Research report

Category-specific modulation of inferior temporal activity during working memory encoding and maintenance

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Abstract

Findings from neurophysiology have supported the view that visual working memory (WM) relies on modulation of activity in object-selective populations of neurons in inferior temporal cortex. Here, using event-related functional magnetic resonance imaging, we investigated whether similar mechanisms support human visual working memory encoding and maintenance processes. We identified regions in inferior temporal cortex that exhibited category-specific responses during perception of faces (fusiform face area [FFA]) or scenes (parahippocampal place area [PPA]) and investigated whether activity in these regions would be modulated by demands to actively encode and maintain faces and scenes. Results showed that independent of perceptual stimulation, the FFA and PPA exhibited greater encoding- and maintenance-related activity when their favored stimulus was relevant to the recognition task. In contrast, maintenance-related activity in the dorsolateral prefrontal cortex (PFC) was modulated by memory load, regardless of the type of information that was task relevant. These results are consistent with the view that visual working memory encoding and maintenance processes are implemented through modulation of inferior temporal activity by prefrontal cortex.

1. Introduction

The on-line maintenance of information in working memory (WM) is thought to rely on a dynamic interaction between perceptual representation and cognitive control mechanisms [17,20,35]. Neuroscientific investigations of WM have generally focused on identifying the neural substrates of executive control, with a predominant emphasis on the functions of the prefrontal cortex (PFC) [8,12,23,38,49,54]. In contrast, research on the controlled processing of visual information has traditionally focused on mechanisms of selection processes within posterior cortical areas [19,22,31,33]. Findings from these studies suggest that attention to visual objects operates through the selection of object representations in inferior temporal cortical regions [11,22,31,33]. Based on results from single-unit recording studies in monkeys [39,41,44], some have speculated that similar processes may support the active encoding and maintenance of task-relevant information in visual WM [10,42]. The idea that object WM maintenance operates through object-based selection mechanisms seems reasonable, in light of findings from behavioral [4], event-related potential [5,24] and neuro-imaging [34,52] studies demonstrating similarities in neural mechanisms for spatial WM and spatial selective attention processes [3]. However, in contrast to results from neurophysiological studies of monkeys [39,41,44], neuroimaging studies of humans have yielded mixed results regarding whether object WM processes operate through activation of representations in inferior temporal cortex [7,13,25,48,55].

For example, one event-related fMRI study reported by Courtney et al. [7] examined activity during a delayed recognition task that required encoding and retention of single faces across an 8-s delay relative to a sensory–motor control task. This report noted that within inferior temporal cortex, activity was primarily observed in response to stimulus presentation, with some degree of sustained activation in anterior fusiform regions associated with active maintenance. Somewhat different results were reported in another study by Jha and McCarthy [25], in which a similar delayed face recognition paradigm was used. Rather than comparing activity to a nonmemory baseline task, Jha and McCarthy [25] examined the effect of increasing memory load (i.e., the number of faces to be retained across the memory delay) on activity observed during memory delays. These researchers found no evidence for load-dependent modulation of inferior temporal activity during the memory delay, suggesting that the results reported by Courtney et al. [7] might have reflected processing of the initial face stimulus, rather than activity associated with active maintenance. Thus, available evidence from prior studies has not lent strong support to the idea that active maintenance of visual objects relies on modulation of activity in inferior temporal cortex.

Furthermore, prior studies have not attempted to identify activity associated with WM *encoding* processes. Results from behavioral studies suggest that after initial perception of a stimulus, a stimulus must be subjected to transient encoding processing so that it may be actively maintained in the absence of bottom–up stimulation [27–29,51]. WM encoding processes have been behaviorally dissociated from initial sensory or perceptual processing of a stimulus [9,27–30,59], but the neural mechanisms for WM encoding have not been extensively investigated. Some evidence implicates the dorsolateral PFC as an area that is robustly activated during WM encoding across a variety of materials [28,51]. However, it is unclear whether visual WM encoding might additionally recruit inferior temporal regions where task-relevant information is represented. At present, little is known about the neural implementation of visual WM encoding processes, because previous fMRI studies of visual WM have not distinguished activity associated with WM encoding processes from activity changes more generally reflective of bottom–up perceptual processing.

Consideration of the neurophysiology of inferior temporal neurons suggests one method to use event-related fMRI to detect activity associated with encoding and maintenance processes, while controlling for bottom–up perceptual processing. Neurophysiological studies suggest that neurons in inferior temporal cortex exhibit a high degree of object selectivity [43], and that active maintenance of object information is associated with stimulus-specific activity in these neurons during retention delays [39,41,44]. We therefore reasoned that the topography of inferior temporal activity associated with WM processes might reflect the type of information that is being maintained.
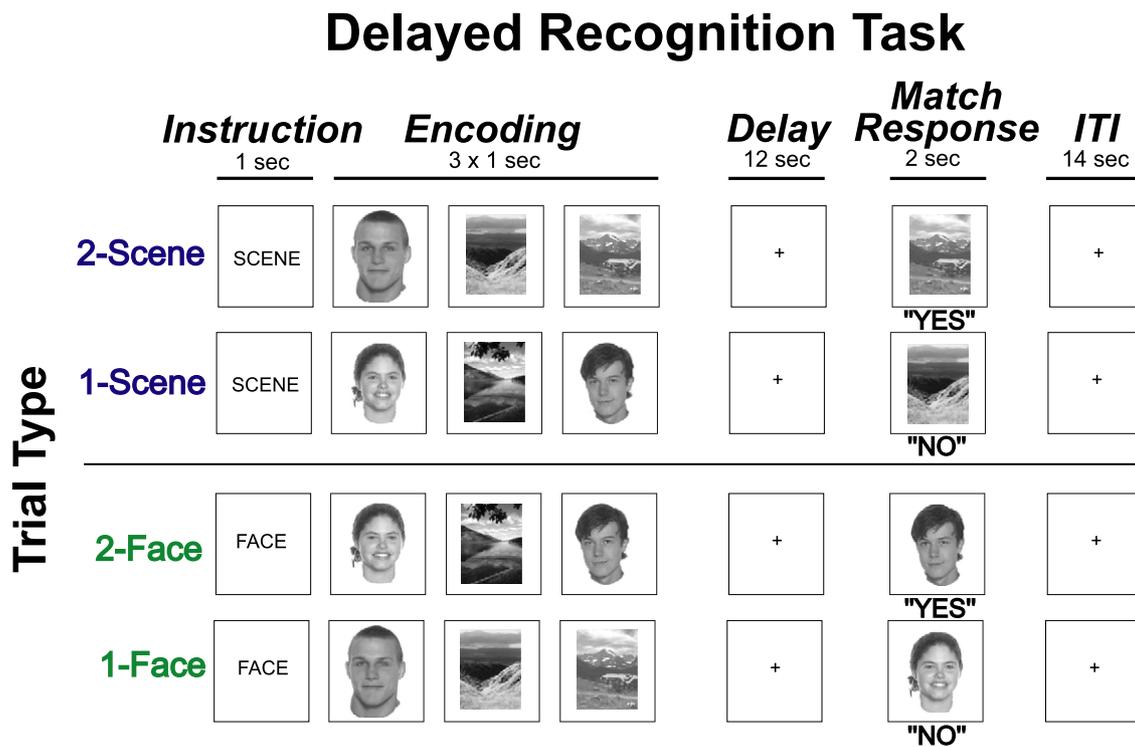
Delayed Recognition Task

Fig. 1. Behavioral paradigm and task design. On each trial, subjects were shown a sequence of three images for 1 s each. Based on the instruction cue, subjects were required to encode and rehearse 1–2 of these items across a 12-s delay. Because the content of the stimulus sets were matched across scene–instruction and face–instruction trials, activity associated with active encoding and maintenance processes could be dissociated from activity associated with perceptual processing.

In the present study, we used event-related fMRI to identify category-specific correlates of WM encoding and maintenance processes within inferior temporal cortex. We focused our analyses on two regions of interest (ROIs): the fusiform face area (FFA)—a region that exhibits larger responses to faces than to other types of stimuli [32] and the parahippocampal place area (PPA)—a region that exhibits larger responses to scenes than to other types of stimuli [14]. Subjects were scanned while they performed a WM task with faces and scenes as stimuli (see Fig. 1). We independently varied the task relevance of faces or scenes (i.e., an instruction to encode and maintain either scenes or faces) and the perceptual content of information presented during the cue phase of each trial (one scene and two faces or two faces and one scene).

With this design, we were able to separate inferior temporal activity associated with visual WM encoding and maintenance processes from activity attributable to stimulus-related perceptual processing. Specifically, one would expect that if inferior temporal activity is solely sensitive to stimulus-related variables, then activity in the FFA and PPA should be sensitive only to the perceptual content of information presented during the cue phase. On the other hand, if, as we hypothesized, visual WM relies on activation of stimulus representations in inferior temporal cortex, we predicted that independent of perceptual stimulation, activity associated with active encoding and maintenance in the FFA and PPA would be modulated by the task relevance of their favored stimulus types (faces and scenes, respectively). Thus, we predicted that independent of perceptual stimulation, activity during the cue *and* delay phases would be enhanced in the FFA when faces were task relevant and enhanced in the PPA when scenes were task relevant. Finally, based on evidence implicating the dorsolateral PFC in WM and cognitive control [20,38,49], we hypothesized that activity in this region would be modulated by the amount of relevant information to be encoded and maintained.

2. Materials and methods

2.1. Subjects

Twelve right-handed subjects ranging in age from 19 to 31 ($M = 22.9$) were recruited from the University of California at Berkeley. All participants were screened against medical, neurological, and psychiatric illnesses, and for use of prescription medications. All subjects gave written informed consent prior to participation in the study according to the procedures approved by the University of California at Berkeley Committee for Protection of Human Subjects.

2.2. Behavioral task

Participants were scanned during performance of a delayed recognition task (Fig. 1). A total of 20 grayscale faces and 20 grayscale scenes (courtesy of N. Kanwisher, MIT) were used as stimuli for these trials. At the beginning of each trial, an instruction (scene or face) was presented for 1 s indicating which type of image was task relevant. This was followed by sequential presentation of three randomly ordered grayscale images (either two faces and one scene or one face and two scenes) presented for 1 s each. Subjects were instructed to fixate on a central cross while rehearsing the task-relevant stimuli (either faces or scenes) across a 12-s delay. Next, a single grayscale face or scene was shown for 2 s and subjects were instructed to make a right-handed button press if the image was in the preceding memory set (50%) or a left-handed button press if it was not (50%). During the 14-s ITI, subjects were instructed to fixate on a centrally presented cross. Twelve trials were presented in each of 8 scanning runs, for a total of 96 trials.

In addition to the delayed recognition task, subjects performed a visuomotor response task used to derive an estimated hemodynamic response function (HRF) [2] and two runs of a localizer task to identify face- and scene-sensitive regions of the inferior temporal cortex [14,32]. In the localizer task, subjects were shown 16-s blocks of either faces, scenes, objects, scrambled objects (courtesy of Nancy Kanwisher, MIT), or a fixation cross on a blank display. During each block, 20 images were shown for 300 ms with a 500-ms fixation cross between each image. To keep attention focused on the images throughout the task, subjects were instructed to press both thumbs on the response pad when the current image was the same as the image immediately preceding it (on the average, one response was required for each block of images).

2.3. MRI acquisition and processing

Functional images were acquired from a Varian INOVA 4T scanner using a gradient echoplanar sequence (TR = 2000 ms, TE = 28 ms, 64×64 matrix, FOV = 2.4 cm) sensitive to BOLD contrast. Each volume consisted of 18 5-mm-thick axial slices with a 0.5-mm gap between each slice. Data processing included motion correction using a six-parameter, rigid body, least-squares alignment procedure [16], and normalization of the time series of each voxel by its mean signal value to attenuate between-run scaling differences. Because data were averaged within functionally defined regions of interest, spatial smoothing was not necessary.

2.4. Data analysis

Our methods for analyzing activation within-trial patterns of activity have been described in detail elsewhere [47,62] and are summarized below. Activation during each phase of each trial was assessed using multiple regression [7,47,53,64]. Separate covariates modeled activation associated with the cue period (0–4 s), late encoding/early delay period (4–6 s), delay period (8–12 s), and response period

(16–18 s) relative to baseline activity during the ITI [47] (see below). Note that the late encoding/early delay period covariate was included to ensure that activity loading on the delay covariate would not be contaminated by activity that could be attributed to prolonged stimulus encoding. Additional nuisance covariates were included to model an intercept and trial-specific baseline shifts. The convolution matrix included a time domain representation of the $1/f$ power structure [63] and filters to remove frequencies above 0.25 Hz and below 0.02 Hz. For each subject, beta values yielded by the GLM for the cue and delay periods were extracted for each covariate and averaged within each functionally defined ROI (see below). These beta values served as the dependent measures for across-subject "random effect" analyses. Because our hypotheses concerned activity changes specific to the encoding and delay periods of each trial, group analyses centered on the covariates modeling these two task periods.

Covariates modeling BOLD responses for each subject during these task phases were derived by convolving the vector of expected neural activity (see above) with an individually derived hemodynamic response function (HRF) [1]. Subject-specific HRFs were used rather than a single canonical HRF, because prior work has demonstrated substantial intersubject variability in the shape of the HRF [1]. One potential concern with using an HRF derived from a subject's motor cortex is that there may be interregional differences in the shape of the HRF within a given subject [36]. However, analyses on this data set and others from our lab suggest that within a subject, HRFs from different regions exhibit similar waveform characteristics, and that these waveforms can differ remarkably from "canonical" HRFs, such as the one included in the SPM99 package ([64]; See also results from another laboratory posted at http://www-psych.stanford.edu/~kalina/SPM99/Tools/eHRF.html). Thus, using an empirically derived HRF enhanced the sensitivity, specificity, and validity of our inferences regarding activation during each task phase.

2.5. Regions of interest (ROIs)

Activity during WM trials was examined within three functionally defined ROIs: the PPA, FFA, and dorsolateral PFC. Time series data were averaged across all voxels within each of these ROIs and submitted to the analyses described above. The PPA and FFA were defined by first delineating anatomical boundaries for the parahippocampal (extending laterally to include the collateral sulcus) and fusiform gyri, respectively. The FFA was defined as all voxels in the fusiform gyrus showing statistically significant activation during the localizer task in a contrast of faces against scenes. Likewise, the PPA was defined as all voxels in the parahippocampal region showing statistically significant activations in the scenes minus faces contrast. Examples of PPA and FFA ROIs for a representative subject are shown in Fig. 2. For the dorsolateral PFC, regions were initially defined by first identifying regions of the middle frontal gyrus corresponding approximately to Brodmann's areas 9 and 46, as defined in the atlas of Talairach and Tournoux [57]. Next, an ROI was defined as all voxels within these regions that exhibited task-related activity during any of the phases of the delayed-recognition task. Although ventrolateral areas of PFC have also been implicated in WM maintenance [50], these areas were not included in the PFC ROI because of signal dropout in these areas for some subjects.

2.6. fMRI planned comparisons

BOLD responses during the WM task were separately analyzed for the FFA, PPA, and dorsolateral PFC ROIs. As noted earlier, the design of the present experiment allowed us to separately examine the effects of stimulus-related processing (the number of faces and scenes that were presented) from effects of WM encoding and maintenance processes (the instruction to remember faces or scenes) during the cue and delay periods. Based on the idea that WM encoding and
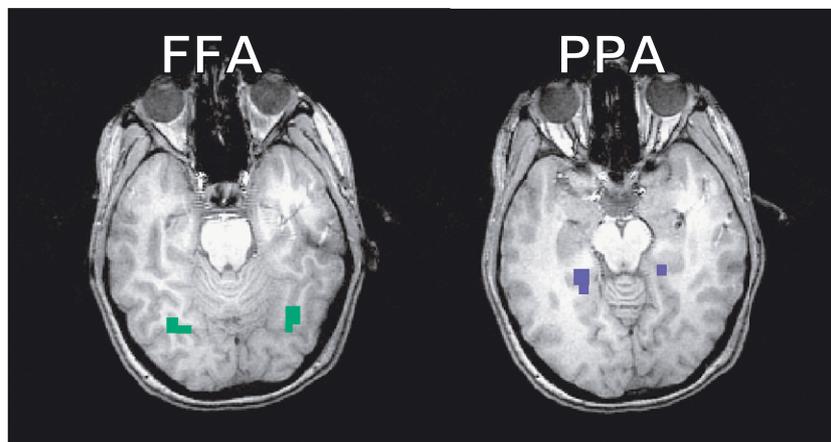

Fig. 2. Locations of the FFA and PPA ROIs are shown on axial slices for one representative subject.

maintenance processes are supported by activation of stimulus representations in inferior temporal cortex, we hypothesized that independent of bottom–up stimulation, FFA and PPA activity during the cue and delay periods should reflect knowledge of the task-relevant category. We directly tested this hypothesis by performing a set of two-way ANOVAs, testing for the effects of instruction type (to remember items from the preferred or nonpreferred category) and stimulus load (the number of items from the preferred category that were presented during the cue phase). These analyses were performed on parameter estimates indexing response amplitudes during the cue and delay periods of the task for each ROI [7,50,53]. We hypothesized that if object WM encoding and maintenance processes operate through activation of stimulus representations in inferior temporal cortex, then we should see either main effects of instruction type or an instruction type by stimulus load interaction during the cue and delay periods.

3. Results

3.1. Behavioral results

As shown in Fig. 3, subjects were highly accurate at performing the WM task ($M = 96.8\%$, S.D. $= 4.6\%$). A two-way ANOVA of memory load (one vs. two items) and instruction type (face vs. scene) showed no significant main effects of accuracy across memory load [$F_{(1,10)} < 1$] or instruction type [$F_{(1,10)} < 1$] or a significant interaction [$F_{(1,10)} = 1.8$]. Consistent with previous studies manipu-
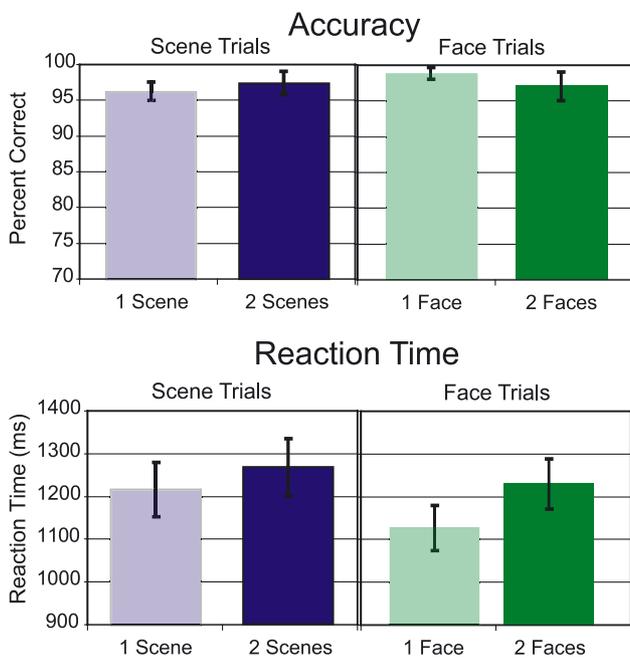
Fig. 3. Behavioral results. Bar graphs show mean accuracy (top) and reaction times (bottom) for each trial type. Error bars denote the standard error of the mean.
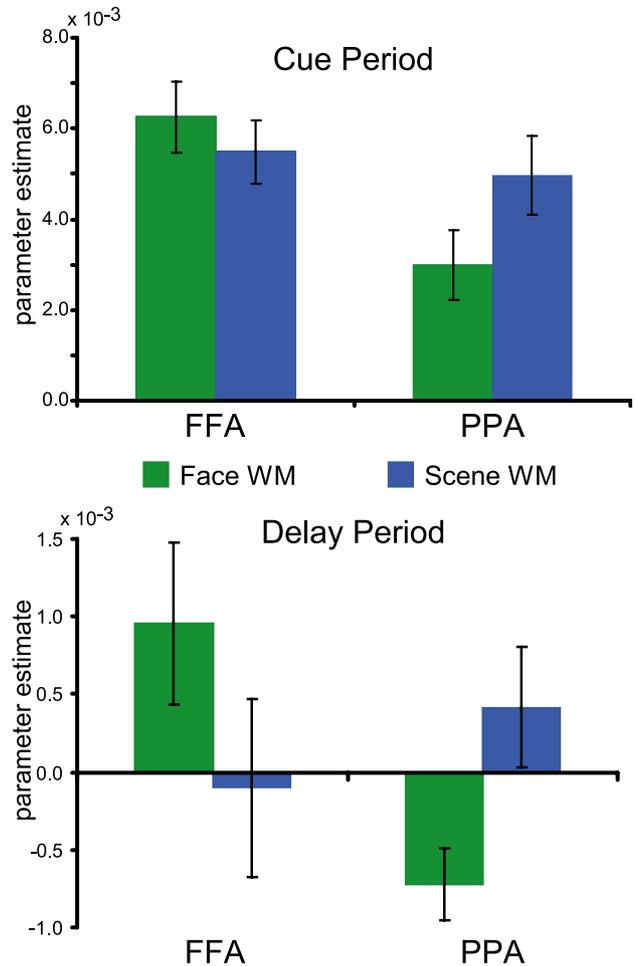
Fig. 4. Modulation of inferior temporal activity associated with active encoding and maintenance. The bar graphs show parameter estimates indexing the magnitude of BOLD responses in the FFA (left) and PPA (right) collapsed across memory load conditions. Cue (top graphs) and Delay (bottom graphs) period responses are shown for trials when faces were relevant (green) and trials when scenes were relevant (blue). Error bars for each ROI and task period denote the standard error of the mean across subjects. These results show that independent of perceptual stimulation, inferior temporal activity was sensitive to the type of information to be encoded and maintained.

lating memory load [56], reaction times (RTs) were significantly slower on two-face and two-scene trials than on one-face and one-scene trials [$F_{(1,10)} = 7.75$, $p < 0.019$]. RTs were significantly slower for scene than for face trials [$F_{(1,10)} = 11.277$, $p < 0.01$], but there was no significant interaction between load and instruction type [$F_{(1,10)} < 1$].

3.2. Imaging data

3.2.1. Inferior temporal ROIs

Results showed that FFA responses during the cue phase were reliably greater when two faces were presented than when one face was presented [$F_{(1,11)} = 18.54$, $p < 0.001$]. Within the PPA, activity during the cue phase was reliably greater when two scenes were presented than when one

scene was presented $[F(1,11) = 21.89, p < 0.001]$. These effects merely confirm the stimulus selectivity of the FFA and PPA ROIs. Independent of this stimulus-related effect, we found that cue and delay period activity in the FFA and PPA was sensitive to the type of information that was task relevant. Specifically, FFA responses during the cue and delay periods were greater when faces were task-relevant than when scenes were task-relevant [cue: $F(1,11) = 11.06$, $p < 0.01$; delay: $F(1,11) = 11.69$, $p < 0.01$], and PPA responses during the cue and delay periods were greater during trials when scenes were task-relevant than during trials when faces were task-relevant [cue: $F(1,11) = 40.29$, $p < 0.001$; delay: $F(1,11) = 16.29$, $p < 0.005$]. No significant interactions between instruction type and stimulus load were observed during any task phase in either ROI. Overall, these findings, summarized in Figs. 4 and 5, demonstrate that, independent of perceptual stimulation, encoding and maintenance-related activity in the FFA and PPA was robustly enhanced by the demand to actively encode and maintain each region's preferred stimulus type.

3.2.2. Dorsolateral PFC ROI

We hypothesized that PFC activity associated with WM processes would be modulated by the amount of information to be actively maintained, independent of the type of material. We directly tested this hypothesis by performing a set of two-way ANOVA assessing the effects of memory
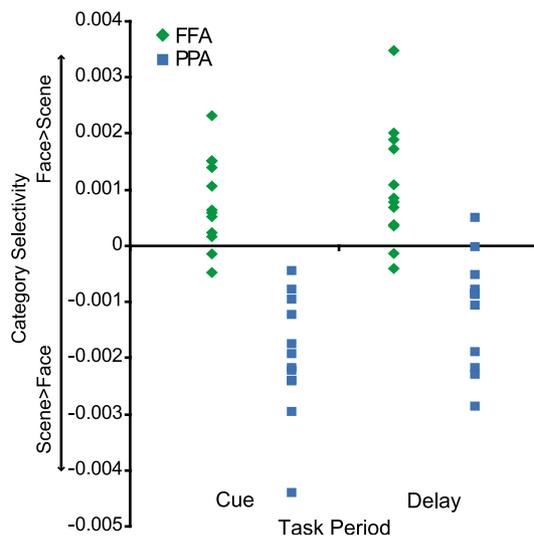

Fig. 5. Category selectivity of inferior temporal activity during WM encoding and maintenance. A scatter plot shows the parameter estimates indexing the face–scene response amplitude difference during the cue (left) and delay (right) periods. Each point represents data from a single subject. Positive values indicate relatively greater activation for face-relevant trials, whereas negative values indicate relatively greater activation for scene-relevant trials (note that because these are contrasts of parameter estimates derived from the GLM, the units are arbitrary). Results plotted for the FFA (blue) and PPA (green) revealed that independent of perceptual stimulation, the majority of subjects exhibited enhanced cue and delay period activity in the FFA and PPA when each region's preferred stimulus was to be encoded and maintained.

load (one vs. two items) and instruction type (rehearse faces or scenes). These analyses were performed on parameter estimates from the cue and delay periods. Results showed that PFC activity during the delay phase was reliably greater when two scenes or two faces were presented than when one scene or one face was presented $[F(1,11) = 21.02, p = 0.001]$. Thus, PFC activity during the delay period was modulated by the amount of information to be retained.

4. Discussion

In the present study, we identified regions of inferior temporal cortex that exhibited category-specific perceptual activity and found that encoding activity within these regions reflected the type of stimulus that was task relevant. Furthermore, our results show that active maintenance of visual information is correlated with category-specific delay period activity in inferior temporal cortex. In contrast to inferior temporal regions, maintenance-related activity in dorsolateral PFC was modulated by the amount of information to be retained. These findings suggest complementary roles for inferior temporal cortex and dorsolateral PFC in visual WM. We expand upon these results and their implications below.

4.1. Neural correlates of WM encoding

Our finding of category-specific modulation of inferior temporal activity during the encoding phase of WM trials may not seem surprising, in light of results from neuroimaging studies of object-based attention. For example, several studies have shown that selective attention to faces or places can modulate activity in the FFA and PPA [45,58,61]. However, in these previous studies, attentional mechanisms were engaged in order to resolve competition between multiple, simultaneously presented objects within a scene. These prior studies showed that modulation of category-specific inferior temporal regions may resolve competition for *perceptual* processing resources.

In contrast, several considerations suggest that visual stimuli in the present experiment did not compete for perceptual processing resources. In our study, each face and scene was shown sequentially, for 1 s each. Current estimates from human electrophysiology suggest that, under normal viewing conditions such as in our study, object recognition is completed between 150 and 300 ms poststimulus [26]. It is therefore reasonable to assume that subjects in our study had ample time to process each stimulus, which in turn suggests that there would be little need for subjects to use the task instruction to resolve competition for perceptual processing resources. Instead, the instruction manipulation in our study primarily biased the degree to which subjects would encode a specific type of stimulus for working memory processing. Thus, in the present study, knowledge of the task-relevant category was used to resolve competition for *mnemonic* processing resources. Accordingly, the finding of category-

specific modulation of inferior temporal encoding activity as a function of task relevance represents a novel demonstration that, independent of perceptual stimulation, biasing of inferior temporal representations supports WM encoding operations. Furthermore, by identifying a neural correlate of WM encoding independent of perceptual processing and competition, our results add support to cognitive theories proposing that the encoding of information into WM may recruit processes that are independent of stimulus-related perceptual processing [27,29].

We can hypothesize two possible mechanisms to account for this pattern of results. One possibility is that knowledge of the task-relevant category served to facilitate encoding of the items from this category. Another possibility is that knowledge of the *irrelevant* category was used to inhibit encoding items from that category. By this view, WM encoding and maintenance operations serve to inhibit distracting information [40,54], instead of or in addition to activating relevant information. This is a reasonable possibility in the present study, given that stimuli were only drawn from two categories (i.e., when instructed to encode faces, it might be beneficial to inhibit scenes). Future research will be necessary to determine the degree to which WM encoding mechanisms reflect selection of task-relevant information vs. inhibition of irrelevant information.

4.2. Neural correlates of WM maintenance

Our findings of category-specific modulation of inferior temporal activity during the delay period are consistent with results from physiological studies of monkeys suggesting that object WM maintenance is accomplished by activating object representations in posterior cortical regions [17,42]. For example, several studies have shown that inferior temporal neurons that exhibit object-selective responses during perception also exhibit sustained responses when the preferred object is retained in memory [39,41,44]. This type of persistent stimulus-specific neural activity is generally interpreted as a correlate of WM maintenance [60], but one might nonetheless question whether this activity actually contributes to WM task performance.

For example, Miller et al. [39] reported that delay period activity in anterior inferior temporal neurons was not evident following the presentation of distracting stimuli. However, the null result reported by Miller et al. [39] should be interpreted with caution. Nakamura and Kubota [44] recorded from anterior inferior temporal cortex in a task similar to that used by Miller et al. [39], but these investigators found that inferior temporal delay period activity remained robust even with presentation of distracting items. Nakamura and Kubota [44] also demonstrated that the duration of delay period activity in these neurons increased with the length of the memory delay. Convergent results were also reported in a human event-related fMRI study of face WM conducted by Postle et al. [48]. Consistent with the results of Nakamura and Kubota [44], and in contrast to the

results of Miller et al. [39], Postle et al. [48] found that the FFA exhibited delay period activity associated with maintenance of faces, and that this activity remained robust even after the presentation of distractor stimuli. Although further investigation will be necessary to resolve these conflicting findings, the preponderance of evidence suggests that the category-specific patterns of inferior temporal activity reported here reflected the active encoding and maintenance of information critical to performance on many WM tasks.

4.3. Frontotemporal networks for visual working memory

Another finding of the present study was that dorsolateral PFC and inferior temporal cortex exhibited distinct response properties across our manipulations of task relevance and memory load. Specifically, we found that inferior temporal activity during the cue and memory delay reflected the type of information that was task relevant, but it was not robustly sensitive to the amount of task-relevant information that was retained (i.e., the memory load). In contrast, in the dorsolateral PFC, activity reflected the amount of task relevant information that was to be encoded and maintained, rather than the type of information that was task relevant. Our findings along with other recent neurophysiological [15] and lesion [46] data suggest complementary roles for these regions in visual WM processes.

For example, Petrides [46] compared the effects of dorsolateral prefrontal and inferior temporal lesions on the performance of visual WM tasks. Results showed that increasing the delay during which information was to be retained significantly impaired performance in monkeys with inferior temporal lesions. In contrast, monkeys with dorsolateral PFC lesions exhibited intact performance regardless of the length of the memory delay; however, these monkeys were impaired when the number of stimuli to be monitored was increased. Based on these findings, Petrides [46] concluded that the inferior temporal cortex and dorsolateral PFC play complementary roles in WM. Whereas sustained activity in inferior temporal cortex may be more critical for maintaining visual object information, the dorsolateral PFC may be more critical for retaining representations of multiple events and their relative status. The findings of the present study are consistent with this conclusion in that functional activity within the human inferior temporal cortex reflected the encoding and retention of specific visual information across the delay, whereas prefrontal activity was sensitive to the number of items to be maintained.

5. General conclusions

A large body of previous work has implicated the dorsolateral prefrontal cortex as a critical component of distributed networks that mediate WM encoding and maintenance processes [6,12,18,20,37,49]. The present findings of memory load-dependent activity in PFC are consistent with this

perspective. In addition, by identifying a role for inferior temporal cortex in visual WM encoding and maintenance operations, the present results clearly demonstrate that high-level visual areas are part of this network. At a higher level, these findings are consistent with the view that WM process-es are mediated by reverberating activity through circuits that represent task-relevant information [17,21].

Acknowledgements

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