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Directing the mind's eye: prefrontal, inferior and medial temporal mechanisms for visual working memory
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Human and nonhuman primates have a remarkable ability to recall, maintain and manipulate visual images in the absence of external sensory stimulation. Evidence from lesion, single-unit neurophysiological and neuroimaging studies shows that these visual working memory processes are consistently associated with sustained activity in object-selective inferior temporal neurons. Furthermore, results from these studies suggest that mnemonic activity in the inferior temporal cortex is, in turn, supported by top-down inputs from multimodal regions in prefrontal and medial temporal cortex, and under some circumstances, from the hippocampus.

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Introduction
Working memory (WM) processes enable one to maintain and manipulate different kinds of information to guide future behavior. The majority of research on WM has examined rehearsal of verbal or spatial information across short delays [1,2]. In these situations, WM maintenance clearly involves interplays between neural systems for perception (phonological or spatial) and neural systems for action (articulatory or oculomotor) [3,4••]. However, our WM abilities extend beyond these situations to allow us to maintain and manipulate vivid mental images of objects that were recently perceived or recalled from long-term memory (LTM) For example, in a typical visual WM task, a sample object is briefly shown, and the sample must be actively maintained across a delay period in anticipation of a subsequent match–nonmatch decision. Recent evidence has demonstrated that visual object WM maintenance is associated with persistent activation of object-selective neurons in inferior temporal

cortex [3,5]. Here, we review this evidence and we highlight the roles of the prefrontal cortex (PFC), the medial temporal neocortex, and the hippocampus in activating inferior temporal memory networks to guide goal-directed behavior (Figure 1).

Inferior and medial temporal neocortical contributions to visual WM maintenance
A wealth of neurophysiological, neuropsychological, and neuroimaging data suggest that the temporal neocortex is critical for representing long-term memories of visual objects [6–9]. Additionally, results from several single-unit recording studies show that temporal lobe neurons exhibit persistent, stimulus-selective activity in tasks requiring the maintenance of visual object information across short delays [10–12]. This type of persistent activity is thought to represent a neural mechanism for visual WM maintenance [13–15]. In addition to persistent activity, temporal neurons exhibit 'match enhancement': an increased response to a test object that matches an actively maintained visual object representation [16].

Many single-unit studies of temporal neurons include recordings from inferior temporal visual area TE and recordings from medial temporal areas (perirhinal areas 35 and 36 and entorhinal area 28; Figure 1a). Some results suggest that activity related to visual WM maintenance might be more prevalent and robust in perirhinal and entorhinal cortices than in area TE. For example, Nakamura and Kubota [11] reported that the proportion of visually responsive neurons that exhibit delay-period activity is larger in the perirhinal (38%) and entorhinal (71%) cortices than in area TE (22%). Furthermore, these areas differ in their ability to maintain visual information in the face of distraction. For example, one study shows that sample-selective delay activity in inferior temporal cortex (collapsed across area TE and perirhinal area 36) was eliminated following presentation of a distracting item [12]. By contrast, sample-selective delay-period activity in entorhinal and perirhinal neurons remains robust even after presentation of distracting stimuli [11,17].

Consistent with the results described above, several [18–21] (but not all [22–24]) human neuroimaging studies report inferior temporal activation during maintenance of visual objects. More recent neuroimaging investigations take into consideration the finding that temporal lobe neurons exhibit activity during retention delays that is object-selective [10–12]. Although neuroimaging methods cannot detect object-selective activity at the

Figure 1
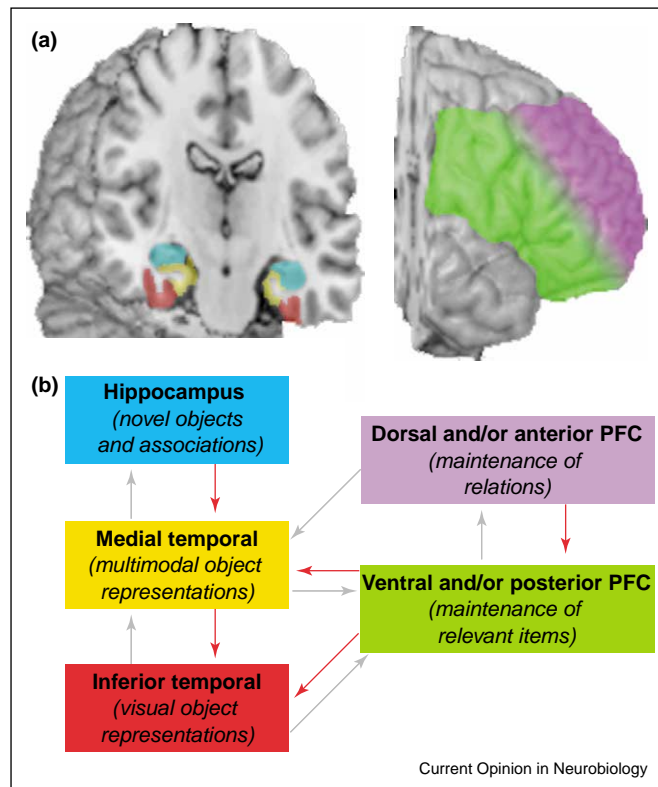
Brain regions implicated in visual WM processing. **(a)** Neural correlates of visual WM maintenance have been observed in inferior (red) and medial (yellow) temporal cortical areas. In addition, recent results suggest that the hippocampus (blue) contributes to maintenance of novel visual objects. Within the lateral PFC, evidence suggests a relative distinction between dorsal and/or anterior regions (BA 9, 10, and 46; purple) and ventral and/or posterior regions (BA 6/8, 44, 45 and 47; green). **(b)** The neuroanatomical connections between these regions, along with the results reviewed here, suggest that inferior temporal visual object representations can be reactivated through feedback from the PFC and/or the medial temporal lobes.

single-neuron level, studies have identified inferior temporal subregions that preferentially respond to categories of objects, such as the fusiform face area (FFA) for faces [25,26] and the parahippocampal place area (PPA) for scenes or buildings [27,28]. Several recent studies examined WM activity in the FFA and show that this area exhibits persistent activity when faces are maintained across memory delays [29••,30•,31,32], that this activity is robust to distraction [32], and that it increases linearly with the number of faces that are actively maintained [30•,33]. In addition to persistent activity, two studies report match enhancement effects in the fusiform gyrus during face WM tasks [34,35].

Another approach that has been used in recent studies is to compare the response properties of different category-specific inferior temporal subregions during encoding and maintenance of preferred and nonpreferred stimuli. Such studies have shown, for example, that independent of perceptual stimulation, encoding and delay period activity in the FFA and PPA is enhanced when their preferred stimuli are task-relevant [31,36•]. Others report activation

of category-specific inferior temporal subregions during mental imagery of faces and buildings [37–39]. Altogether, these recent neuroimaging findings concur with the results of monkey physiology studies to suggest that visual WM operations are supported by activation of object representations in the temporal cortex.

The hippocampus and the medial temporal neocortex contribute to active maintenance of novel objects

It has been suggested that medial temporal cortical areas (perirhinal, parahippocampal, and entorhinal cortices) and the hippocampus comprise a 'medial temporal lobe memory system' that is not involved in WM [40,41]. However, studies of monkeys [42–44] and humans [45–49] with extensive medial temporal lesions suggest that these regions are necessary for maintaining representations of novel, complex objects even across short delays. It is generally believed that the rate of neuronal plasticity is faster within the hippocampus and the perirhinal cortex than in posterior neocortical areas such as TE. Accordingly, it is likely that novel visual objects do

not have a strong pre-existing representation in inferior temporal cortex, and that active maintenance of novel objects would therefore depend on the activation of newly formed memory representations in the hippocampus and perirhinal cortex.

Consistent with this idea, several studies report increased hippocampal and/or perirhinal activity during WM tasks with novel visual objects [50,51,52•,53], faces [49,54], or scenes [55,56•]. Furthermore, hippocampal and medial temporal cortical activation during WM delays appears to be specific to novel stimuli, [52•,54,55], and enhanced for items that are successfully remembered after long delays [49,52•,56•,57]. More recent results suggest that the hippocampus exhibits enhanced functional connectivity to the inferior temporal cortex during working memory delays [58••]. These results are consistent with the view that the hippocampus and the perirhinal cortex play a role in new LTM formation, and that sustained activation of these new LTM traces additionally facilitates active maintenance during WM tasks [52•].

Prefrontal regions contribute to visual WM maintenance

Whereas temporal cortical neurons are likely to encode the object representations that are activated during visual memory maintenance, PFC neurons appear to play a significant role in top-down control processes that facilitate WM maintenance [1,59]. For example, prefrontal lesions in humans do not eliminate WM maintenance, but they do selectively impair executive processes necessary for maintaining relevant information in the face of distraction [60]. Regarding visual WM, results suggest that the PFC might facilitate maintenance through top-down modulation of object representations in temporal cortex. For example, prefrontal neurons (such as those in entorhinal cortex) exhibit object-specific delay-period activity that is robust to distraction [61]. Furthermore, one study demonstrates that cooling of the PFC impairs behavioral performance and attenuates sample-specific delay-period activity in inferior temporal neurons during a delayed matching to sample (DMS) task [62]. Similar network level interactions appear to occur in humans [58••,63••]; for example, Mechelli et al. [63••] find that category-specific activity in the FFA and PPA during imagery of faces and houses is mediated by top-down feedback from the PFC.

Recent evidence suggests that more dorsal and/or anterior (Brodman's areas [BA] 9, 10, 46) and more ventral and/or posterior (BA 6/8, 44, 45, and 47) prefrontal subregions might make different contributions to WM. Based on neurophysiological and neuroimaging studies, some suggest that ventral and dorsal PFC might be differentially specialized for maintaining object and spatial information, respectively [64,65]. Others suggest that different ventral prefrontal regions might be important for maintaining different types of information, but that dorsal prefrontal regions might be differentially specialized for monitoring or manipulating this information [66–68]. Although these hypotheses are typically contrasted with one another, it is possible that both are partly correct. Many spatial WM tasks involve processing spatial relations between items that are active in memory; many WM tasks that investigate manipulation or monitoring usually involve processing abstract relations (semantic, temporal, etc.) between items that are active in memory. Thus, it is possible that ventral and/or posterior prefrontal regions are specialized for activating representations of relevant items (e.g. objects, words, etc.), and that dorsal and/or anterior prefrontal regions are specialized for activating spatial and nonspatial relations between items that are active in memory [69].

Recent results from single-unit recording studies are remarkably consistent with this hypothesis [70••,71•]. In one study, monkeys were presented a sequence of three objects, and after a delay were required to touch the objects in the order that they were shown [70••]. Neurons in the dorsal PFC responded selectively during the encoding phase according to each item's ordinal position in the sequence, irrespective of its visual features, whereas ventral prefrontal neurons responded in an object-selective manner. Another study examined dorsal prefrontal neurons during the performance of a 'self-ordered' task, in which monkeys made successive saccades to three distinct objects [71•]. Almost half of these neurons exhibited responses that were modulated according to whether the object was the first, second, or third saccade target. These findings suggest that the dorsal PFC is particularly important for maintaining relations amongst objects that are being actively maintained.

Activating visual memories by association: roles of the inferior and medial temporal cortices, hippocampus, and PFC

In addition to showing persistent activity during maintenance of a preferred object, temporal lobe neurons can exhibit activity in response to an initially non-preferred object if that object has been repeatedly associated with a preferred object [72–75]. For example, Sakai and Miyashita [76] trained monkeys to learn associations between pairs of visual objects and recorded from temporal neurons during a delayed paired associate (DPA) task, in which one object was used to cue recall of its associate from memory. These investigators identified 'pair coding' neurons that selectively responded to both objects in the pair, and 'pair recall' neurons that exhibited sustained delay-period activity when their preferred object was recalled in response to its associate.

Recent evidence from lesion, physiological, and neuroimaging studies suggest that visual associative memory retrieval requires top-down modulation of neurons in

Figure 2
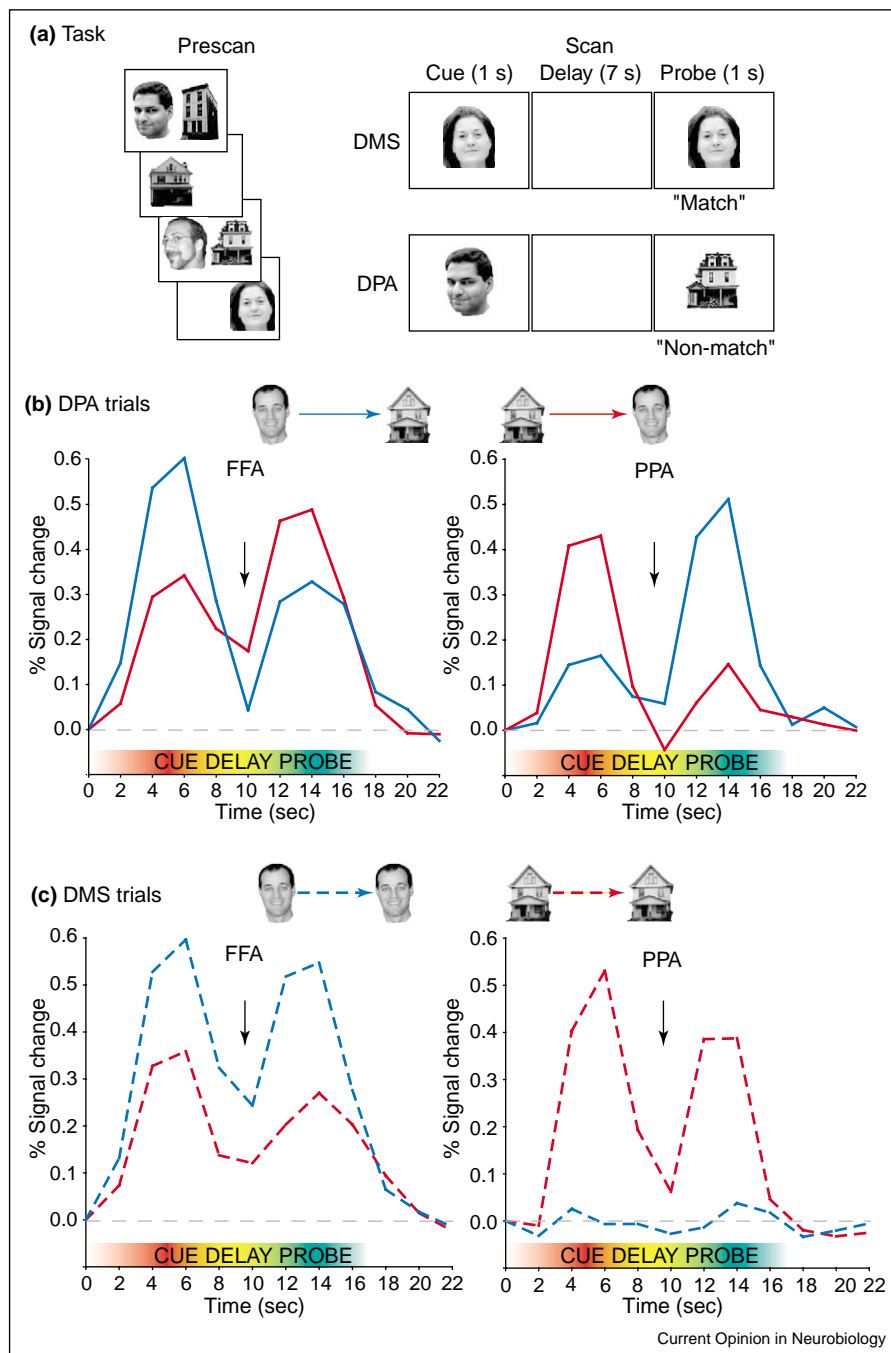
Human inferior temporal activity during visual WM maintenance and associative memory retrieval. **(a)** In an event-related fMRI study, subjects were trained to learn a set of faces, houses, and face–house associations and were scanned while performing two tasks. On DMS trials, subjects were shown a 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 a house. **(b)** On DPA trials, activity during the cue phase in the FFA (left) and PPA (right) was enhanced when the preferred stimulus of each region 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 DPA and DMS trials, cue and delay period activity in the FFA and PPA was enhanced when subjects maintained each region's preferred stimulus type. Adapted from [29••].

inferior temporal area TE. For example, lesion studies show that eliminating feedback from prefrontal [77–80], perirhinal [81–83], or entorhinal [84•] cortices to inferior temporal area TE impairs visual associative memory. Neurophysiological studies show some distinctions between each of these areas. For example, pair coding neurons are relatively abundant in the perirhinal cortex [85•], but such cells are rare in area TE [85•] and PFC [86]. Furthermore, during performance of the DPA task, delay-period activity in perirhinal neurons reflects both the cue stimulus and the retrieved associate [87••]. By contrast, delay-period activity in PFC [86] and area TE [87••] switches, such that, in the initial part of the delay, activity in neurons selective for the cue object predominate, whereas later in the delay, activity in neurons selective for the associate are more active. Collectively, these results seem to suggest that top-down influences from the medial temporal region reflect representations of the relevant association, whereas top-down influences from the PFC to area TE reflect the object that is currently task relevant.

Neuroimaging studies of humans reveal further insights into the neural mechanisms for visual associative memory retrieval [29••,88]. In one study [29••], subjects learned a series of faces, houses, and face–house associations; they were then scanned while performing DMS and DPA tasks with these stimuli (Figure 2). Results show that delay-period activity within category selective inferior temporal subregions reflects the type of information that is currently active in memory: the FFA showed enhanced activity when subjects maintained previously shown faces on DMS trials and when subjects recalled faces in response to a house cue on DPA trials; the PPA showed enhanced activity when subjects maintained previously shown houses on DMS trials and when they recalled houses in response to a face cue on DPA trials. Further analyses differentiated between two types of top-down influences that facilitate task performance: regions in posterior, ventral PFC exhibited persistent activity during the memory delays of both DPA and DMS trials, suggesting that these areas provide top-down activation of task-relevant object representations. By contrast, anterior PFC (BA 10) and the hippocampus exhibited selective activity increases during the cue period of DPA trials, suggesting that these areas are preferentially involved in retrieving the relation between the cue and its associate.

Conclusions and future directions
Overall, available evidence points strongly to the idea that visual WM processes are supported by activation of visual LTM representations in the inferior temporal cortex. These visual object representations can be activated by inputs from prefrontal regions [89] and by inputs from the hippocampus and medial temporal neocortex [52•,54] (Figure 1b). An important direction for future work will be to understand how these and other areas functionally interact during different types of visual WM processes.

Update
Lee *et al*. [90] report that humans with lesions to the medial temporal neocortex are impaired at making fine discriminations among visual objects, scenes and faces that have a high degree of feature overlap. Additionally, patients with more selective hippocampal damage are more specifically impaired at visual scene discrimination. These data suggest that the medial temporal neocortex is a site for detailed visual object representations that might contribute to the visual WM processes reviewed here.

Acknowledgements

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