neurons with Attention Selectivity

2-means classification

Narrow criteria classification

Match vs. NonMatch Preference in Attention Selective Neurons
Selectivity for match vs. nonmatch stimuli

Neurons within the attention selective population could be modulated differentially by the match and nonmatch stimuli; some demonstrated increased firing when the test stimulus was a match while others were activated preferentially by the nonmatch stimulus. Intuitively, one might speculate that a greater number excitatory type II neurons would be active during a match presentation and that more interneurons might be recruited when a non-match stimulus (to which a response is suppressed) appeared. We tested this hypothesis on the data pooled from both tasks and compared responses to match and nonmatch stimuli that appeared during trials in when the fixation did not move. The population of neurons that responded preferentially to the match under fixed conditions was then further broken down by preference to the behavioral match vs. nonmatch in trials with moving fixation.

When we considered the 81 attention selective neurons classified as type I or II, we found 49 (60%) that preferred the match stimulus in stationary fixation trials (fixed match trials). Fifteen of the 27 (56%) type I units responded better to a match stimulus than a nonmatch stimulus. Thirty-four of 54 (63%) type II neurons were match-preferring. These percentages were not significantly different from one another (Chi-square, \( P = .52 \)). Figure 10, bottom panel, demonstrates these results. When we looked at the subset of 54 attention selective neurons categorized by the narrow criteria, we found 34 units (63%) that were selective for the match under stationary fixation conditions. Only 4 neurons were categorized as FS, 2 of which (50%) responded preferentially to the fixed nonmatch stimulus. Thirty-two (64%) of the 50 RS neurons demonstrated fixed
match selectivity. The differences between FS and RS neurons also did not reach significance (Fisher’s exact t-test, $P = 0.62$).

When the subset of neurons selective for the fixed match were examined further, we found that 33 units (67%) also preferred the behavioral match, which constituted a screen match for those neurons recorded in the Screen Match task, or the retinal match in the Retinal Match task. Eleven of 15 fixed match preferring type I neurons (73%) and 22 of 34 type II units (65%) preferred the behavioral match. As was the case for the stationary match, these results conformed to what would be expected if type I and type II neurons are equally activated by the behavioral match (Chi-square, $P = 0.55$). Twenty-three of the 34 units (68%) classified under the FS/RS rubric responded better to the behavioral match, including one of the two fixed match selective FS units (50%) and 22/32 RS neurons (69%). These percentages that did not differentiate behavioral match selectivity between the populations in any way (Fisher’s exact t-test, $P = 1.0$).

**Discussion:**

Here we investigate differences in putative excitatory and inhibitory interneurons in posterior parietal cortex utilizing classification methods similar to those pioneered by Patrica Goldman-Rakic’s lab in dorsolateral prefrontal cortex (Constantinidis and Goldman-Rakic, 2002). This research is the first to show that putative interneurons in posterior parietal cortex demonstrate spatial tuning, sustained activity during the delay and responses that can be modulated by attention. Our first objective was to describe the tuning curve properties of posterior parietal interneurons in detail and how these might differ from those of excitatory pyramidal neurons in PPC. Secondly, we wished to
elucidate the contribution that each neuron type makes to spatial working memory by examining activity profiles during the delay following the cue. These issues were specifically addressed by our NoJump task. Finally, we wanted to determine if attention modulates interneuron responses differentially from those of pyramidal neurons in PPC, as has been shown in areas mediating earlier stages of visual processing. In V1, task difficulty increases attentional gain more for units exhibiting narrow waveform than for those with wider waveforms while in V4, interneurons demonstrate a greater attention dependent increase in absolute firing rate and reduction in response variability than their excitatory counterparts (Mitchell et al., 2007; Chen et al., 2008). The question of attentional modulation is investigated by means of our second task, the JumpFix paradigm, in which the test stimulus is identical in all cases, but can be either a match or a nonmatch stimulus depending on the behavioral context in which it appears.

*Spatial Selectivity*

Putative interneuron and pyramidal neuron types that we recorded in posterior parietal cortex demonstrated spatial selectivity in approximately equal proportions. Furthermore putative interneurons, designated as FS or type I, demonstrated distinct visual spatial tuning curves. We compared the tuning curve widths between type I/type II units classified by k-means clustering and the FS/RS neurons categorized by the narrow criteria to determine whether putative interneuron types display tuning curve profiles that differ from those of excitatory pyramidal neurons. Because there was some overlap in type I/RS classifications resulting from the two methods, we considered FS/RS and type I/type II groupings separately.
Within visually the responsive population and the spatially selective subpopulation, the average widths at half height for FS neurons was generally broader than for RS neurons, but this difference did not reach statistical significance. It should be noted however, that small sample sizes for FS units may have resulted in a lack of statistical power to discern intrinsic variation between the two types. The differences also tended to wash out as the number of FS units dwindled in the increasingly smaller subpopulations that displayed specific modulation, such as by cue delay activity. On the other hand, comparison of widths at height between type I and type II neurons yields very close averages across the overall population, and within most of the subpopulations. These findings in PPC differ from those of previous work in dlPFC, where putative interneurons display statistically wider tuning curves (Constantinidis and Goldman-Rakic, 2002), an attribute that has been shown theoretically to be a prerequisite in prefrontal cortex for the maintenance of stable working memory (Compte et al., 2000).

One reason for the lack of difference in PPC that was observed for PFC may be that all neurons in the prefrontal study that were classified using both methods were grouped into the same respective classes, i.e, all FS neurons were also type I neurons and all RS neurons were grouped with type II. As previously mentioned, this was not the case for our data set. While the WHH differences between RS and FS types in our work did more closely resemble those observed in prefrontal cortex, type I and type II were undistinguishable. Interestingly, tuning profile differences between putative primate prefrontal interneurons and pyramidal cells are not limited to visual spatial processing, but have also been described in abstract numerical categorization where interneurons are
more able to discriminate between categories while pyramidal neurons are more selective for a particular category (Diester and Nieder, 2008).

*Working memory*

Putative posterior parietal interneuron and pyramidal neurons types both demonstrate activity during the delay period, indicating that both appear to contribute to working memory function. We found that the percentages of type I/type II and FS/RS neurons that display working memory characteristics were essentially equal. As we might expect, the majority of neurons that demonstrated statistically significant activation during the delay following the cue were also modulated by the cue itself. This was especially true for spatially selective populations. Since the working memory traces observed in posterior parietal cortex are often associated with visual spatial stimuli, spatial selectivity and working memory issues are to some extent, interconnected.

Previous studies have sought to understand the nature of the signals arising in the posterior parietal cortex and to discern to what extent these they may merely be relayed from processes in PFC; working memory is one such function that has been under scrutiny in PPC. Our finding of lack of difference in WWH for tuning curves could be interpreted to mean that some aspects of spatial working memory function seen in PPC may in fact be such a top down signal. However, it is useful to consider the differences in working memory previously described between the regions. In posterior parietal cortex, the memory trace is associated with the most recently viewed stimulus and is quickly abolished by a novel stimulus that directs attention away from the previous locus of attention (Constantinidis and Steinmetz, 1996), whereas in PFC, neuron discharges after a
relevant cue stimulus remain high even after intervening non-match stimuli (di Pellegrino and Wise, 1993; Miller et al., 1996). One large scale computational model of multiple cortical areas including PFC operating during a delay match-, and delay nonmatch-to-sample paradigms may offer insight into the mechanism underlying this phenomenon. Tonic dopamine release at the onset of the task switches the prefrontal networks in this simulation into a state where memoranda can be retained. (Chadderdon and Sporns, 2006). The lack of difference in tuning curve widths observed in PPC may reflect such a functional segregation.

**Attention modulation**

We found that both putative interneuron and pyramidal neuron types demonstrated attention modulation in statistically equivalent percentages, indicating that the both types of neurons operate within the networks mediating attention in the same constituent proportions. In stationary fixation trials, the proportion of both neuron types activated by a match vs. a non-match stimulus in the neuron’s receptive field was also essentially the same. When we further examined the subset of neurons that preferred the fixed match, we discovered that in moving fixation trials, putative interneurons and pyramidal neurons expressed preference for the behavioral match in relatively equal proportions. Though we report the pooled data from both paradigms in the results section, we should point out that we compared percentages of neuron types expressing fixed match preference and behavioral match preference in each task paradigm separately and found that they were also not statistically different (data not shown). The largest disparity we encountered was for match vs. nonmatch responses in the Screen Match paradigm when the fixation did
not move. Under this condition we observed 4/11, 36% of type I neurons and 17/24, 71% of type II neurons that preferred the match, producing a P value of 0.073 (Fisher’s exact test).

Classification methods to identify neuron types recorded in vivo

The two-means system used to classify neuron types in this and previous studies has its obvious shortcomings in that there are more than two neuron categories in the cortex. Interneurons take on many forms and are differentiable into more tightly defined groups. While some neurons in our study may have been misclassified as putative excitatory units because of their regular spiking characteristics when in fact they are interneurons, work in vitro indicates that RS interneurons are in the minority (Krimer et al., 2005). Furthermore all fast- and intermediate-spiking units categorized in vitro fall into some class of interneuron (Krimer et al., 2005).

The narrow classification system might provide better estimate the actual number of FS neurons, but its drawbacks are evident in the fact that it missed 33% of the neurons under study, similar to what was reported in dlPFC (Constantinidis and Goldman-Rakic, 2002). This problem arises from the fact that setting threshold limits on two orthogonal parameters results in the division of space into four distinct quadrants, only two of which contain data that pass the threshold criteria (figure 3 A).

While the narrow criteria may categorize RS neurons as such more accurately than the 2-means algorithm, it cannot discern which RS neurons are interneurons. It may be the case that the type I neurons identified by two-means classification that were also categorized as RS by the narrow criteria belong to the RS interneuron group. Though the
classification along the narrow criteria yields incomplete results, it provides the empirical basis behind the use of the two-means algorithm. As exemplified in figure 3 C-D, there is clear bimodal delineation that occurs along the waveform width dimension, thus providing a natural division into two categories.

Despite its shortcomings, the 2-means system provides a reliable excitatory neuron/interneuron classification system that is sufficient for understanding many of the regional cortical differences in information processing. It is also useful in planning constructing of large scale neural network models or verifying their counterparts in biological systems. For this reason, the two-means system provides a good classification basis for this and preceding studies, and allows for more in-depth comparisons between cortical areas than had previously been possible.
References:


CHAPTER IV

DISCUSSION

Justin Rawley
Posterior parietal cortex is one of the fundamental elements in a network of modular cognitive areas that encompasses the broader spectrum of mammalian intelligence. In the previous sections we describe what is known about posterior parietal cortical involvement in a variety of mental operations ranging from coordinate transformation and visual-spatial attention to working memory and learning. Its feedforward afferents from sensory modalities, in particular visual areas, and reciprocity with prefrontal and subcortical structures put this region at the forefront of cognitive visual processing. As the extent to which its connections and interactions with other brain areas has become evident, so has the scope of its participation in the more wide-ranging aspects that are unified into higher processing. This research deals with two such functions directly, visual-spatial coordinate reference frame encoding and visual attention in area 7a. Corollary objectives are defined by the interrelated components of the cognitive processes under study, which also include working memory, learning and rule encoding.

Importance of posterior parietal cortex

Posterior parietal cortex is the focal point of convergence for input from several sensory modalities, each of which may be encoded in a different spatial frame of reference. These divergent streams of information must be integrated in such a way that the viewer is immerse in a unified three dimensional map of the surroundings that allows for seamless interaction with the immediate world. Damage to this region can cause the fracture of the sensory experience into isolated pieces and disjoined events that no longer convey relationships between object locations and features or how they are laid out with respect to the viewer. The resulting clinical manifestations often include spatial neglect,
extinction and apraxia. In the worst case, Balint’s syndrome occurs in which a patient has little control to allocate attention willfully and can only perceive one object at a time. For this reason, it becomes essential to understand how sensory signals are transformed to construct a common frame of reference, not only from which motor output can be planned and executed, but from which the animal can understand its relationship with its environment.

The position PPC occupies makes it one of the main focuses of investigators wishing to unravel the mysteries of higher cognitive function, as well as those trying to understand the neural mechanisms that make possible uninhibited daily human activity. Lesion, neurpsychological, and imaging studies all underscore the importance of PPC’s contribution in information processing, command and control; by understanding how this region accomplishes what it does, clinicians can develop treatment strategies to help those with parietal dysfunction while engineers can build neuroprosthetics that may be able to take the place of damaged tissue. Because of its role in coordinate transformation, PPC has garnered much interest as the biological starting point for constructing interfaces between the brain and prosthetic limb/movement devices (Mojarradi, 2003; Andersen, 2004b, c, a; Musallam et al., 2004; Mulliken et al., 2008).

*Human interface and intelligent systems*

From a robotics and engineering perspective, complex artificial intelligent systems will need an analogue to posterior parietal cortex in order to interact with full self-sufficiency with the environment in the same way that humans do. Another field that stands to gain from posterior parietal exploration is ergonomics and human factors research, where
optimizing the designs of, for example, automobile and aircraft cockpits can make a huge impact on the safe operation of such vehicles. Elucidating the biological underpinnings of visual perception and attention can result in the creation of avionics, air traffic control and collision avoidance systems that maximize the salience of the highest priority objects/targets/bogies while minimizing distracting factors and reducing the load on human operators.

As for the potential contribution of neurophysiological research on machine intelligence, one could consider as a simple example, an analogy in which posterior parietal cortex is compared to the combat information center (CIC) on a modern warship. As its name implies, the CIC receives information from a variety of modalities encompassing passive and active modes of sonar and radar, as well as electronic information from other sources including airborne and satellite observation platforms. These information input streams are somewhat analogous to the sensory systems of developed mammals in that information gathered in the CIC is integrated into a form which can be used to direct operations of the vessel in the wartime/maritime environment. The CIC is in constant communication with the bridge, from which decisions are made and commands are issued directing the course of the ship. In this respect, the bridge could provide a loose analogue for the prefrontal and motor cortices. As in biological systems, these elements work together as an organic whole that is capable of action. However, as sophisticated as these inventions are now, the human factor is still an integral part of the final decision pathway.

It has been put forth that cognitive processing in humans and higher mammals arises as a function of complex interaction between highly developed but specialized
brain regions (Hazy, 2006; Postle, 2006; D'Esposito, 2007). The realization of truly cognizant artificial intelligent systems may also come about as an emergent characteristic of large scale implementations of modular networks simulating the centers of human cognition. It is entirely imaginable that an aircraft, spaceship or naval destroyer could operate with unrestricted autonomy given a sophisticated enough approximation of the mammalian central nervous system at its core.

**Human and machine learning**

Understanding the role that posterior parietal cortex plays in learning and memory can aid in the establishment of more effective teaching methodologies that take advantage of the natural biological tendencies to group or chunk information into related subsets (Miller, 1956; Gobet et al., 2001). Taking advantage of existing top down and bottom up processes during the presentation of new material can increase saliency of items to be learned and reduce the time it takes to train human expert systems. This knowledge can also be carried over into the organization of large database structures and machine expert systems so that inherent complexity in the interface between machine and operator is minimized. Creation of more realistic virtual environments for training real world missions can also benefit from knowledge of how the brain, and in particular, the posterior parietal cortex processes visual spatial information.

**Organization of research**

The first chapter outlines what is already known about the posterior parietal cortex including anatomical connections, comparative differences between human and monkey
physiology, pathology in humans, and function. We present an overview of some seminal
studies as well as more recent investigations that have lead to the current understanding
of the posterior parietal cortex. We also attempt to address the direction of future research
in this area.

In our second chapter, we investigate the coordinate reference frame in which
visual spatial information is encoded, and what happens when behavioral conditions
necessitate a shift in the coordinate reference system used to assess relevance of an
object. A related and equally important issue concerns the behavioral component of
visual attention and how the immediate importance of a stimulus may enhance or
decrease the strength of the signal. We also discuss how the magnitude of response is
affected by the order in which the stimuli are shown, comparing late vs. early match
stimuli (those with several intervening nonmatch stimuli vs. those that immediately
follow the cue in the same location). Since the subjects were trained to perform two
separate paradigms that were the same in all respects except for which coordinate
reference frame is used to report the match, an element of learning and rule encoding is
necessary for accurate execution of these tasks. This is a corollary factor that we also
touch upon briefly in the second chapter.

The third chapter addresses differences in response properties of putative
inhibitory interneurons and excitatory pyramidal neurons, defined as such by
physiological characteristics, and their respective contributions to networks that mediate
visual perception and attention. This part of our investigation centers on the participation
of the two neuron types in visual spatial processing, including the assessment of visual
tuning curves for each type of neuron. Another facet of this inquiry focuses on attention
selectivity, the basic principle being that interneurons and excitatory neurons in posterior parietal cortex may be differentially modulated by the behavioral consequence of a stimulus, specifically, whether it dictates immediate action, or is to be ignored. We discuss the implication of our findings in the context of spatial selectivity, working memory, and attention selectivity, and relate these results to what has been discovered in other regions, such as early visual and prefrontal cortices.

*Visual spatial attention*

Previous research in monkeys demonstrates that allocation of attention to a location in space can occur naturally as a bottom up process to the appearance of salient stimuli in that location (Constantinidis and Steinmetz, 2005). In the early stages of visual processing, objects in the environment “compete” on the basis of their intrinsic saliency to be carried to the next higher level up the visual stream. At some point in this hierarchy “attention” is allocated to a stimulus in such a way that further processing is transferred into the realm of top down control. The communication between bottom up and top down control is bidirectional; sensitivity gain is increased in those neurons located along the V1-V4 pathway, representing an area of visual space that is currently being actively monitored by intrinsic allocation of attention (Kastner et al., 1999; Ogawa, 2004; Silver, 2007; Li et al., 2008). Furthermore, top down attention that is already allocated to one location or feature can attenuate responses that would otherwise occur in the presence of salient bottom up signals (Einhauser, 2008). In the other direction, a novel stimulus appearing at a new location can disrupt neural responses in posterior parietal cortex to previously viewed stimuli, possibly serving as a switch to reorient attention (Corbetta et
Both suggest that there is a fine balance between intrinsic and external forces that mediate attention, and that behavioral relevance is a strong factor in determining where and how attention is allocated.

In monkeys, pop-out stimuli embedded in arrays of distractors invoke much higher neural responses in animals trained to use the stimulus as a behavioral indicator, than in subjects who passively view them (Constantinidis and Steinmetz, 2005). In human studies, activity within the temporal parietal junction (TPJ), an area thought to be the analogue of monkey area 7a, can be modulated in some circumstances only in the presence of a stimulus that has behavioral significance (Corbetta et al., 2000; Kincade et al., 2005).

Our research indicates that behavioral significance indeed plays an important role in modulating posterior parietal responses in area 7a. We demonstrate that the same object presented in the exact same location can induce entirely different responses in the same neuron depending on the behavioral context in which the stimulus is viewed.

*Coordinate reference frame encoding of visual spatial attention*

The first question our research on attention attempts to address is that of coordinate reference encoding. Previous research in area 7a suggests that visual signals encoded in this area are world referenced (Snyder et al., 1998). However, these experiments probed the consequence of active versus passive body and head rotation on neural responses rather than the effect that a stimulus in behaviorally relevant location might elicit after an eye movement. In this respect, our research addresses the reference frame of visual attention *per se*. We investigated the alternative possibilities that neurons in area 7a
encode stimulus location with respect to position on the retinal, or can switch coordinate reference frame encoding depending upon the context of the situation, in this case, the demands of our task. Our experimental paradigm incorporates an eye movement requirement that changes retinal position with respect to the head and body, thus introducing a shift in the world view. We trained animals to attend to objects in the retinal (egocentric) view, and the screen (world) view and compared posterior parietal neuron responses under each of the coordinate reference reporting systems.

From our observations we concluded that the attentional reference frame in 7a is predominantly represented in screen coordinates. In the Screen Match task, most neurons that preferred the absolute match also preferred a match in screen coordinates (the behavioral match) after an eye movement was executed. Response modulation to the behavioral match condition was more ambiguous among the population of fixed match preferring neurons recorded during the Retinal Match task. Here, almost equal numbers of neurons demonstrated response enhancement for one behavioral condition verus another (screen match vs. retinal match). While the preference for the behavioral match was more robust across the population recorded in the Screen Match task, a regression analysis indicates that response differences between the screen match and retinal match conditions were overall still positively correlated with those of the fixed match and nonmatch responses in both tasks, regardless of the behavioral significance of the former. Because we could not record the same neurons during performance of both tasks, we cannot be certain that some neurons do not switch coding preference as the demands of the task change. Noteworthy is the fact that because animals learned the screen match task first, there is the possibility that the effects of training this task never washed out
entirely when the animals learned the second task. We can be certain however, that animals are capable of performing both tasks and that populations of neurons in area 7a can respond preferentially to fixed match stimuli under both reference systems. These results also confirm that learning in posterior parietal cortex is flexible, and that the imposition of a particular behavioral rule can govern the responses of neurons in this region.

Working memory

Working memory is another aspect of posterior parietal function that has been explored in physiological, imaging and neuropsychological literature, with recent contributions opening up new avenues in our understanding of this realm of processing. Examples of neurons that display continued activity during the delay after the offset of a cue stimulus have been observed in both prefrontal and posterior parietal cortices, as well as in other areas. This sustained activity in the absence of a stimulus has been hailed as the physiological correlate of working memory, but as we have noted in the first chapter, there exist functional differentiation between the type of working memory seen in prefrontal and posterior parietal neurons (di Pellegrino and Wise, 1993; Constantinidis and Steinmetz, 1996; Miller et al., 1996). Though not the main focus of our present research, working memory is nevertheless essential to the performance of delay matching to sample tasks of the type we used in the experimental paradigm. Not surprisingly, our neuron database contains many examples where activity was sustained during the delay phase after the offset of the cue (figure 8C, chapter 3). In chapter 3, we consider working memory in the context of differential contribution of Type I versus Type II, or FS versus
RS (depending upon classification method) to the memory trace held in 7a during the execution of such tasks.

**Concluding Remarks**

Posterior parietal cortex, in particular area 7a, is becoming the subject of increasing interest, not only because of its place in dorsal visual processing, but because of the similarities that it shares with the human temporal parietal junction (TPJ), an area implicated in neglect syndromes. Our research has focused on discerning the coordinate reference frame of visual attention, a vital first step in unraveling and ameliorating the often devastating syndromes that follow injury to the parietal cortex. In addition, understanding parietal function, may be fundamental to optimizing human and machine learning, organizing knowledge based systems and constructing artificial intelligence capable of self-navigation.

Considering the interconnectedness of PPC with regions including prefrontal, sensory (including late stages of the ventral visual pathway) limbic and other subcortical structures, some have proposed that higher cognitive function arises as an emergent property of a complex system formed by these networks. Characterizing the role that PPC plays within this system may help elucidate the neural mechanisms underlying not only the concrete cognitive functions that we address here, but also some of the deeper mysteries of human consciousness.
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CURRICULUM VITAE

WAKE FOREST SCHOOL OF MEDICINE

Justin Rawley

RESIDENCE:       2307 Sherwood Drive
                  Winston-Salem, NC 27103
                  (336) 408-5062

BUSINESS:        Program in Neuroscience
                  Wake Forest University School of Medicine
                  Medical Center Blvd.
                  Winston-Salem, NC 27157

BIRTHPLACE:      High Point, North Carolina

BIRTHDATE:       January 2, 1969

CITIZENSHIP:     USA

MARITAL STATUS:  Single

EDUCATION:

2009  Wake Forest University School of Medicine
       Winston-Salem, North Carolina
       Ph.D. (Neuroscience, will receive in 2009)

2002  Wake Forest University School of Medicine
       Winston-Salem, North Carolina
       M.S. (Neuroscience)

1995  Eastman School of Music
       Rochester, New York
       M.M. (Music performance)

1991  Salem College
       Winston-Salem, North Carolina
       B.M. (Music performance)
EMPLOYMENT:

2004-2005 Research Assistant, Wake Forest University
2001-2004 Platoon Leader, Ground Ambulance Company Medical Service Corps, USAR

TEACHING EXPERIENCE:

2006 Guest Lecturer, Course Planner Professional Development Dept. of Neuoscience Wake Forest University
1997 Laboratory Instructor Medical Neuroscience Wake Forest University School of Medicine
1989- 1990 Substitute Lecturer, Music History Salem College

LEADERSHIP:

2006-2008 Graduate Student Association Member
2007-2008 Chairman of the GSA Professional Development Committee; Organizer 2008 Graduate School Forum

AWARDS:

2006 Student Travel Award Fine Science Tools, Dept. Neurobiology and Anatomy, WFUSM Society for Neuroscience Annual Meeting, Washington, DC
1996-2000 Graduate Fellowship Neuroscience Program Wake Forest University School of Medicine
1991 President’s Prize in Music Salem College
1987-1991 Fogle Organ Scholarship Salem College
**BIBLIOGRAPHY:**

**Journal Articles:**

**Abstracts:**


**Presentations:**

**LANGUAGES:** English, Russian, Belarusian

**TECHNICAL SKILLS:**

**Computer Languages:** Matlab, Basic, C++

**Design:** Adobe: Photoshop, Illustrator, Premiere, InDesign, Dreamweaver; HTML

**Surgical:** Recording well in the macaque monkey and cat, headpost holder in the macaque, chronic multi-electrode electrode array in the rat.

**Electrophysiology:** Acute multi-electrode recording in the macaque, acute single electrode recording in cat, whole cell recording in ferret slice preparation, chronic multi-electrode in the rat.