

WORKING MEMORY FOR VISUAL OBJECTS: COMPLEMENTARY ROLES OF INFERIOR TEMPORAL, MEDIAL TEMPORAL, AND PREFRONTAL CORTEX

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Abstract—Humans have an extraordinary ability to maintain and manipulate visual image information in the absence of perceptual stimulation. The neural substrates of visual working memory have been extensively researched, but there have been few attempts to integrate these findings into a model of how different cortical areas interact to form and maintain visual memories. In this paper, I review findings from neurophysiological, neuropsychological, and neuroimaging studies of visual working memory in human and non-human primates. These data support a model in which visual working memory operations rely on activation of object representations in inferior temporal cortex, via top-down feedback from neocortical areas in the prefrontal and medial temporal cortex, and also from the hippocampus. © 2005 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: memory, prefrontal, temporal, hippocampus, visual, working.

In the past 30 years, there has been an explosion of research on the cognitive neuroscience of working memory (WM) in human and nonhuman primates. Much of this interest has focused on the prefrontal cortex (PFC), which is not surprising, as the PFC has been shown to contribute to numerous cognitive activities (Stuss and Benson, 1986; Fuster, 1997), including WM maintenance (e.g. Jacobsen, 1936; Fuster and Alexander, 1971; Kubota and Niki, 1971; Funahashi et al., 1993; Rao et al., 1997). Nonetheless, it is clear that functions of the PFC are not limited to WM maintenance (D'Esposito et al., 1998b; Lebedev et al., 2004), and that WM processes are dependent on a distributed network of cortical regions extending well beyond the PFC (Fuster, 1995; Wager and Smith, 2003; Pasternak and Greenlee, 2005; Ranganath and D'Esposito, 2005; Ranganath and Blumenfeld, 2005). Recent papers have focused on the nature of these networks for spatial (Curtis and D'Esposito, 2003; Constantinidis and Wang, 2004) and verbal (Ruchkin et al., 2003) WM, demonstrating a clear link between WM maintenance and neural systems

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Abbreviations: BA, Brodmann's area; DMS, delayed-matching-to-sample; DNMS, delayed non-matching to sample; DPA, delayed-paired associate task; FFA, fusiform face area; LTM, long-term memory; PFC, prefrontal cortex; PPA, parahippocampal place area; WM, working memory.

specialized for perception and action (Fuster, 1995, 2003, Postle, in press).

Here, I will introduce a model of the neural mechanisms of processes that support the maintenance and manipulation of visual images. I will first review results implicating the inferior temporal cortex, medial temporal cortex and hippocampus, and the PFC in visual WM processes (Fig. 1). Next, I will propose a model to understand how interactions between these areas support visual WM operations under different conditions. Finally, I will review new results showing how this model can illuminate not only WM, but also the relationship between WM processes and long-term memory (LTM) formation and retrieval.

Inferior temporal cortex and visual WM maintenance

Inferior temporal area TE is considered to be the final stage of the ventral visual processing pathway (Ungerleider and Mishkin, 1982), and is thus well suited to process and represent information about complex visual objects. Single-unit recording studies in monkeys have shown that temporal lobe neurons exhibit object-selective visual responses (Baylis et al., 1987; Nakamura et al., 1994), and that this selectivity can be modified through perceptual (Logothetis et al., 1995; Sigala and Logothetis, 2002) or associative (Miyashita, 1988; Erickson and Desimone, 1999; Messinger et al., 2001) learning.

Additional work has shown that inferior temporal cortex is critical for short-term maintenance of information about visual objects (Ranganath and D'Esposito, 2005). For example, inactivation (Fuster et al., 1981; Horel and Pytko, 1982; Horel et al., 1987) or lesions (Petrides, 2000) of the inferior temporal cortex severely impair short-term retention of visual object features. Single-unit recording studies have shown that inferior temporal neurons exhibit persistent, object-selective activity during the retention of visual objects across short delays (Miyashita and Chang, 1988; Miller et al., 1993; Nakamura and Kubota, 1995). Although results from one study showed that persistent object-selective activity in temporal neurons is attenuated following presentation of a distracting stimulus (Miller et al., 1993), this finding should not be taken to suggest that this region plays no role in visual WM maintenance. As I discuss later in this paper, objects can be coded and maintained at a number of different levels, and presenting a distracting stimulus might interfere with maintenance of coherent visual object representations while sparing maintenance of other relevant representations (Ranganath et al., 2005). Thus, although it is of interest that inferior temporal neu-

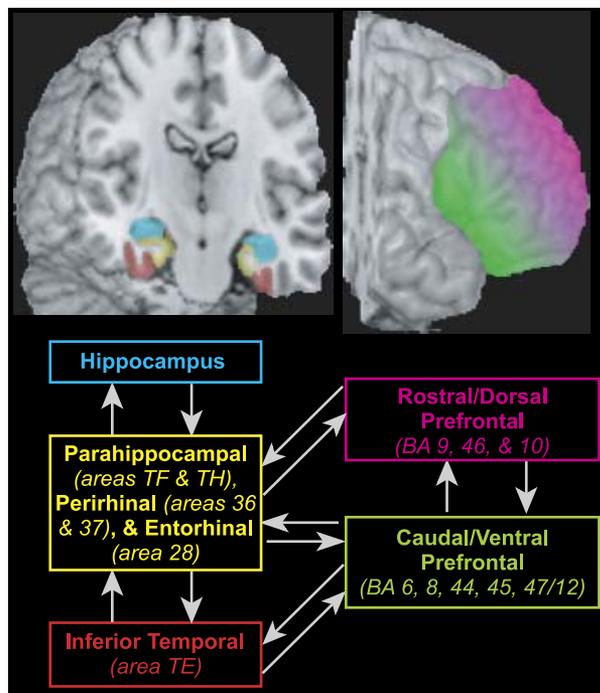


Fig. 1. Brain regions implicated in visual WM processing: (A) At left, locations of inferior temporal (red) and medial temporal (yellow) neocortical areas and the hippocampus (blue) are shown. At right, relative locations of rostral/dorsal (BA 9, 10, and 46, shown in magenta) and caudal/ventral prefrontal regions (BA 44, 45, and 47/12, shown in green) are shown. (B) Neuroanatomical connections between these regions are schematically depicted. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

rons differ from those in medial temporal (Suzuki et al., 1997) and prefrontal (Miller et al., 1993) neurons with respect to their ability to exhibit persistent activity following presentation of distracting objects, these differences do not mean that inferior temporal neurons do not play an important role in visual WM maintenance.

In addition to persistent activity, temporal lobe neurons have shown another form of activity relevant to visual WM, termed “match enhancement.” Match enhancement is an increased response to a test object that matches an actively maintained object representation (Miller and Desimone, 1994). Interestingly, match enhancement effects in inferior temporal neurons are robust to the presentation of distracting objects (Miller et al., 1993).

Finally, it should be noted that some temporal cortical neurons exhibit reduced activity in response to recently presented items relative to items that are relatively novel (Baylis and Rolls, 1987; Miller et al., 1991a,b; Fahy et al., 1993; Miller and Desimone, 1994; Ringo, 1996). Collectively, each of these types of neural signals represents a potential mechanism for retention of visual object information across short delays (Baylis and Rolls, 1987; Suzuki, 1999; Ranganath and Blumenfeld, 2005).

A number of human neuroimaging studies have also examined inferior temporal activity during visual WM maintenance. Initial work revealed mixed results, as some stud-

ies reported sustained inferior temporal activity during memory delays (Courtney et al., 1997; Postle and D’Esposito, 1999; Postle et al., 2003; Sala et al., 2003; Rama and Courtney, 2005), whereas others reported only transient, stimulus-related activity in inferior temporal cortex (Jha and McCarthy, 2000; Munk et al., 2002; Linden et al., 2003). More recent neuroimaging investigations have taken into consideration the fact that inferior temporal activity during retention delays is object-selective (Miyashita and Chang, 1988; Miller et al., 1993; Nakamura and Kubota, 1995). To the extent that neurons selective for maintained objects are disproportionately distributed across the inferior temporal cortex (Haxby et al., 2001), conventional neuroimaging methods might not be sufficiently sensitive to detect persistent, object-selective activity during memory delays (Ishai et al., 2000). One way to address this issue is to identify inferior temporal subregions that preferentially and maximally respond to categories of objects, such as the fusiform face area (FFA) for faces (Puce et al., 1995; Kanwisher et al., 1997) and the parahippocampal place area (PPA) for scenes or buildings (Aguirre et al., 1998; Epstein and Kanwisher, 1998). Once these areas are identified with high spatial resolution in each individual subject, they can be probed as regions of interest for activity during maintenance of preferred and non-preferred stimuli.

Using this approach, several studies have examined WM activity in the FFA, showing that this area exhibits persistent activity when faces are maintained across memory delays (Druzgal and D’Esposito, 2003; Ranganath et al., 2004a,b). Additionally, persistent FFA activity increases linearly with the number of faces that are actively maintained (Druzgal and D’Esposito, 2001a, 2003). In addition to persistent activity, two studies reported match enhancement effects in the fusiform gyrus during face WM tasks (Jiang et al., 2000a; Druzgal and D’Esposito, 2001b). Other studies have compared the response properties of the FFA and PPA to characterize the selectivity of mnemonic activity in inferior temporal cortex during WM encoding and maintenance. These studies have consistently shown that even when perceptual input was identical, encoding and delay period activity in the FFA and PPA was enhanced when their preferred type of stimulus was currently task-relevant, relative to non-preferred items (Ranganath et al., 2004b; Gazzaley et al., 2005). In a similar vein, researchers have reported activation of category-specific inferior temporal subregions during mental imagery of faces and buildings (Ishai et al., 2000, 2002; O’Craven and Kanwisher, 2000). These neuroimaging findings converge with the results of single-unit recording studies in monkeys to suggest that visual WM maintenance is consistently associated with persistent activation of object representations in the inferior temporal cortex.

Roles of hippocampus and medial temporal cortex in maintenance of novel objects

Although it is commonly suggested that medial temporal cortical regions such as the perirhinal cortex (areas 35 and 36), entorhinal cortex (area 28) and parahippocampal cor-

tex (areas TF and TH) are not important for WM (Alvarez et al., 1994; Ryan and Cohen, 2004), single-unit recording studies have reported robust neural correlates of WM maintenance in these regions. In fact, comparisons between areas suggest that activity related to visual WM maintenance might be more prevalent and robust in perirhinal and entorhinal cortex than in area TE. For example, Nakamura and Kubota (1995) reported that, of the visually responsive neurons that were identified, the proportion of cells that exhibited persistent delay-period activity was significantly larger in the perirhinal (38%) and entorhinal (71%) cortices than in area TE (22%). Some results suggest that these areas differ in their ability to maintain information in the face of distraction. For example, one study showed that sample-selective delay activity in inferior temporal (collapsed across area TE and perirhinal area 36) cortex was eliminated following presentation of a distracting item (Miller et al., 1993). In contrast, sample-selective delay-period activity in entorhinal neurons remained robust even after presentation of intervening stimuli (Nakamura and Kubota, 1995; Suzuki et al., 1997). Thus, medial temporal cortical areas might be particularly critical for visual WM maintenance in the face of distraction.

Evidence from lesion studies and neuroimaging studies suggests that the medial temporal lobe region might also be critical for visual WM maintenance when one needs to actively maintain information about novel, complex objects (Ranganath and Blumenfeld, 2005). For example, extensive medial temporal lobe lesions in monkeys (Zola-Morgan and Squire, 1985; Murray and Mishkin, 1986; Eacott et al., 1994) and humans (Holdstock et al., 1995; Owen et al., 1995; Buffalo et al., 1998) impair retention of novel objects even across short delays of 7–10 s¹ (see Ranganath and Blumenfeld, 2005, for review). Additionally, imaging studies have reported increased hippocampal and/or perirhinal activity during WM tasks with novel visual objects (Eliot and Dolan, 1999; Sybirska et al., 2000; Davachi and Goldman-Rakic, 2001; Ranganath et al., 2005), faces (Ranganath and D'Esposito, 2001; Nichols et al., 2004), or scenes (Stern et al., 2001; Schon et al., 2004). Hippocampal and medial temporal cortical activation during WM delays appears to be specifically enhanced during maintenance of novel stimuli relative to familiar stimuli, (Ranganath and D'Esposito, 2001; Stern et

al., 2001; Ranganath et al., 2005). Interestingly, one recent study found that the hippocampus exhibits enhanced functional connectivity with inferior temporal cortex during WM delays (Gazzaley et al., 2004), suggesting that the hippocampus might provide feedback to posterior cortical areas in order to guide WM maintenance.

Roles of prefrontal regions in visual WM maintenance

Whereas temporal lobe regions are the likely sites of object representations that are activated during visual WM maintenance, the PFC appears to play a significant role in cognitive control processes that select or inhibit relevant object representations based on behavioral relevance (Miller, 1999; Rainer and Ranganath, 2002; Curtis and D'Esposito, 2003; Ranganath and D'Esposito, 2005, Postle, in press). For example, prefrontal lesions in humans do not eliminate short-term memory, but instead selectively impair cognitive control processes necessary for actively maintaining or manipulating relevant information in the face of distraction (Chao and Knight, 1998; D'Esposito and Postle, 1999, D'Esposito et al., in press). Converging evidence comes from single-unit results showing that prefrontal neurons, like those in entorhinal cortex, exhibit persistent object-specific delay-period activity that remains robust even after presentation of distracting stimuli (Miller et al., 1996).

Several lines of evidence suggest that PFC contributes to WM by modulating activity in posterior cortical areas (Mechelli et al., 2004; Gazzaley et al., 2005). Mechelli et al. (2004) used dynamic causal modeling of functional magnetic resonance imaging (fMRI) data to show that FFA and PPA activity during imagery of faces and houses was mediated by top-down feedback from PFC. Convergent evidence comes from studies examining functional correlates of PFC dysfunction. For example, Fuster and colleagues (Bauer and Fuster, 1976; Fuster et al., 1985) have shown that cooling of the PFC impaired behavioral performance and attenuated sample-specific delay-period activity in inferior temporal neurons during a delayed-matching-to-sample (DMS) task. In another study, event-related potential (ERP) recordings were used to monitor posterior cortical responses to distracting sounds presented during the delay period of an auditory WM task (Chao and Knight, 1998). Patients with prefrontal lesions exhibited significantly impaired WM performance when distracting sounds were presented during the delay, and this effect was accompanied by increased neural responses to the distracters. Collectively, these results suggest that the PFC supports WM by regulating activity in posterior cortical areas.

One current controversy regards the functional organization of the PFC, and the relative roles of different subregions in visual WM (Courtney et al., 1998a; Miller, 2000; Postle and D'Esposito, 2000; Rainer and Ranganath, 2002; Ranganath et al., 2003; Ranganath and Knight, 2003). Based on the neuroanatomical organization of the PFC in monkeys, these debates have generally focused on differences between relatively dorsal (Brodmann's areas [BA] 9 and 46) and ventral (BA 44, 45, and 47/12) areas of

¹ These studies used the "delayed non-matching to sample" (DNMS) paradigm with trial-unique objects (Konorski, 1959; Gaffan, 1974; Mishkin and Delacour, 1975). In this task, a sample object is shown, and then after a brief retention delay, the subject must choose a novel object over a previously studied object. It is usually assumed that this test taps familiarity-based recognition memory, and accurate performance on the task does not require active maintenance of the sample. Nonetheless, WM maintenance can, in principle, be used to solve the task when the retention delays are relatively short (Pascalis and Bachevalier, 1999; Ranganath and Blumenfeld, 2005). Accordingly, studies showing effects of perirhinal or parahippocampal lesions on DNMS performance when delays are relatively short suggest that these regions may be necessary for active maintenance of novel objects as well as discrimination between novel and familiar objects. This issue is discussed in more depth in another review (Ranganath and Blumenfeld, 2005).

PFC. As shown in Fig. 2, the homologous areas in human PFC lie in relatively rostral and dorsal regions (BA 9, 10, and 46) and caudal/ventral regions (BA 6/8, 44, 45, and 47). Human neuroimaging studies have revealed fairly consistent evidence that these prefrontal areas exhibit different response properties.

I suggest that all PFC subregions play a role in “selecting” (i.e. accentuating or inhibiting the activation of) memory representations, (Goldman-Rakic, 1987; Cohen and Servan-Schreiber, 1992; Fuster, 1997; Kimberg et al., 1997; Thompson-Schill et al., 1997; Wagner, 1999; Miller,

2000; Curtis and D’Esposito, 2003; Passingham and Sakai, 2004, Postle, in press), but that different subregions may be selecting information at different levels of analysis. More specifically, I propose that caudal/ventral regions may be selecting representations of relevant “items” (i.e. objects, spatial locations, words, etc.), whereas relatively rostral/dorsal regions may select representations of abstract relations between items that are currently active. Based on the neuroanatomical connectivity of homologous areas in the monkey (Miller, 2000), it is likely that the selection processes implemented by of caudal/ventral PFC

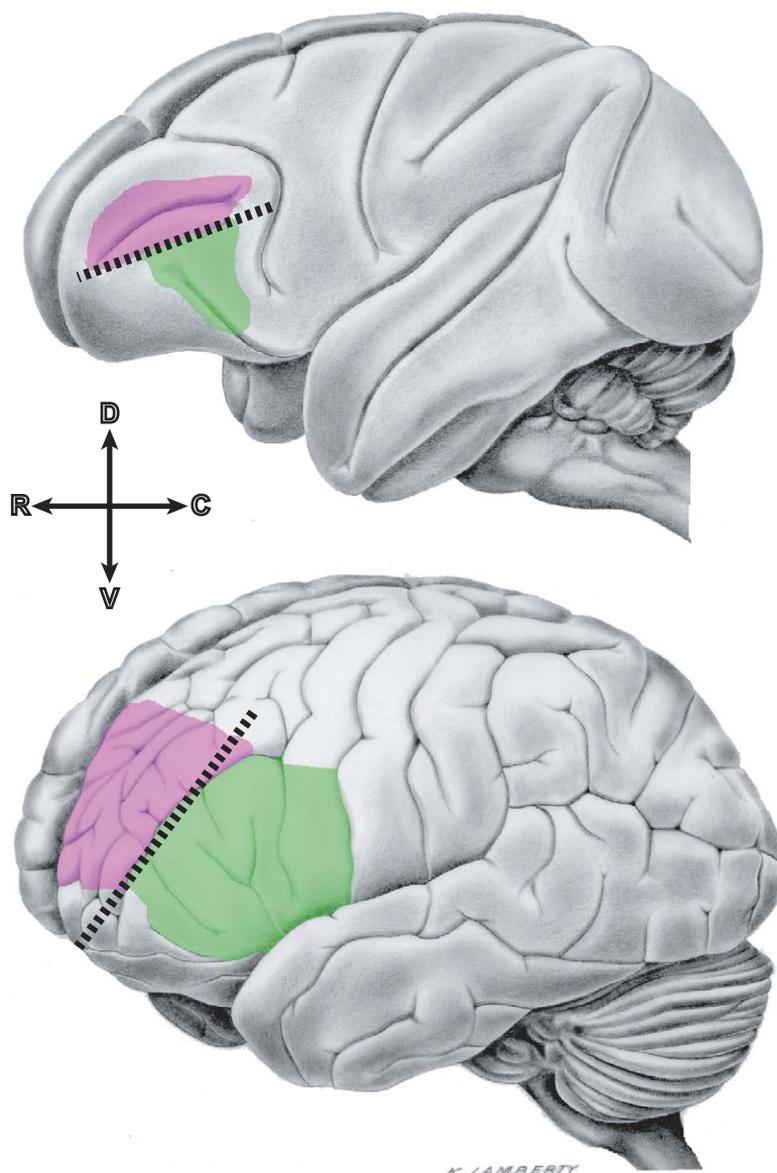


Fig. 2. Differences in relative locations of prefrontal regions between the macaque and human brain. (A) Cytoarchitectonic analyses of the monkey cortex have led many researchers to postulate functional differences between regions in and around the sulcus principalis (BA 9 and 46), shown in magenta, and regions in and around the inferior convexity (BA 44, 45, and 47/12), shown in green. A dashed line schematically illustrates the division between these areas. (B) The relative locations of homologous areas are shown for the human brain, based on published cytoarchitectonic analyses of the human PFC (Rajkowska and Goldman-Rakic, 1995; Amunts et al., 1999; Petrides and Pandya, 2002), and a dashed line schematically illustrates the division between these areas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

involve modulations of activity in posterior cortical areas, whereas selection processes implemented by rostral/dorsal PFC involve modulations of activity in caudal/ventral PFC and/or posterior parietal cortex (Wendelken, 2001).

Numerous fMRI studies have reported that caudal/ventral PFC regions are recruited across a variety of task domains that engage item selection processes, including when a task requires transient encoding of a relevant item (Paller and Wagner, 2002), sustained maintenance of an item representation (Curtis and D'Esposito, 2003; Ranganath et al., 2004a), and inhibition of irrelevant or potentially distracting items (Konishi et al., 1999). Critically, the topography of caudal/ventral PFC activation has paralleled the representation of different item features in posterior cortex. For example, tasks requiring selection, encoding, or maintenance of spatial (BA 6/8: Courtney et al., 1998b), semantic (left BA 45 and 47: Thompson-Schill et al., 1997; Wagner et al., 2001b), phonological (left BA 44: Schumacher et al., 1996; Poldrack et al., 1999), and visual non-verbal (right BA 44 and 47: Kelley et al., 1998; Wagner et al., 1998; Braver et al., 2001) information tend to recruit different caudal/ventral prefrontal subregions.

Results from several imaging studies are also consistent with the idea that rostral/dorsal PFC regions (BA 9, 10, and 46) are recruited during tasks that require selection of relations between items that are active in memory. For example, these regions are activated during tasks that require reasoning based on abstract relations (Christoff et al., 2001; Kroger et al., 2002; Badre and Wagner, 2004; Bunge et al., 2004b), encoding of relations among items that are active in memory (Davachi et al., 2001; Wagner et al., 2001a; Blumenfeld et al., 2004), grouping of items in WM based on higher order relations (Bor et al., 2003, 2004), inhibition of previously learned associations (Dolan and Fletcher, 1997; Henson et al., 2002; Anderson et al., 2004), or sequencing of information that is being maintained in WM (i.e. “manipulation,” D'Esposito et al., 1999; Postle et al., 1999; Barde and Thompson-Schill, 2002; Blumenfeld et al., 2004). In contrast to the results for caudal/ventral PFC, rostral/dorsal PFC activation does not seem to be sensitive to the kind of information that is being processed, suggesting that these regions act at a more abstract level (D'Esposito et al., 1998a; Smith and Jonides, 1999; Wagner, 1999; Christoff and Gabrieli, 2000; Koechlin et al., 2003; Fuster, 2004; Ramnani and Owen, 2004).

The model described above potentially reconciles competing theories of prefrontal function. For example, some researchers have suggested that rostral/dorsal PFC subregions (e.g. BA 46) might be specialized for spatial WM processing (O'Scalaidhe et al., 1997; Courtney et al., 1998b) or response selection (Rowe et al., 2000; Bunge et al., 2004a), whereas several findings firmly suggest that this region does not exhibit content- or modality-based specialization (Rao et al., 1997; Postle and D'Esposito, 1999). Other researchers have suggested that dorsal PFC regions may be specialized for monitoring (Petrides, 1989; Owen, 1997) or manipulating (D'Esposito et al., 1999; Postle et al., 1999) information in WM. A common theme among both the “spatial” and the “manipulation/monitoring”

models described above is that they each involve active processing of relations: Many spatial WM tasks involve processing of the spatial relations among items that are active in memory (Jiang et al., 2000b), whereas many tasks that investigate manipulation or monitoring usually involve processing of more abstract relations (semantic, temporal, etc.) between items that are active in memory (Wendelken, 2001; Ranganath and D'Esposito, 2005). Thus, the idea that relatively rostral/dorsal prefrontal regions are specialized for activating spatial and nonspatial relations among items that are active in memory provides a parsimonious account for a wide range of findings in the imaging literature.

A model for visual WM

Earlier, I have described evidence regarding the roles of inferior temporal, medial temporal, and prefrontal regions in visual WM (Gazzaley et al., 2004; Ranganath and D'Esposito, 2005). To integrate these findings into a specific model, we next need to specify some principles regarding the nature of visual WM. I propose that two basic principles can be proposed based on theoretical accounts of visual perception.

The first principle is that visual WM maintenance reflects the outcome of processing at multiple, hierarchical levels. Visual information is analyzed by a hierarchy of cortical areas, such that low-level features are analyzed in early stages and these features are integrated into higher-level representations at late stages of the cortical hierarchy (Ungerleider and Mishkin, 1982; Van Essen et al., 1992). The implications of this idea for visual WM are that visual information can potentially be maintained at multiple levels of analysis (i.e. ranging from low-level retinotopic features, to viewpoint-independent object representations, to representations of flexible relations between parts of objects that are perceived as separate, etc.). Accordingly, interfering with maintenance at one level of analysis—through lesions or behavioral distraction—can still preserve maintenance at other levels of analysis. It follows that null effects in lesion (e.g. failure to find significant effects of lesions on visual WM performance, as in Alvarez et al., 1994) or single-unit recording (e.g. failure to find persistent activity during memory delays following distractions, as in Miller et al., 1991b) studies of visual WM should be interpreted with caution.

The second principle is that visual WM maintenance, like visual perception, is constructive in nature. Recent theories have emphasized the role of feedback interactions in visual processing (Lamme and Roelfsema, 2000; Grossberg, 2001; Bar, 2004; Deco and Rolls, 2004; Murray et al., 2004) and several lines of evidence suggest that top-down knowledge is used to guide visual object recognition (Bar, 2003). If higher-order knowledge is used to process visual images during perception, it is reasonable to suggest that similar processes may support visual WM maintenance. That is, in many situations, recently perceived visual stimuli are “recoded” (Miller, 1956) so that they can be actively maintained (Jolicoeur and Dell'Acqua, 1998; Raye et al., 2002; Ranganath et al., 2005). Recoding

a visual image should involve activation of relatively high level visual and supramodal representations that may, in turn, reinstate activity in earlier visual areas. The implications of this idea are that, under certain circumstances, WM maintenance may involve multiple stages of processing. During the initial few seconds of WM maintenance, neural systems involved in “top-down” cognitive control processes and high-level visual areas should be recruited in order to reconstruct a stable mental representation of the previously seen image. Once a pattern of activity corresponding to the relevant image is re-instantiated, this image could be maintained with little effort in the absence of external stimulation.

Based on the principles described above and based on neuroanatomical considerations, I can now outline a basic model of visual WM (Fig. 1). First, I propose that the visual aspects of an image are maintained through persistent activity in visual cortical areas (Ranganath et al., 2005)—maintenance of coherent visual object representations could occur through persistent object-specific activity in inferior temporal cortex (Ranganath and D'Esposito, 2005), whereas lower-level features could be maintained through persistent activity in areas such as V4 (Tallon-Baudry et al., 2001, 2004; Lee et al., 2005; Pasternak and Greenlee, 2005), and possibly even V1 (Super et al., 2001). Of course, it is likely that relevant aspects of visual objects can additionally be maintained through activation of semantic or other non-visual representations.

I additionally propose that there are top-down mechanisms that facilitate activation of representations in visual cortical areas. For example, feedback from medial temporal lobe regions should be required to reconstruct aspects of a novel visual image (Rolls, 2000). This is because medial temporal lobe regions are unique in their ability to rapidly encode representations of novel information (Rolls, 2000; O'Reilly and Norman, 2002). Because novel visual images may not correspond to established visual object representations in inferior temporal cortex, feedback from medial temporal lobe regions may be necessary in order to reconstruct a high-resolution mental image (Ranganath and D'Esposito, 2001). I propose that representations of novel objects are rapidly formed in the perirhinal cortex (Murray and Bussey, 1999). This area is ideally suited for forming new object representations, as this region receives massive cholinergic inputs from the nucleus basalis, which are thought to facilitate rapid neocortical plasticity in response to novel stimuli or events (Easton and Parker, 2003; Ranganath and Rainer, 2003; Turchi et al., 2005). The hippocampus proper complements the perirhinal cortex, in that it is ideally suited to rapidly encode the relations between objects in a visual scene (Gaffan, 1991; Nadel, 1991; Eichenbaum and Cohen, 2001; O'Reilly and Rudy, 2001).

Finally, top-down input from the PFC can additionally promote maintenance of complex visual images in the face of distraction (Miller et al., 1996; Sakai et al., 2002). For example, top-down input from caudal/ventral prefrontal areas should facilitate activation of relevant visual object representations and inhibit representations of distracting or

irrelevant information. Rostral/dorsal prefrontal areas can facilitate reconstruction or manipulation of a complex visual image by enhancing or reducing the activation of relations between features of an image based on prior knowledge.

Interactions between visual WM and LTM

The model described above suggests that the specific neural circuits recruited to implement visual WM processes will depend on whether one is attempting to maintain a simple, highly familiar object or a novel, detailed visual image. In the former case, the model suggests that visual WM maintenance will be associated with persistent activity in caudal/ventral prefrontal and occipito-temporal cortical areas. However, when complex, novel images are being maintained, an additional mechanism should be necessary, because these images would not be associated with stable representations in inferior temporal cortex. In the latter situation, rapidly formed LTM traces in medial temporal areas could be used to provide top-down feedback to inferior temporal and earlier visual areas in order to initiate visual WM maintenance processes. Additionally, rostral/dorsal prefrontal areas would be expected to complement the roles of medial temporal regions by enhancing the activation of relations between specific aspects of a visual image, in order to minimize conjunction errors in the reconstructed image.

The model I have described suggests that the recruitment of rostral/dorsal prefrontal and medial temporal areas during on-line maintenance of a visual image should be directly correlated with whether or not the image is successfully encoded into LTM. A number of neuroimaging studies have empirically validated this prediction by demonstrating that persistent activity in prefrontal and medial temporal areas during maintenance of novel information is enhanced for items that are successfully remembered even after long retention delays (Davachi and Goldman-Rakic, 2001; Davachi et al., 2001; Nichols et al., 2004; Schon et al., 2004; Ranganath et al., 2005; Takashima et al., unpublished observations).

In one recent study, my colleagues and I specified the time course and functional significance of hippocampal and prefrontal recruitment during maintenance of novel stimuli (Ranganath et al., 2005). Specifically, we used event-related fMRI to examine brain activity during active maintenance of novel visual objects (see Fig. 3) and then administered a surprise post-scan recognition memory test consisting of objects that were presented in the scanning session and foil objects that were not previously shown. We then averaged activity during WM trials as a function of whether or not each object was remembered on the subsequent LTM test.

We reasoned that subjects could perform the visual WM task simply by actively maintaining low-level features of each object, but the similarity of these features across successive objects would make them insufficient to support accurate LTM performance. In order to recognize an object on the subsequent LTM test, subjects would have needed to rapidly construct a stable representation of that

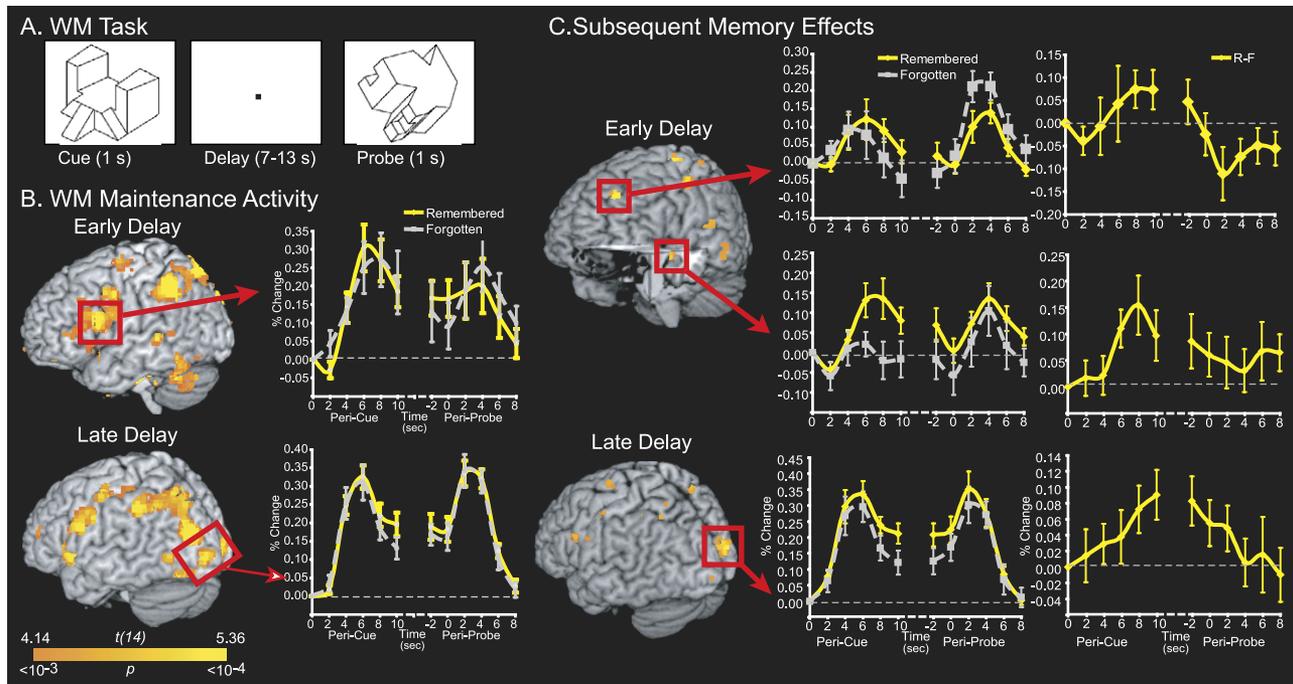


Fig. 3. fMRI results relating activity during WM maintenance to LTM formation. (A) On each trial of the WM task, subjects actively maintained a novel 3d object across a delay period in order to make a match–nonmatch decision. After the scan session, subjects were given a surprise LTM test and activity during the WM trials was averaged separately for subsequently remembered and forgotten objects. (B) Areas showing persistent delay period activity for both remembered and forgotten objects. Note that activity in both left ventral prefrontal and left occipital regions was quite robust throughout the memory delay. (C) Areas showing differential delay period activity for remembered and forgotten objects. During the early part of the delay period, the left hippocampus and dorsolateral PFC (BA 9) exhibited greater activity for subsequently remembered than for forgotten objects. Note the robust difference between the time courses 8–10 s following cue onset. During the late part of the delay, bilateral occipital regions exhibited subsequent memory effects. The subsequent memory effect in this region, unlike the hippocampus and dorsolateral PFC, was quite robust throughout the memory delay. Adapted from Ranganath et al. (2005) with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

object during the WM trial. The model described above would therefore predict that: (1) subjects should exhibit persistent delay-period activity in caudal/ventral PFC and in occipito-temporal cortex regardless of whether each object was subsequently remembered or forgotten, and (2) for objects that were subsequently remembered on the LTM test, rostral/dorsal prefrontal and medial temporal areas should be recruited during the early part of the delay period, when subjects were actively reconstructing a representation of the cue object.

As shown in Fig. 3B, we found that ventral prefrontal and early visual cortical areas were recruited during maintenance of each object, regardless of whether the item was subsequently remembered on the LTM test. However, when we identified areas in which activity during the early part of the delay period was correlated with subsequent LTM performance, we observed activation in the left dorsolateral PFC (BA 9) and the left anterior hippocampus (similar, but subthreshold effects were observed in the perirhinal and parahippocampal cortices). As shown in Fig. 3c, these areas exhibited maximal activation during maintenance of subsequently remembered objects during the early part of the memory delay; differences between remembered and forgotten objects were not apparent in the late part of the memory delay. In contrast, activation differences between remembered and forgotten objects were

also seen during the late part of the memory delay in occipito-temporal visual areas.

We next ran a second behavioral experiment (Ranganath et al., 2005), testing whether processing during the early delay period functionally contributed to LTM formation.² We reasoned that if this is the case, then interfering with controlled processing during the early part of the memory delay should significantly impair LTM formation.

² In cognitive psychology, there has been a long history of research on the role of WM maintenance in LTM formation (Craik and Lockhart, 1972; Craik and Watkins, 1973; Woodward et al., 1973; Naveh-Benjamin and Jonides, 1984; Greene, 1987; Davachi et al., 2001; Craik, 2002; Raye et al., 2002; Dobbins et al., 2004; Ranganath et al., 2005). Most published studies on the topic used verbal stimuli and have concluded that, when subjects do not engage in spontaneous elaboration of stimuli, active maintenance does not improve performance on free recall tests, but does improve performance on recognition memory tests (Greene, 1987). This pattern of results suggests that WM maintenance improves familiarity-based memory, but has little effect on recollection (Dobbins et al., 2004). However, results from some studies suggests that processing during the initial few seconds of WM maintenance is dissociable from the processes engaged later in WM maintenance (Naveh-Benjamin and Jonides, 1984; Raye et al., 2002; Ranganath et al., 2005). The initial stage of WM maintenance has been shown to disproportionately improve LTM performance (Naveh-Benjamin and Jonides, 1984; Ranganath et al., 2005) relative to more extended WM maintenance. Further work needs to be done to establish the degree to which processing during the initial stage of WM maintenance impacts recollection or familiarity-based recognition.

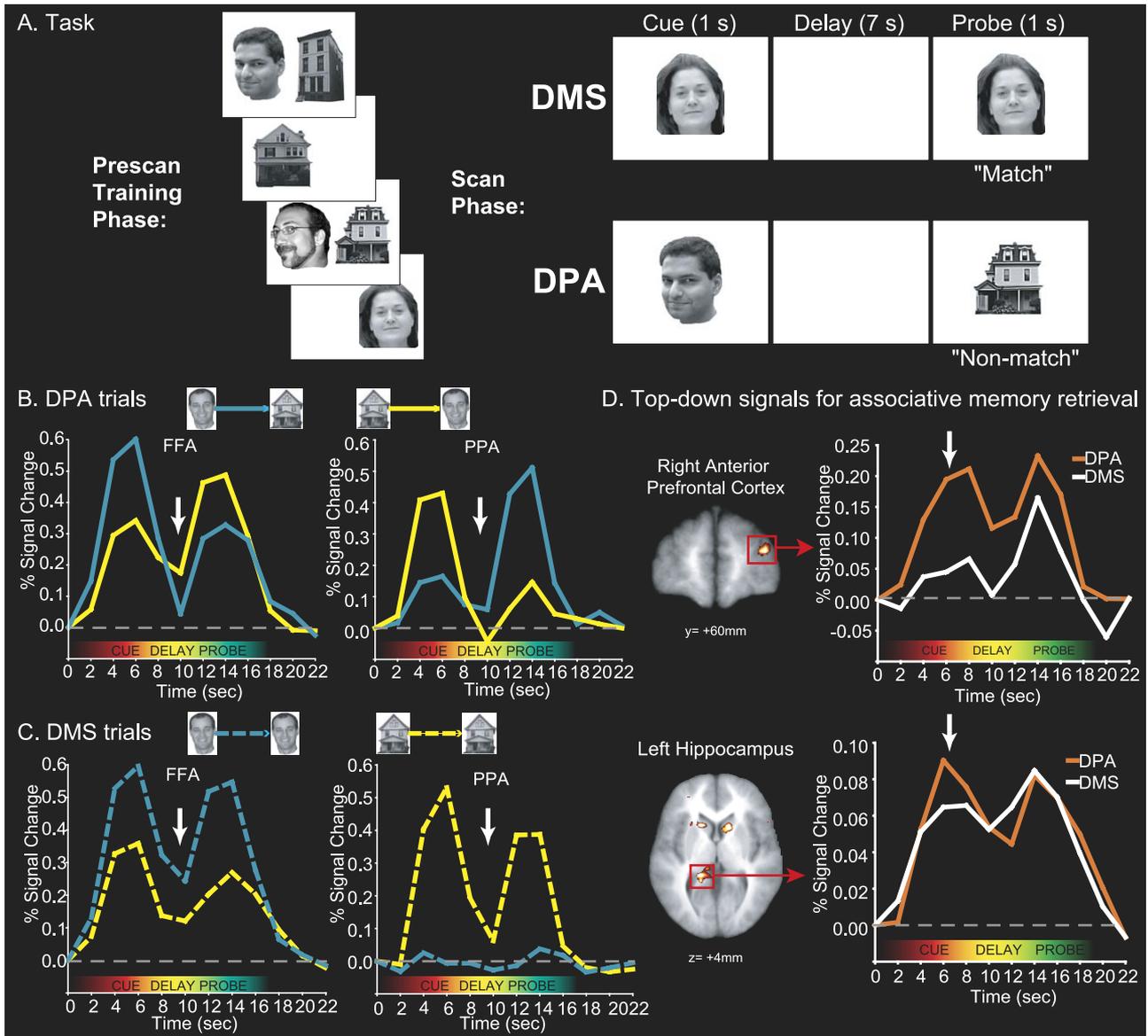


Fig. 4. Human brain activity during visual WM maintenance and associative memory retrieval. (A) In this event-related fMRI study, subjects were trained to learn a set of faces, houses, and face-house associations and were scanned while performing two tasks. On DMS trials, subjects were shown a previously studied face or house and required to maintain it across a delay. On DPA trials, subjects 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. In a separate scan, tasks were performed to identify the locations of the FFA and PPA. Activity in these category-specific inferior temporal subregions was then examined during the DPA and DMS tasks separately according to whether the cue stimulus was a face or house. (B) On DPA trials, activity during the cue phase in the FFA (left) and PPA (right) was enhanced when each region's preferred stimulus was presented. However, during the delay period, activity in these regions 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 and delay activity in the PPA was greater when a house was recalled in response to a face cue. (C) On DMS trials, cue and delay period activity in the FFA and PPA was enhanced when subjects maintained each region's preferred stimulus type. (D) Regions in anterior PFC and the hippocampus exhibited greater activity during the cue period of DPA trials than during the cue period of DMS trials, suggesting that these areas were involved in activating appropriate object representations based on the previously learned associations. Adapted from Ranganath et al. (2004a) with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Accordingly, subjects in this study performed the same WM task as in the fMRI study, but they were additionally required to perform an interfering task during the memory delay. Results showed that interfering with processing during the early delay period substantially impaired subse-

quent LTM performance, but interfering with processing later in the delay did not have any effect.

Putting the findings from the two experiments (Ranganath et al., 2005) together, we can see that low-level object features could be temporarily maintained through top-

down modulation of activity in early visual areas by caudal/ventral prefrontal regions. However, on trials when the hippocampus and dorsolateral PFC were successfully recruited during the early delay, a new object representation was actively constructed, and this representation could support performance on both the WM decision and on a subsequent LTM test.

Visual WM and visual associative LTM retrieval

People not only have the ability to maintain visual images corresponding to recent percepts but also to maintain visual information recalled from memory. For example, one could maintain a mental image of a recently seen face or recall a mental image of a face that is associated with a name. The model of visual WM that I have described suggests that medial temporal and rostral/dorsal prefrontal areas should be disproportionately critical for reactivation of associative memories, but that once activated, these memories could be maintained via top-down feedback from caudal/ventral PFC to inferior temporal cortex. Results consistent with these predictions were reported in a recent study in which we compared the response properties of different cortical areas during visual WM maintenance and associative memory retrieval tasks (Ranganath et al., 2004a). In this study, subjects learned a series of faces, houses, and face-house associations and they were scanned while performing a DMS and a delayed-paired associate task (DPA) with these stimuli (Fig. 4). Both tasks involved the maintenance of a house or a face, but on DMS trials, subjects maintained an object that was recently perceived, whereas on DPA trials, subjects maintained an object that was recalled via a previously learned association. We then examined activity in the category-selective inferior temporal subregions (the FFA and PPA) as a function of what was active in memory during the delay period. Within the FFA, we found that activity during the delay period was enhanced when subjects maintained a face on DMS trials and when subjects maintained a face that was recalled in response to a house cue on DPA trials. Within the PPA, we found that activity was enhanced when subjects maintained a house on DMS trials and when they recalled a house in response to a face cue on DPA trials. In other words, delay period activity within inferior temporal subregions reflected the type of information that was currently active in memory.

Further analyses differentiated between two types of top-down influences that facilitated task performance: Anterior PFC (BA 10) and the hippocampus exhibited selective activity increases during the cue period of DPA trials, suggesting that these areas were preferentially involved in activating the relation between the cue and its associate. This processing would be critical for activating the appropriate object representation during the memory delay. Regions in caudal/ventral PFC exhibited persistent activity during the memory delays of both DPA and DMS trials, suggesting that these areas provided top-down activation of representations of task-relevant objects that were recently perceived (DMS) or retrieved (DPA).

CONCLUSIONS

In conclusion, evidence from cognitive neuroscience has identified a distributed network of frontal and posterior cortical areas that support visual WM processes. However, this distributed network is not undifferentiated—different areas make specific and complementary contributions to visual WM processes. Maintenance of visual information appears to be implemented through sustained activation of visual object representations in inferior temporal cortex and additionally through sustained activation in earlier visual areas (Tallon-Baudry et al., 1999, 2001, 2004; Super et al., 2001; Rainer et al., 2004; Lee et al., 2005). Caudal/ventral prefrontal regions are likely to play a role in supporting this persistent activity and inhibiting the influence of distracting information. In some situations, a visual mental image must be actively constructed or arbitrary relations between visual objects must be used to activate relevant representations in inferior temporal cortex. In these cases, top-down feedback from regions in medial temporal cortex, hippocampus, and PFC should be critical for visual WM (Ranganath and D'Esposito, 2001; Ranganath et al., 2005).

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