PREFRONTAL AND PARIETAL CONTRIBUTIONS TO SPATIAL WORKING MEMORY

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Abstract—Functional neuroimaging studies consistently implicate a widespread network of human cortical brain areas that together support spatial working memory. This review summarizes our recent functional magnetic resonance imaging studies of humans performing delayed-saccades. These studies have isolated persistent activity in dorsal prefrontal regions, like the frontal eye fields, and the posterior parietal cortex during the maintenance of positional information. We aim to gain insight into the type of information coded by this activity. By manipulating the sensory and motor demands of the working memory task, we have been able to modulate the frontal eye fields and posterior parietal cortex delay-period activity. These findings are discussed in the context of other neurophysiological and lesion-based data and some hypotheses regarding the differential contributions of frontal and parietal areas to spatial working memory are offered. Namely, retrospective sensory coding of space may be more prominent in the posterior parietal cortex, while prospective motor coding of space may be more prominent in the frontal eye fields. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: frontal eye field, saccade, fMRI, TMS, functional connectivity, working memory.

Working memory allows animals to use information that is not currently available in the environment but is crucial for adaptive behavior. Therefore, an internal representation of relevant information must be created and maintained until it can be used to guide behavior. Persistent neural activity during the delay period between a sensory cue (e.g. the position of a briefly flashed spot of light) and a later motor response (e.g. a shift of gaze to the remembered location) is the most compelling evidence that this activity reflects some form of a memory representation (Fuster and Alexander, 1971; Kubota and Niki, 1971; Gnadt and Andersen, 1988; Funahashi et al., 1989). This observation, however, does not answer what is actually being remembered or coded for by this activity (Curtis and D'Esposito, 2003). During a memory delay, one can look back to a past event, a *retrospective* code, or can look forward to a future event, a *prospective* code, in order to link events that are separated in time but are contingent upon one another (Con-

stantinidis and Steinmetz, 1996; Quintana and Fuster, 1999; D'Esposito et al., 2000; Boussaoud, 2001; Takeda and Funahashi, 2002, 2004; Curtis et al., 2004). Both coding schemes are likely mechanisms of working memory.

Investigators interested in the mechanisms of working memory are particularly interested in the maintenance of *spatial* information because good evidence already exists about how space is represented by the brain. Many parts of the striate and extrastriate visual cortex are topographically organized in eye-centered or retinal coordinates (i.e. retinotopy) (Van Essen, 2004). The spatial position of stimuli in discrete parts of the visual field is encoded by corresponding neural activity in discrete parts of the visual cortex. Similarly, portions of the motor and premotor cortices, for example the frontal eye fields (FEF), are also organized according to a functional topography, some of which is in eye-centered coordinates (Schall, 2002). The FEF may use an additional mechanism for coding space by representing locations in motor or saccadic coordinates. The spatial position of a stimulus can be represented by the activation of FEF neurons that code for a saccade that moves the eyes to the location of the stimulus. Indeed, the FEF contains neurons that code for saccade endpoints of all portions of retinal space (Bruce et al., 2004). The maintenance of a spatial location can theoretically be accomplished through the sustained activation of both sensory and motor representations.

With these potential mechanisms in mind, this review will summarize the human and non-human primate studies that have used oculomotor delayed-response tasks, often referred to as delayed-saccade tasks, to probe the functions of the frontal and parietal cortices (Fig. 1). The review focuses on our recent functional magnetic resonance imaging (fMRI) studies and places these findings in the context of other related work.

Human neuroimaging

Sweeney and colleagues (1996) were the first to image the brain during delayed-saccades. In this important study, PET images of memory-guided saccades were subtracted from visually-guided saccades identifying a widespread network of regions including dorsal prefrontal cortex (PFC), bilateral FEF, and the intraparietal sulcus (IPS). Other blocked-design fMRI studies that used various types of spatial working memory tasks followed (Belger et al., 1998; Nystrom et al., 2000; Postle et al., 2000a; Simon et al., 2002) replicating the results of Sweeney and colleagues (1996). These block design studies, however, rely on the assumptions of cognitive subtraction and "pure insertion," which are particularly untenable in the case of

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Abbreviations: FEF, frontal eye field; fMRI, functional magnetic resonance imaging; IPS, intraparietal sulcus; LIP, lateral intraparietal; PFC, prefrontal cortex; PPC, posterior parietal cortex; TMS, transcranial magnetic stimulation.
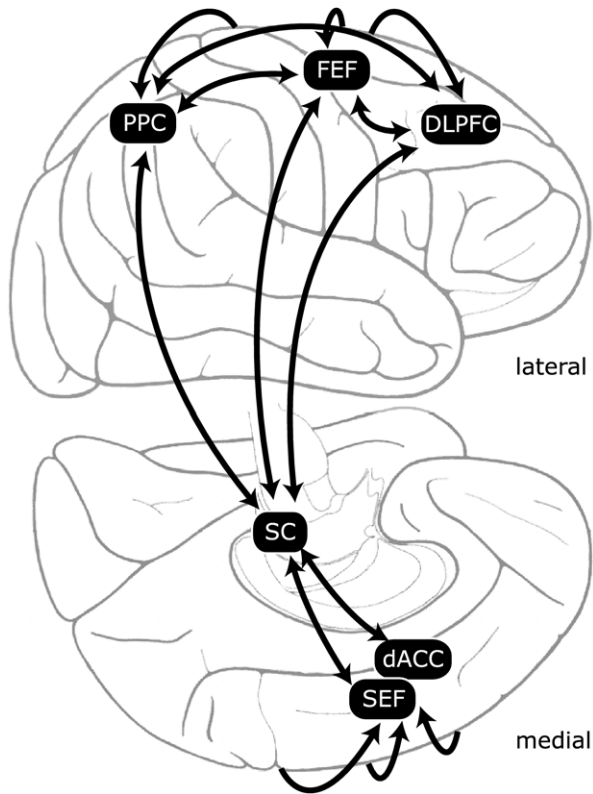
Fig. 1. Key connections between nodes of the oculomotor network in the human brain. This network, with the superior colliculus (SC) serving as the final common pathway, is thought to govern the generation of saccades. Together, these areas are also thought to play important roles in visuospatial and visuomotor behavior, such as that required during spatial working memory. Abbreviations: dACC, dorsal anterior cingulate cortex; DLPFC, dorsal lateral prefrontal cortex; SEF, supplementary eye fields.

delayed-response tasks (Zarahn et al., 1999). Specifically, cognitive subtraction assumes that the presence or absence of a cognitive factor does not influence other factors; they can be independently manipulated. In the case of a delayed-response task, the critical assumption is that the presence of a retention interval does not influence encoding or response factors. Intuitively, just knowing that a retention interval exists will surely affect how the information to-be-remembered is encoded.

The next generation of fMRI studies of spatial working memory used event-related designs that have the potential to isolate delay period activity from visual encoding and motor response, thereby dodging the assumptions of cognitive subtraction. These studies have provided consistent evidence that signals in the FEF, nearby posterior portions of superior frontal sulcus (area 8 in the dorsal PFC), and the IPS persist throughout the entire delay period of spatial working memory tasks (Courtney et al., 1998; Zarahn et al., 1999, 2000; Rowe et al., 2000; Leung et al., 2002; Sakai et al., 2002; Brown et al., 2004; Curtis et al., 2004). The persistent activity in these areas in one way or another is thought to support maintenance processes. Presumably, each area is not representing completely redundant informa-

tion and thus, a key goal is to now decipher what is being coded for by these persistent signals. To these ends, our recent work has focused not on which parts of the brain are active during working memory delays, but instead on what might persistent activity represent. As mentioned above, persistent signals may reflect the neuronal activity necessary to sustain representations of sensory or motor information. These signals may also reflect the retrospective coding or prospective coding of information.

To address this important question, we recently performed an event-related fMRI study of oculomotor delayed-response tasks in which subjects were biased toward or against the use of a prospective motor code (Fig. 2a) (Curtis et al., 2004). In one condition (match), subjects could plan a saccade to acquire the target as soon as it appeared and could simply delay the initiation of the saccade until after the delay. Delay period activity should reflect this strategy, the maintenance of a prospective motor code or motor intention. In a comparison condition (non-match), a saccade was made after the retention interval to an unpredictable location that did not match the location of the sample. The subjects still had to remember the location of the sample so that they could discern between the matching and non-matching targets. But because a saccade was never made to the sample location and the non-matching location was unpredictable, we reasoned that this manipulation biased the subject away from maintaining a motor code during the delay. Instead, it encouraged the maintenance of a retrospective sensory code, which is probably akin to sustained covert spatial attention (Awh and Jonides, 2001; Corbetta and Shulman, 2002).

We found that activity specific to the delay period was greater for the match compared with non-match conditions in the FEF (Fig. 2b). This suggested a plausible mechanism by which the FEF contributes to spatial working memory. We proposed that the sustained activity in the FEF likely reflects the representation of the saccade vector to acquire the location of the sample. Conversely, delay period activity was greater for the non-match compared with match trials in the IPS suggesting that when a motor intention cannot be maintained another mechanism is available, such as maintenance of spatially directed covert attention at the location of the visual cue (Fig. 2b). Support for these interpretations comes from both monkey and human studies (discussed below).

These findings led us to propose that a network of brain areas maintains the task relevant information, where different nodes in this network maintain relatively different representational codes, such as motor and sensory representations. Inherent in this proposition is that these nodes are interacting in some way, passing, transforming, and/or sustaining representations. However, we could only assume but not directly measure the functional interactions between the identified nodes of the putative network. In a follow-up study (Curtis et al., 2005), we used a novel multivariate technique, *coherence*, to formally characterize functional interactions between the FEF and other brain
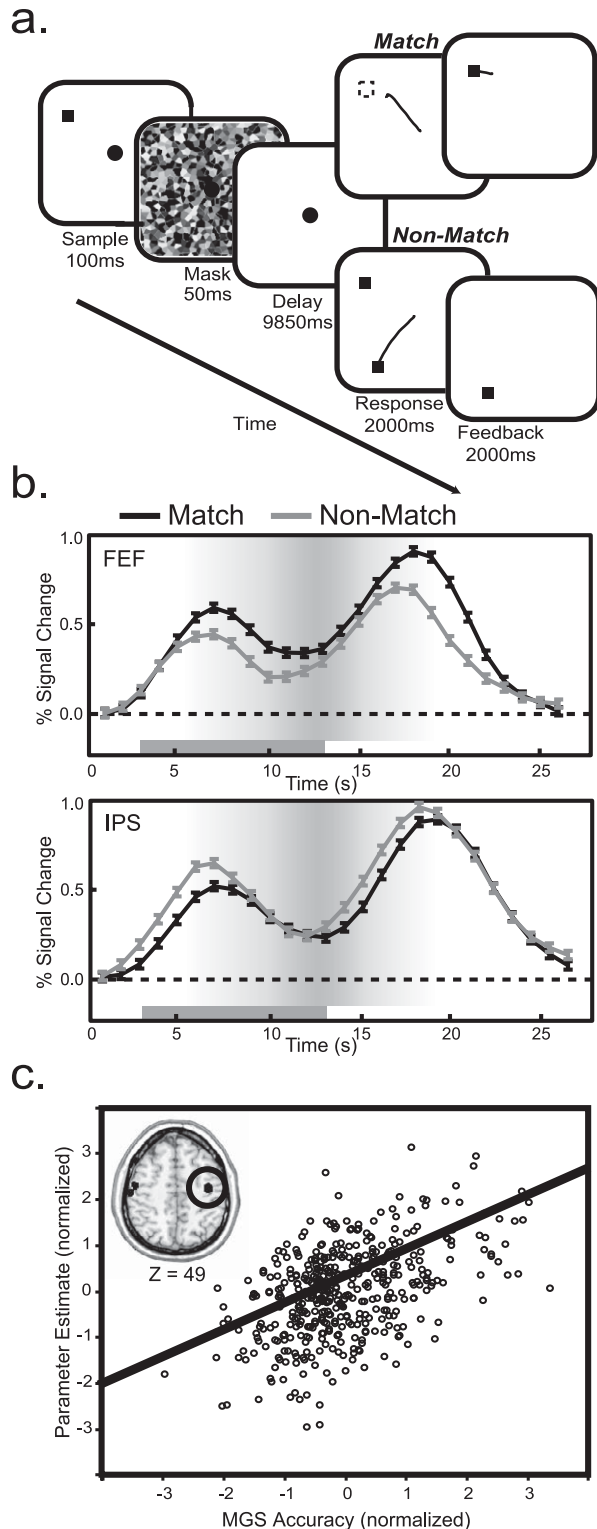
Fig. 2. Event-related study of spatial working memory by Curtis et al. (2004). (a) Schematic depiction of the delayed saccade tasks where subjects used the cue's location to make a memory-guided saccade (MGS). Both the matching-to-sample (top) and non-matching-to-sample (bottom) tasks began with the brief presentation of a small square target. During matching trials, the subject made a MGS (depicted by the thin black line) after the disappearance of the fixation cue marking the end of the delay period. Feedback was provided by the re-presentation of the

areas. The coherence statistic, which can be thought of as a correlation in frequency space (Sun et al., 2004), allowed us to identify brain areas that changed their functional connectivity with the FEF as a function of the matching and non-matching-to-sample task demands.

We found that the type of representational codes that were being maintained in working memory biased frontal–parietal interactions (Fig. 3). A network of oculomotor areas was found to be especially interactive during the match compared with non-match trials. Specifically, coherence between FEF and the supplementary eye fields and dorsal anterior cingulate was greater when a motor representation was an efficient strategy to bridge the delay. We proposed that this network of oculomotor areas supports working memory by representing and maintaining saccade goals. Another network composed primarily of hetero-modal prefrontal and parietal areas was found to be highly interactive during the nonmatch trials. Coherence between the FEF and the dorsolateral PFC, superior frontal sulcus, and posterior parietal cortex (PPC), was greater during non-match compared with match trials. This network may support working memory by sustaining covert attention at a particular location (Corbetta et al., 2002). Therefore, different nodes in a larger overlapping network change their relative patterns of interaction depending on the strategy employed during spatial working memory tasks.

We also performed a correlation analysis between memory-guided saccade accuracy, measured with a MR compatible eye-tracker, and the magnitude of delay period activity (Curtis et al., 2004). This analysis identified voxels whose trial-by-trial delay activity scaled linearly with the accuracy of the memory-guided saccade made seconds later. This correlation was based on how accurate the saccade was in continuous degrees of visual angle. Significant brain-behavior correlations were found in FEF bilaterally (Fig. 2c), the right IPS, and the right superior frontal sulcus. Therefore, the fidelity of the mnemonic representation can be predicted by the degree of delay period activity in a small number of regions that have been implicated repeatedly in the maintenance of spatial information. This correlation provides strong evidence that the sustained activity is critical to successfully representing the spatial information.

cue. At this point, the subject corrected any errors by shifting gaze to the cue. The difference between the endpoint fixation after the MGS and the fixation to acquire the feedback cue was used as an index of memory accuracy. During non-matching trials, the subject made a saccade to the square that did not match the location of the sample cue. (b) Average (±S.E. bars) BOLD time series data for matching (black) and non-matching-to-sample (gray) oculomotor delayed response tasks. The solid gray bar represents the delay interval. The gray gradient in the background depicts the probability that the BOLD signal is emanating from the delay period, where darker indicates more probable. The FEF show greater delay period activity during the matching task where an oculomotor strategy is efficient. The right IPS shows greater delay period activity during the non-matching task when subjects are biased from using such a strategy. (c) Scatter plot showing the correlation between MGS accuracy and the magnitude of the delay period parameter estimates in the right FEF. More accurate MGS were associated with greater delay-period activity.
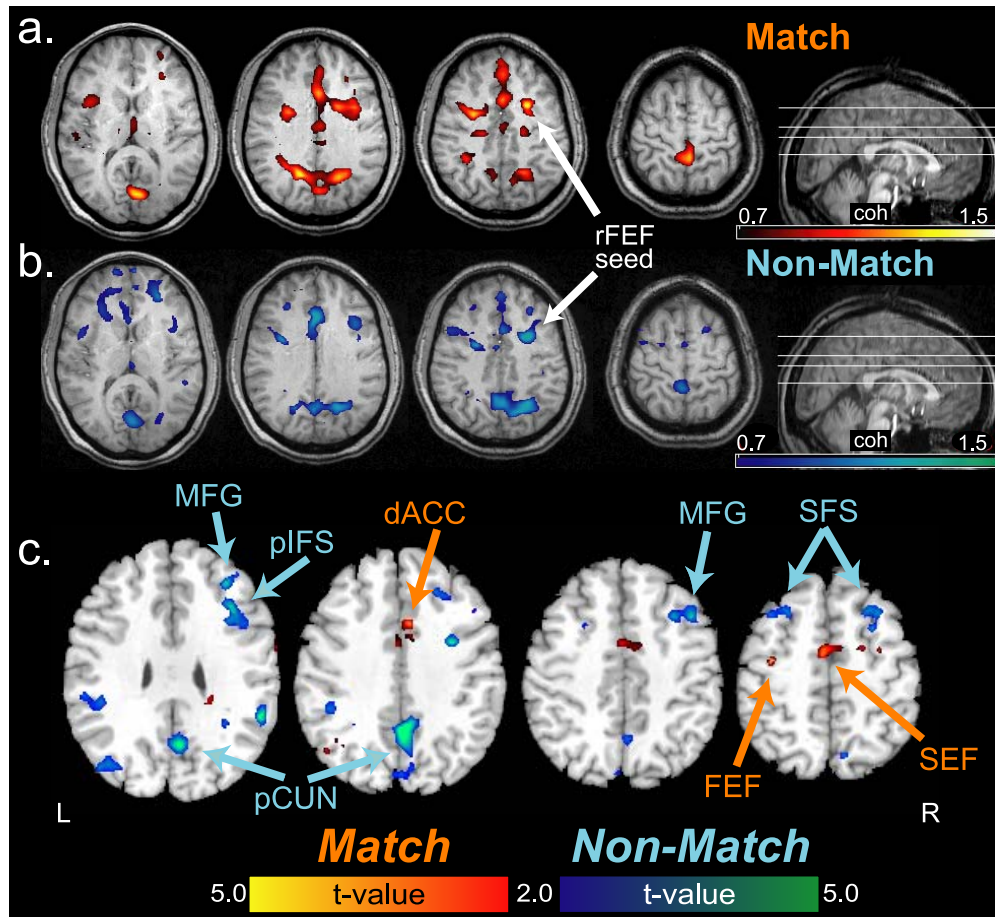
Fig. 3. Statistical coherence maps from Curtis et al. (2005). Representative subject's coherence map for (a) match trials and (b) nonmatch trials overlaid on the subject's anatomy. Notice the overlapping pattern of the network of regions. (c) *t*-Statistics showing the reliability of right FEF coherence difference. These were created by subtracting the match and nonmatch coherence maps for each subject. Warm colors indicate regions that show greater coherence with the right FEF seed on match compared with nonmatch trials. Cool colors indicate regions that show greater coherence with the right FEF seed on nonmatch compared with match trials. dACC, dorsal anterior cingulated cortex; dlPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus; preCU, precuneous; SEF, supplementary eye fields; SFS, superior frontal sulcus; vlPFC, ventrolateral prefrontal cortex.

Monkey electrophysiology

The monkey FEF contains an organized map of visual space defined in oculomotor coordinates and is thought to be an important area for transforming visual signals into saccadic commands (Bruce and Goldberg, 1985; Schall, 1991; Sommer and Wurtz, 2000). Neurons in the FEF increase in the rate of firing just prior to saccade initiation if the movement is directed into the neuron's response field (Bruce and Goldberg, 1985; Hanes et al., 1998). Electrical stimulation of the FEF causes saccades that are indistinguishable from natural saccades (Robinson and Fuchs, 1969; Bruce et al., 1985). This indicates an important role in saccade programming. Some FEF neurons also appear to be visual in nature; they respond when a visual stimulus is present in their receptive fields (Bruce and Goldberg, 1985; Schall et al., 1995). Moreover, robust persistent activity of FEF neurons has been reported many times now during spatial working memory delay periods (Bruce and Goldberg, 1985; Funahashi et al., 1989; Chafee and Goldman-Rakic, 1998; Sommer and Wurtz, 2001; Umeno and Goldberg, 2001). This activity is spatially selective in that it

is greater during trials in which the position of the remembered stimulus matches the neuron's response field. Therefore, the persistent activity in the human FEF that we have measured with fMRI during delayed-saccade tasks could reflect the activity of neurons that are responsible for moving the eyes to the remembered location. This type of coding of space could be used in memory tasks even when no eye-movement is ever made as the saccade can simply be suppressed.

The monkey lateral intraparietal (LIP) area of the PPC shares many of the same features with the FEF. Specifically, LIP neurons a) increase their rate of firing when a visual stimulus appears in its receptive field (Robinson et al., 1978), b) increase before saccades to spatially specific locations (Barash et al., 1991), c) LIP neuronal microstimulation evokes saccades (Thier and Andersen, 1998), and d) their activity sustains throughout delayed-saccade retention intervals (Gnadt and Andersen, 1988). Overall, the physiology of FEF and LIP neurons is remarkably more similar than it is different. Moreover, they send and receive projections to and from almost the same set of cortical and

subcortical areas and are highly interconnected with one another (Fig. 1). The functional interconnectedness of FEF and LIP is demonstrated by the fact that if one area is cooled it causes disturbed neural firing in the other during a delayed-saccade task (Chafee and Goldman-Rakic, 2000). Theoretically, both areas are presumed to play important roles in the representation of space and in the transformation of spatial information into a motor coordinate framework (Colby and Goldberg, 1999; Andersen and Buneo, 2002; Goldberg et al., 2002). At the population level, FEF and LIP neuronal activity may form topographical maps that represent the most salient objects and portions of space. Salience, as evidenced by enhanced neuronal firing, is modulated by bottom-up and top-down mechanisms that attract attention as well as the mechanisms that direct intentions, or plan movements (Gottlieb et al., 2005; Lebedev et al., 2004; Takeda and Funahashi, 2004). How these areas cooperate with one another and how they differ in their roles in spatial working memory remain unknown. For instance, almost all human functional imaging studies of spatial working memory co-activate the FEF and PPC, but have provided little empirical evidence for how they might functionally differ. The results of our fMRI study of delayed-matching and non-matching saccades (Curtis et al., 2004), nonetheless, suggest that relative differences in the way in which these two areas code spatial information may exist.

Although human studies have been somewhat mixed on whether they find activation of the dorsolateral PFC anterior to the human FEF during the maintenance of spatial locations (Courtney et al., 1998; Zarahn et al., 1999; Postle et al., 2000b; Rowe et al., 2000; Leung et al., 2002; Curtis and D'Esposito, 2003; Brown et al., 2004; Curtis et al., 2004), monkey electrophysiology has provided compelling data demonstrating a critical role of principal sulcus neurons in spatial working memory (Fuster and Alexander, 1971; Kojima and Goldman-Rakic, 1982; Funahashi et al., 1989, 1993a; di Pellegrino and Wise, 1993; Ferrera et al., 1999; Constantinidis et al., 2001; Takeda and Funahashi, 2002, 2004). Data from several of these studies suggest that the majority of dlPFC neurons that show delay-period activity code for the spatial position of the cued location and not the planned movement. This viewpoint may be an oversimplification of the data since Takeda and Funahashi (2004) have recently demonstrated that at the population level, dlPFC initially codes for the spatial location of the cue and then later codes for the location of the memory-guided saccade. They disassociated the cued location and movement direction by requiring monkeys to make a saccade to a location that was 90° rotated from the cued location. The population vector initially pointed toward the cued location and then turned toward the direction of the upcoming memory-guided saccade halfway through the delay period. Therefore, at the population level persistent activity in dlPFC neurons may code for different aspects of the task as sensory information is transformed into motor plans. Next, relevant lesion studies that may provide a more direct assessment are discussed.

Lesions to the PFC and PPC

Functional MRI and electrophysiological techniques depend on correlating activity and behavior but cannot be used to determine whether a brain region is actually necessary for a given behavior. Lesion methods remain the gold standard for discerning necessity and can be especially useful to arbitrate between hypotheses about the meaning of observed responses from electrophysiology and functional neuroimaging (Curtis and D'Esposito, 2004).

Humans and monkeys with PFC (including FEF) and PPC lesions show very subtle disturbances in the metrics of saccades to external visual stimuli (Schiller et al., 1987; Pierrot-Deseilligny et al., 1991; Lynch, 1992; Funahashi et al., 1993b; Rivaud et al., 1994; Sommer and Tehovnik, 1997; Heide and Kompf, 1998; Dias and Segraves, 1999; Gaymard et al., 1999, 2003; Li et al., 1999; Li and Andersen, 2001). *Visually-guided* saccades are slow to initiate but are mostly accurate suggesting that the FEF and PPC play important roles in saccade triggering probably through their direct projections to the superior colliculus. Lesions to the PFC, FEF, and PPC all cause decreased accuracy of *memory-guided* saccades (Funahashi et al., 1993b; Rivaud et al., 1994; Dias and Segraves, 1999; Gaymard et al., 1999; Li et al., 1999; Ploner et al., 1999). Analysis of the types of errors following cortical damage suggests that the FEF and PPC tend to cause systematic errors that are hypometric (i.e. saccades fall short of cued location), while PFC damage can result in memory-guided saccades that are variably scattered around the cued location (Funahashi et al., 1993b; Dias and Segraves, 1999; Li et al., 1999; Ploner et al., 1999). This suggests that these regions may make separate contributions to delayed-saccade task performance (see below). Moreover, the accuracy of delayed-saccades worsens as the retention interval is increased (Funahashi et al., 1993b; Gaymard et al., 1999), an effect that is yet to be demonstrated in the PPC. Such a *delay-dependency* strongly indicates a critical role in the maintenance of spatial information and not just oculomotion.

Transcranial magnetic stimulation (TMS) permits the application of temporary "virtual" lesions in humans and has been used to study the effects of disrupting the PFC and PPC during delayed-saccade tasks. Application of TMS does not induce eye movements (Zangemeister et al., 1995), but it does normally delay or in some cases facilitate saccade triggering during both visually and memory-guided saccades if applied shortly after the signal to move the eyes is given (Muri et al., 1996; Ro et al., 1999; Kapoula et al., 2001; Wipfli et al., 2001; Coubard et al., 2003; Kapoula et al., 2004; Yang and Kapoula, 2004). Again, this finding is consistent with the proposed role in saccade triggering. Although the accuracy of visually-guided saccades is not affected by TMS of the PFC and PPC, the accuracy of memory-guided saccades decreases, but this effect critically depends on which part of the cortex is stimulated and depends on when stimulation is applied. During delayed-saccade tasks, accuracy wors-

ens when the PPC is stimulated early in the delay (~200–300 ms), just after the visual cue is presented. However, accuracy worsens when the PFC is stimulated in the middle to later portions of the delay (Muri et al., 1996, 2000; Brandt et al., 1998). Early in the delay, sensory data are represented until that information can be transformed into a motor plan. The selective effect of PPC stimulation early in the delay may suggest an important role in the retrospective sensory coding of visual space. However, it may simply suggest that the PPC representations are more transient than those in the PFC. The selective effect of PFC stimulation late in the delay period is more difficult to interpret because it is unknown whether the FEF and/or more anterior dorsolateral PFC were disrupted by the TMS. A caudal–rostral gradient may exist along the dorsolateral PFC (e.g. areas 46 and 9/46) to the premotor cortex (e.g. FEF) where neurons represent progressively greater degrees of visuospatial to visuomotor information (di Pellegrino and Wise, 1993). Interestingly, Ploner et al. (1999) described patients with selective FEF damage and patients with FEF damage that extended into anterior dorsal PFC. Both sets of patients were impaired on a delayed-saccade task, but the pattern of errors suggested two mechanisms affected by the lesions. FEF lesions caused systematic errors (i.e. saccade endpoints were consistently hypometric with regard to the target), but dorsal PFC lesions caused variable errors (i.e. saccade endpoints fluctuated with regard to the target). The authors concluded that the FEF and dorsal PFC make distinct contributions to the maintenance of positional information, presumably related to the caudal–rostral functional gradient in the dorsal PFC. If true, systematic errors may result from errors in translating spatial information into a motor plan, a known role of the FEF. Variable errors may result from difficulties maintaining the exact spatial position of cued locations, a known role of the dorsolateral PFC (Funahashi et al., 1993a). Consistent with this hypothesis is the finding that FEF lesions in the monkey primarily cause hypometric memory-guided saccades (Sommer and Tehovnik, 1997; Dias and Segraves, 1999) and dorsolateral PFC lesions cause additional variability in the saccade endpoints (Sawaguchi and Goldman-Rakic, 1991; Funahashi et al., 1993b). Therefore, the delay-specific deficit following TMS when applied over human PFC may be the result of FEF disruption, a possibility that should be addressed by future work.

Spatial working memory, attention, and intention

Large-scale cortical and subcortical networks support diverse and complex behaviors like spatial working memory, spatial attention, and spatially-directed actions (i.e. intentions). However, it has been pointed out, based on the patterns of overlap from neuroimaging studies, that some of the processes implicated may share common neural resources (Awh and Jonides, 2001; Corbetta et al., 2002). With this idea in mind, the mechanisms that the FEF use to support spatial working memory, spatial attention, and spatial intention may be similar. This idea has support beyond simply the patterns of co-activation in functional imaging studies. Electrical microstimulation of monkey FEF neurons, at a level that does not induce a saccade, improves target detection at a location that matches the response field of the neuron that was microstimulated (Moore and Fallah, 2004). In other words, "activation" of a FEF neuron that would move the eyes to a specific location results in performance enhancements that are similar to those found after subjects are cued to covertly attend to a specific location. These data suggest that saccade planning is a viable mechanism that underlies spatial attention (Kowler et al., 1995). That is, neurons in the FEF may form a map of salient portions of space in oculomotor coordinates that can be read out to indicate the cued location in a spatial working memory task, the current direction of spatially-directed attention, or the direction toward which a movement is planned. In fact, there are probably many such maps of space that all code for saliency in some form or another. The different contributions of the PFC, FEF, and PPC to spatial behavior are likely to be dependent upon the area's differential connectivity; which types of information are sent to the area that form the basis of the map and which areas have access to the readout will determine its role.

Summary and conclusions

Functional neuroimaging of humans and electrophysiological recordings from monkeys implicate a widespread network of cortical and subcortical brain areas that together support the various sensory, motor, and memory functions required by tests of spatial working memory. The oculomotor network is an ideal system for the study of spatial working memory since it is arguably the best understood response output system in the primate. The oculomotor delayed-response task has been instrumental in attempts to differentiate the specific contributions of these brain structures to spatial working memory. Most importantly, maintenance-related activity during the retention interval can be separated from the visual and motor components of delay-response tasks (Hikosaka and Wurtz, 1983). Using this approach a small subset of regions, most notably the PFC, FEF, and PPC, shows evidence of persistent delay period activity. Studies of humans with brain damage and monkeys with experimental lesions have confirmed that damage to the PFC, FEF, and PPC does indeed cause impairments in the accuracy of delayed-saccades. Therefore, these areas are necessary for intact spatial working memory. The question of what type of information is carried by persistent activity still remains. Our recent fMRI studies, in which we have used modified versions of delayed-saccade tasks, indicate that persistent activity in the FEF and PPC may carry relatively different types of information. Retrospective sensory coding of space may be more prominent in the PPC, while prospective motor coding of space may be more prominent in the FEF. The disassociation is far from absolute, but the relative difference that we detect with fMRI is supported by TMS studies that have compared PFC/FEF and PPC stimulation during portions of the delay period in which visuospatial or motor planning is emphasized. Support has also come from the

different types of errors made during delayed-saccade tasks following lesions to the FEF and PPC. Studies are currently under way to further test these hypotheses with a special emphasis on the task parameters that modulate persistent signals in the brain.

REFERENCES

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220.

Awh E, Jonides J (2001) Overlapping mechanisms of attention and spatial working memory. Trends Cogn Sci 5:119–126.

Barash S, Bracewell RM, Fogassi L, Gnadt JW, Andersen RA (1991) Saccade-related activity in the lateral intraparietal area. II. Spatial properties. J Neurophysiol 66:1109–1124.

Belger A, Puce A, Krystal JH, Gore JC, Goldman-Rakic P, McCarthy G (1998) Dissociation of mnemonic and perceptual processes during spatial and nonspatial working memory using fMRI. Hum Brain Mapp 6:14–32.

Boussaoud D (2001) Attention versus intention in the primate premotor cortex. Neuroimage 14:S40–S45.

Brandt SA, Ploner CJ, Meyer BU, Leistner S, Villringer A (1998) Effects of repetitive transcranial magnetic stimulation over dorsolateral prefrontal and posterior parietal cortex on memory-guided saccades. Exp Brain Res 118:197–204.

Brown MR, DeSouza JF, Goltz HC, Ford K, Menon RS, Goodale MA, Everling S (2004) Comparison of memory- and visually guided saccades using event-related FMRI. J Neurophysiol 91:873–889.

Bruce CJ, Goldberg ME (1985) Primate frontal eye fields. I. Single neurons discharging before saccades. J Neurophysiol 53:603–635.

Bruce CJ, Goldberg ME, Bushnell MC, Stanton GB (1985) Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. J Neurophysiol 54:714–734.

Bruce CJ, Friedman HR, Kraus MS, Stanton GB (2004) The primate frontal eye field. In: The visual neurosciences (Chalupa LM, Werner JS, eds), pp 1428–1448. Cambridge, MA: The MIT Press.

Chafee MV, Goldman-Rakic PS (1998) Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J Neurophysiol 79:2919–2940.

Chafee MV, Goldman-Rakic PS (2000) Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. J Neurophysiol 83:1550–1566.

Colby CL, Goldberg ME (1999) Space and attention in parietal cortex. Annu Rev Neurosci 22:319–349.

Constantinidis C, Steinmetz MA (1996) Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. J Neurophysiol 76:1352–1355.

Constantinidis C, Franowicz MN, Goldman-Rakic PS (2001) The sensory nature of mnemonic representation in the primate prefrontal cortex. Nat Neurosci 4:311–316.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215.

Corbetta M, Kincade JM, Shulman GL (2002) Neural systems for visual orienting and their relationships to spatial working memory. J Cogn Neurosci 14:508–523.

Coubard O, Kapoula Z, Muri R, Rivaud-Pechoux S (2003) Effects of TMS over the right prefrontal cortex on latency of saccades and convergence. Invest Ophthalmol Vis Sci 44:600–609.

Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV (1998) An area specialized for spatial working memory in human frontal cortex. Science 279:1347–1351.

Curtis CE, D'Esposito M (2003) Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 7:415–423.

Curtis CE, D'Esposito M (2004) The effects of prefrontal lesions on working memory performance and theory. Cogn Affect Behav Neurosci 4:528–539.

Curtis CE, Rao VY, D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944–3952.

Curtis CE, Sun FT, Miller LM, D'Esposito M (2005) Coherence between fMRI time-series distinguishes two spatial working memory networks. NeuroImage 26:177–183.

D'Esposito M, Ballard D, Zarahn E, Aguirre GK (2000) The role of prefrontal cortex in sensory memory and motor preparation: an event-related fMRI study. Neuroimage 11:400–408.

di Pellegrino G, Wise SP (1993) Visuospatial versus visuomotor activity in the premotor and prefrontal cortex of a primate. J Neurosci 13:1227–1243.

Dias EC, Segraves MA (1999) Muscimol-induced inactivation of monkey frontal eye field: effects on visually and memory-guided saccades. J Neurophysiol 81:2191–2214.

Ferrera VP, Cohen JK, Lee BB (1999) Activity of prefrontal neurons during location and color delayed matching tasks. Neuroreport 10:1315–1322.

Funahashi S, Bruce CJ, Goldman-Rakic PS (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol 61:331–349.

Funahashi S, Chafee MV, Goldman-Rakic PS (1993a) Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. Nature 365:753–756.

Funahashi S, Bruce CJ, Goldman-Rakic PS (1993b) Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas." J Neurosci 13:1479–1497.

Fuster JM, Alexander GE (1971) Neuron activity related to short-term memory. Science 173:652–654.

Gaymard B, Ploner CJ, Rivaud-Pechoux S, Pierrot-Deseilligny C (1999) The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. Exp Brain Res 129:288–301.

Gaymard B, Lynch J, Ploner CJ, Condy C, Rivaud-Pechoux S (2003) The parieto-collicular pathway: anatomical location and contribution to saccade generation. Eur J Neurosci 17:1518–1526.

Gnadt JW, Andersen RA (1988) Memory related motor planning activity in posterior parietal cortex of macaque. Exp Brain Res 70:216–220.

Goldberg ME, Bisley J, Powell KD, Gottlieb J, Kusunoki M (2002) The role of the lateral intraparietal area of the monkey in the generation of saccades and visuospatial attention. Ann N Y Acad Sci 956:205–215.

Gottlieb J, Kusunoki M, Goldberg ME (2005) Simultaneous representation of saccade targets and visual onsets in monkey lateral intraparietal area. Cereb Cortex 15:1198–1206.

Hanes DP, Patterson WF 2nd, Schall JD (1998) Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. J Neurophysiol 79:817–834.

Heide W, Kompf D (1998) Combined deficits of saccades and visuospatial orientation after cortical lesions. Exp Brain Res 123:164–171.

Hikosaka O, Wurtz RH (1983) Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. J Neurophysiol 49:1268–1284.

Kapoula Z, Isotalo E, Muri RM, Bucci MP, Rivaud-Pechoux S (2001) Effects of transcranial magnetic stimulation of the posterior parietal cortex on saccades and vergence. Neuroreport 12:4041–4046.

Kapoula Z, Yang Q, Coubard O, Daunys G, Orssaud C (2004) Transcranial magnetic stimulation of the posterior parietal cortex delays the latency of both isolated and combined vergence-saccade movements in humans. Neurosci Lett 360:95–99.

Kojima S, Goldman-Rakic PS (1982) Delay-related activity of prefrontal neurons in rhesus monkeys performing delayed response. Brain Res 248:43–49.

Kowler E, Anderson E, Dosher B, Blaser E (1995) The role of attention in the programming of saccades. Vision Res 35:1897–1916.

Kubota K, Niki H (1971) Prefrontal cortical unit activity and delayed alternation performance in monkeys. J Neurophysiol 34:337–347.

Lebedev MA, Messinger A, Kralik JD, Wise SP (2004) Representation of attended versus remembered locations in prefrontal cortex. PLoS Biol 2:e365

Leung HC, Gore JC, Goldman-Rakic PS (2002) Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda. J Cogn Neurosci 14:659–671.

Li CS, Andersen RA (2001) Inactivation of macaque lateral intraparietal area delays initiation of the second saccade predominantly from contralesional eye positions in a double-saccade task. Exp Brain Res 137:45–57.

Li CS, Mazzoni P, Andersen RA (1999) Effect of reversible inactivation of macaque lateral intraparietal area on visual and memory saccades. J Neurophysiol 81:1827–1838.

Lynch JC (1992) Saccade initiation and latency deficits after combined lesions of the frontal and posterior eye fields in monkeys. J Neurophysiol 68:1913–1916.

Moore T, Fallah M (2004) Microstimulation of the frontal eye field and its effects on covert spatial attention. J Neurophysiol 91:152–162.

Muri RM, Vermersch AI, Rivaud S, Gaymard B, Pierrot-Deseilligny C (1996) Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. J Neurophysiol 76:2102–2106.

Muri RM, Gaymard B, Rivaud S, Vermersch A, Hess CW, Pierrot-Deseilligny C (2000) Hemispheric asymmetry in cortical control of memory-guided saccades. A transcranial magnetic stimulation study. Neuropsychologia 38:1105–1111.

Nystrom LE, Braver TS, Sabb FW, Delgado MR, Noll DC, Cohen JD (2000) Working memory for letters, shapes, and locations: fMRI evidence against stimulus-based regional organization in human prefrontal cortex. Neuroimage 11:424–446.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y (1991) Cortical control of memory-guided saccades in man. Exp Brain Res 83:607–617.

Ploner CJ, Rivaud-Pechoux S, Gaymard BM, Agid Y, Pierrot-Deseilligny C (1999) Errors of memory-guided saccades in humans with lesions of the frontal eye field and the dorsolateral prefrontal cortex. J Neurophysiol 82:1086–1090.

Postle BR, Stern CE, Rosen BR, Corkin S (2000a) An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. Neuroimage 11:409–423.

Postle BR, Berger JS, Taich AM, D'Esposito M (2000b) Activity in human frontal cortex associated with spatial working memory and saccadic behavior. J Cogn Neurosci 12:2–14.

Quintana J, Fuster JM (1999) From perception to action: temporal integrative functions of prefrontal and parietal neurons. Cereb Cortex 9:213–221.

Rivaud S, Muri RM, Gaymard B, Vermersch AI, Pierrot-Deseilligny C (1994) Eye movement disorders after frontal eye field lesions in humans. Exp Brain Res 102:110–120.

Ro T, Cheifet S, Ingle H, Shoup R, Rafal R (1999) Localization of the human frontal eye fields and motor hand area with transcranial magnetic stimulation and magnetic resonance imaging. Neuropsychologia 37:225–231.

Robinson DA, Fuchs AF (1969) Eye movements evoked by stimulation of frontal eye fields. J Neurophysiol 32:637–648.

Robinson DL, Goldberg ME, Stanton GB (1978) Parietal association cortex in the primate: sensory mechanisms and behavioral modulations. J Neurophysiol 41:910–932.

Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE (2000) The prefrontal cortex: response selection or maintenance within working memory? Science 288:1656–1660.

Sakai K, Rowe JB, Passingham RE (2002) Active maintenance in prefrontal area 46 creates distractor-resistant memory. Nat Neurosci 5:479–484.

Sawaguchi T, Goldman-Rakic PS (1991) D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251:947–950.

Schall JD (1991) Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. J Neurophysiol 66:559–579.

Schall JD (2002) The neural selection and control of saccades by the frontal eye field. Philos Trans R Soc Lond B Biol Sci 357:1073–1082.

Schall JD, Hanes DP, Thompson KG, King DJ (1995) Saccade target selection in frontal eye field of macaque. I. Visual and premovement activation. J Neurosci 15:6905–6918.

Schiller PH, Sandell JH, Maunsell JH (1987) The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. J Neurophysiol 57:1033–1049.

Simon SR, Meunier M, Piettre L, Berardi AM, Segebarth CM, Boussaoud D (2002) Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI. J Neurophysiol 88:2047–2057.

Sommer MA, Tehovnik EJ (1997) Reversible inactivation of macaque frontal eye field. Exp Brain Res 116:229–249.

Sommer MA, Wurtz RH (2000) Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. J Neurophysiol 83:1979–2001.

Sommer MA, Wurtz RH (2001) Frontal eye field sends delay activity related to movement, memory, and vision to the superior colliculus. J Neurophysiol 85:1673–1685.

Sun FT, Miller LM, D'Esposito M (2004) Measuring interregional functional connectivity using coherence and partial coherence analyses of fMRI data. Neuroimage 21:647–658.

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR (1996) Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol 75:454–468.

Takeda K, Funahashi S (2002) Prefrontal task-related activity representing visual cue location or saccade direction in spatial working memory tasks. J Neurophysiol 87:567–588.

Takeda K, Funahashi S (2004) Population vector analysis of primate prefrontal activity during spatial working memory. Cereb Cortex 14:1328–1339.

Thier P, Andersen RA (1998) Electrical microstimulation distinguishes distinct saccade-related areas in the posterior parietal cortex. J Neurophysiol 80:1713–1735.

Umeno MM, Goldberg ME (2001) Spatial processing in the monkey frontal eye field. II. Memory responses. J Neurophysiol 86:2344–2352.

Van Essen DC (2004) Organization of visual areas in macaque and human cerebral cortex. In: The visual neurosciences (Chalupa LM, Werner JS, eds), pp 507–521. Cambridge, MA: The MIT Press.

Wipfli M, Felblinger J, Mosimann UP, Hess CW, Schlaepfer TE, Muri RM (2001) Double-pulse transcranial magnetic stimulation over the frontal eye field facilitates triggering of memory-guided saccades. Eur J Neurosci 14:571–575.

Yang Q, Kapoula Z (2004) TMS over the left posterior parietal cortex prolongs latency of contralateral saccades and convergence. Invest Ophthalmol Vis Sci 45:2231–2239.

Zangemeister WH, Canavan AG, Hoemberg V (1995) Frontal and parietal transcranial magnetic stimulation (TMS) disturbs programming of saccadic eye movements. J Neurol Sci 133:42–52.

Zarahn E, Aguirre GK, D'Esposito M (1999) Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. Brain Res Cogn Brain Res 7:255–268.

Zarahn E, Aguirre G, D'Esposito M (2000) Replication and further studies of neural mechanisms of spatial mnemonic processing in humans. Brain Res Cogn Brain Res 9:1–17.