THE COGNITIVE NEUROSCIENCE OF WORKING MEMORY

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Abstract

For over 50 years, psychologists and neuroscientists have recognized the importance of a "working memory" to coordinate processing when multiple goals are active, and to guide behavior with information that is not present in the immediate environment. In recent years, psychological theory and cognitive neuroscience data have converged on the idea that information is encoded into working memory via the allocation of attention to internal representations – be they semantic long-term memory (e.g., letters, digits, words), sensory, or motoric. Thus, information-based multivariate analyses of human functional MRI data typically find evidence for the temporary representation of stimuli in regions that also process this information in nonworking-memory contexts. The prefrontal cortex, on the other hand, exerts control over behavior by biasing the salience of mnemonic representations, and adjudicating among competing, context-dependent rules. The "control of the controller" emerges from a complex interplay between PFC and striatal circuits, and ascending dopaminergic neuromodulatory signals.

Keywords

working memory; short-term memory; cognitive control; top-down; prefrontal cortex; connectivity; dopamine

INTRODUCTION

The introduction of the term "working memory" into the behavioral literature can be traced back to a passage in Miller, Galanter and Pribram's book "Plans and the Structure of Behavior" (1960). In it, the authors state:

> "Without committing ourselves to any specific machinery, therefore, we should like to speak of the memory we use for the execution of our Plans as a kind of quick access, "working memory". There may be several Plans, or several parts of a single Plan, all stored in working memory at the same time. In particular, when one Plan is interrupted by the requirements of some other Plan, we must be able to remember the interrupted Plan in order to resume its execution when the opportunity arises. When a Plan has been transferred into the working memory we recognize the special status of its incompleted parts by calling them "intentions."
> (p. 65)

Soon thereafter, Pribham and colleagues (1964) posited that the neural machinery supporting working memory might include the prefrontal cortex (PFC). They did so based on the deficits that PFC lesions were known to produce on various tests that imposed a delay between the target stimulus and the subsequent target-related response. (Or, in the case of delayed alternation, between the execution of one action and the execution of a subsequent action that depended on the former.)

The most enduring conceptualization of working memory, however, has been that of the *multicomponent* model, introduced in 1974 by experimental psychologists Alan Baddeley and Graham Hitch (1974). The model was developed to address two factors in the literature of the time. One was Baddeley and Hitch's assessment that contemporary models of short-term memory (STM) did not capture the fact that mental operations performed on information in conscious awareness can be carried out independent of interaction with, or influence on, long-term memory (LTM); for example, "maintenance rehearsal" had recently been shown not to enhance encoding into LTM.) A second factor was that their own work indicated that performance on each of two tasks under dual-task conditions could approach levels of performance under single-task conditions if the two engaged different domains of information, specifically verbal and visuo-spatial. Thus, the original version of their model called for two STM buffers (dubbed the "phonological loop" and the "visuospatial sketchpad", respectively) that could operate independently of each other and independently of LTM, although both under control of a separate system that they dubbed the "Central Executive".

From a functional perspective, the *multicomponent* model of working memory accomplished the buffering and coordinating operations that Miller et al. (1960) had identified as critical if one is to be able to simultaneously maintain, and successfully carry out, multiple behavioral goals. In 1986, Baddeley summarized it as "a system for the temporary holding and manipulation of information during the performance of a range of cognitive tasks such as [language] comprehension, learning and reasoning". The following year, Patricia Goldman-Rakic (1987) echoed these ideas in an influential synthesis of cognitive and neurobiological perspectives, stating that "the evolution of a capacity to guide behavior by [mnemonic] representation of stimuli rather than by the stimuli themselves introduces the possibility that concepts and plans can govern behavior". Thus, "the ability to guide behavior by representations of discriminative stimuli rather than by the discriminative stimuli themselves is a major achievement of evolution". What is captured in each of these seminal writings is that working memory underlies the successful execution of complex behavior, regardless of the cognitive domain or domains that are being engaged. When working memory fails, so too does the ability to carry out many activities of daily living. Viewed from this perspective, it is not surprising that working memory can be shown to be impaired in many neurological and psychiatric syndromes that are characterized by disordered behavior (Devinsky & D'Esposito, 2003). The centrality of working memory to understanding normal, as well as pathological, behavior is presumably reflected in the intensity with which it has been studied: In mid-2014, a search of the term "working memory" in PubMed retrieved 17,597 citations and in Google Scholar 1,580,000 results were returned. Although we cannot hope to do justice to such a vast literature in just one review, what we hope to

accomplish here is to highlight what we consider to be important developments in working memory research from a cognitive neuroscience perspective.

COGNITIVE MODELS OF WORKING MEMORY

As we write this review the *multicomponent* model of working memory is marking its 40th anniversary, and from roughly 1985 through 2005 – what one might consider the first 20 years of the cognitive neuroscience study of working memory – this was the dominant theoretical framework. More recently, however, what might be called *state-based* models have taken on increased prominence. As a class, these models assume that the allocation of attention to internal representations – be they semantic long-term memory (LTM; e.g., letters, digits, words), sensory, or motoric – underlies the short-term retention of information in working memory. These models conceptualize information being held "in" working memory as existing in one of several states of activation established by the allocation of attention.

Our brief review of state-based models will organize these into two categories: "activated LTM" models and "sensorimotor recruitment" models. Although these two types of models have arisen within different literatures, the principal difference between them seems to be simply the class of stimuli for which each has been proposed. That is, activated LTM models have by-and-large been articulated for, and tested with, symbolic stimuli typically considered to be "semantic" (e.g., letters, words, digits). Sensorimotor recruitment models, on the other hand, have typically been invoked for classes of stimuli considered to be "perceptual" (e.g., visual colors and orientations, auditory pitches, tactile vibrational frequencies). Despite these surface-level differences, however, both of these classes of state-dependent models of working memory are grounded in the idea that the attentional selection of mental representations brings them into working memory, and that the consequences of attentional prioritization explains such properties as capacity limitations, proactive interference from no-longer-relevant items, and so on.

The temporary activation of LTM representations

The subset of *state-based* models that has been formalized to the highest degree are those pertaining to working memory for information for which there exists a semantic representation in LTM. In perhaps the most well-known of the state-based models, Cowan (1995) describes two distinct states in STM: a small, capacity-limited state referred to as the focus of attention (FoA) and a more expansive state referred to as the activated portion of LTM ("activated LTM"). In this model, the FoA corresponds to approximately four chunks of information that one can hold in working memory at any moment in time using top-down attentional control. When attention subsequently shifts to other information, the items that were previously in the FoA transition into activated LTM. Activated LTM has no capacity limit per se, but is susceptible to temporal decay and interference effects. A variant on this two-level model has been proposed by Oberauer (2002, 2009) in a three-embedded-components theory. In it, the four-item FoA from Cowan's model is recast as a *region of direct access* from which a narrower FoA can efficiently select information.

Capacity limits, per se, do not exist for either of these two hypothesized states in working memory. Rather, the amount of information that can be retained in the region of direct access and the FoA is limited only by interference from bindings between object features being retained in working memory (Oberauer, 2013). A third model, advocated by McElree (1998, 2006), posits two states of memory: a FoA with a strict capacity limit of one item, and LTM, in which all items exist along a graded continuum of "memory strength", with memory strength (which we construe as level of activation) of an item falling off as a function of how recently it was in the FoA, and from which all items are equally accessible.

Setting aside some differences in terminology, these models all posit the following: When we are presented with symbolic information that is to-be-remembered (e.g., a list of names or a telephone number), the LTM representations of this information are accessed during the process of perceptual recognition, and they are subsequently maintained in an elevated state of activation, via attention, until this information is no longer needed to achieve some proximal goal. (For our purposes, we will gloss over whether there may exist one or more distinct states of attentional prioritization, and summarize all as a FoA.) These models account for extensive behavioral findings suggesting the existence of different states of representation of information being held in working memory. For example, Oberauer and colleagues (2001, 2002, 2005) have made clever use of the Sternberg effect, whereby reaction time for a recognition judgment about a memory probe increases linearly with the number of items concurrently held in working memory. The Oberauer studies have modified the basic Sternberg memory paradigm by introducing a retrocue during the memory delay that informs the subject that only a subset of the initially presented memory items will be relevant for an upcoming probe. Given sufficient time to process this retrocue, subjects respond more quickly to memory probes of the cued items (i.e., as would be predicted if they were now holding a smaller memory set). The uncued items are not fully forgotten, however, and continue to influence ongoing processing in the form of intrusion costs on response times when they are presented as negative (to-be-rejected) memory probes. This intrusion effect persists for 5 seconds, long after the uncued items cease to affect response times for the cued items. The uncued items are therefore hypothesized to have been removed from the FoA, but to persist in activated LTM (Oberauer, 2001). By varying the retrocue-to-memory probe asynchrony, it has been estimated that it takes approximately 1 second to remove uncued items from the FoA (Oberauer, 2005). Questions about whether there exists one or more qualitatively discrete states of activation outside of the FoA remain a topic of active research.

Sensorimotor recruitment

The basic premise of *sensorimotor recruitment* models of working memory is that the same systems and representations that are engaged in the perception of information can also contribute to the short-term retention of that information. An early, paradigmatic example of such models is that of attention-based rehearsal, whereby a location in space can be held in working memory via the covert allocation of attention to that location (e.g. Awh & Jonides, 2001). For other domains of sensory information, such as visually perceived spatial frequency, contrast, orientation, or motion, behavioral evidence indicates that each is retained in a highly stimulus-specific manner (Magnussen, 2000, Magnussen & Greenlee,

1999, Zaksas et al. 2001) that is most parsimoniously explained as the persistent activation of the sensory representations themselves. We shall see in the next section that a growing body of neural evidence supports this contention.

In the literature, the label "sensory recruitment" is much more common than is "sensorimotor recruitment". We prefer the latter, however, to accommodate the intimate, often inextricable, coupling between sensory attention and motor intention. This is particularly important in the context of spatial working memory, which is not only disrupted by drawing attention to a distracting location (e.g., Awh et al. 1998), but also by concurrent performance of task-irrelevant motor sequences, such as eye movements, tapping, and so on (reviewed in Postle et al. 2006). Conversely, motoric activity, such as the trajectory of a saccade, can be altered when one is concurrently holding a location in working memory (Theeuwes et al. 2005). These results support the idea that the coordinates of a to-be-remembered location are immediately incorporated into a salience map that simultaneously holds them in brain systems that represent them as a percept and as a target for action by any of various motor effectors (Postle 2011).

Capacity limits of visual working memory

A focus of intensive investigation for sensorimotor recruitment models has been the factors that explain capacity limitations. Much of this work has followed from Luck and Vogel's (1997) experiments with a "change detection" task in which a target array of colored squares (varying across trials from a single square to 10 or more) is presented for a few hundred milliseconds, followed by a brief (roughly 1-second) blank delay, followed by a probe array containing the same number of items, but with one item appearing in a different color on half the trials (a "Yes/No recognition" procedure). By applying a simple algebraic formula to the results, they estimated that subjects had a visual STM capacity of between 3 and 4 items. Importantly, they found that an individual's capacity did not change with number of features used to individuate objects, up through objects defined by conjunctions of 4 features. This led them to hypothesize that the capacity of visual STM is constrained by a finite number of hypothetical "slots", each one capable of storing an object representation, regardless of the complexity of any single object (Vogel et al. 2001).

This "slots model" has been challenged from at least two perspectives and, at the time of this writing, the nature of visual STM capacity limits remains a topic of vigorous debate. One open question is that of the influence of object complexity – contrary to the findings of Vogel et al. (2001), others have found that visual short-term memory capacity declines with increasing object complexity (e.g., Alvarez & Cavanagh, 2004). A second challenge arises from the perspective that visual STM capacity may not depend on a finite number of slots but, instead, on a single attentional resource. Evidence for this latter view is marshaled when the procedure for testing visual STM is changed from recognition to recall. This procedural change allows for the estimation of the precision of a mnemonic representation, by measuring the error in the recall response. With STM for the orientation of one or more line segments, for example, the average error in recalling the orientation of the probed stimulus is larger when subjects are remembering several stimuli simultaneously, in comparison to when they are remembering just one (Bays and Hussain, 2008). That is, mnemonic precision

(the inverse of recall error) declines monotonically as a function of memory set size, an outcome that one would expect if STM were supported by a limited resource that must be apportioned ever more thinly as the number of items in the memory set increases. Slots models have been modified to allow for variable representational precision within a slot, but one contentious question that remains is how to best explain capacity limitations: As an individual approaches the limit of the amount of information that she can retain in STM, is it because she has run out of slots (in which case an absolute ceiling in performance is predicted), or because her attentional resources have been spread so thin that any one item's mnemonic fidelity is too poor to be retrievable? For excellent reviews on these issues see Ma et al. 2014 and Luck & Vogel 2013.

NEURAL MECHANISMS UNDERLYING WORKING MEMORY

There are many grains of detail at which a "mechanism" – "the process by which something takes place" – can be considered. Here we will first consider evidence for the general ideas of activated LTM and of sensorimotor recruitment, at a relatively abstract level. Subsequently, we will consider specific systems-level neural mechanisms that may underlie these phenomena. To anticipate one conclusion, it is likely that there are numerous neural mechanisms that can support the short-term retention of information in working memory, and many likely operate in parallel.

The "neural plausibility" of state-based accounts of working memory

One reason that state-based models of working memory have gained prominence in recent years is that cognitive neuroscience research has shown them to do a good job of accommodating neural data. This is particularly true since the advent of applying multivariate pattern analysis (MVPA) techniques to human functional neuroimaging data. (These techniques have been summarized in many places, one of them being Lewis-Peacock and Postle, 2012). With regard to the idea of the temporary activation of LTM, for example, Lewis-Peacock and Postle (2008) have done the following. First, they scanned subjects with functional magnetic resonance imaging (fMRI) while the subjects made judgments that required accessing information from LTM: the likability of famous individuals; the desirability of visiting famous locations; the recency with which they had used a familiar object. Next, outside the scanner, they taught subjects arbitrary paired associations among items in the stimulus set. Finally, they scanned subjects a second time, but this time while performing delayed recognition of paired associates (i.e., see one item from the LTM memory set at the beginning of the trial, and indicate whether or not the trial-ending probe is that item's associate). The finding was that multivariate pattern classifiers trained on data from the first scanning session, when subjects were accessing and thinking about information from LTM, were successful at decoding the category of information that subjects were holding in working memory in the second scanning session. Such an outcome could only be possible if the working memory task and the LTM task drew on the same neural representations.

MVPA has also been used to generate compelling evidence for sensorimotor recruitment models of working memory. Thus, for example, two studies have demonstrated that primary visual cortex (V1) supports the delay period-spanning representation of the color or

orientation of target stimuli on tests of delayed recognition (Harrison & Tong 2009, Serences et al. 2009). This pattern of results has been replicated with other classes of stimuli: the short-term retention of motion can be decoded from lateral extrastriate cortex, including area MT+, as well as from medial calcarine and extracalcarine cortex (Riggall & Postle, 2012, Emrich et al. 2013); the short-term retention of complex visuospatial patterns can be decoded from occipital and parietal cortex (Christophel et al. 2012); and the short-term retention of familiar objects, faces, houses, scenes, and body stimuli can be decoded from ventral occipitotemporal cortex (Han et al. 2013, Lee et al. 2013, Nelissen et al. 2013, Sreenivasan et al. 2014). Finally, in relation to the frontoparietal salience map, Jerde and colleagues (2012) have demonstrated that a classifier trained only on performance of a test of attention to location, or only on performance of oculomotor delayed response, or only on performance of spatial delayed recognition, can recover trial-specific target direction from any of the three trial types. That is, for example, a classifier trained to discriminate leftward from rightward sustained attention can also correctly discriminate leftward from rightward motor preparation, and leftward from rightward spatial STM, even though it has never been trained on the latter two. Thus, the functions that we label *attention*, *intention*, and *retention* may be treated identically by the brain.

Perhaps the most compelling evidence in support of sensorimotor recruitment models of working memory derive from two studies using multivariate approaches that have linked the precision of the delay-period neural representation of target stimuli in sensory cortex with behavioral estimates of mnemonic precision, showing that "the relative 'quality' of … patterns [of activity in sensory cortex] determine the clarity of an individual's memory" (Ester et al. 2013). In one, Ester and colleagues (2013) showed that the precision of population tuning curves in V1 and V2v estimated from the delay-period signal from these regions predicted the fidelity with which a subject was able to reconstruct the target orientation at the end of the delay period. In another, Emrich et al. (2013) varied from trial to trial the number of directions of motion that had to be remembered, and found a reliable within-subject correlation between the load-related decline in delayed-recall precision, and a load-related decline in MVPA decoding performance.

Complementing these fMRI studies are results of studies using transcranial magnetic stimulation (TMS) to alter activity in sensorimotor regions during the delay period of tests of working memory for visually presented stimuli. Hamidi and colleagues (2008; 2009), for example, have shown that delay-period repetitive TMS of parietal cortex and frontal eye fields selectively affects spatial working memory performance. A more nuanced approach, taken for working memory for visual motion, has leveraged the fact that TMS of visual area MT can produce the percept of a "moving phosphene" – a flash of light that contains coherent motion within the area of the flash. The perceived direction of motion is reproducibly toward the periphery, away from the fovea, in the visual field contralateral to the side of stimulation. Silvanto and Cattaneo (2010) demonstrated that this percept is systematically influenced when TMS is delivered while the subject is engaged in STM for the direction of motion of a target stimulus. When the target motion is in the same direction as the expected motion of the phosphene, the perception of the moving phosphine is enhanced. However, when the target motion is in the opposite direction, perception of the

moving phosphene is reduced. These results indicate that the physiological state of MT varies systematically as a function of the direction of motion being remembered, just as it does, when a stimulus is present, as a function of the direction of motion being perceived.

Working memory at the systems level

Working memory does not derive from a discrete system, as do vision and motor control. Rather, working memory is a property of the brain that supports successful attainment of behavioral goals that are being carried out by any of several systems, including sensory systems, those that underlie semantic and episodic memory, and motor systems. We next review five neural mechanisms that likely underlie working memory function.

Persistent Neural Activity—The study of the neural underpinnings of working memory took a significant leap forward in 1971 with the publication of two studies featuring extracellular recordings from the PFC in monkeys performing working memory tasks. In one, Fuster and Alexander (1971) reported that PFC neurons exhibited persistent activity during the stage of a delayed-response task in which the monkey had to actively maintain information that was no longer present, yet relevant for successfully completing the task. In the second, Kubota and Niki (1971) reported a comparable finding during the delay period of a delayed alternation task. The ability of neurons to generate persistent activity in the absence of external stimuli is likely of fundamental importance to the neural basis of working memory. Following on these landmark discoveries, many other labs have found such "working memory-related" neurons within the PFC (e.g. Funahashi et al. 1989; Miller et al., 1996). With the advent of fMRI in the early 1990s, it was subsequently demonstrated that human PFC also exhibits persistent neural activity that appeared to be coding task-relevant information during working memory tasks (see Courtney et al., 1997 and Zarahn et al., 1997 for the first of such studies). Many characteristics of this activity seems consistent with the notion that it reflects the maintenance of representations critical for guiding behavior. First, it endures throughout the entire length of the delay-period until it can be presumably used to guide a response (Fuster & Alexander, 1971 Funahashi et al. 1989). Second, it directly relates to behavior. For example, during the performance of an oculomotor delayed-response task, the magnitude of fMRI signal in frontal cortex reflects the fidelity of the maintained representation (Curtis et al., 2004). An open question that cannot be answered with fMRI is the mechanism that underlies persistent neural activity. Specifically, the relative importance of cortico-cortical loops (long-range recurrent interactions), thalamo-cortical loops, or local cortical mechanisms (such as excitatory reverberation), for the generation of persistent neural activity has yet to be determined (Wang 2001; Pesaran et al. 2002).

In addition to the circuit-level questions summarized above, recent research applying MVPA to fMRI and electroencephalography (EEG) data has raised intriguing questions about the functions supported by persistent neural activity. These questions fall into two categories, one relating to the nature of the persistent delay-period activity that supports the short-term retention of information, the second relating to the very necessity of this activity. The first question arises from dissociations between the elevated activity that is classically observed in frontoparietal regions, and subthreshold patterns of activity that MVPA detects in sensory

processing-related regions. As first described by Tong (2009) and by Serences (2009), the delay-period retention of visual stimulus information can be decoded from primary visual cortex, despite the absence of sustained, elevated signal levels of signal in this region. Subsequent studies by Riggall & Postle (2012), and by Emrich et al. (2013) replicated these findings, and also explicitly failed to find evidence for stimulus information in the elevated delay-period activity that was present in frontal and parietal regions. Further, Sreenivasan et al. (2014) showed that the magnitude of above-threshold delay-period activity does not correlate positively with the feature weightings that underlie MVPA classification. One implication of all these studies is that above-threshold delay-period activity may support functions other than information storage per se. What these functions may be is the topic of the final section of this review. A second implication is that the neuronal processes that drive the MVPA-decodable activity in sensory areas are operating at a level that is subthreshold from the perspective of traditional univariate statistics. Thus, an important focus of future research will be to understand the nature of this "subthreshold" delay-period activity. One candidate explanation is that it simply reflects reduced spiking at the population level, as would be expected for a sensory area in the absence of a bottom-up drive. A second possibility, mutually compatible with the first, is that MVPA may be detecting regional heterogeneity in oscillations of local field potentials (LFPs). That is, delay-period stimulus representations may be encoded in LFPs that persist in the same networks that exhibit elevated firing when the stimulus is present.

A second question highlighted by MVPA of fMRI and EEG data is whether persistent activity is even necessary for the retention of information in working memory. This was raised when Lewis-Peacock and colleagues (2012) scanned subjects performing a multistep delayed-recognition task that first presented two sample stimuli, then a retro-cue indicating which of the two would be relevant for the first memory probe, then, following this first probe, a second retro-cue indicating which stimulus would be relevant for the trial-ending second memory probe. With this procedure, an item could be irrelevant for the first memory probe (an "unattended memory item"), but then relevant for the second memory probe. Although the authors initially predicted that MVPA evidence for unattended memory items would take on an intermediate level between the item that was in the FoA and baseline, this is not what they found. Instead, in response to the retro-cue, MVPA evidence for the unattended memory item dropped to baseline levels. This item nonetheless remained "in" working memory, as evidenced by its successful retrieval if cued by the second retro-cue. This finding has been replicated in an EEG study, thereby discounting the possibility that the unattended memory item may be transferred to an oscillatory code to which fMRI is insensitive (LaRocque et al. 2013). These findings, therefore, highlight the intriguing possibility that persistent neural activity may not be necessary for maintaining representations held in working memory. Indeed, this possibility has also been explored by researchers working at other levels of investigation, including computational modeling, in vitro electrophysiology, and extracellular recordings in the behaving monkey. Computationally, it has been suggested that information can be sustained over brief intervals via rapid shifts in synaptic weights. In such a scenario, the encoding of the sample stimulus would be accomplished via a transient reconfiguration of synaptic weights in the networks engaged in its initial processing. The contents of working memory could then be read out

when the network was activated by a subsequent sweep of activation through this network (Itskov et al. 2011, Mongillo et al. 2008, Sugase-Miyamoto et al. 2008). Empirical evidence that is consistent with such a mechanism has been recorded from ventral temporal cortex (Sugase-Miyamoto et al. 2008) and PFC (Stokes et al. 2013) in monkeys. What mechanism could support the short-term synaptic facilitation that would be needed to implement such a scheme? Theoretically, "residual" presynaptic calcium levels have been proposed (Mongillo et al. 2008). Empirically, an associative short-term potentiation has been demonstrated to be gluR1-dependent in an in vitro preparation (Erickson et al. 2010) Clearly, the relative contribution of persistent neural activity versus other mechanisms that do not rely on above-baseline activity to sustain working memory representations should be a high priority for future research.

Whether or not WM representations are maintained via persistent neural activity, synaptic mechanisms, or some combination of both, these storage mechanisms are consistent with *state-based* models of working memory, which eliminate the need for currently relevant representations to be transferred to a limited number of dedicated, specialized buffers (Postle 2006, D'Esposito 2007). In neural terms, any population of neurons can serve as a buffer. Moreover, the ability to exhibit persistent neural activity, or a shift in synaptic weights, is likely a property of all neurons, from primary cortex to multimodal association cortex. In other words, networks of neurons located anywhere in the brain can potentially store information that can be activated in the service of goal-directed behavior.

Hierarchical representations in prefrontal cortex—What is the nature of the neural code within PFC? Some have put forth the idea that persistent activity in PFC represents sensory features of information maintained in working memory (Goldman-Rakic 2005). Indeed, in the systems and cognitive neuroscience literatures, one can see that the waxing and waning of popularity of "stimulus representation" models of the PFC tracked very closely the multicomponent model of working memory. More recently, there has been greater emphasis on the fact that PFC actually exhibits at best, coarse selectivity for items and features maintained in working memory (Constantinidis et al. 2001). Further, PFC delay-period activity can represent a broad range of task variables that are not directly related to the to-be-remembered stimuli. For example, lateral PFC neurons recorded from monkeys exhibit differential preferences for task rules (Warden & Miller 2010), contingent motor responses (Romo et al. 1999), and stimulus–response mappings (Wallis et al. 2001). Studies examining population coding of lateral PFC delay activity have similarly found information about stimuli (Stokes et al. 2013), rules (Riggall & Postle 2012), and object categories (Meyers et al. 2008) throughout the delay period of working memory tasks. In fact, Rigotti and colleagues have recently demonstrated that neuronal activity within PFC is tuned to mixtures of multiple task-related variables, suggesting that PFC representations exhibit high-dimensionality (Rigotti et al. 2013). That is, a high number of dimensions is needed to characterize the distinct (multivariate) patterns that can be taken on by the sampled population of neurons across a variety of experimental conditions. Moreover, it was shown that this dimensionality is predictive of the animal's behavior, in that the population of PFC neurons exhibited a decrease in dimensionality on error trials. Interestingly, the authors of the very first reports of persistent activity within the PFC offered interpretations

that are in line with many current models. For example, Fuster and Alexander [1971] wrote that:

> The temporal pattern of firing frequency observed in prefrontal and thalamic units during cue and delay periods suggest the participation of these units in the acquisition and temporary storage of sensory information which are implicated in delay response performance. Their function, however, does not seem to be the neural coding of information contained in the test cues, at least according to a frequency code, for we have not found any unit showing differential reactions to the two positions of the reward.It is during the transition from cue to delay that apparently the greatest number of prefrontal units discharge at firing levels higher than the intertrial baseline… We believe that the excitatory reactions of neurons in MD and granular frontal cortex during delayed response trials are specifically related to the focusing of attention by the animal on information that is being or has been placed in temporary memory storage for prospective utilization." (p. 654)

Several human fMRI studies have directly investigated the nature of representations being maintained in PFC as compared to posterior cortical regions. In one study, subjects viewed a sample display of dot motion, then, halfway through the delay period, were cued as to whether they would be probed on memory for the speed or the direction of the sample motion. Delay-period MVPA decoding of stimulus direction was only successful at lateral and medial regions of occipital cortex that are associated with visual perception. PFC, however, was seen to represent a more abstract level of task performance: whether a trial was a "speed" trial or a "direction" trial (Riggall & Postle, 2012). A different study using different stimuli but a similar procedure, found analogous results. In it, subjects first viewed a common object, and were then cued as to whether the memory probe would require a fine-grained perceptual judgment or a category-membership judgment. On perceptual trials, MVPA decoded stimulus identity in ventral occipitotemporal cortex, but not PFC. On category trials, MVPA decoded stimulus category from PFC, but not occipitotemporal cortex (Lee et al. 2013). These two findings are consistent with prior studies demonstrating that the lateral PFC preferentially encodes and maintains arbitrary and abstract representations of object category over representations of visual similarity (Meyers et al. 2008, Freedman et al. 2001, 2003, Chen et al. 2012). Further support for the distinction between stimulus-selective lateral PFC representations and sensory representations comes from a second fMRI study that required subjects to remember over a short interval either faces, scenes or both categories of information (Sreenivasan et al. 2014). It was reasoned that if a region supports a sensory representation of working memory stimuli, then the "remember faces" trials should be incorrectly classified as "remember both" trials more often than they should be misclassified as "remember scenes" trials, because the sensory representation of faces is more similar to the representation of remembering faces and scenes together than it is to remembering only scenes. Similarly, "remember scenes" trials should also be disproportionately misclassified as "remember both" trials if activity patterns encode sensory representations. The findings from this fMRI study suggested that what is represented by PFC is higher-order information, such as task rules, goals, or abstract representations of the categories, as compared to what is represented by extrastriate cortex, which may be more stimulus-specific (e.g., the identity of specific faces).

These empirical findings fit nicely with the original theoretical notions put forth by Fuster (1990), and Miller and Cohen (2001), that integrated representations of task contingencies and rules are maintained in the PFC, which is critical for the mediation of events separated in time but contingent on one another. This formulation of PFC function places less emphasis on a storage role and instead emphasizes its role in providing top-down control over all other brain regions where information is actually stored (Smith & Jonides, 1999; D'Esposito et al. 2000, Petrides 2000). Thus, the sustained activity in the PFC does not reflect the storage of representations, per se; it reflects the maintenance of high-level representations that provide top-down signals that can guide the flow of activity across brain networks. This idea will be expanded upon in the next section. However, first, we must consider the nature of the information represented within PFC with respect to the functional organization of PFC as a whole.

The PFC is a heterogeneous region covering a significant amount of territory in the brain. In this review we are focusing on lateral PFC, and not medial or orbital PFC regions, which likely have distinct yet complementary functions (Cummings 1993). Any understanding of the nature of the representations stored and maintained in PFC necessary for goal-directed behavior must consider sub-regional differences in both cellular makeup and connectivity. Numerous neuropsychological, physiological, imaging studies support the general idea that as one moves rostral (anteriorly) in the frontal cortex, from premotor cortex to frontopolar cortex, the processing requirement of these regions necessary for planning and selection of action are of higher-order (Burgess et al. 2007, Christoff et al. 2003, Ramnani & Owen, Koechlin and colleagues (2003) have put forth a hypothesis that frontal cortex may be organized from rostral to caudal in a hierarchical fashion en route to action (also see Fuster (2004) for earlier formulation of a similar idea). Specifically, a 'cascade model' is proposed (Koechlin & Summerfield, 2007) that predicts that competition among alternative action representations is resolved based on mutual information with various contextual information, termed control signals. Using fMRI in healthy subjects, Koechlin and colleagues (2003) found support for their predictions by demonstrating that as contextual information required to select a response was more abstract and relevant over a longer temporal interval, fMRI activation progressed from caudal to more rostral regions of frontal cortex.

In an fMRI study (Badre & D'Esposito, 2007), we aimed to replicate and extend Koechlin's findings regarding the proposed rostral-caudal functional gradient along frontal cortex. We specifically tested an alternative idea that this gradient derives from a hierarchy ranked by the abstractness of the representation to be selected. In this study healthy subjects performed a response selection task that required more abstract action decisions to be made across behavioral conditions. The lowest level of the task performed was called the *Response* task where subjects learned that a colored square corresponded to a particular finger response. At the next level called the *Feature* task, each colored square corresponded to a particular shape, and then subjects chose their motor response if the colored square matched the shape. Thus, at this level, there is not enough information in color alone to determine the correct response. The object shape had to be considered in conjunction with the color to make a response. The only difference from the *Response* task was that the colors now mapped to

relevant shapes that cued a correct response, rather than mapping directly to the correct response. In other words, an action decision must be based on a more abstract action representation. At the next level called the *Dimension* task, subjects learned that a particular color corresponded to a particular dimension of an object (shape or orientation), and they were required to compare the two objects along a particular dimension and indicate with a motor response whether the objects matched or mismatched along only the relevant dimension. The subject knew which dimension was relevant based on the color of the square bounding the objects. Hence, the design for the mappings was identical to the *Feature* and *Response* task, except that now color mapped to dimension rather than feature or response. Again, the action decision must be based on more abstract representation. The final and highest level was called the *Context* task where subjects performed the *Dimension* task, however, conflict was manipulated by varying the frequency of the sets of color to dimension mappings. In this case, the temporal context was required to select the appropriate context (the color cue) for determining the dimension. Thus, selection of the relevant context was more abstract.

During the lowest level *Response* task, activation was found in posterior frontal cortex within premotor cortex (PMd, area 6). At the next higher level *Feature* task, activation was found anterior to premotor cortex within pre-premotor cortex (pre-PMd; area 8). On the next higher level *Dimension* task, activation was noted anterior to this location within the inferior frontal sulcus (IFS) on the border of areas 45 and 9/46. Finally, activation on the highest level *Context* task was found in the most anterior location within frontopolar cortex or area 10. Thus, as action representations became more abstract, activation within frontal cortex moved anteriorly (or rostrally). Importantly, this progression of activation from posterior to anterior portions of frontal cortex was not simply due to the task becoming more complex or difficult, because we also varied the difficulty within each individual task (e.g. *Response*, *Feature*, *Dimension* or *Context*), and found that activation within that particular region engaged by each task increased in magnitude with difficulty but did not change it's location within frontal cortex. In contrast to the emphasis of Koechlin et al. (2003) on temporal and contextual factors in differentiating regions of frontal cortex, these results suggest that regions of PFC may be differentiated by the level of abstraction at which the action representations must be selected over competition.

Thus, human fMRI studies support the notion that there is a functional gradient along the anterior-to-posterior axis of the frontal lateral cortex. A similar functional gradient relating to motivational aspects of cognitive control has been identified along the medial PFC axis (Kouneiher at al., 2009, Venkatraman et al., 2009) and functional connectivity between medial and lateral PFC has been observed (Blumenfeld et al. 2013). It is important to point out that consensus has not been reached regarding the specific details of functional gradient observed in PFC (see Badre 2008 for review). Nevertheless, an important component of emerging models of the organization of lateral PFC is that a hierarchy exists. A processing hierarchy within the frontal cortex requires that anterior regions influence the processing in posterior regions more than posterior regions influence anterior regions. How can one obtain direct evidence to support this claim? Essential clues (albeit indirect ones) regarding a hierarchical rostro-caudal organization of the frontal lobe can be derived from its anatomical

organization. If there were a hierarchical arrangement, anatomical connectivity among PFC subregions would likely display a pattern where area 10, at the highest level would have projections back down to area 6 at the lowest level. However, area 6 would not necessarily project back up to area 10. Such a pattern does appear to exist, at least in rhesus monkeys (Badre & D'Esposito, 2009). Barbas and Pandya (1991) have also noted that different frontal regions have different degrees of differentiation at the columnar level. More differentiated regions are more laminated (e.g. aggregation of cells into cortical layers). Caudal areas with well-developed laminar differentiation (such as area 8 or caudal 46) have restricted connections mostly to neighboring regions. In contrast, rostral areas that have less laminar differentiation (such as area 10) have widespread connections to other areas. In this scheme, less differentiated areas such as those in rostral PFC (areas 10, 9, 46), which have more diffuse projections, are well situated to be the top of a hierarchy. In contrast, more differentiated areas such as those in caudal PFC (area 9/46, 8) have more intrinsic connections and are well situated to be lower in a hierarchy.

Further indirect evidence for a hierarchical organization within lateral PFC derives from functional neuroimaging studies examining effective connectivity, or the causal influence that one brain region may have on another. For example, in the Koechlin et al. (2003) study previously mentioned, structural equation modeling of the imaging data showed that activation in rostral frontal regions accounted for variance in activation in caudal frontal regions but not vice versa. Direct evidence for a hierarchical organization within lateral PFC requires lesion data. That is, a rostral to caudal flow of control processing within the frontal lobes predicts that performance on tasks requiring higher order control should be impaired by disruptions to lower order processors, even when the higher order processors are intact. However, when a higher order control processor is disrupted, performance should be unaffected on tasks that require only lower order control. This hypothesized asymmetric pattern of deficit cannot be directly tested with neurophysiological methods such as fMRI, EEG, and single-unit recording. Rather, it requires a lesion method that leads to isolated disruption of specific processors along the proposed hierarchical gradient.

Additionally, using the cognitive tasks we implemented in the fMRI study, we have carried out a behavioral study of patients with focal frontal lesions to test the hypothesis that there is a hierarchical organization in frontal cortex (Badre et al. 2009). Specifically, we tested whether a lesion to the pre-PMd region of frontal cortex (area 8), assumed to damage a 2nd level processor, would impair performance on the *Feature* task as well as the *Dimension* and *Context* tasks, but would not affect performance on the *Response* task. The reasoning was that disruption of the 2nd level of a hierarchy should interfere with processing at higher levels (*Feature*, *Dimension*, and *Context* tasks at the 3rd and 4th levels), but not at lower levels (*Response* task, 1st level). By contrast, a more anterior IFS lesion (areas 45; 9/46), which would damage a 3rd level processor, should impair performance on the *Dimension* task (3rd level) as well as the *Context* task (4th level), but not on the *Feature* (2nd level) or *Response* (1st level) tasks. Such a pattern of behavioral results in patients with focal frontal lesions would be direct evidence for a hierarchical organization of frontal lobe function. We predicted that because of the asymmetric dependencies predicted by a hierarchy, deficits in higher level tasks will be more likely across patients, regardless of the site of their lesion,

than deficits in lower level tasks. Thus, the presence of an impairment at any level should increase the likelihood of an impairment at all higher levels, but should not increase the odds of an impairment at a lower level. We observed that the probability of a deficit on any task was 62% across the patients. Critically, however, the probability of a deficit at any level given a deficit at a lower level was 91% across patients, a significant change over the probability of a deficit on any task. By contrast, the probability of a deficit at any level given a deficit at a higher level was only 76%, a weak change over the prior probability of a deficit on any task. This asymmetry provides initial support for the hierarchical dependencies among behavioral deficits at the different levels of the task and the aggregation account of the group data. Recently, this pattern of findings supporting a frontal hierarchy has been replicated in another group of patients with focal frontal lesions (Azuar et al. 2014).

Hierarchical organization of rules and goals has many advantages. For example, increasingly abstract representations of rules and goals could serve as different top-down signals that could bias particular but different action pathways over competitors allowing for flexible goal-directed behavior. Take the example of the seemingly simple act of hitting a golf ball. Hitting the ball in the proper direction requires temporary maintenance of the location of the flag on the green – a relatively concrete representation. If the golf ball is in a fairway bunker, it also requires the temporary maintenance of more abstract representation of the golf rule stating that the golf club cannot touch the sand before hitting the ball, or a penalty will be assessed. Finally, throughout this act of hitting the ball it might also be beneficial to maintain an even more abstract representation of the knowledge that golf provides exercise and is a healthy behavior. In this way, simultaneous maintenance of hierarchically organized representations within PFC can provide independent, yet likely interactive top-down bias signals that may (or may not) lead to a successful goal-directed behavior!

Top-down signaling—The PFC has long been implicated as a source of top-down signals that can influence processing in other cortical and subcortical brain regions (Duncan 2001, Fuster 2008, Shallice 1982, Braver et al. 2008). One type of PFC top-down signal likely provides direct feedback to posterior cortical regions that process incoming sensory input from a particular modality (e.g., visual or auditory). For example, when a person is looking into a crowd of people, the visual scene presented to the retina may include a vast array of visual information. However, if someone is searching for a friend, some top-down mechanism must exist that allows for suppressing irrelevant visual information while enhancing task-relevant information allowing for an efficient yet effective search. In this way, the maintenance and representation of the goal (e.g. find your friend) by PFC serves as a bias signal. As Miller and Cohen (2001) have stated, "cognitive control stems from the active maintenance of patterns of activity in the prefrontal cortex that represent goals and the means to achieve them. They provide bias signals to other brain structures whose net effect is to guide the flow of activity along neural pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task". As described earlier in this review, given that the PFC represents rules and goals at multiple levels of abstraction, it is in an ideal position to influence processing in downstream brain regions that receive its anatomical projections.

We have used fMRI and evoked-related potentials (ERP) in humans to investigate such top-down mechanisms (Gazzaley et al. 2005). In this study, during each trial of a working memory task participants observed sequences of two faces and two natural scenes presented in a randomized order. In separate blocks of trials subjects were required to *Remember Faces and Ignore Scenes*, *Remember Scenes and Ignore Faces*, or *Passively View* faces and scenes without attempting to remember them. Since each trial had equivalent bottom-up visual information (e.g. faces and scenes), we could directly determine if top-down signals were engaged. Moreover, the inclusion of a passive baseline allowed for the dissociation of possible enhancement and suppression mechanisms. With both fMRI and ERP we obtained activity measures from areas of visual association cortex specialized in face and scene processing. For fMRI, we used an independent functional localizer to identify both stimulus-selective *face* regions (within the fusiform face area or FFA; Kanwisher et al. 1997) and *scene* regions (within the parahippocampal place area or PPA; Epstein & Kanwisher, 1998). For ERP, we utilized a face-selective ERP, the N_{170}, a component localized to posterior occipital electrodes reflecting visual association cortex activity with face specificity (Bentin et al. 1996). Our fMRI and ERP data revealed top-down modulation of both activity magnitude and processing speed that occurred above and below the perceptual baseline depending on task instruction. That is, during the encoding period of the delay task, FFA activity was enhanced, and the N_{170} occurred earlier, when faces had to be remembered as compared to a condition where they were passively viewed. Likewise, FFA activity was suppressed, and the N_{170} occurred later, when faces had to be ignored compared to a condition where they were passively viewed. These results suggest that there are least two types of top-down signals, one that serves to enhance task-relevant information, and the other that serves to suppress task-relevant information. By generating contrast via enhancing and suppressing activity magnitude and processing speed, top-down signals can bias the likelihood of successful representation of relevant information in a competitive system (Hillyard et al. 1973, Moran & Desimone 1985, Corbetta et al. 1990).

With fMRI or any type of neurophysiological method applied to animals or humans, there is no direct way to determine the source of top down signals. Thus, to obtain evidence that the PFC is the source of top-down signals that modulate visual association cortex, the physiological responses of visual association cortex must be examined after disruption of PFC function (Miller & D'Esposito, 2005). The first attempt at such an approach was performed by Joaquin Fuster and colleagues (1985) in monkeys where the effect of PFC inactivation by cooling on spiking activity in inferotemporal cortex neurons during a delayed-match-to-sample color task was investigated. During the delay interval in this task – when persistent stimulus-specific activity in inferotemporal cortical neurons is observed – PFC inactivation caused attenuated spiking activity and a loss of stimulus-specificity of inferotemporal cortical neurons. These two alterations of inferotemporal cortex activity strongly implicated the PFC as a source of top-down signals necessary for maintaining robust sensory representations in the absence of bottom-up sensory activity.

Many years passed before any other attempt was made with animals or humans to follow-up this landmark finding by Fuster. In fact, the combined lesion/electrophysiological approach continues to be rarely implemented. Translating this approach to humans, Chao and Knight

(1998) investigated patients with lateral PFC lesions during delayed match-to-sample tasks. It was found that when distracting stimuli are presented during the delay period the amplitude of the ERP recorded from posterior electrodes was markedly increased in patients with frontal lesions compared to controls. These results were interpreted as demonstrating disinhibition of sensory processing supporting a role of the PFC in suppressing the representation of task-irrelevant stimuli. Recently, we investigated the causal role of the PFC in the modulation of evoked-activity in human extrastriate cortex during the encoding of faces and scenes (Miller, et al. 2011). We employed two experimental approaches to disrupt PFC function: TMS of PFC in healthy subjects and focal PFC lesions in stroke patients. We then investigated the effect of disrupted PFC function on the selectivity of category representations (faces or scenes) in temporal cortex. Different object categories, like faces and scenes are represented by spatially distributed, yet overlapping, assemblies in extrastriate visual cortex (Haxby, et al. 2001). Thus, we reasoned that disruption of PFC function would lead to higher spatial correlations between scene- and face-evoked activity in extrastriate cortex, suggesting a decrease in category selectivity. Consistent with our predictions, following disruption of PFC function (i.e., TMS session vs. baseline, or lesion vs. intact hemisphere in stroke patients), stimulus-evoked activity in extrastriate cortex exhibited less distinct category selectivity to faces and scenes (more spatial overlap). In a follow-up study (Lee & D'Esposito, 2012), we were able to further demonstrate that the decreased tuning of extrastriate cortex response coincided with decrements in working memory performance. This work extended the findings of Fuster and colleagues (1985) in monkeys to humans and suggests that the PFC may sharpen the representations of different object categories in extrastriate cortex by increasing the distinctiveness of their distributed neural representations. These findings are also consistent with other recent combined TMS/fMRI and TMS/EEG studies demonstrating decreased attentional modulation of stimulus-selective visual regions following PFC disruption (Feredoes et al. 2011, Higo et al. 2011, Zanto et al. 2011). Together, such causal evidence clearly supports the notion that the PFC is the source of top-down signals that act via both gain and selectivity mechanisms.

A key to understanding the role of the PFC in cognition likely rests in its connectivity with other regions (Yeterian et al., 2012). Any top-down signal from a particular PFC region, representing a particular goal, could have a different influence and behavioral consequence depending on what brain regions are recipients of these signals. For example, PFC top-down signals could enhance internal representations of relevant sensory stimuli in extrastriate cortex or anticipated motor plans in premotor cortex. It is likely that multiple top-down signals are engaged in a parallel fashion during the evolution of any goal-directed behavior. Moreover, other cortical regions, such as the parietal cortex and hippocampus have also been proposed to provide top-down signals during cognition (Eichenbaum, Ruff 2013). Consideration of the mechanisms by which multiple higher-order brain regions can influence lower-order brain regions highlights the enormous complexity of the human brain, and how much further we must travel to understand it.

Long-range connectivity—Another mechanism critical for working memory is the synchronization of activity among distributed brain regions. Owing to the limitations in available methodology in both animals and humans, only a limited number of studies to date

have been able to assess if and how neurons and brain regions communicate and interact to support working memory. We developed a multivariate method designed specifically to characterize functional connectivity in event-related fMRI data that can measure inter-regional correlations during the individual stages of a cognitive task (Rissman et al. 2004). Using this method, we specifically sought to characterize the network of brain regions associated with the maintenance of a representation of face stimuli over a short delay interval. With this approach (Gazzaley et al., 2004), we found significant functional connectivity between the FFA and the PFC and parietal cortex during the delay period of the task, which supports the notion that higher order association cortices interact with posterior sensory regions to facilitate the active maintenance of a sensory percept. Similarly, we have also found that posterior language-related areas involved in the maintenance of words in the absence of visual input also exhibit increased functional connectivity with the PFC (Fiebach et al. 2006).

Distributed synchronized activity could occur via synaptic reverberations in recurrent circuits (Wang 1999, Durstewitz et al. 2000), or synchronous oscillations between neuronal populations (Buzsaki & Draguhn, 2004, Fries, 2005, Singer 2009). In humans, electroencephalographic (EEG) magnetoencephalographic (MEG) and electrocorticographic (ECoG) recordings have been utilized to investigate which particular frequencies of oscillations may be related to working memory. Activity in low and high frequencies in the theta (4–7 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–200 Hz) ranges have all been found to be modulated during working memory tasks (for a comprehension review of 26 studies see Roux & Uhlhaas, 2014). Roux and Uhlhaas (2014) have proposed a different functional role for each of these frequency bands. Specifically, they propose that gamma-band oscillations are involved in the active maintenance of working memory information, theta-band oscillations are specifically involved in the temporal organization of working memory items and alpha-band oscillations are involved in the inhibition of task-irrelevant information. These notions are based on studies that have demonstrated amplitude modulation of neural oscillations presumably emanating from particular brain regions involved in working memory. For example, during a delayed match to sample task while recording human EEG it was observed that occipital gamma and frontal beta oscillations were sustained across the retention interval. Moreover, as this delay interval lengthened, these oscillations decreased in parallel with decreased performance on the task (Tallon-Baudry et al., 1999). In a recent study (Anderson et al., 2014), it was shown the spatial distribution of power in the alpha frequency band (8 –12 Hz) tracked both the content and quality of the representations stored in visual WM. These empirical findings support the notion that neural oscillations are critical for working memory maintenance processes.

It is likely that long-range synchronization of these oscillations between brain regions also plays an important role in working memory function (Sauseng et al. 2010, Crespo-Garcia et al., 2013). For example, in a human MEG study, synchronized oscillations in the alpha, beta and gamma bands was observed between frontoparietal and visual areas during the retention interval of a delayed match-to-sample visual working memory task. Moreover, these observed synchronized oscillations were sustained and stable throughout the delay period of the task, memory load dependent, and correlated with an individuals working memory capacity (Palva et al., 2010). Monkey physiology data have also provided considerable

insight into the possible mechanisms underlying communication between brain regions during working memory. For example, in one study (Liebe et al. 2011), neural interactions between visual area V4 and lateral PFC were investigated during the performance of a visual delayed match to sample task. During the retention interval of the task, these two areas exhibited synchronization of local field potentials in the theta frequencies. Moreover, there was phase-locking of neuronal spiking activity in these two regions to these observed theta oscillations. Most importantly, the strength of this inter-cortical locking was predictive of the animal's performance, that is, higher for subsequently correctly remembered stimuli and session-to-session variability in memory performance. The authors concluded that these findings reflect a mechanism for effective communication between brain regions involved in the temporary maintenance of relevant visual information, an idea also put forth by others (Fries 2005, Fell & Axmacher 2011). An intriguing recent finding suggests a critical role for the thalamus in regulating information transmission across cortical regions, at least at the local level (Saalmann et al. 2012).

Brainstem Neuromodulators—In many models of cognition, neuromodulators such as dopamine, serotonin, norepinephrine or acetylcholine, play a limited role, if any role at all. Yet, given that brainstem neuromodulatory neurons send projections to all areas of brain, their influence on cognitive function is without question. For working memory, there is abundant evidence from both animal and human studies that dopaminergic modulation of fronto-striatal circuitry in particular, is critical for its function (Cools & D'Esposito 2009).

Dopaminergic neurons in the human brain are organized into several major subsystems (mesocortical, mesolimbic and nigrostriatal). The mesocortical and mesolimbic dopaminergic systems originate in the ventral tegmental area of the midbrain and project to the frontal cortex, anterior cingulate, nucleus accumbens, and anterior temporal structures such as the amygdala, hippocampus and entorhinal cortex (Bannon & Roth, 1983). Across the cerebral cortex, the concentration of dopamine is highest within the frontal cortex (Brown et al. 1979, Williams & Goldman-Rakic 1993). However, there is also a strong dopaminergic input into the hippocampus (Samson et al 1990), and there is abundant evidence from both animal and humans studies that dopamine is involved in hippocampal-dependent long-term memory (for a review of this topic see Shohamy & Adcock, 2010).

The functional importance of dopamine to working memory and PFC function has been demonstrated in several ways. First, in monkeys depletion of PFC dopamine or pharmacological blockade of dopamine receptors induces working memory deficits (Brozoski et al. 1979; Sawaguchi & Goldman-Rakic 1991). These deficits are as severe as in monkeys with PFC lesions, and are not observed in monkeys in which other neurotransmitters, such as serotonin are depleted. Furthermore, dopaminergic agonists administered to monkeys with dopamine depletion reverses their working memory deficits (Brozoski et al. 1979, Arnsten et al. 1994). Likewise, numerous studies have shown that administration of dopamine receptor agonists to healthy young human subjects improves working memory performance (Luciana & Collins, 1992, Kimberg, et al. 1997, Muller et al. 1998, Kimberg & D'Esposito, 2003). An important feature of the dopaminergic system is that it exhibits a U-shaped dose-response curve which leads to specific dosages of dopaminergic drugs producing optimal performance on working memory tasks (Arnsten et

al. 1997, Kimberg et al. 1997, reviewed in detail in Cools, 2011). These observations illustrate that "more" is not "better" but rather an optimal brain dopamine concentration is necessary for optimal working memory function.

Different classes of dopamine receptors exist in varying concentrations throughout the brain. D-2 dopamine receptors are present in much lower concentrations in the cortex than D-1 receptors, and are mostly within the striatum (Camps et al. 1989). However, D-2 receptors are at their highest concentrations in the PFC (Goldman-Rakic et al. 1990). Moreover, dopamine release in the brain can be either transient (phasic) or sustained (tonic). Grace (2000) has proposed that these two mechanisms of action of dopamine are functionally distinct and antagonistic. Specifically, it is proposed that tonic dopamine release is mediated by D1 receptors whereas D2 receptor mediated effects are phasic. In support of this notion, during performance of a working memory task in monkeys, a dopamine D2 receptor agonist selectively modulated the phasic component of the task yet had little effect on the persistent mnemonic-related activity, which was instead modulated by a D1 receptor agonist (Sawaguchi et al 2001, Wang et al. 2004). Thus, these two dopamine receptors likely have complementary functions, which serve to modulate active memory representations stored within PFC (Cohen et al. 2002). The dual-state theory of PFC dopamine function put forward by Durstewitz and Seamans (2008) states that a D1-dominated state favors robust online maintenance of information, while a D2-dominated state is beneficial for flexible and fast switching among representational states.

Regarding working memory function, it is proposed that tonic dopamine effects may increase the stability of maintained representations whereas phasic dopamine effects may serve as a gating signal, indicating when new inputs should be encoded and maintained, or when currently maintained representations should be updated (Braver & Cohen 1999). In this way, two separate mechanisms underlie cognitive flexibility and stability that nevertheless must work together: dopamine would promote stability or flexibility of maintained representations depending on the neural site of modulation (Cools & Robbins, 2004). Specifically, dopamine receptor stimulation in the PFC would promote stability by increasing distractor-resistance (Durstewitz et al., 2000). Conversely, dopamine receptor stimulation in the striatum would promote flexibility by allowing the updating of newly relevant representations (Frank et al. 2001, Bilder et al., 2004). In the context of real world situations, demands for cognitive flexibility and stability are reciprocal: if we are too flexible, we are likely to become distracted; if we are too stable, we become inflexible and unresponsive to new information.

We have tested this dopaminergic model of working memory with a human pharmacological fMRI study (Cools et al. 2007). Healthy young subjects underwent fMRI scanning on two occasions, once after intake of the dopaminergic agonist bromocriptine and once after placebo (in a double-blind, cross-over design). During scanning, subjects performed a working memory task that allowed the separate investigation of working memory updating and maintenance processes. Specifically, subjects had to encode, maintain and retrieve visual stimuli over a short delay. Two faces and two scenes were always presented during the encoding period and subjects were instructed to remember either the face or scenes. During the retention period another stimulus was presented, which subjects were instructed

to ignore. This distractor was either a scrambled image or a novel face or scene. The critical measure of working memory updating was the behavioral switch-cost, which was calculated by subtracting performance (error rates and reaction times measured at probe) on trials where they switched to a new instruction as compared to remaining with the same instruction. The critical measure of working memory maintenance was the behavioral distractor-cost, which was calculated by subtracting performance (measured at probe) after scrambled as compared to non-scrambled distractors. We predicted that bromocriptine would modulate PFC activity during the epoch of the task following distraction, but the striatum would be modulated during the instruction epoch. This is exactly what we observed which is is consistent with the hypothesis that working memory maintenance and updating processes are modulated by differential dopaminergic stimulation of the PFC and striatum, respectively. This finding suggests that high levels of dopamine within the PFC (and lower levels in the striatum) optimizes the maintenance of task-relevant representations, whereas high levels of dopamine within the striatum (and low levels in the PFC) optimizes the flexible updating of information (for a more detailed review of dopaminergic functions, see Cools & D'Esposito, 2009). The functional opponency between stability and flexibility of working memory representations maps well onto the neurochemical reciprocity between DA in the PFC and the striatum: increases and decreases in PFC dopamine leads to decreases and increases in striatal dopamine respectively (Pycock et al. 1980, Meyer-Lindenberg et al, 2005, Akil et al, 2003).

A working memory "gate" provides a computationally efficient mechanism for allowing information necessary for goal-directed behavior to be updated when it is open, but preventing current information to be sustained and irrelevant information to be kept out when it is "closed" (O'Reilly & Frank 2006, Badre 2012). Using high-resolution MRI of the midbrain, D'Ardenne (2008) and colleagues demonstrated activation in a region likely comprising the substantia nigra and ventral tegmental area during trials on a task that required working memory updating. Midbrain activity also correlated with PFC activity as well as with behavior. These findings support the idea that dopamine acts as a gating signal to the PFC when updating of maintained representations are required. Recently, Badre and Frank have provided computational and empirical evidence for the possible mechanisms underlying working memory gating (Badre & Frank, 2012, Frank and Badre 2012, Chatham et al., 2013). Specifically, as a refinement of the original O'Reilly and Frank model that proposed that the striatum can deliver selective gating inputs into the PFC, Frank and Badre propose two types of striatal gating signals. The first type provides gating of inputs to be maintained by frontal cortex (input gating) and the second type of gating signal determines which of these maintained representations will have an influence on particular actions that are selected (output gating). Selective gating (rather than a global mechanism arising from midbrain dopaminergic input that would update everything) allows for some information to be maintained by PFC while other information is updated. The idea of selective striatal gating also allows for a hierarchy within fronto-striatal circuitry such that contextual representations in rostral frontal cortex can influence striatal gating of contextual representations in caudal frontal cortex. An MRI study using diffusion tractography has demonstrated that the proper wiring is in place for such a mechanism in that there is a

rostral-caudal correspondence in the connectivity pattern between frontal and striatal regions (Verstynen et al. 2012).

CONCLUSIONS

Working memory is a construct that has motivated research in many domains – cognitive, neuroscientific, clinical – for the past 50 years. The results from this half-century of research, cumulatively, have reinforced the centrality, articulated in seminal writings from the 1960s, 70s, and 80s, of working memory in the control of behavior. The past decade has witnessed many exciting advances in our understanding of the mechanisms that underlie working memory, and these have necessarily prompted the near-continuous updating of our models of how working memory works. At a broader level, however, one could make the case that our current neural systems-level models were foreshadowed by a core feature of the Baddeley and Hitch (1974) multiple component model, and that is the important distinction between stimulus representation, on the one hand, and the control of behavior with those representations, on the other. Baddeley has always been clear that his construal of the Central Executive of the multiple-component model was of something akin to Shallice's Supervisory Attentional System. That is, a control system that was not in any sense "specialized for" or "dedicated to" working memory operations, but one that could use and/or manipulate the contents of working memory storage to more effectively guide behavior. The prefrontal, basal ganglia, thalamic, and brainstem systems reviewed here can be construed as a neural substrate for this Central Executive. We believe that a conceptual error at the root of some of the systems- and cognitive-neuroscience research from the 1980s–2000s was misattribution of PFC activity to the functioning of one of the storage buffers from the multicomponent model, rather than to the Central Executive. The research that we have reviewed here makes it clear that the functions of PFC (and related systems) are too flexible, and operate on too abstract a level, to be construed as simply performing a buffering role.

The past ten years have also witnessed considerable progress in our understanding of how the function of buffering is accomplished in the primate brain. In digital computers, this function is carried out by random access memory (RAM), circuitry that is physically distinct from "hard drive" storage, and that is specialized for and dedicated to this role. The analogy to computer architecture may have, at least implicitly, influenced previous thinking about biological working memory. What recent research has established, however, is that there are no dedicated "RAM" circuits in the primate brain. Rather, the operation of holding information "in" working memory occurs within the same circuits that process that information in non-mnemonic contexts. For symbolic information, this has been captured by models of activated semantic LTM. For sensorimotor information, by sensorimotor recruitment models.

In this review, we have emphasized the fundamental importance of working memory for cognitive control. It is our belief that any understanding of the basic mechanisms of working memory leads directly to a further understanding of the most complex aspects of human cognition. The frontal cortex continues to be a primary area of focus in attempts to uncover the neural mechanisms that support component processes that are necessary for cognitive

control. The frontal cortex is hierarchically organized and provides critical bias signals that sculpt goal-directed behavior. Much work is still needed regarding the nature of these signals, and the mechanisms by which the frontal cortex maintains relevant information and communicates with other brain regions. Moreover, ascending brainstem neuromodulatory systems, such as the dopaminergic system, likely influence most of the cognitive processes mentioned in this review. A consideration of all of these mechanisms together, rather than in isolation, should provide a clearer picture of the neural bases of cognitive control.

Acknowledgments

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SUMMARY POINTS

1. An enduring principle of the multiple-component model of working memory (Baddeley and Hitch, 1974) is that the short-term retention of information (a.k.a. "working memory storage") and the control of how that information is used to guide behavior are subserved by distinct processes. With regard to the former, however, earlier ideas of specialized buffers have been largely superceded by state-based models.

2. Although state-based models of working-memory storage are often categorized as "activated LTM" models or "sensorimotor recruitment" models, all are grounded in the idea that the attentional selection of mental representations brings them into working memory, and that the consequences of attentional prioritization explain such properties as capacity limitations, proactive interference from no-longer-relevant items, and so on.

3. Recent research applying multivariate pattern analysis (MVPA) to fMRI and EEG data has provided compelling neural evidence for state-based models of working memory storage.

4. Some recent findings from computational modeling, extracellular electrophysiology, fMRI, and EEG, suggest that working memory storage may depend on the transient reorganization of synaptic weights, rather than on sustained, elevated activity.

5. The PFC likely represents higher-order information, such as task rules, goals, or abstract representations of categories, as compared to feature- and stimulus-specific representations in posterior cortex. Moreover, a critical mechanism for working memory function is the synchronization of PFC activity with activity in other brain regions.

6. One dimension of functional organization of PFC is a hierarchical caudal-to-rostral gradient of the level of abstraction of the rules and goals that guide behavior.

7. Top-down control signals emanating from PFC likely take at least two forms: signals that modulate gain by either enhancing task-relevant information or suppressing task-irrelevant information, and signals that can modulate the selectivity of information represented in posterior cortical regions.

8. Dopamine plays a critical role in working memory function. The complex interplay of midbrain dopamine in prefrontal and striatal circuits underlies "tonic maintenance" and "phasic gating" functions that govern the balance between cognitive flexibility and stability.

FUTURE ISSUES

1. How is the focus of attention organized? Does it have a strict capacity limit of one item or can it contain multiple items? Are there multiple distinct levels within the focus of attention (or levels of activation within working memory), or is everything outside a unitary focus of attention in the same state of long-term memory?

2. What class of models better account for capacity limitations in visual STM – slots models, single-resource models, a hybrid of the two, or some as-yet-to-be-described alternative?

3. Because recent MVPA studies have dissociated working-memory storage from sustained, elevated delay-period activity, what functions does the latter subserve?

4. Is it possible, as suggested by recent experiments, that all delay-period activity that is decodable with MVPA, even activity that is below univariate statistical thresholds, corresponds to the focus of attention, rather than the storage of information per se? If so, is that the latter accomplished via the transient reorganization of synaptic weights?

5. Is the high dimensionality that has been ascribed to ensembles of PFC neurons a property that is unique to that region, or is the property also characteristic of other brain regions?

6. What are the different functional roles of particular frequencies of oscillations (e.g. theta (4–7 Hz), alpha (8–13 Hz), and gamma (30–200 Hz)) for working memory?

7. Does dopamine play a similar role in both "input" and "output" working memory gating signals?

8. What is the role of other neurotransmitters and hormones, in addition dopamine, in working memory function?