

WORKING MEMORY

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ABSTRACT

Working memory is an evolving concept that refers to the short-term storage of information that is not accessible in the environment, and the set of processes that keep this information active for later use. From a psychological perspective, working memory has been conceptualized as comprising multiple components such as executive control and active maintenance processes. This chapter will review functional neuroimaging studies (PET and fMRI) that have provided evidence that prefrontal cortex is a critical node in the functional neural network that supports working memory function. Also, recent data will be reviewed regarding the functional organization of prefrontal cortex.

1. INTRODUCTION

Working memory refers to the temporary representation of information that was just experienced or just retrieved from long-term memory but no longer exists in the external environment. These internal representations are short-lived, but can be maintained for longer periods of time through active rehearsal strategies, and can be subjected to various operations that manipulate the information in such a way that makes it useful for goal-directed behavior. Working memory is a system that is critically important in cognition and seems necessary in the course of performing many other cognitive functions such as reasoning, language comprehension, planning, and spatial processing. Although working memory is an evolving construct, most often definitions include both storage and (executive) control components (Miyake and Shah, 1999). Cognitive neuroscientists are searching for ways to disassociate the separable components of working memory in such that these separate functions can be localized within separate brain regions (i.e., *brain mapping*). Equally important is the goal of engineering models of the mechanisms by which the brain uses to support high-level cognitive processes like working memory.

INSERT FIGURE 1 HERE

The prefrontal cortex (PFC) appears to be the most important brain regions necessary for working memory (Figure 1). Two consistent findings from studies of monkeys performing delayed response tasks suggest a critical role for the PFC in working memory. First, experimental lesions of the principal sulcus in the dorsolateral prefrontal cortex (DLPFC) impair performance on working memory tasks (Jacobsen, 1936; Fuster, 1997; Curtis and D'Esposito, in press) and that exacerbate with increasing

memory retention intervals (Miller and Orbach, 1972; Bauer and Fuster, 1976; Funahashi et al., 1993). That is, forgetting increases not only when a delay is imposed but increases with the length of the delay. Second, electrophysiological single unit recordings from the DLPFC often show persistent, sustained levels of neuronal firing during the retention interval of delayed response tasks (Fuster and Alexander, 1971; Kubota and Niki, 1971; Funahashi et al., 1989). This sustained activity is thought to provide a bridge between the stimulus cue, for instance, the location of a flash of light, and its contingent response, for instance, a saccade to the remembered location. Persistent activity during blank memory intervals is a very powerful observation and established a strong link implicating the DLPFC as a critical node supporting working memory.

Subcomponents of working memory

A solid understanding of how working memory processes are implemented in the brain may hinge on our ability to resolve the nature of stored representations in addition to the types of operations performed on such representations necessary for guiding behavior (Curtis and D'Esposito, 2003a; Wood and Grafman, 2003). This is essentially restating in traditional cognitive science terminology that we must be able to dissociate storage functions (representations) and executive control functions (operations). *Representations* are symbolic codes for information stored either transiently or permanently in neuronal networks. Maintenance and storage are not synonymous. Storage, in the context of working memory, is the representation of memoranda through neuronal activity (i.e., an activity based definition (Miller and Cohen, 2001)). The term maintenance is used more broadly to describe both the active representation and any

processes that influences which items survive passive decay and distraction. *Operations* are processes or computations performed on representations. Examples of control processes or operations include the modification, transformation, integration, or manipulation of the originally encoded item.

Besides the representation-operation distinction, another key way to fractionate working memory into subcomponents is by considering the type of information that is being represented. This separation is essentially a further fractionation of the representation or storage subcomponent. In this regard, separate working memory subsystems selectively process and store different domains of information (e.g., space, object, verbal, visual, auditory, etc.). The most important distinction that has been made is between spatial and non-spatial visual information given the extensive literature showing segregated processing streams of visual information. A ventral “what” pathway primarily performs analyses of visual features eventually leading to object recognition as information from V1 travels through the occipital lobe to the inferior temporal lobe (Ungerleider and Mishkin, 1982). A dorsal “where” pathway primarily processes signals relating to motion and space often in service of visually guided actions as information travels from V1 through MT and the posterior parietal cortex finally to M1 and the dorsal premotor cortex (Milner and Goodale, 1995).

Models of working memory (Baddeley, 1986; Miyake and Shah, 1999) and models of PFC function (Goldman-Rakic, 1987; Passingham, 1993; D'Esposito et al., 2000a; Miller, 2000; Petrides, 2000a; Fuster, 2001; Miller and Cohen, 2001) vary substantially in the relative importance given to representations and operations (Curtis and D'Esposito, 2003a; Wood and Grafman, 2003). For example, Baddeley's model (Baddeley, 1986) of working memory proposes that information is represented in

various storage buffers depending on the form of the information (e.g., verbal or visuospatial). A central executive, similar to Norman and Shallice's supervisory attentional scheduler (Shallice and Burgess, 1996), is proposed to coordinate operations performed on the contents of information represented in memory. Some models attribute storage functions or representations to posterior cortical areas (e.g., premotor, parietal, and temporal cortex) and reserve the collection of "executive" operations for the PFC (Smith and Jonides, 1999; D'Esposito et al., 2000a; Petrides, 2000a).

Models of dorsolateral prefrontal cortical function

Founded on experimental lesion and unit recording data in awake-behaving monkeys, Goldman-Rakic (Goldman-Rakic, 1987) formalized her highly influential theory of PFC function. In this model, lesions of Brodmann's area 46 in the DLPFC impair the ability to maintain on-line sensory representations that are no longer present in the environment but are necessary for adaptive performance. Damage to the DLPFC results in the *forgetting* of relevant information. Persistent delay-period activity reflects the temporary storage of some stimulus feature like its position or shape (Funahashi et al., 1993; Chafee and Goldman-Rakic, 1998; Constantinidis et al., 2001). Although local operations permit for the feeding of sensory representations to neurons that control effectors, for example, the primary function of the DLPFC is proposed to create and maintain internal representations of relevant sensory information. Miller and Cohen (Miller and Cohen, 2001) extend this idea by suggesting that in addition to recent sensory information, integrated representations of task contingencies and even abstract rules (e.g., if this object then this later response) are also maintained in the prefrontal

cortex. This notion is similar to what Fuster has long emphasized (Fuster, 1997). Namely, that the PFC is critically responsible for temporal integration, the mediation of events separated in time but contingent on one another. Sustained delay-period activity may reflect the maintenance of several goal-directed representations including past sensory events (i.e., a retrospective code), but also representations of anticipated action and preparatory set (i.e., prospective codes) (Quintana and Fuster, 1999; D'Esposito et al., 2000b). All of these models emphasize that the DLPFC plays a prominent storage role in the temporary maintenance of relevant information through persistent neural activity.

However, other models place less emphasis on a storage role for the DLPFC and instead (or additionally) emphasize its role in providing top-down control over more posterior regions where information is actually stored (Smith and Jonides, 1999; D'Esposito et al., 2000a; Petrides, 2000b; Miller and Cohen, 2001). Thus, the sustained activity in the DLPFC does not reflect the storage of representations, *per se*; it reflects some maintenance operation or top-down process that influences which aspects of our external or internal milieu is actively maintained by other posterior areas. Studies showing the enhancement of task performance and changes in the properties of extrastriate cortex attributable to the focusing of visual attention have been influential in developing this viewpoint (Desimone and Duncan, 1995; Kastner and Ungerleider, 2001).

Although clearly we are able to perform a variety of high-level tasks that require “executive” control processes, this does not imply that a homunculus-like entity exists in the brain. In fact, among researchers a strong sentiment against the notion that an “executive control” module exists in the brain is best summarized by Goldman-Rakic,

“based on anatomical, physiological, and lesion evidence in both monkeys and humans, “a central-executive” in the form of an all-purpose polymodal processor may not exist, and to the contrary, a strong case can be made for the view that the substrates of cognition reside in a the parallelism of the brain’s modularized information processing systems” (Goldman-Rakic, 1996). Therefore, we must not confuse postulating that the PFC plays an important role in “executive control” processes and postulating that the PFC is the site of the central executive.

In summary, working memory is not a unitary system and can be viewed as a set of properties that characterize how this cognitive system makes use of temporarily activated representations to guide behavior. These properties may be behaviorally and neurally dissociable. Many methods exist to examine the neural basis of working memory in humans. The lesion method, for example, has been helpful in establishing the necessity of PFC in working memory function (for a review see (D’Esposito and Postle, 1999). However, since injury to PFC in humans is rarely restricted in its location, testing ideas about the necessity of a specific region of PFC for specific components of working with lesion studies in humans is difficult. Functional neuroimaging, such as positron emission tomography (PET), or functional MRI (fMRI), provides another means of testing such ideas and in fact are currently the best methods we have for investigating the physiology of the human brain (reviewed in the next section). It is important to realize however, that unlike lesion studies, imaging studies only support inferences about the *engagement* of a particular brain system by a cognitive process, but not about its *necessity* to these processes (Sarter et al., 1996). That is, neuroimaging studies cannot, alone, tell us whether the function of a neural system represents a neural substrate of that function, or rather a nonessential process that is

associated with that function. Moreover, this observation applies equally to all methods of physiological measurement, such as single- and multiunit electrophysiology, EEG or MEG. Thus, data derived from neuroimaging studies provide one piece of converging evidence that is being accumulated to determine the neural basis of working memory.

2. FUNCTIONAL NEUROIMAGING STUDIES OF WORKING MEMORY

Maintenance processes

There is now a critical mass of studies (i.e. more than 100 studies) that have used functional neuroimaging in humans to investigate brain regions engaged during working memory tasks (for review, see Curtis & D'Esposito, 2003; (D'Esposito et al., 1998b). Review of the details of each of these studies is beyond the scope of this chapter, however, those studies that highlight the critical advancements to our understanding of the neural basis of working memory will be considered. For example, Jonides and colleagues (1993) performed the first imaging study, using PET, which showed that PFC was activated during performance of a spatial working memory task that was analogous to the one used in the monkey studies. In this study, subjects were presented with two types of trials. In the memory condition, subjects were required to maintain the spatial location of three dots appearing on a visual display across a three second delay. After this delay, a probe for location-memory consisted of a single outline circle that either encircled the location of one of the previous dots or not. In the perception condition, the three dots were again presented on a visual display but immediately following their presentation, a probe circle appeared simultaneously with the dots, and the subject merely made a perceptual judgment as to whether or not the probe encircled a dot.

The rationale of this study was that “subtraction” of images obtained during the perceptual condition from images obtained from the memory condition would reveal brain regions that require the storage of spatial information during the retention interval, and not sensorimotor components of the task. Comparison of the block of trials with a delay period to a block of trials without a delay period produced activation within PFC, as well as occipital, parietal and premotor cortices. The location of the PFC activation in this study was within right Brodmann’s area 47 (inferior frontal gyrus), which is inferior to proposed homologous regions to the principal sulcus (area 46), the site of spatial working memory in monkeys (Funahashi et al., 1989; Funahashi et al., 1993). Nevertheless, this study was an important demonstration that human PFC, like monkey PFC, may be critical for maintaining internal representations across time. Subsequently, numerous other imaging studies have utilized delayed response tasks with requirements for storage of spatial (Jonides et al., 1993; McCarthy et al., 1994; Goldberg et al., 1996; McCarthy et al., 1996; Smith et al., 1996; Sweeney et al., 1996; Belger et al., 1998; Courtney et al., 1998; Petit et al., 1998; Awh et al., 1999; Postle and D’Esposito, 1999; Nystrom et al., 2000a; Postle et al., 2000b; Rowe et al., 2000; Zarahn et al., 2000; Pochon et al., 2001; Rowe and Passingham, 2001; Corbetta et al., 2002; Glahn et al., 2002; Leung et al., 2002; Sakai et al., 2002; Simon et al., 2002; Zald et al., 2002; Postle and D’Esposito, 2003; Brown et al., 2004; Curtis et al., 2004; Postle et al., 2004) as well as nonspatial (i.e. letters, words, faces, objects) information (Paulesu et al., 1993; Petrides et al., 1993; Awh et al., 1996; Fiez et al., 1996; Schumacher et al., 1996; Smith et al., 1996; Braver et al., 1997; Desmond et al., 1997; Jonides et al., 1997; Jonides et al., 1998; Rypma et al., 1999; Nystrom et al., 2000a; Chein and Fiez, 2001; Davachi et al., 2001; Barde and Thompson-Schill, 2002; Chein et al., 2002; Gruber and

von Cramon, 2003; Walter et al., 2003; Crottaz-Herbette et al., 2004). Also, many other studies have been performed using more complex types of working memory tasks such as n-back tasks (e.g. (Petrides et al., 1993; Cohen et al., 1994; McCarthy et al., 1994; Owen et al., 1996; Salmon et al., 1996; Smith et al., 1996). Consistent across these studies is the demonstration of lateral PFC activation, in a comparison between blocks of trials designed to have greater memory requirements than a matched control task.

A potential problem in interpretation of an imaging study such as that of Jonides, or the many others that were subsequently reported, is that they each rely on the assumptions of the method of cognitive subtraction. Cognitive subtraction attempts to correlate brain activity with specific processes by pairing two tasks that are assumed to be matched perfectly for every sensory, motor and cognitive process except the process of interest (Posner et al., 1988). For example, in the Jonides study it was assumed that the only difference between the two experimental conditions was the delay period, and therefore the process of memory storage. Although the application of cognitive subtraction to imaging was a major innovation when originally introduced (Petersen et al., 1988), it has become clear that it is a potentially flawed methodology that may lead to erroneous interpretation of imaging data.

The assumptions that must be relied upon for cognitive subtraction methodology can be faulty for at least two reasons. First, it involves the assumption of *additivity* (or *pure insertion*), the idea that a cognitive process can be added to a pre-existing set of cognitive processes without affecting them (Sternberg, 1969). For example, the delayed-response paradigm typically used to study working memory is comprised of a memory-requiring delay period between a “perceptual” process (the presentation of the item(s) to be stored) and a “choice” process (a required decision based upon the item

that was stored). The neural substrates of the memory process are proposed to be revealed by a subtraction of the integrated (i.e., averaged, summed, or totaled) functional hemodynamic signal during a no-delay condition (i.e., a block of trials without a delay period) from that during a delay condition (i.e. a block of trials with a delay period). In this example, failure to meet the assumptions of cognitive subtraction will occur if the insertion of a delay period between the “perceptual” and “choice” processes interacts with these other behavioral processes in the task. The non-memory processes may be different in delay trials as compared to no-delay trials; for example, more activation may be expected during the perceptual encoding epoch when the subject is aware that they are going to have to remember the spatial locations over a delay period.

A second reason that cognitive subtraction methodology can be faulty is that in neuroimaging, an additional requirement must be met in order for cognitive subtractive methodology to yield non-artifactual results: the transform between the neural signal and the neuroimaging signal must be linear. In two studies thus far using functional MRI (fMRI), some non-linearities have been observed in this system (Boynton et al., 1996; Vazquez and Noll, 1998). In our example of a delayed-response paradigm, failure will occur if the sum of the transform of neural activity to hemodynamic signal for the “perceptual” and “choice” processes differs when a delay is inserted as compared to when it is not present. In this example, artifacts of cognitive subtraction might lead to the inference that a region displayed delay-correlated increases in neural activity when in actuality it did not.

To overcome these potential problems, “event-related” fMRI designs were developed that do not rely on cognitive subtraction (for review, see (D'Esposito et al., 1998b; Rosen et al., 1998). These designs allow one to detect changes in fMRI signal

evoked by neural events associated with single behavioral trials as opposed to blocks of such trials, or as we will see even specific events within a trial. Event-related fMRI designs are somewhat analogous to designs employed in event-related potential (ERP) studies in that the functional responses occurring during different temporal portions of within trial can be analyzed.

As mentioned, spatial delayed-response tasks typically have a stimulus presentation period, an ensuing delay (of a few seconds), and a choice period. Changes in single unit neural activity have been observed during each of these task components in electrophysiological studies of non-human primates. For example, Fuster and colleagues, using a visual delayed-response task, observed that responses of single PFC neurons to the initial stimulus presentation ended within a few hundred milliseconds of stimulus offset (Fuster et al., 1982). They also observed changes in firing rate in single neurons in lateral PFC during the delay period that were sustained for several seconds. If these results also characterize human PFC function, it should be possible with an event-related fMRI design to resolve temporally functional changes correlated with the delay period from those correlated with the stimulus presentation/early delay period.

The logic of one implementation of an event-related fMRI design is as follows (Zarahn et al., 1997; Postle et al., 2000a) and is illustrated in Figure 2. A single behavioral trial may be hypothesized to be associated with one brief neural event, or several brief neural events that are subcomponent processes that are engaged within a trial (i.e. encoding or retrieval in a delayed-response task). A neural event will cause a brief fMRI signal change, which is called the hemodynamic response. If we wish to detect and differentiate the fMRI signal evoked by a series of sequential neural events

(i.e., such as the presentation of the stimulus and, seconds later, the execution of the response), one method would be to statistically model the evoked fMRI signal using a pair of hemodynamic responses as covariates, each shifted to the appropriate time period where the event of interest is thought to occur. Importantly, covariates shaped like hemodynamic response functions could theoretically be used to model any neural event, even if the event is sustained, such as delay period activity.

INSERT FIGURE 2 HERE

Analyzed in the manner described above, during the performance of a spatial delayed-response task, we observed that several brain regions, including PFC, consistently displayed activity that correlated with the delay period across subjects (Zarahn et al., 1996, 1999). This finding suggests that these regions may be involved in temporary maintenance of spatial representations in humans. With this event-related fMRI design, we could be confident that activity observed was not due to differences in other components of the task (i.e., presentation of the cue or motor response) during the behavioral trials. Most importantly, these results do not rely on the assumptions of cognitive subtraction. An example of the time series of the fMRI signal averaged across trials for a PFC region displaying delay-correlated activity is shown in Figure 3a.

INSERT FIGURE 3 ABOUT HERE

In this same study, we also found direct evidence for the failure of cognitive subtraction (see Figure 3b). We found a region in PFC that did not display sustained activity during the delay (in an event-related analysis) yet showed greater activity in the delay trials as compared to the trials without a delay. In any blocked neuroimaging

study, such as those reviewed above, that compares delay versus no-delay trials with subtraction, such a region would be detected and likely assumed to be a “memory” region. Thus, this result provides empirical grounds for adopting a healthy doubt regarding the inferences drawn from imaging studies that have relied on cognitive subtraction.

Other studies using event-related designs have also investigated the temporal dynamics of neural activity but during working memory tasks using non-spatial information. For example, Courtney and colleagues (Courtney et al., 1997) utilized a delayed response task that required the maintenance of faces. Ventral occipito-temporal regions exhibited predominantly transient responses to the stimuli, consistent with a role in perceptual processing, whereas PFC demonstrated sustained activity over the memory delay, consistent with a role in active maintenance of face information. We now briefly summarize major findings from imaging studies of working memory categorized by the type of information that is being maintained (i.e., verbal, spatial, object). We focus on studies that used event-related designs that allowed the investigators to separate maintenance activity during delay periods from the encoding and response periods of delayed-response type tasks.

Spatial working memory maintenance

Past human neuroimaging studies have generally implicated widespread and distributed frontal-parietal networks during the performance of spatial working memory tasks (Jonides et al., 1993; McCarthy et al., 1994; Goldberg et al., 1996; McCarthy et al., 1996; Smith et al., 1996; Sweeney et al., 1996; Belger et al., 1998; Courtney et al., 1998; Petit et al., 1998; Awh et al., 1999; Postle and D'Esposito, 1999; Nystrom et al.,

2000a; Postle et al., 2000b; Rowe et al., 2000; Zarahn et al., 2000; Pochon et al., 2001; Rowe and Passingham, 2001; Corbetta et al., 2002; Glahn et al., 2002; Leung et al., 2002; Sakai et al., 2002; Simon et al., 2002; Zald et al., 2002; Postle and D'Esposito, 2003; Brown et al., 2004; Curtis et al., 2004; Postle et al., 2004). Event-related fMRI studies that have isolated delay period activity have provided consistent evidence that signals in the frontal eye fields (FEF), nearby posterior portions of superior frontal sulcus (area 8), and the intraparietal sulcus (IPS) persist throughout the entire delay period (Courtney et al., 1998; Zarahn et al., 1999; Postle et al., 2000b; Rowe et al., 2000; Zarahn et al., 2000; Leung et al., 2002; Sakai et al., 2002; Brown et al., 2004; Curtis et al., 2004). For example, Curtis et al., (2004) scanned subjects while they performed oculomotor delayed response tasks that required maintenance of the spatial position of a single dot of light over a delay period after which a memory-guided saccade was generated. Both the FEF and IPS time courses showed activity that spanned the entire delay period (Figure 4). Importantly, we were also able to demonstrate that the magnitude of FEF and IPS delay period activity predicted the accuracy of the memory-guided saccade generated later after the delay. This relationship suggests that the fidelity of the stored location is reflected in the delay period activity. Therefore, both the FEF and the IPS may be involved in the storage of spatial information.

INSERT FIGURE 4 HERE

Findings from monkey (Bruce and Goldberg, 1985; Schlag and Schlag-Rey, 1987; Schall and Thompson, 1999; Andersen and Buneo, 2002) and human (Sweeney et al., 1996; Luna et al., 1998; Grosbras et al., 2001; Connolly et al., 2002; Cornelissen

et al., 2002; Curtis and D'Esposito, 2003b; DeSouza et al., 2003) studies suggest that the FEF contain representations of saccadic intentions. The FEF contains an organized map of visual space defined in oculomotor coordinates (Bruce and Goldberg, 1985). Therefore, the activity in the FEF during spatial working memory tasks could reflect the activity of neurons that are responsible for moving the eyes to the remembered location, referred to as a *prospective motor code*. 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. Curtis et al., (2004) provide evidence for this type of motor coding of space by comparing two conditions in which subjects were biased towards or against the use of a prospective motor code. In one condition (match), subjects can plan a saccade to acquire the target as soon as it appears and can 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, a saccade was made after the retention interval to an unpredictable location that did not match the location of the sample (non-match-to-sample). The subject 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, or sustained spatial attention. Delay period activity was greater for the match compared to non-match conditions in the FEF suggesting a plausible mechanism by which the FEF contributes to spatial working memory. The sustained activity in the FEF likely reflects the representation of the saccade vector to acquire the target location of the sample.

Support for this interpretation comes from monkey (Bruce and Goldberg, 1985; Schlag and Schlag-Rey, 1987; Schall and Thompson, 1999; Andersen and Buneo, 2002) and human (Sweeney et al., 1996; Luna et al., 1998; Grosbras et al., 2001; Connolly et al., 2002; Cornelissen et al., 2002; Curtis and D'Esposito, 2003b; DeSouza et al., 2003; Brown et al., 2004) studies that suggest that the FEF contains representations of saccade intentions. Indeed, FEF contains an organized map of visual space defined in oculomotor coordinates (Bruce and Goldberg, 1985). Delay period activity was greater for the non-match compared to match trials in the IPS suggesting that when a motor intention cannot be maintained and another mechanism is enacted such as maintenance of spatially directed covert attention. Activity in posterior parietal cortex has consistently been linked to the representation of space in electrophysiological studies of monkeys (Gnadt and Andersen, 1988; Constantinidis and Steinmetz, 1996; Gottlieb and Goldberg, 1999; Goldberg et al., 2002) and imaging studies of humans (Heide et al., 2001; Sereno et al., 2001; Merriam et al., 2003; Brown et al., 2004).

Again, activity in the FEF was greater during the delay period on trials when subjects knew the direction of the memory-guided saccade (match) compared to trials when subjects did not know the direction of the memory-guided saccade (non-match, see Figure 4). Therefore, a plausible mechanism for spatial maintenance is the sustained activation of oculomotor neurons whose response field matches the location of the memory cue. Another possibility exists that must also be considered. The activation of the FEF neurons could be a form of spatial rehearsal, similar to the way that Broca's area is thought to support verbal rehearsal with subvocal motor articulations that refresh phonological representations stored in posterior parietal cortex. The FEF could refresh the spatial representations stored in posterior parietal cortex via

subthreshold activation of FEF neurons coding for tagged portions of space. Importantly, humans with lesions in the FEF have impaired visually guided (Rivaud et al., 1994) and memory guided saccades (Pierrot-Deseilligny et al., 1991).

Verbal working memory maintenance

In no other area of working memory research has Baddeley and colleagues' model (1986) been more influential. This stems from the fact that the most formalized aspect of their model is the *phonological loop*, a subsystem of working memory that is proposed to maintain verbal information. The phonological loop is thought to operate via two mechanisms. First, a *phonological store* is thought to contain representations of speech sounds (phonemes) whose activations decay passively and rapidly over time. Second, an *articulatory rehearsal process* is thought to actively refresh the phonological representations that need to be maintained and is primarily a subvocal process that we all can observe through introspection. Data from both PET and fMRI studies suggest that separate frontal and parietal regions may support these separate storage and rehearsal processes. Inferior posterior parietal cortex (i.e., areas 39 and 40) is thought to be the most important substrate for phonological storage of verbal information, while cortical areas that support the motor aspects of speech production (i.e., Broca's area 44, SMA, and cerebellum) are thought to be critical for articulatory rehearsal (Paulesu et al., 1993; Petrides et al., 1993; Awh et al., 1996; Fiez et al., 1996; Schumacher et al., 1996; Smith et al., 1996; Braver et al., 1997; Desmond et al., 1997; Jonides et al., 1997; Jonides et al., 1998; Rypma et al., 1999; Nystrom et al., 2000a; Chein and Fiez, 2001; Davachi et al., 2001; Barde and Thompson-Schill, 2002; Chein et al., 2002; Gruber and von Cramon, 2003; Walter et al., 2003; Crottaz-Herbette et al., 2004). Although the

evidence linking the frontal premotor areas with articulatory rehearsal processes is particularly consistent, establishing that the inferior parietal cortex does indeed serve as a phonological storage area, consistent with Baddeley's model, continues to be debatable. Several studies have failed to find predicted activation in the left inferior posterior parietal cortex (Jonides et al., 1998; Becker et al., 1999; Chein and Fiez, 2001). Nonetheless, much of the data support such a relationship. Using an event related design, Chein and Fiez (2001) reported that Broca's area and area 40 of the inferior parietal cortex showed a pattern of sustained activity during the delay period of a verbal working memory task (See Figure 5). This was a critical demonstration that was required if these regions are indeed involved in verbal storage during the memory delay.

INSERT FIGURE 5 HERE

The investigators also tested two other important predictions that are made by Baddeley's model that states that the phonological loop is actually composed of distinct storage and rehearsal mechanisms. Performance on tests of verbal working memory is better for phonologically distinct words compared to performance when the words are phonologically similar (e.g., toy, boy, joy). The so-called *word-similarity effect* is thought to stem from confusions in the storage of overlapping representations and is predicted to tax the phonological storage system. Performance on verbal working memory tasks is also worse when words that are longer, or have more syllables, are used. The so-called *word-length effect* is thought to stem from the increased time it takes to subvocalize the words, allowing more time for passive decay of the stored representations. Thus, the word-length effect is predicted to tax articulatory rehearsal processes. Chein and Fiez (2001) showed that the signal in Broca's area was greater

during the delay period on trials in which subjects were maintaining 3-syllable words compared to 1-syllable words. The sustained activity in Broca's area was consistent with articulatory rehearsal because it showed a word-length effect. The left inferior parietal cortex (area 40) showed a word-similarity effect – activity was greater on trials when the words were phonological related compared to when they were distinct. The increased signal for pseudo words (e.g., blick, rame, scote) is also consistent with a phonological storage role because increased demands are placed on phonological storage when semantic representations are absent (Jonides et al., 1998). Therefore, frontal premotor regions, especially Broca's area, and the inferior parietal cortex are the key substrates implicated in processes necessary for the maintenance of verbal material.

Object working memory maintenance

A number of studies have now accumulated that investigated the maintenance of objects, mostly visually presented faces, houses, and line drawings that are not easily verbalizable (Courtney et al., 1994; Haxby et al., 1994; Smith et al., 1995; Courtney et al., 1996; McCarthy et al., 1996; Courtney et al., 1997; Belger et al., 1998; Cullen et al., 1998; Postle and D'Esposito, 1999; Curtis et al., 2000b; Curtis et al., 2000a; Haxby et al., 2000; Jha and McCarthy, 2000b; Jiang et al., 2000; Mecklinger et al., 2000; Pollmann and von Cramon, 2000; Postle et al., 2000c; Druzgal and D'Esposito, 2001; Rama et al., 2001; Mecklinger et al., 2002; Druzgal and D'Esposito, 2003; Linden et al., 2003; Postle et al., 2003; Sala et al., 2003). Consistently, posterior cortical areas along the inferior temporal lobe that normally respond to the visual presentation of select objects also tend to activate during object working memory tasks. Therefore, the

temporal lobe appears to play an important role in short-term storage of object features. For example, the fusiform gyrus, the ventral convexity surface of the temporal lobe, activates to a greater extent when a subject is shown pictures of faces compared to other types of complex visual stimuli like pictures of houses or scenes or household objects (Kanwisher et al., 1997) and given its somewhat selective response properties has been termed the “fusiform face area” or FFA.

There are four important findings that indicate that posterior extrastriate cortical regions like the FFA play an important role in the mnemonic storage of object features. First, the FFA shows persistent delay period activity (Druzgal and D'Esposito, 2001; Rama et al., 2001; Druzgal and D'Esposito, 2003; Postle et al., 2003) during working memory tasks. Second, the activity in the FFA is somewhat selective for faces; it is greater during delays in which subjects are maintaining faces compared to other objects (Sala et al., 2003). Third, as the number of faces that are being maintained increases, the magnitude of the delay period activity increases in the FFA (Jha and McCarthy, 2000a; Druzgal and D'Esposito, 2001, 2003). Such *load-effects* strongly suggest that a role in short term storage because as the number of items that must be represented increases so should the storage demands and so should the measured fMRI signals. Fourth, using a delayed paired associates task, Ranganath et al., (2004) has shown that the FFA responds during an unfilled delay interval following the presentation of a house that the subject has learned is associated with a certain face. Therefore, the delay period FFA activity likely reflects the reactivated image of the associated face that was retrieved from long-term memory (see Figure 6) despite that no face was actually presented before the delay. Together, these studies suggest that posterior regions of visual association cortex, like the FFA, participate in the internal storage of specific

classes of visual object features. Most likely, the mechanisms used to create internal representations of objects that are no longer in our environment are similar to the mechanisms used to represent objects that exist in our external environment.

INSERT FIGURE 6 HERE

There have been several reports of delay period specific activations in the PFC during object working memory tasks as well (Smith et al., 1995; Courtney et al., 1996; McCarthy et al., 1996; Smith et al., 1996; Courtney et al., 1997; Manoach et al., 1997; Belger et al., 1998; Cohen et al., 1998; Courtney et al., 1998; Postle and D'Esposito, 1999; Jha and McCarthy, 2000b; Nystrom et al., 2000a; Postle et al., 2000c; Stern et al., 2000; Rama et al., 2001; Munk et al., 2002; Pessoa et al., 2002; Druzgal and D'Esposito, 2003; Ranganath et al., 2003; Sala et al., 2003). However, the localization of the delay period activity appears varied across the dorsal, ventral, and medial portions of the PFC. The most consistent finding in that regard may be a greater bias towards right hemisphere activation for object working memory compared to verbal working memory.

3. CURRENT ISSUES AND FUTURE DIRECTIONS

What is the meaning of persistent activity during working memory delays?

Working memory allows animals to use information that is not currently present in the environment but is vital to adaptive behavior. Internal representations must be formed and sustained such that the cross-temporal contingencies can be established. Sustained neural activity during the delay period between a sensory cue, say the position of a briefly flashed spot of light, and a later motor response, say a shift of gaze

to the remembered location, is compelling evidence that this activity is a memory representation (Fuster and Alexander, 1971; Kubota and Niki, 1971; Gnadt and Andersen, 1988; Funahashi et al., 1989). Over 30 years has elapsed since these initial observations, but the nature of these signals remains elusive. What is actually being represented in various brain regions during working memory delays? For example, during a memory delay, one may need to look back to a past perceptual event in order to maintain a *retrospective* sensory code, or may need to look forward to a future action to maintain a *prospective* motor code, in order to link events that are separated in time but are contingent upon one another (Boussaoud and Wise, 1993; Funahashi et al., 1993; Quintana and Fuster, 1999; Rainer et al., 1999; D'Esposito et al., 2000b; Curtis et al., 2004). It is likely that different brain regions represent different types of memory codes. As Fuster has written, ongoing behavior can be thought of as a stage of a chained perception-action cycle, and the brain represents information at many different levels. There are several different strategies that functional neuroimaging studies can use to attempt determine the code represented in different brain regions.

A good example of one strategy has already been discussed. The Curtis et al. (2004) (see Figure 4) study experimentally manipulated factors that biased subjects towards or against the use of a prospective motor code. The nature of the persistent signals could be inferred from brain areas that were sensitive to this manipulation. That example demonstrates how one might begin to test hypotheses about the mechanisms that give rise to delay period activity. Another method is to systematically manipulate factors that affect storage and evaluate whether or not delay activity is similarly affected. This idea has been explored by increasing the memory load by increasing the number items to represent in memory, which should tax storage mechanisms. Several studies

now have manipulated load to test whether the persistent activity in the dorsolateral PFC that has been repeatedly noted reflects the storage of visually presented material. Three event-related fMRI studies that manipulated memory load have failed to find that the delay period activity was affected by load (Rypma and D'Esposito, 1999; Jha and McCarthy, 2000a; Postle et al., 2000b). For example, Jha and McCarthy (Jha and McCarthy, 2000a) reported that remembering 3 faces did not evoke greater delay period activity in the DLPFC than remembering 1 face at any point during 15 or 24 s memory delays. These findings, thus, are contrary to the view that the DLPFC simply maintains task relevant representations. However, Leung, Gore, and Goldman-Rakic (Leung et al., 2002) recently demonstrated that the DLPFC does not sustain a significant level of activity throughout a 18 s delay when maintaining 3 faces in memory, but does so if 5 faces are required to be remembered. Two recent studies from our laboratory have also detected significant effects of memory load on delay period DLPFC activity during a face (Druzgal and D'Esposito, 2003) and letter (Rypma et al., 2002) working memory task. Although mixed, some studies find that DLPFC activity increases when the number of items to be maintained increases. This seems to support the conclusion that the DLPFC plays an important role in memory storage – since increasing the demands of storage should be expected to increase BOLD signal in a region where representations are being actively stored – but there are equally plausible explanations that need to be investigated. First, the DLPFC activity may reflect top-down biasing signals to more posterior regions where the representations are actually stored (Miller and Cohen, 2001; Curtis and D'Esposito, 2003a). Second, the large memory loads could be beyond the capacity of working memory and might invoke strategic changes in the way information is represented (Cowan, 2001). Rypma et al. (Rypma and

D'Esposito, 1999; Rypma et al., 2002) have argued that the increased signal changes with increased load in the DLPFC are the consequence of the strategic process of data compression (e.g., chunking) because these effects are most prominent during the cue period when encoding takes place. Strategic organization of memoranda is a control process that is distinct from raw storage of representations.

Another method for determining the nature of the representations in different brain regions is to disrupt maintenance and look for dissociations of brain activity. For example, the level of activity in area 46 correlates with how resistant the memory representation is to performance degradation caused by distraction (Sakai et al., 2002). Subjects first encoded the order and spatial position of 5 cues and before memory was tested, subjects performed a secondary spatial distraction task. In area 46, but not premotor area 6/8 or IPS, the level of persistent activity prior to the distraction correlated with memory performance after the distraction (Figure 7). The increased level of activity may have reflected the amount of rehearsal or some other process that transformed the representations into a form that was less susceptible to distraction. Overall, the goal of future research in this area should focus on the meaning of persistent signals in the PFC since these signals are key to understanding the implementation of working memory in the brain.

INSERT FIGURE 7 HERE

What is the functional organization of the lateral PFC?

While there is strong support that lateral PFC is critical for WM maintenance processes, it is unclear whether functional subdivisions within PFC exist. Goldman-Rakic

and colleagues first put forth a proposal that different PFC regions are critical for active maintenance of different types of information. Based on monkey electrophysiological and lesion studies (Funahashi et al., 1989; Wilson et al., 1993), it was proposed that persistent activity within ventrolateral PFC reflects the temporary maintenance of nonspatial codes (such as an object's color and shape) whereas dorsolateral PFC activity reflects maintenance of spatial codes (such as the location of an object in space). This hypothesis had the appeal of parsimony, as a similar organization exists in the visual system which is segregated into "what" and "where" pathways (Ungerleider and Haxby, 1994). Also, anatomical studies in monkeys have demonstrated that parietal cortex (i.e., spatial vision regions) predominantly projects to a dorsal region of lateral PFC (Petrides and Pandya, 1984; Cavada and Goldman-Rakic, 1989), whereas temporal cortex (i.e., object vision regions) projects more ventrally within lateral PFC (Barbas, 1988).

Numerous functional neuroimaging studies of humans have attempted to test this hypothesis regarding PFC organization (for a review, see (D'Esposito et al., 1998a)). For example, in a blocked design PET study of delayed-response tasks using faces and locations of faces as stimuli (Courtney et al., 1996), it was found that a direct comparison of the two memory conditions revealed that the spatial working memory task resulted in greater activation within left superior frontal sulcus (Brodmann's areas 8,6) and the face working memory task resulted in greater activation in a more ventral right PFC region (areas 9,45,46). In a follow-up study using an event-related fMRI design (Courtney et al., 1998), a double dissociation was found between face and spatial working memory. It was observed that within the superior frontal sulcus in both hemispheres there significantly more sustained activity during spatial, than during face working memory

delay periods. By contrast, left inferior frontal gyrus showed significantly more sustained activity during face than during spatial working memory delay periods.

Another possible axis along which human lateral PFC may be organized is according to the type of operations performed upon information being actively maintained, rather than the type of information being maintained. For example, Petrides proposed that there are two processing systems, one dorsal and the other ventral, within lateral PFC (Petrides and Pandya, 1994). It was proposed that ventral PFC (Brodmann's areas 45, 47) is the site where information is initially received from posterior association areas and where active comparisons of maintained information are made. In contrast, dorsal PFC (areas 9, 46, 9/46) is recruited only when "monitoring" and "manipulation" of this information is required.

This model received initial support from an empirical PET study performed by Owen, Petrides and colleagues (Owen et al., 1996) in which dorsal PFC activation was found during three spatial working memory tasks thought to require greater monitoring of remembered information than two other memory tasks, which activated only ventral PFC. We also tested this model of process-specific PFC organization using event-related fMRI (D'Esposito et al., 1999). In our study, subjects were presented two types of trials in random order in which they were required to either (1) *maintain* a sequence of letters across a delay period or (2) *manipulate* (alphabetize) this sequence during the delay in order to respond correctly to a probe. In every subject, delay-period activity was found in both dorsal and ventral PFC in both types of trials. However, dorsal PFC activity was greater in trials during which actively maintained information was manipulated. These findings suggest that dorsal PFC may exhibit greater recruitment during conditions where

additional processing of actively maintained information is required supporting a process-specific PFC organization.

On the surface, these two models of PFC organization seem incompatible, and to this day papers continue to be published pitting one against the other. However, a closer look at the empirical data from human functional imaging, and monkey physiology studies, over the past 10 years leads to the conclusion that both models accurately describe PFC organization. Part of the reason for the persistence of the notion that these models are orthogonal to each other resulted from a lack in preciseness of the anatomical definitions of dorsal and ventral PFC that were being used. For example, as reviewed above, the principal evidence cited to support the “domain-specific” PFC organization (Goldman-Rakic and Leung, 2002) derives from studies by Courtney and colleagues who found that the superior frontal sulcus (area 6/8) appears specific to spatial working memory whereas regions within inferior frontal gyrus (areas 45, 47) appears specific to nonspatial information (e.g. faces). Unquestionably, the superior frontal sulcus is anatomically “dorsal” to the inferior frontal gyrus, Thus, on the surface these data provide strong support for a dorsal-what vs. ventral-where, domain-specific PFC organization.

However, other evidence from monkey physiological and human functional imaging studies seem inconsistent with the domain-specific hypothesis because they provide evidence that certain dorsal and ventral PFC regions do not appear specific to a one domain of information. For example, several single-unit recording studies during delayed response tasks have found a mixed population of neurons throughout dorsal and ventral regions of lateral PFC that are not clearly segregated by the type of

information (i.e. spatial versus nonspatial) that is being stored (Rosenkilde et al., 1981; Fuster et al., 1982; Quintana et al., 1988; Rao et al., 1997). Also, cooling of PFC (Fuster and Bauer, 1974; Bauer and Fuster, 1976; Quintana and Fuster, 1993) and dorsal PFC lesions cause impairments on nonspatial working memory tasks (Mishkin et al., 1969; Petrides, 1995). and ventral PFC lesions cause spatial impairments (Mishkin et al., 1969; Iversen and Mishkin, 1970; Butters et al., 1973). Finally, another study found that ventral PFC lesions in monkeys did not cause delay-dependent defects on a visual pattern association task and color matching task (Rushworth et al., 1997). Also, there are numerous human functional imaging studies that have failed to find different patterns of PFC activation during spatial vs. non-spatial working memory tasks (e.g. (Owen et al., 1998; Postle et al., 1999; Nystrom et al., 2000b).

How can we reconcile all of these findings? The answer emerges from a close examination of the particular PFC regions that do, or do not exhibit persistent activity that is specific to a particular type of information. Thus, domain-specificity may exist within the superior frontal sulcus (area 6/8) and portions of the inferior frontal gyrus (areas 44, 45, 47) but other lateral PFC regions, such as middle frontal gyrus (areas 9, 46, 9/46) may not show domain-specificity. Thus, a coarse subdivision of PFC into dorsal and ventral regions fails to account for the possibility that both domain-specific and process-specific organization may exist. Thus, a hybrid model of PFC organization could accommodate the empirical findings (Postle and D'Esposito, 2000).

A problem with a hybrid model is that it is extremely difficult to capture, in cognitive or neural terms, the specific type of processes that are being attributed to the middle frontal gyrus (areas 9, 46, 9/46). Are the processes attributed to this region, e.g.

“monitoring” and “manipulation”, distinct from active maintenance processes? For example, one possibility is that “monitoring” and “manipulation” tasks recruit middle frontal gyrus because they require active maintenance of more abstract relations (e.g., semantic, temporal, etc) between items (Wendelken, 2001). In this view, the PFC is not organized by different types of processing modules, but by the abstractness of the representations being actively maintained. This organization could be hierarchic, ranging from features of an object (e.g., red), to more abstract dimensions (e.g., color), to superordinate representations such as goals or task context (e.g., color naming task). Recent evidence from functional neuroimaging studies has begun to provide support for this idea.

Considerable evidence exists that premotor cortex (BA 6) is involved in the selection of responses when guided by simple stimulus features (Schumacher and D'Esposito, 2002; Jiang and Kanwisher, 2003a, b; Schumacher et al., 2003). For example, Schumacher and D'Esposito (2002) manipulated the difficulty of response-selection based on two factors: the compatibility of a spatial location and a manual response and the ease with which a cue stimulus could be perceptually discriminated from surrounding distractor stimuli. In contrast to ventral PFC regions, which showed little sensitivity to either manipulation, and to the dorsal PFC, which was exclusively sensitive to compatibility, premotor cortex was additively sensitive to both spatial and visual manipulations of the cue features. Similarly, evidence from single-unit recording of monkey suggests that premotor cortex, and not dorsal PFC, encodes simple response mappings (Weinrich et al., 1984; Wallis and Miller, 2003). In contrast to premotor cortex, several studies have shown that dorsal PFC encodes the abstract relationship between a stimulus and a response based on a contextual cue (Bunge et al., 2003; Wallis and

Miller, 2003; Boettiger and D'Esposito, in press). And finally, frontopolar cortex (BA 10; FPC) has been implicated in relying on a high-level goal or task context in order to interpret a cue during selection of an action. Such processing is critical to the extent that a cue does not map directly to a response, but requires the subject to reflect on additional, remembered contextual information or goals to interpret the cue (Koechlin et al., 1999; Koechlin et al., 2003; Sakai and Passingham, 2003). For example, Badre and Wagner (Badre and Wagner, 2004) observed greater FPC activation when a cue for the response was symbolic and arbitrary, in contrast to directly naming the response, and so had to be verified with respect to the remembered trial context (in this case the serial order in which the appropriate response had been recently presented). Furthermore, this activation in FPC was evident even when simpler order response selection demands were minimal, as the appropriate response had been prepared in advance.

A recent neuroimaging study has tested this model of hierarchical PFC organization all within one set of experiments (Koechlin et al., 2003). In this fMRI study, the frequency of to-be-selected representations was manipulated in an effort to impact levels of PFC processing. Manipulation of the number of responses within a block primarily affected premotor cortex. Manipulation of the number of relevant stimulus dimensions within a block impacted dorsolateral PFC. Finally, manipulation of the across-block frequency of cue-to-response or cue-to-dimension mappings impacted FPC responses. Interestingly, structural equation modeling of the fMRI data revealed path coefficients from FPC to dorsal PFC to premotor cortex but not in the opposite direction, broadly consistent with a hierarchic organization. An important contribution from this study is that it considers the entire frontal cortex, from premotor regions to the most anterior portion of prefrontal cortex (area 10), an area that has been relatively ignored in

working memory research. This type of PFC organization is also consistent with data derived from a connectionist model (O'Reilly et al., 2002) which demonstrated that a connectionist model possessing a concrete feature level and an abstract dimension level in its "PFC" could produce the double dissociations reported in the monkey data.

Miler and Cohen (2001) have presented a synthesis of empirical findings with a theoretical model regarding how basic maintenance processes subserved by the PFC can exert cognitive control. They propose PFC delay activity is specific to those representations that are behaviorally relevant, enabling an animal or human to prospectively integrate across time when selecting an action. Automatic behaviors can be mediated by computations in posterior neocortices with little influence from internal goals maintained by the PFC. When "bottom-up" processes are insufficient for or in conflict with current goals, available cues may be insufficient to uniquely specify a response. Under such circumstances, the active maintenance of behavioral relevant representations permits the appropriate selection for action.

The PFC has extensive reciprocal connections with most of the brain and is situated at the apex of mnemonic, affective, perceptual, and motor pathways arising from posterior and subcortical processors. Thus, it is in a privileged position to store behaviorally relevant representations and exert cognitive control. Frontal cortex appears hierarchically organized, not simply in a dorsal/ventral fashion, but in a posterior/anterior direction from premotor regions to frontopolar cortex (Figure 8). Future research must continue to determine the regional distinctions that define functional topography of frontal cortex, and the principles by which these regions interact to produce controlled behavior. A critical mass of human functional imaging studies, combined with monkey lesion and

physiological studies of monkeys, have begun to call into question traditional distinctions in PFC organization. A newer framework suggests there is flexibility in functional boundaries and that function versus content theoretical accounts may fail to be mutually exclusive where boundaries exist (Badre and Wagner, 2004).

INSERT FIGURE 8 HERE

In summary, goal-directed behavior, which is both intentional and flexible, requires the active maintenance of a broad range of perceptual, mnemonic, and motor representations. For example, imagine hitting a golf ball. If your ball is in the woods, you may need to maintain the location of the flag in the distance as you keep your eye on the ball. As you prepare to hit your ball, you also have to maintain the rules of the game, since any movement of the ball as you address it may result in a penalty stroke. And finally, if you are playing poorly, it is important to maintain the original goal for taking up the game – to exercise and enjoy yourself.

How does the PFC interact with other brain regions to support working memory?

The first step in neuroimaging is necessarily one of localization of function where we often attempt to ascribe a particular cognitive function, such as a component of working memory, to a brain region. Nonetheless, neuroimaging scientists are at the same time well aware that the implementations of discrete cognitive functions are almost surely distributed across many nodes in a network. One of the next steps in afunctional neuroimaging is likely to be attempts to characterize networks of cortical activity associated with cognition. Importantly, fMRI has the unique ability to simultaneously image multiple regions of the brain. Thus, it has the often-touted

potential that is just currently being realized (McIntosh, 2000; Friston, 2002; Sun et al., 2004) to characterize interactions between the nodes in neural networks, such as the network that supports working memory.

For example, we described above how different cortical areas might maintain relatively different codes across a memory delay in an oculomotor spatial delayed-response task (Curtis et al., 2004). Recall that the frontal eye fields (FEF), for example, were more active during the delay when the direction of the memory-guided saccade was known compared to when it was not known throughout the delay. Other areas showed the opposite pattern. Despite these task-dependent differences in regional activity, we could only assume but not address the functional interactions between the identified nodes of the putative network. Standard univariate analysis of fMRI data, in which each brain voxel is analyzed independently of all others, reveal no more than independent activity within these regions. In a follow-up study, we used a multivariate technique, coherence, to formally characterize functional interactions between the FEF and other brain areas (Curtis et al., in review). Coherence is a statistic that is analogous to correlation, but is performed on the time-series data once it has been fast Fourier transformed into frequency space (Sun et al., 2004). Using coherence, we found that the type of representational codes that are being maintained in working memory biases frontal-parietal interactions and therefore influence network dynamics. For example, coherence between FEF and other oculomotor areas was greater when a motor representation was an efficient strategy to bridge the delay period. However, coherence between the FEF and higher-order multimodal areas, e.g., dorsolateral prefrontal cortex, was greater when a sensory representation must be maintained in working memory.

With similar goals, Gazzaley, Rissman, and D'Esposito (Gazzaley et al., in press) utilized another type of multivariate analysis method that allowed them to explore functional connectivity between brain regions during the distinct stages of a delayed face recognition task. They modeled the individual trial components of the task for every single trial separately, not averaged across the whole trial as is usually done. In order to assess network interactions, they correlated the parameter estimates for every trial derived from the FFA with all other brain voxels. High correlations indicate that the trial-to-trial variability in the magnitude of the parameter estimates between two regions was high, suggesting functional connectivity. This analysis revealed a network of brain regions with significant correlations with the FFA during the retention interval. This maintenance network included the dorsolateral and ventrolateral PFC, premotor cortex, intraparietal sulcus, caudate nucleus, thalamus, hippocampus, and occipitotemporal regions.

Functional MRI is uniquely suited to measure network dynamics since it simultaneously records correlates of neural activity throughout the entire functioning brain with high spatial resolution. Together, the findings from these initial two studies (Gazzaley et al., in press; Curtis et al., in review) support the notion that the coordinated functional interaction between nodes of a widely distributed network underlies the active maintenance of internal representations. Moreover, they may signal the beginning of a new generation of multivariate studies that use fMRI to characterize network dynamics.

Summary and conclusions

Elucidation of the cognitive and neural architectures underlying human working memory has been an important focus of cognitive neuroscience for much of the past

decade. One conclusion that arises from this research is that working memory, a faculty that enables temporary storage and manipulation of information in the service of behavioral goals, can be viewed as neither a unitary, nor a dedicated system. Data from numerous imaging studies has been reviewed that has demonstrated that a network of brain regions, including the PFC, is critical for the active maintenance of internal representations. Moreover, it appears that the PFC has functional subdivisions that are organized by the abstractness of these representations (e.g. features, rules, goals). Finally, working memory function is not localized to a single brain region but likely an emergent property of the functional interactions between the PFC and other poster regions. Numerous questions remain regarding the neural basis of this complex cognitive system, but imaging studies such as those reviewed in this chapter should continue to provide converging evidence for such questions.

FIGURE LEGENDS

FIGURE 1 Schematic parcellation of the human brain based on cytoarchitecture divisions of Brodmann (1909). In the frontal cortex, premotor areas (6 and 44) include the frontal eye fields (FEF; circled “F”) bilaterally and Broca’s area (circled “B”) in the left hemisphere. Multimodal association frontal cortex includes dorsolateral prefrontal cortex (DLPFC), which refers to areas 46 and 9, ventrolateral prefrontal cortex (VLPFC), which refers to areas 45 and 47 and frontopolar or anterior PFC, which refers to area 10.

FIGURE 2 Delayed-response task and modeling within trial components of event related fMRI data. A) A prototypic oculomotor delayed-response task, like all delayed-response tasks, has three main epochs, a sample cue period where stimuli to-be-remembered are presented, an unfilled delay period where stimuli are retained in memory, and finally a response period where a memory-guided response (i.e., saccade) is required. Event-related designs for fMRI have the ability to statistically disambiguate the hemodynamic signals specifically related to encoding the cue stimuli and generating memory-guided responses from the maintenance-related activity present in the retention interval. B) When multiple sequential neural events occur within a trial, the resulting fMRI response is a mixture of signals emanating from more than one time and more than one trial component. The gradient under the curve schematically represents the mixing or temporal overlap of the various signal components. For example, the white region at the peak of the first hump is almost exclusively evoked from neural processing during the cue phase of the task. However, just a few seconds later, in the darker portion just to the right, the signal is a mixture of processing at the cue phase and the beginning of the delay period. C) In order to resolve the individual components of the mixed fMRI signal, separate regressors can be used to independently model the cue, delay, and response phases of the trial. D) The magnitudes of the regressors scale with the degree to which they account for variance in the observed time series data. The magnitude of the delay regressor can be used as an index for maintenance-related activity.

FIGURE 3 (A) An example of the time series of the fMRI signal averaged across trials for a PFC region that displayed delay-correlated activity is shown (filled black circles represent activity for delay trials and open circles are trials without a delay). (B) An example of a time series where the integrated activity for the presentation of the cue and response during the delay trials (filled black circles) is greater than that observed during the combined presentation of the cue and response in the no delay trials (open circles). This reflects a violation of the assumptions of cognitive subtraction that are made by most block design experiments. The solid gray bar represents the duration of the delay period of the behavioral task.

FIGURE 4 Event related study of spatial working memory by Curtis et al. (2004). a) Schematic depiction of the oculomotor delayed response tasks where subjects used the cue’s location to make a memory-guided saccade. Both the matching-to-sample (top) and non-matching-to-sample (bottom) tasks began with the brief presentation of a small. During matching trials, the subject made a memory-guided saccade (depicted by the

thin black line) after the disappearance of the fixation cue marking the end of the delay. Feedback was provided by the re-presentation of the cue. At this point, the subject corrected any errors by shifting gaze to the cue. The difference between the endpoint fixation after the memory-guided saccade 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 (\pm 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 frontal eye fields (FEF) show greater delay period activity during the matching task where an oculomotor strategy is efficient. The right intraparietal sulcus (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 memory-guided saccade (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.

FIGURE 5 Main results from Chein and Fiez (2001) study of verbal working memory. The circled regions on the right depict Broca's and inferior parietal cortex. On the left are time series data from these regions. Both Broca's area (a) and inferior parietal cortex (b) show sustained activity during the maintenance of verbal material. Consistent with an important role in articulatory rehearsal processes, Broca's area showed a word-length effect – activity was greater during the delay period on trials in which subjects were maintaining 3-syllable words compared to 1-syllable words. The left inferior parietal cortex (area 40) showed a word-similarity effect – activity was greater on trials when the words were phonological related compared to when they were distinct.

FIGURE 6 Human inferior temporal activity during visual associative memory retrieval and maintenance from Ranganath et al., (2004). In this event-related fMRI study, subjects were scanned while they were shown a face or a house that was previously learned in a face-house pair and asked to recall and maintain its associate across a delay period. Activity during the initial cue phase in the fusiform face area (FFA) was greater when the cue was a face compared to when it was a house. However, during the delay period, activity reflected the type of information that was active in memory, rather than the previously presented cue stimulus—that is, delay activity in the FFA was greater when a face was recalled in response to a house cue. Grey lines represent time series from FFA when a house was presented at cue and its face pair was tested at the probe phase. Black lines represent the face-house pairing order.

FIGURE 7 An event related study by Sakai et al. (2002) had subjects first encode the order and spatial position of 5 cues (gray bar). Subjects had to maintain this information for several seconds and then encountered a secondary spatial distraction task (black bar). Then memory performance was tested. On correct trials, when the subjects successfully maintained the stimuli, the activity in area 46 was greater as can be seen by the average (\pm S.E. bars) BOLD time series data. In area 46, but not premotor area

6/8 or IPS, the level of persistent activity prior to the distraction correlated with memory performance after the distraction.

FIGURE 8 Simplified schematic depicting the hierarchical organization of key areas critical for working memory. The frontal cortex appears hierarchically organized, not simply in a dorsal/ventral fashion, but in a posterior/anterior direction from premotor regions to anterior frontopolar cortex. Non-spatial, especially verbal, working memory depends on a network of ventral cortical regions including the ventrolateral PFC (VLPFC, areas 45 & 47), Broca's area (area 44), and posterior parietal and temporal cortex. This network maintains information by the activation of stored semantic representations and subvocal articulatory rehearsal processes. Similarly, spatial working memory depends on a network of dorsal cortical regions including the superior frontal sulcus (SFS, area 8), FEF (area 6), and the superior portions of parietal cortex (SPL, area 7). This network maintains positional information through the shifting and maintenance of spatial attention and motor intention. Anterior PFC regions like the dorsolateral PFC (DLPFC, area 46) and frontopolar cortex (FPC, area 10) interact with both of these networks and appear to maintain more abstract representations, such as task goals and behaviorally relevant contexts.

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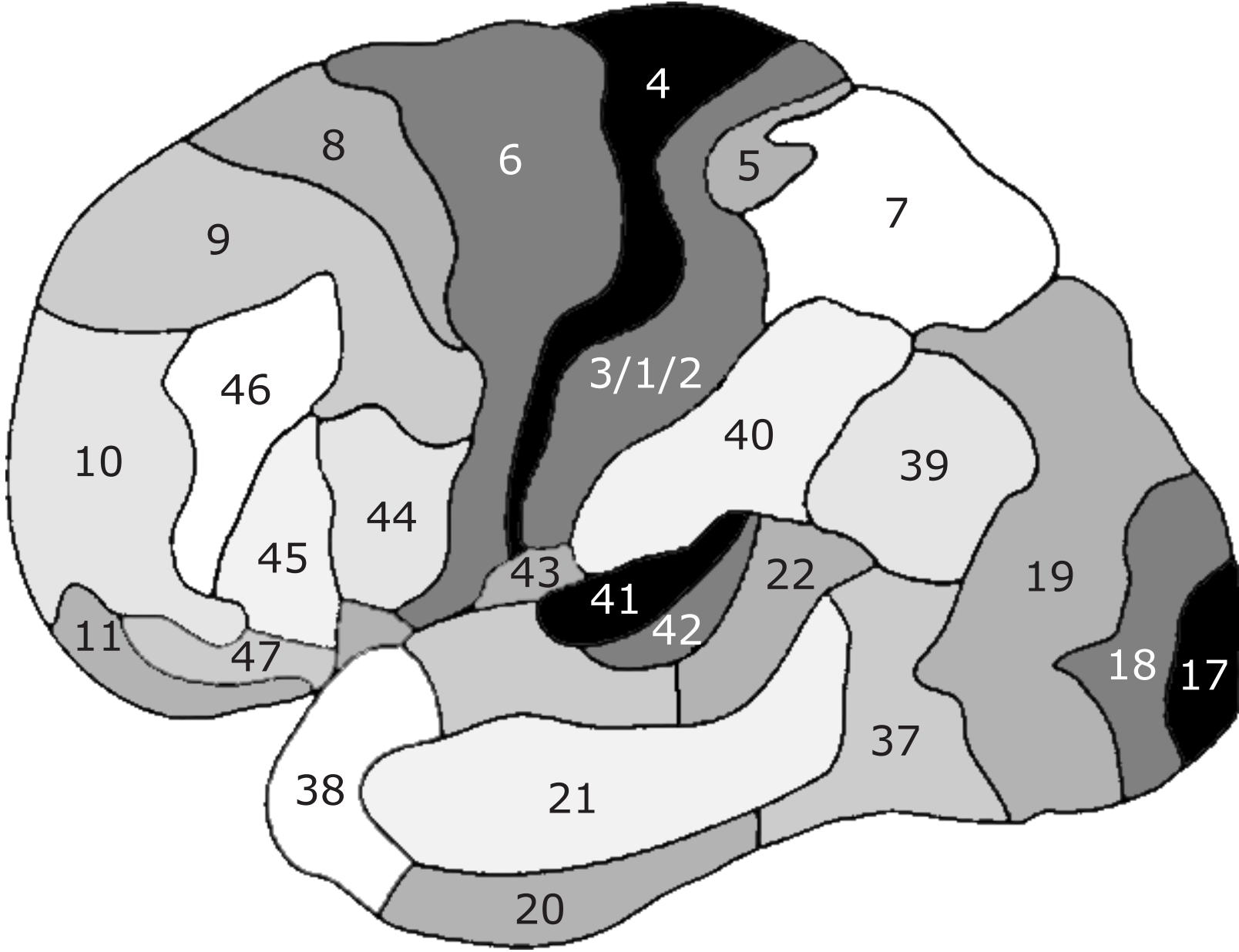
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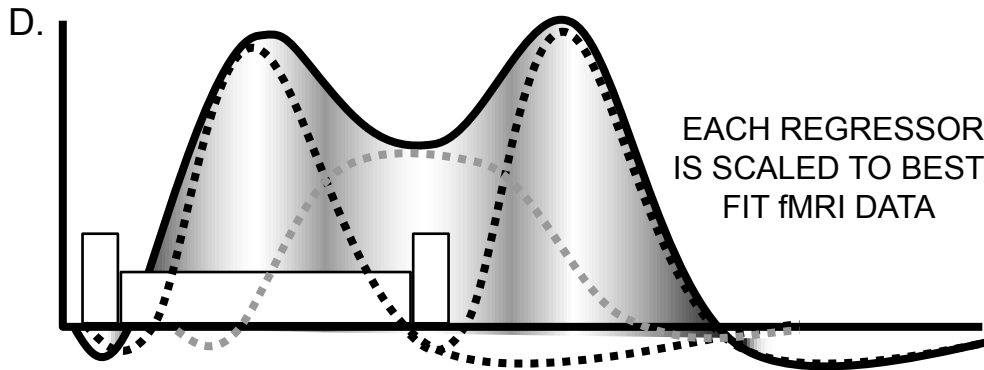
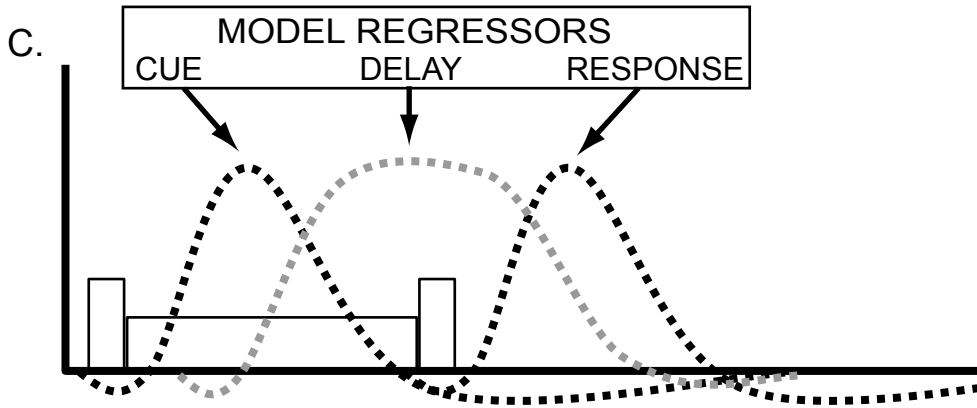
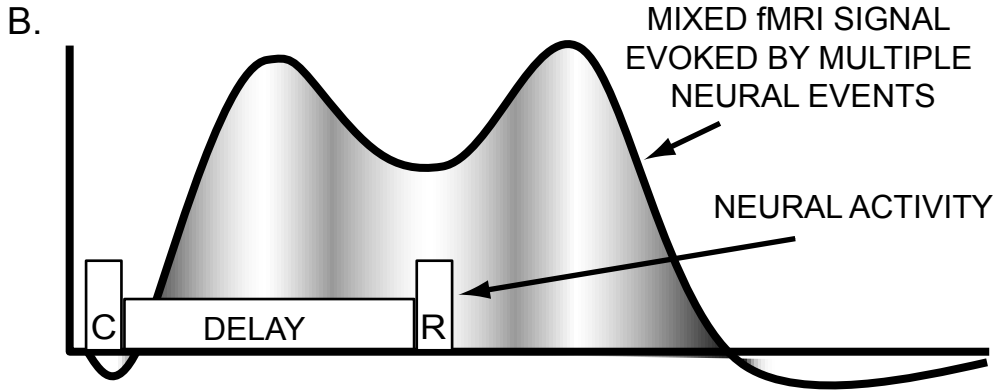
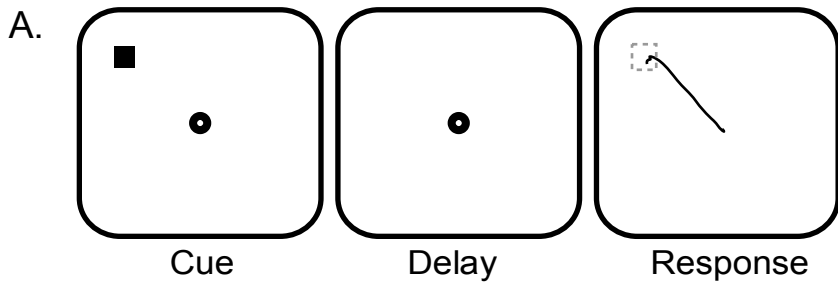
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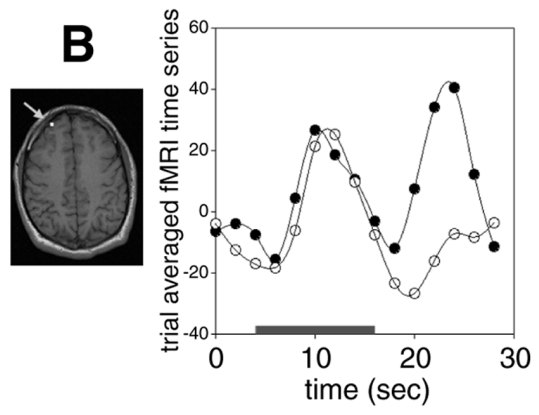
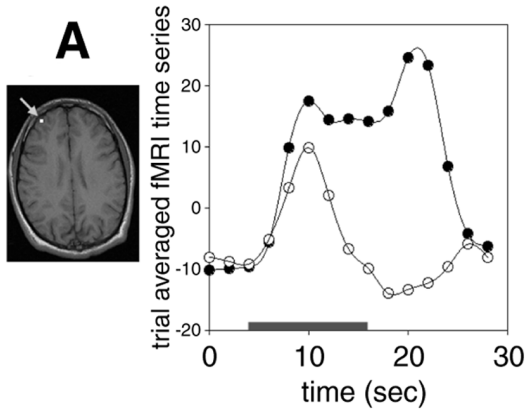
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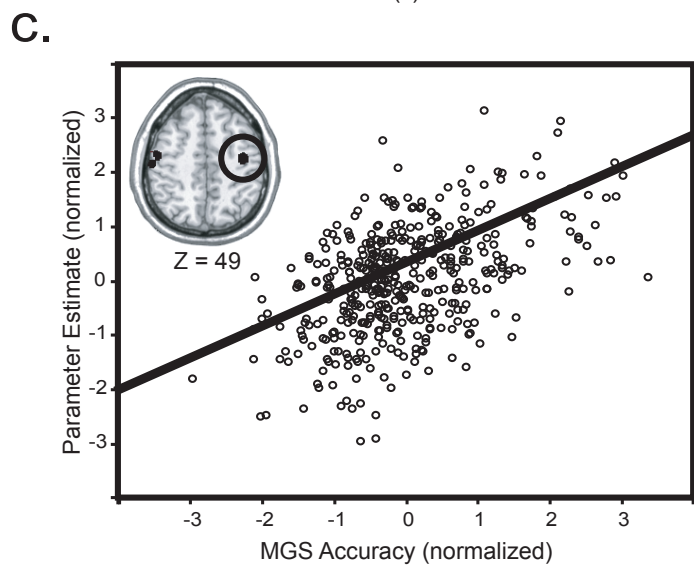
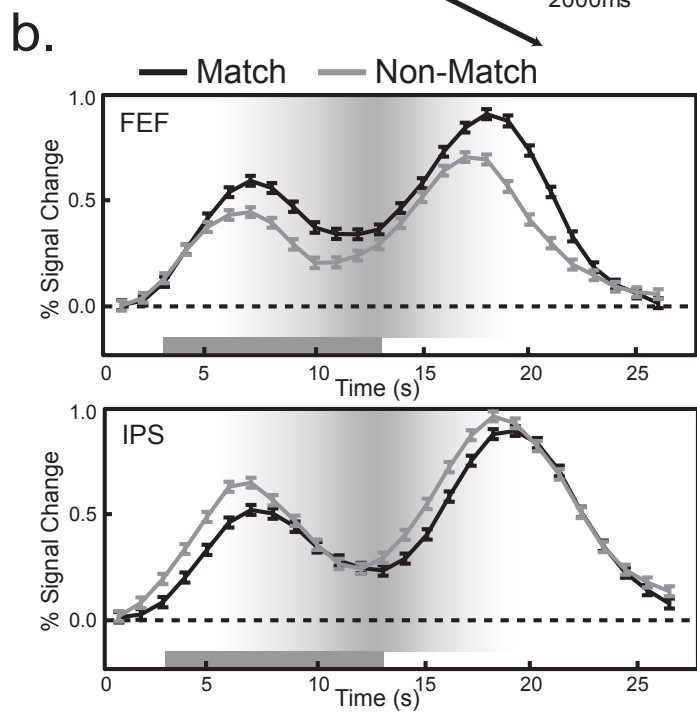
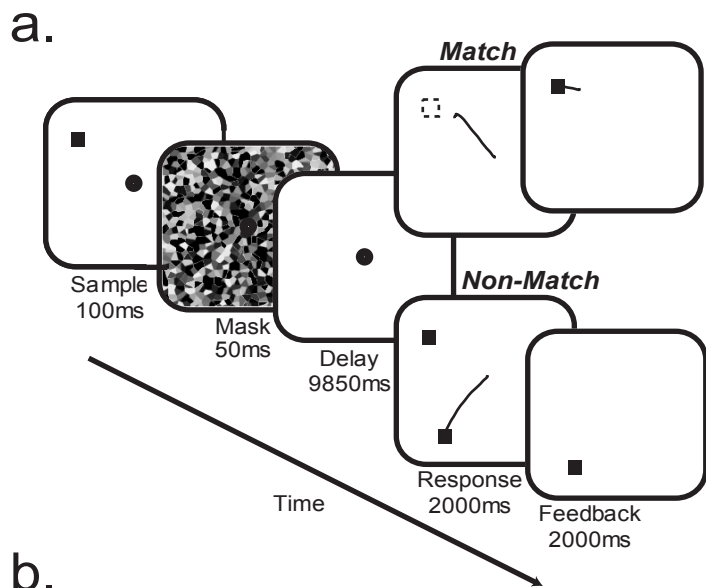
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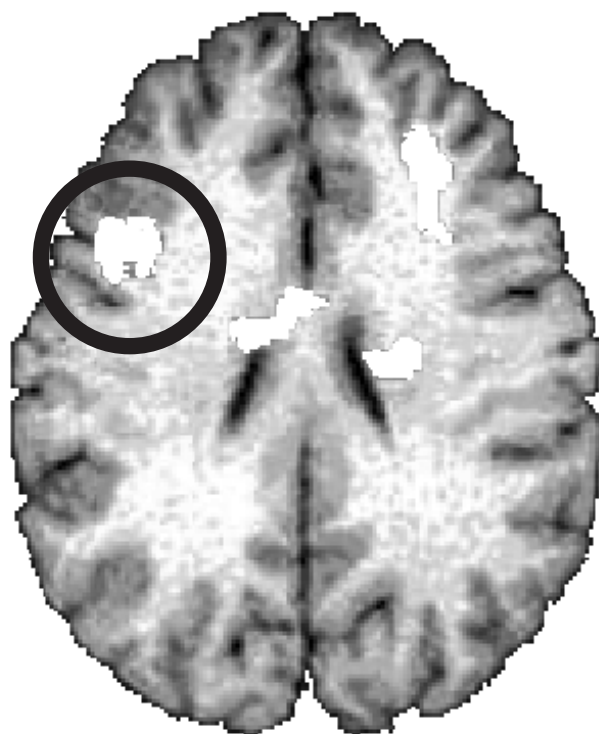
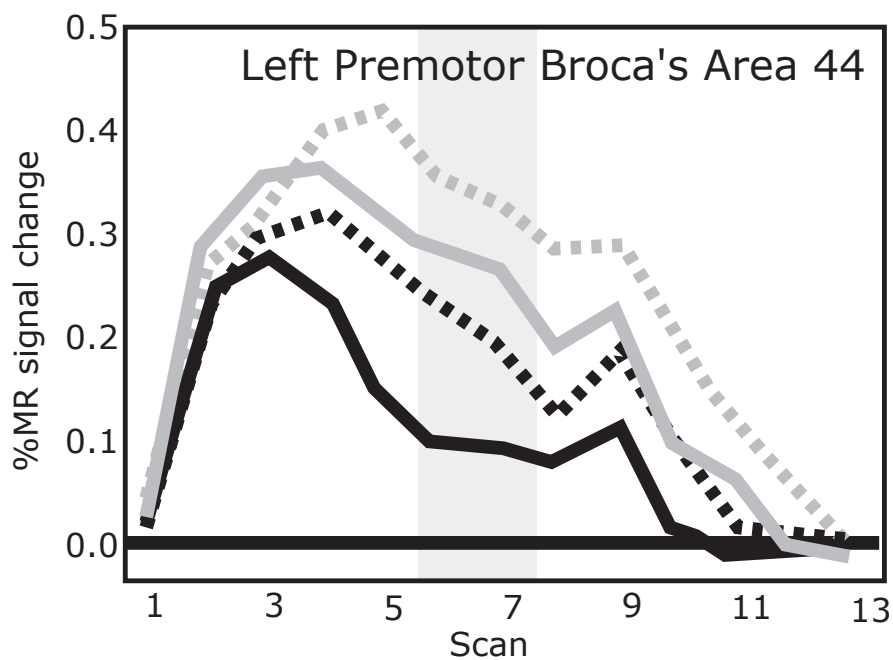
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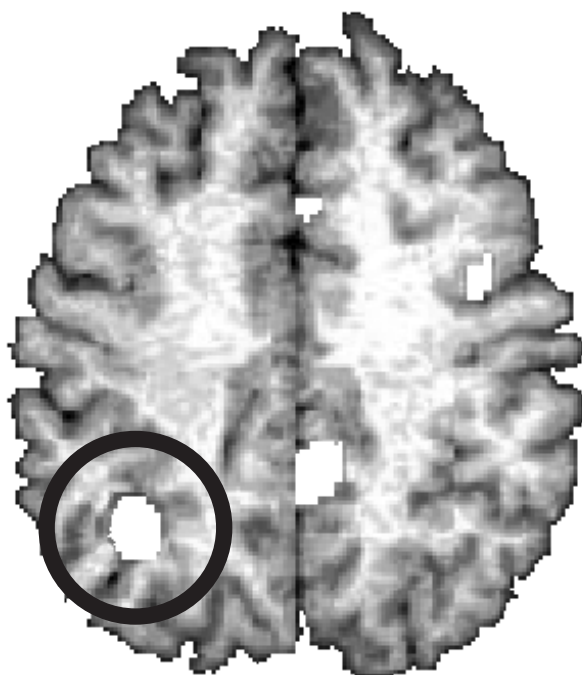
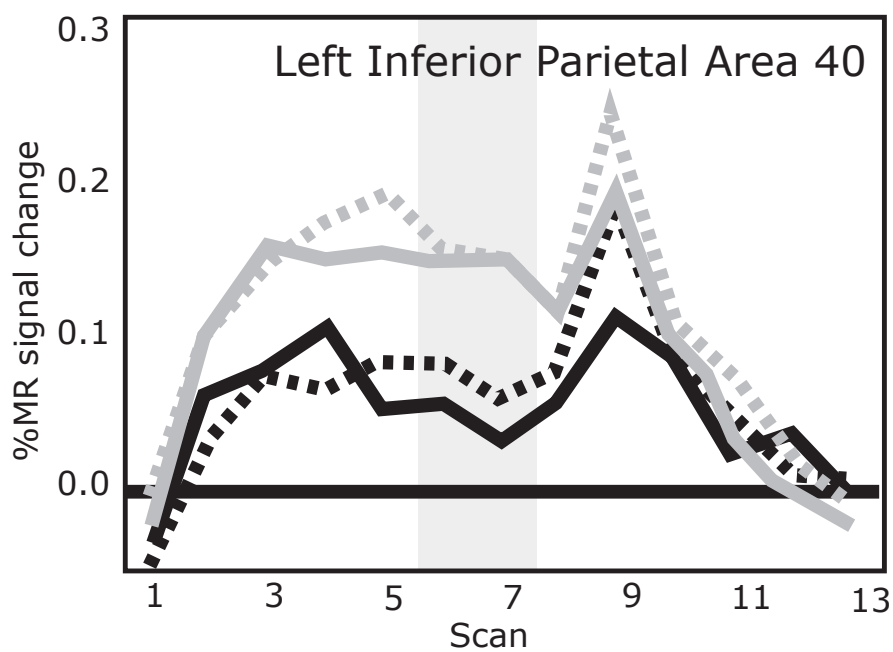


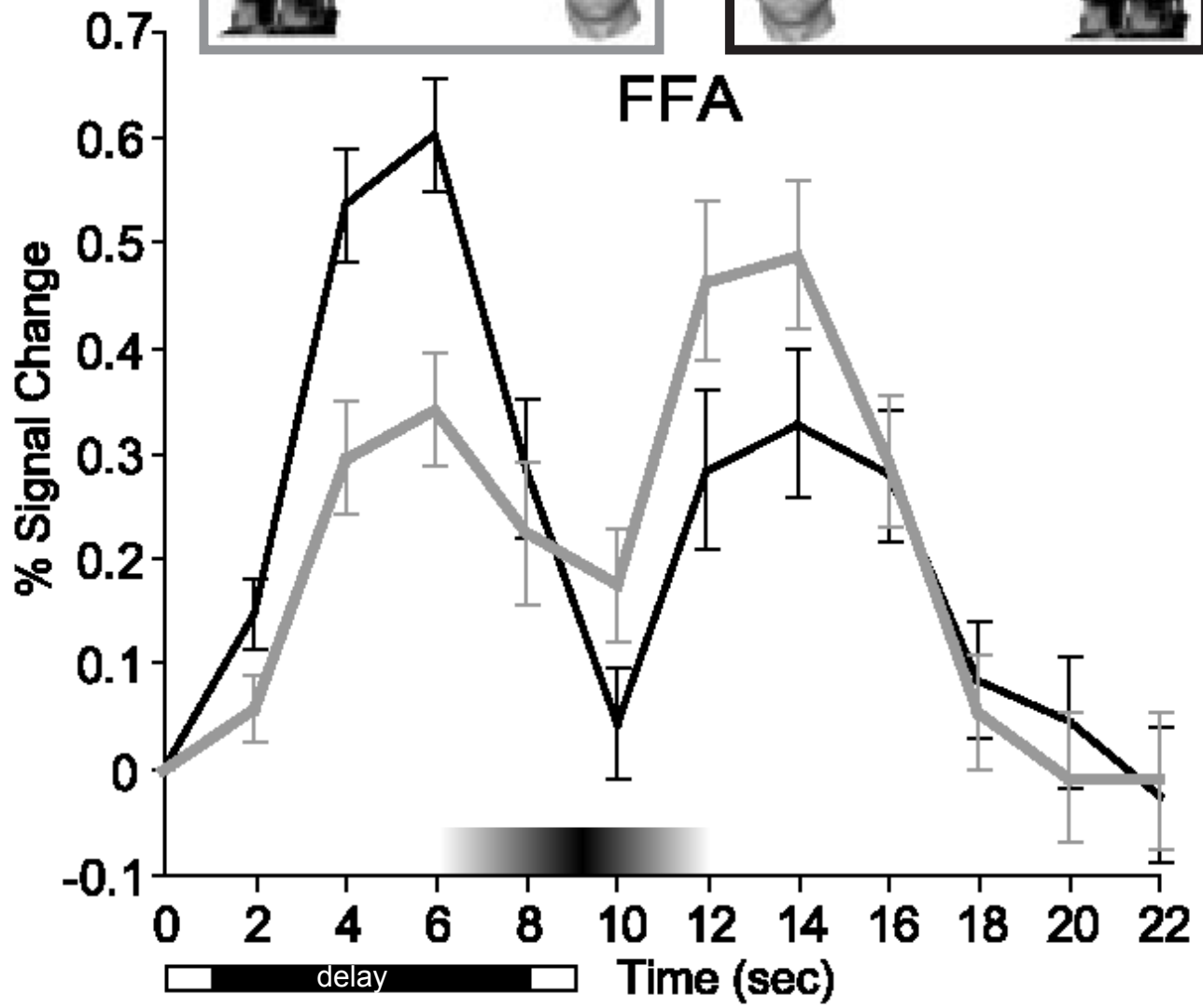
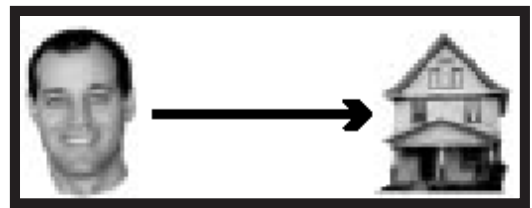
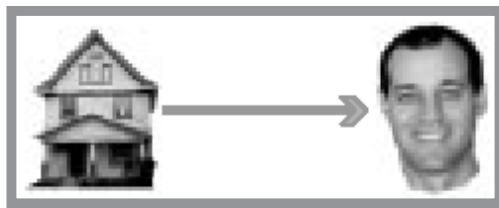




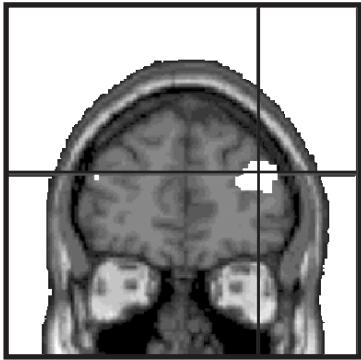


- 1-syllable phonologically distinct words
- 3-syllable phonologically distinct words
- 1-syllable phonologically similar words
- 1-syllable pseudo words

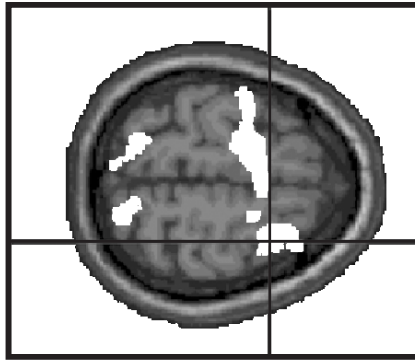




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