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Complementary roles of medial temporal lobes and mid-dorsolateral prefrontal cortex for working memory for novel and familiar trial-unique visual stimuli

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Abstract

It has been suggested that working memory (WM) for novel information requires the medial temporal lobes (MTL), but is not necessary for WM for familiar stimuli. In previous studies that directly compared WM for novel and familiar stimuli, only the novel stimuli were trial-unique. Here, 16 young human subjects performed a Sternberg WM task with visual scenes while in a functional magnetic resonance imaging scanner. All task stimuli were trial-unique, but were either new (Novel condition) or previously learned (Familiar condition). This design allowed investigation of whether MTL and prefrontal cortex (PFC) activity is related specifically to the novelty/familiarity of the stimuli or to their trial-unique status during WM. We observed greater hippocampal and parahippocampal activity during encoding and maintenance for novel than for familiar stimuli. In contrast, right mid-dorsolateral PFC (dlPFC) activity was greater during encoding of familiar than novel stimuli. The mid-dlPFC was not recruited during maintenance or for retrieval when the Familiar condition was contrasted with the Novel condition. However, left mid-dlPFC activity was present at retrieval when correct Match trials (i.e. hits) were contrasted with correct Non-match trials (i.e. correct rejections) for the Novel condition. The results support the hypothesis that MTL regions are required for the encoding and maintenance of novel stimuli during WM, demonstrating that the observed MTL activity is not related to the trial-uniqueness of the stimuli *per se*. Furthermore, the observed activation pattern in mid-dlPFC suggests a role for the mid-dlPFC in executive control-associated processes related to monitoring of scene familiarity at encoding and retrieval during WM.

Introduction

Computational models and experimental evidence has suggested that working memory (WM) for novel information requires the medial temporal lobes (MTL), but is not necessary for WM for familiar stimuli (Hasselmo & Stern, 2006). In some of these WM models, familiar trial-unique stimuli can be maintained by previously modified recurrent excitatory connections (Amit & Brunel, 1997; Durstewitz *et al.*, 2000). This circuit mechanism allows already connected, reactivated networks of neurons to remain active in the absence of stimulus exposure, giving rise to active stimulus maintenance during WM. In contrast, novel stimuli do not match any synaptic connectivity from previously encoded stimuli, and therefore require maintenance mechanisms that are independent of prior synaptic modification (Lisman & Idiart, 1995), such as the persistent spiking in entorhinal cells (Egorov *et al.*, 2002; Hasselmo & Stern, 2006). These models suggest that novel and familiar trial-unique stimuli may require different mechanisms for stimulus maintenance (for review, see Hasselmo, 2012). Experimentally, previous studies have contrasted novel stimuli that have never been seen before with familiar stimuli that are shown multiple times in a single experimental session. Yet there is a fundamental difference between a stimulus being novel and being trial-unique. A novel stimulus has never been seen previously, whereas a trial-unique stimulus can be highly familiar, but is only seen once during testing.

Data suggest that parahippocampal regions might mediate WM for novel stimuli, but previous studies have not always distinguished trial-unique from novel stimuli. Monkeys with parahippocampal lesions perform poorly on WM tasks with trial-unique stimuli (Gaffan & Murray, 1992; Eacott *et al.*, 1994), but not with familiar, repeating stimuli (Correll & Scoville, 1965; Eacott *et al.*, 1994). Single parahippocampal neurons in monkeys performing WM tasks with trial-unique objects show persistent spiking (Suzuki *et al.*, 1997). In humans, WM for novel, trial-unique but not familiar, repeating visual stimuli recruits MTL regions (Ranganath & D'Esposito, 2001; Stern *et al.*, 2001; Hannula & Ranganath, 2008; Schon *et al.*, 2008).

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Recent work suggests that MTL regions, including the hippocampus, support not only WM for novel information, but also WM for trial-unique complex or relational/contextual information (Ranganath *et al.*, 2005; Piekema *et al.*, 2009; Bergmann *et al.*, 2012), even if the items that are associated during WM are highly familiar and repeatedly presented, such as location–number associations (Piekema *et al.*, 2006). These functional magnetic resonance imaging (fMRI) results are consistent with findings from studies in patients with MTL lesions showing impaired short-term retention for relational information (Hannula *et al.*, 2006; Olson *et al.*, 2006; Finke *et al.*, 2008; Jeneson *et al.*, 2011), especially when WM capacity is exceeded (Jeneson *et al.*, 2010, 2012) or when the WM delay is long (Finke *et al.*, 2008; Jeneson *et al.*, 2011). The findings from these studies are consistent with the purported role of the hippocampus in relational binding of episodic events (Eichenbaum *et al.*, 1994; Eichenbaum, 2000), and suggest together with our own work (Schon *et al.*, 2004, 2005) that MTL regions support long-term encoding and relational binding during WM.

In contrast, WM for familiar, repeating visual stimuli recruits posterior parietal, inferior temporal and prefrontal cortex (PFC), but not the MTL (Postle & D'Esposito, 1999; Postle *et al.*, 2000; Wager & Smith, 2003; Schon *et al.*, 2008). This work suggests that the PFC and posterior cortex may be sufficient for WM for familiar, repeating information, while the MTL are recruited for WM for novel information (Hasselmo & Stern, 2006). However, the familiar stimuli used in these studies were not trial-unique.

Monitoring and manipulation of small sets of familiar stimuli during WM recruit the mid-dorsolateral PFC (mid-dlPFC; Petrides, 1995, 2000; Owen *et al.*, 1996, 1998; Stern *et al.*, 2001; Schon *et al.*, 2008), but stimulus maintenance *per se* does not (Petrides, 2000). In addition, dlPFC supports both episodic and WM encoding (Blumenfeld & Ranganath, 2006; Qin *et al.*, 2007; Hales & Brewer, 2010) and retrieval (Buckner *et al.*, 1998; Henson *et al.*, 1999; Ranganath *et al.*, 2003), as well as familiarity monitoring in episodic memory tasks (Henson *et al.*, 2000; Bunge *et al.*, 2004; Dobbins *et al.*, 2004). These previous studies suggest that scene familiarity may modulate dlPFC activity during WM retrieval, but not during the delay-period if both novel and familiar stimuli are trial-unique.

Here, we investigated whether stimulus novelty drives MTL recruitment during encoding and maintenance, and stimulus familiarity drives PFC recruitment during retrieval when both novel and familiar stimuli are trial-unique.

Materials and methods

Subjects

Sixteen healthy young subjects (13 female; age 21 ± 4 years) were recruited from the Boston University Charles River Campus (BU-CRC). Vision was normal or corrected to normal. Subjects did not have any history or current neurological or psychiatric disorders. They were not claustrophobic and were not taking any psychoactive medication. In addition, subjects were screened for MRI environment compatibility before entering the magnet room using standard screening criteria for MRI. All study procedures conform with The Code of Ethics of the World Medical Association (Declaration of Helsinki; printed in the *British Medical Journal* 18 July 1964). All subjects provided signed informed consent in a manner approved by the Partners Human Research Committee and by the BU-CRC Institutional Review Board.

Task design and procedures

We developed a Sternberg WM task with trial-unique complex visual scenes. There were two conditions: scenes were either unfamiliar (Novel condition); or learned 1 day before task performance (Familiar condition). Here, a novel stimulus is defined as an unfamiliar stimulus that has not been seen previously. All stimuli were trial-unique and were presented only once during the fMRI task unless they were shown again at test (Match). Extensive behavioral piloting was performed to determine: (i) how many stimuli subjects could learn and retain after a 24-h interval; (ii) the most appropriate procedure for learning the familiar stimulus set; (iii) to determine the WM load for each condition (Novel vs. Familiar) for the Sternberg task such that reaction times and accuracy would not differ as a function of condition, and such that ceiling and floor effects would be avoided. The study was performed on two consecutive days. The following paragraphs describe task design and procedures.

Stimuli

We used digital photographs of unfamiliar visual outdoor scenes (width 10.23 cm; height 6.81 cm; resolution 72 pixels/inch) as stimuli (Fig. 1). Stimuli were randomly drawn from a large set of 1260 scenes and were obtained from various internet sources. Scenes with people and faces or a single nameable object in the foreground were discarded. The familiar and novel stimulus sets used for the Sternberg task were each composed of 180 stimuli ($N = 360$). The remaining five sets of 180 stimuli were used as lures for five subsequent memory assessments: three of these sets were used to test retention of the familiar stimulus set on the day before fMRI scanning; one set was used to test retention of the familiar stimulus set immediately before fMRI scanning; and one set was used to test incidental encoding of the novel stimulus set from the Sternberg task (see Procedures, below) after fMRI scanning.

Sternberg task

Subjects performed 80 trials of the Sternberg task with a WM load of four stimuli (Fig. 1B). There were eight runs and 10 trials per run. On each trial, subjects initially saw four sequentially presented scenes (2 s per scene; encoding), followed by a variable delay-period (6, 10, 14 or 18 s, randomly intermixed; maintenance). After the delay-period, a test picture was presented and subjects had to indicate with a button press whether the test stimulus matched one of the four sample scenes seen during encoding of that trial (2 s; retrieval). The retrieval phase was then followed by a variable-length inter-trial interval (ITI) during which the subjects had to focus their gaze on a fixation cross (ITI; 6, 10, 14 or 18 s). The key feature of the Sternberg WM task was that each stimulus was trial-unique. Stimuli were encountered only once in the case of Non match trials or twice in the case of Match trials regardless of whether they were familiar or unfamiliar (novel). This way, novel and familiar Sternberg trials were equated for the number of times a stimulus was seen during the Sternberg WM task. Thus, novel and familiar trials differed only in whether the stimuli were previously seen (familiar stimulus set) or never encountered previously (novel stimulus set), but not in whether the stimuli used were trial-unique. Stimuli included in the familiar stimulus set were seen seven times before Sternberg task performance (six times during learning on Day 1, and once during testing on Day 2; see below). Of the 80 total trials, 40 were novel trials (i.e. stimuli were drawn from the trial-unique novel stimulus set; 20 Match trials and 20 Non match trials) and 40

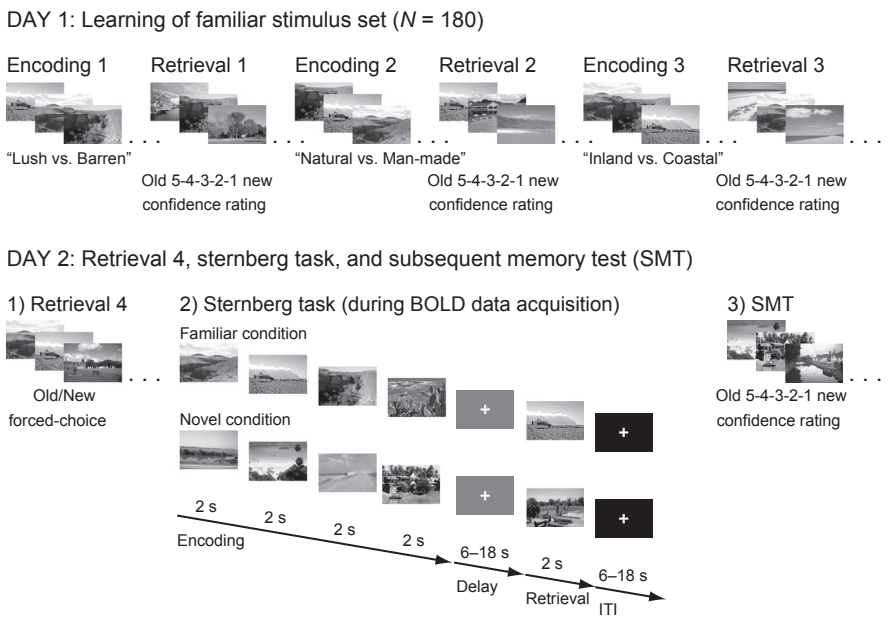

FIG. 1. Memory tasks. (A) On Day 1, subjects learned the familiar stimulus set (N = 180) by alternating three encoding sessions with three retrieval test sessions. During encoding, subjects made subjective judgments about the stimuli (e.g. 'Lush vs. Barren', 'Natural vs. Man-made', 'Inland vs. Coastal'). The order of the three subjective judgments was randomized across subjects. During each retrieval test, subjects saw all 180 stimuli from the familiar stimulus set randomly intermixed with 180 new stimuli (lures). Subjects indicated their level of confidence about the old/new status of each scene ('5', 'high-confidence old'; '4', 'low-confidence old'; '3', 'unsure'; '2', 'low-confidence new'; and '1', 'high-confidence new'). (B) On Day 2: (1) subjects' retention of the familiar stimulus set was assessed prior to acquisition of BOLD images using an old/new forced-choice recognition procedure; (2) subjects performed a Sternberg task while BOLD images were acquired. Subjects were instructed to remember a set of four sequentially presented complex visual scenes over a brief variable-length delay-period. At test, they were required to indicate whether the presented scene matches one of the four sample scenes presented immediately before the delay-period. Each trial ended with a variable-length ITI. There were two conditions. In the Novel condition, stimuli were drawn from a set of new, not previously seen stimuli (N = 180). In the Familiar condition, stimuli were drawn from the familiar stimulus set learned on Day 1 (N = 180). For both conditions, stimuli were trial-unique, unless they were seen again a second time at retrieval (Match trial); (3) After fMRI scanning, subjects performed a surprise subsequent recognition memory task to assess retention of the stimuli from the Novel condition using the same confidence rating scales as for the retrieval tests (see above).

were familiar trials (i.e. stimuli were drawn from the trial-unique familiar stimulus set; 20 Match trials and 20 Non match trials). For Match trials, the temporal location of the matching stimulus shown during encoding (shown 1st, 2nd, 3rd or 4th) was pseudo-randomized with the restriction that each position occurred 10 times (40 Match trials total). For each delay length (6 vs. 10 vs. 14 vs. 18 s), 50% of the trials were novel trials and 50% of the trials were familiar trials. In addition, for each combination of delay length and condition (Novel vs. Familiar), 50% of the trials were Match trials and 50% of the trials were Non match trials. Trials were pseudo-randomized with the restriction that the above criteria were met.

Procedures

On Day 1, subjects learned the familiar stimulus set by alternating three encoding runs with three retrieval runs (encoding 1–retrieval 1 –encoding 2–retrieval 2–encoding 3–retrieval 3; Fig. 1A). During encoding, each scene from the familiar stimulus set was displayed on the computer screen for 2 s. Subjects were instructed to remember the stimuli for a later memory test and to make a forced-choice subjective response to each of the 180 stimuli. The required subjective response was different for each of the three encoding tasks, and included 'Natural vs. Man-made', 'Inland vs. Coastal' and 'Lush vs. Barren', and was counterbalanced across subjects. During the retrieval tasks, subjects saw each scene again from the familiar stimulus set plus an equal number of new scenes (lures). They were instructed to rate their level of confidence on a 5-point scale whether a given picture was old or new (Schon *et al.*, 2004). A response of '1' indicated that they were highly confident the given picture was not seen during encoding ('high-confidence new'), a response of '2' indicated 'low-confidence new', a response of '3' indicated 'unsure', a response of '4' indicated 'low-confidence old', and a response of '5' indicated 'high-confidence old'. On Day 2, subjects first practiced the Sternberg task. Immediately before the functional scans were collected, subjects performed a 4th recognition memory task while the high-resolution structural scans were acquired (Fig. 1B). Subjects performed forced-choice, old/new judgments. All subjects reached a predetermined criterion of $\geq$ 75% correct. Approximately 15–20 min after the end of the functional data acquisition, subjects performed a surprise subsequent recognition memory assessment designed to assess incidental encoding of the stimuli from the novel stimulus set (Fig. 1B). Each scene from the novel stimulus set and an equal number of new pictures ('Lures') were presented randomly on a computer screen. Subjects were required to rate their memory of each picture using the same 5-point confidence rating scale used during training.

fMRI data acquisition

fMRI and structural MRI data were acquired at the Athinoula A. Martinos Center for Biomedical Imaging of the Massachusetts General Hospital in Charlestown, MA, USA, using a 3 Tesla MAGNETOM Trio scanner (Siemens AG, Medical Solutions, Erlangen, Germany) with a 12-channel head coil. Across eight acquisition runs per subject, 1364 blood oxygen level-dependent (BOLD) echo-planar images consisting of 30 interleaved slices each were acquired

perpendicular to the long axis of the hippocampus (repetition time, 2000 ms; time to echo, 30 ms; flip angle, 90°; field of view, 200 ms; matrix size, 64 × 64 mm^2; in-plane resolution, 3.125 mm^2; slice thickness, 5 mm; skip between slices, 1 mm). Each run included four initial dummy scans to allow for T1 equilibration that were discarded before data analysis. In addition, for each subject one T1-echo planar scan (repetition time, 10 000 ms; time to echo, 34 ms; field of view, 200 mm; matrix size, 64 × 64 mm^2; in-plane resolution, 3.125 mm^2; slice thickness, 5 mm; skip between slices, 1 mm) and two high-resolution magnetization prepared rapid gradient echo structural scans with generalized autocalibrating partially parallel acquisitions (Griswold *et al.*, 2002; repetition time, 2530 ms; time to echo, 3.44 ms; flip angle, 7°; field of view, 256 mm; matrix size, 256 × 256 mm^2; in-plane resolution, 1 mm^2; slice thickness, 1 mm) were acquired.

fMRI data preprocessing

Preprocessing was performed with SPM8 software (Friston *et al.*, 1994, 1995a,b). Preprocessing included reorienting of all BOLD images such that the origin was at the anterior commissure, averaging of the two structural scans for each subject, motion correction with unwarping to correct for variance due to movement-by-susceptibility interactions (Andersson *et al.*, 2001), co-registration of the averaged structural scan and the BOLD scans to the T1-echo planar scan, and segmentation of structural scans into gray and white matter images. At this stage a bias-corrected structural scan was also created using the default tissue probability maps as priors. Bias correction of smooth image intensities may allow for more accurate spatial registration (Ashburner & Friston, 2005). The gray and white matter images were then imported into DARTEL-readable files. Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) is a collection of tools that allow for more accurate inter-subject registration (Ashburner, 2007). All subjects' gray and white matter images were simultaneously registered in several iterative steps into subject-space-specific gray and white matter templates. This normalization into subject space was then followed by normalization into MNI space. All normalized BOLD images were spatially smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel. All normalized structural scans were averaged across subjects for statistical overlay.

Data analysis

Behavioral data analysis

For each subject and each retrieval test, response proportions, hit rates, correct rejection rates, false alarm rates, miss rates and discriminability (d') were calculated. To investigate the effects of condition (Novel vs. Familiar) and of retrieval type (Match vs. Non match) on reaction times and proportion of correct responses from the Sternberg task, we used a two-factor repeated-measures analysis of variance (ANOVA).

fMRI data analysis

Two statistical analyses were performed using the modified General Linear Model approach of SPM8 (Friston *et al.*, 1994, 1995a,b). The first analysis assessed whether encoding, maintenance and retrieval activity differed as a function of condition (Novel vs. Familiar; Novel vs. Familiar analysis), and a follow-up analysis assessed familiarity monitoring by contrasting correct Match with correct Non match trials as a function of condition (Novel vs. Familiar; WM retrieval analysis). For the Novel vs. Familiar analysis, 16 regressors were created by crossing the two conditions (Novel and Familiar) with four events (encoding, maintenance, retrieval and ITI) and two hemodynamic response functions (canonical hemodynamic response function and time derivative). Only correct trials were included. Incorrect trials were not analysed because subjects made only very few errors (Fig. 2B). In addition, to control for spurious effects due to subject movement, for each subject the six movement parameters (three translations, three rotations) were included in the statistical model. Contrasts of interest included: (1) encoding – Novel > Familiar; (2) maintenance – Novel > Familiar; and (3) retrieval – Novel > Familiar as well as the reverse contrasts. Additional contrasts included: (1) encoding > ITI (fixation), across Novel and Familiar conditions; (2) maintenance > ITI (fixation), across Novel and Familiar conditions; and (3) retrieval > ITI (fixation), across Novel and Familiar conditions. The regressors of interest were orthogonal or nearly orthogonal as shown by Pearson's correlations. The Pearson's correlation coefficients were $r = -0.19$ for the correlation between the Novel encoding and Novel maintenance regressors; $r = 0.01$ for the correlation between the Novel maintenance and Novel retrieval regressors; $r = -0.11$ for the correlation between the Familiar encoding and Familiar maintenance regressors; and $r = 0.02$ for the correlation between the Familiar maintenance and Familiar retrieval regressors across subjects. For the WM retrieval analysis, 20 regressors were created by splitting up the retrieval regressors into Match vs. Non match regressors, yielding eight total retrieval regressors (2 retrieval types × 2 conditions × 2 hemodynamic response functions). Regressors of no interest included regressors modeling error trials, the six movement parameters and one dummy regressor for each run. Contrasts of interest included: (1) Non match – Novel > Familiar; (2) Match – Novel > Familiar; (3) Novel – Match > Non match; and (4) Familiar – Match > Non match. Contrasts 3 and 4 assessed retrieval success (hits vs. correct rejections) for the Novel and Familiar conditions, respectively. The analyses described above were performed on the single-subject level. Subsequent group analyses were performed by entering the resulting contrast images of each subject into second-level one-sample *t*-tests. In addition, three conjunction analyses were performed at the group level by entering contrast images from the Novel vs. Familiar analysis into full-factorial repeated-measures ANOVA with non-sphericity correction. The first conjunction analysis assessed whether the activity in the MTL was present for encoding and maintenance [(encoding - Novel > Familiar) ∩ (maintenance - Novel > Familiar)]. A second conjunction analysis investigated whether an effect of Novel condition > Familiar condition was present at retrieval for both Match and Non match trials [(Match - Novel > Familiar) ∩ (Non match - Novel > Familiar)]. And, finally, a third conjunction analysis assessed whether a retrieval success effect (Match > Non match) was present regardless of condition (Novel vs. Familiar) [(retrieval success, Novel condition) ∩ (retrieval success, Familiar condition)]. For conjunctions, the SPM software does not allow the use of a cluster-extent threshold. Therefore, an uncorrected $P < 0.01$ was used for each contrast, yielding a $P < 0.0001$, uncorrected, for the conjunction.

A cluster-extent-corrected alpha of 0.01 was used to correct for multiple comparisons (Forman *et al.*, 1995; Saad *et al.*, 2006). Smoothness of the residual (error) image was first determined with the AFNI program 3DFWHMx (Cox, 1996; Cox & Hyde, 1997). Then, 10 000 Monte Carlo simulations were run using the AFNI AlphaSim program to estimate the cluster-extent threshold using a whole-brain mask, the residual smoothness FWHM estimates and an

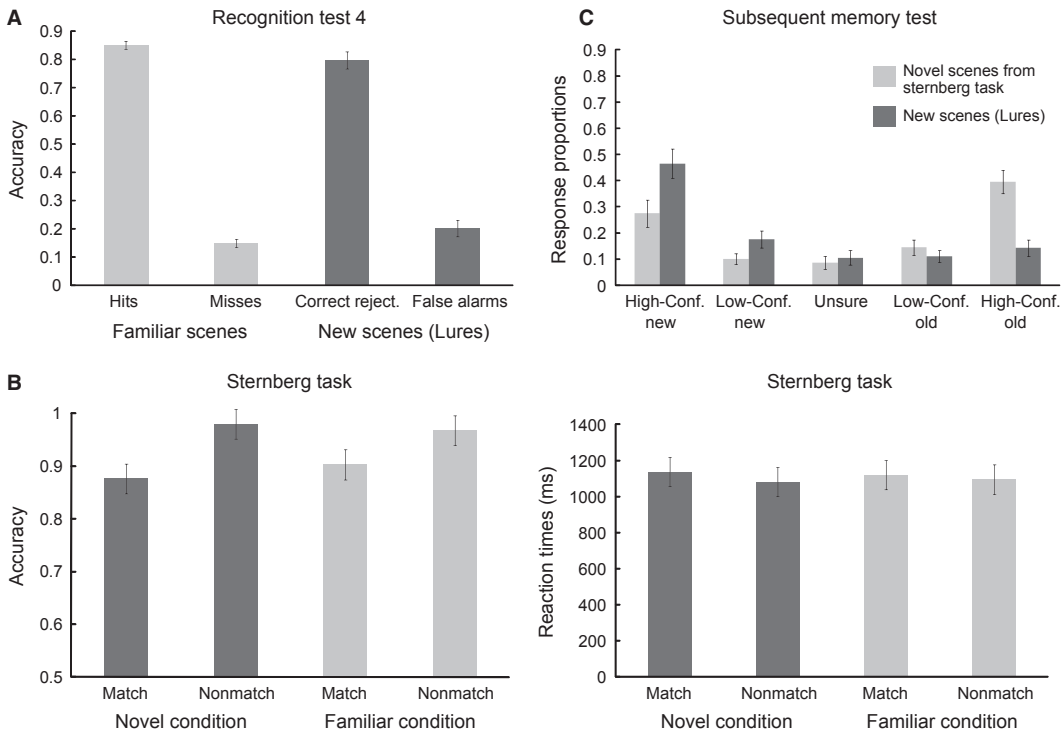

FIG. 2. Behavioral data. (A) Proportion of correct responses for recognition test 4. This test assessed 24-h retention of the familiar stimulus set vs. not previously seen scenes. (B) Response proportions and reaction times of Sternberg task as a function of type of retrieval (Match vs. Non match). Left panel – proportion of correct responses. Right panel – reaction times of correct trials (in ms). (C) Proportion of correct responses for the post-scan subsequent memory test. This test assessed retention of the novel stimulus set vs. not previously seen scenes (lures) using a 5-point confidence rating scale (see *x*-axis).

assumed individual voxel type I error of $P = 0.01$. This yielded a cluster-extent of 71 voxels for the Novel vs. Familiar analysis, and a cluster-extent of 83 voxels for the WM retrieval analysis.

Parameter estimates (β-values) are included simply to illustrate whether the observed differential activation patterns were positive or negative (i.e. activated or deactivated). They were extracted from 5-mm spheres around peak activations in areas of interest that included the MTL and the lateral PFC. Parameter estimates were extracted and averaged across voxels within each sphere using the Volumes toolbox of SPM5. The parameter estimates were selectively averaged by condition, event and/or retrieval type.

Results

Behavioral results

Figure 2A illustrates the average hit rate (mean ± SD 85 ± 6%), false alarm rate (21 ± 12%), correct rejection rate (79 ± 12%) and miss rate (15 ± 6%) of the familiar stimuli on Day 2. The corrected recognition rate (hits minus false alarms) of the familiar stimuli on Day 2 was 64 ± 12% (test 4). All subjects reached the criterion of a hit rate of ≥ 75% (recognition test 4). Similarly, the average discrimination index d' [z (hit rate) – z (false alarm rate)] was 1.02 ± 0.6.

The proportion of correct responses and reaction times for correct trials of the Sternberg task are displayed in Fig. 2B as a function of condition (Novel vs. Familiar) and retrieval type (Match vs. Non match). For both, only the main effect of retrieval type was significant ($F_{1,15} = 14.97$, $P < 0.05$; $F_{1,15} = 4.90$, $P < 0.05$ for proportion of correct responses and reaction times, respectively), demonstrating fewer errors and faster reaction times for Non match trials than for Match trials.

Figure 2C illustrates the response distribution of the novel Sternberg stimulus set and the lures (new stimuli) on the subsequent recognition memory test. The average hit rate was 57 ± 20% (mean ± SD; rating of 4 or 5 for novel Sternberg stimuli), the false alarm rate (rating of 4 or 5 for lures) was 28 ± 15%, the correct rejection rate (rating of 1 or 2 for lures) was 67 ± 15% and the miss rate (rating of 1 or 2 for novel Sternberg stimuli) was 38 ± 20%. The corrected recognition rate (hits minus false alarms) for the novel stimuli from the Sternberg task was 31 ± 15% (test 5). These results indicate that the majority of scenes from the novel stimulus set were encoded into long-term memory (LTM), with the false alarm rate only being 7% higher than that of test 4 (see above).

fMRI results

MTL activation for encoding of novel scenes is sustained during maintenance

We contrasted activity during encoding of novel stimuli (Novel condition) with activity during encoding of familiar stimuli (Familiar condition). This contrast showed activity in the MTL that included the left hippocampus ([x y z] = [−30 −24 −12], $Z = 3.25$, $P_{COR} < 0.01$) and bilateral parahippocampal cortex (PHC; right [x y z] = [30 −51 −3], $Z = 3.47$; $P_{COR} < 0.01$; left [x y z] = [−21 −33 −18], $Z = 3.10$, $P_{COR} < 0.01$; Fig. 3A and B).

During maintenance similar regions within the MTL were activated for the Novel > Familiar contrast. These areas included the left hippocampus ([x y z] = [−27 −15 −15], $Z = 3.03$, $P_{COR} < 0.01$) and bilateral PHC (right [x y z] = [21 −42 −12], $Z = 3.25$, $P_{COR} < 0.01$; left [x y z] = [−24 −33 −18], $Z = 3.43$, $P_{COR} < 0.01$; Fig. 3C and D).

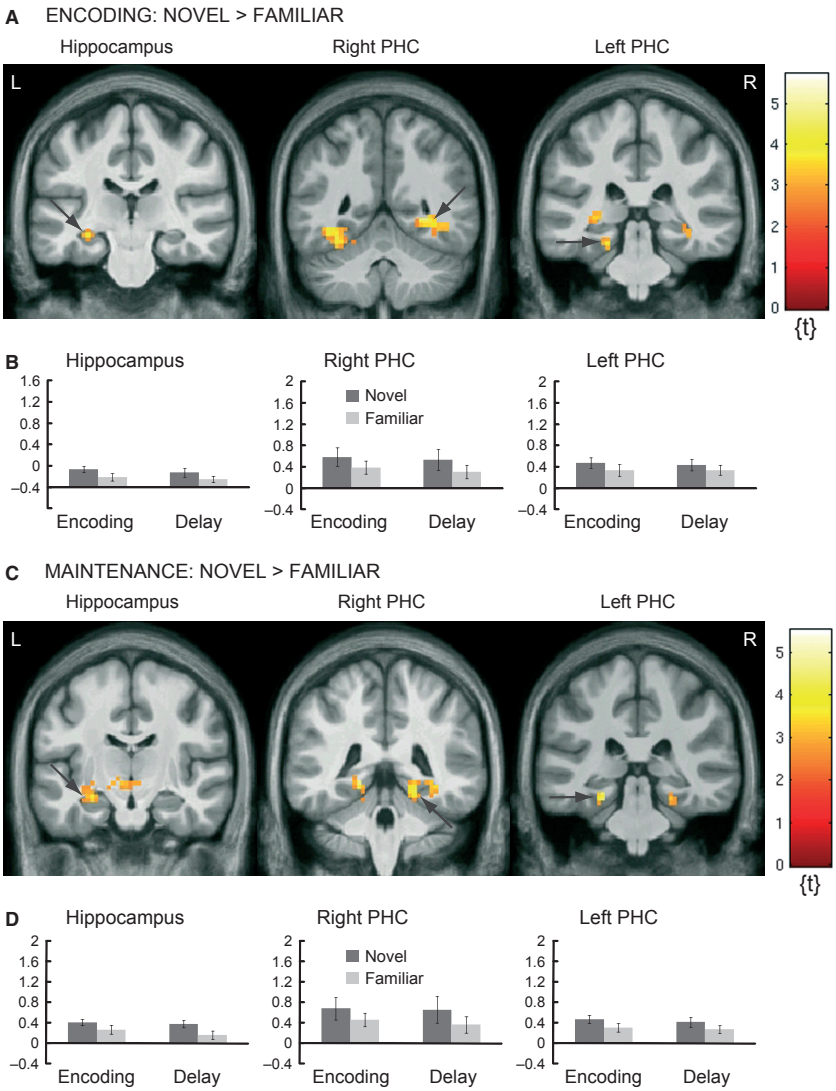

FIG. 3. Greater MTL activity during encoding and maintenance (delay-period) for the Novel condition than for the Familiar condition. (A) Statistical parametric *t*-maps show MTL activity during encoding in the left hippocampus (left; arrow), in the right PHC (center; arrow) and in the left PHC (right; arrow) as a function of novelty (Novel > Familiar). (B) Graphs show parameter estimates (beta-weights) from the left hippocampus (left), the right PHC (center) and the left PHC (right) as a function of novelty (dark gray bars, Novel; light gray bars, Familiar) and event (encoding; delay); peaks are from the Novel encoding > Familiar encoding contrast (see arrows in A). (C) Statistical parametric *t*-maps show MTL activity during the delay-period (maintenance) in the left hippocampus (left; arrow), in the right PHC (center; arrow) and in the left PHC (right; arrow) as a function of novelty (Novel > Familiar). (D) Graphs show parameter estimates (beta-weights) from the left hippocampus (left), the right PHC (center) and the left PHC (right) as a function of novelty and event; peaks are from the Novel maintenance > Familiar maintenance contrast (see arrows in C). Statistical parametric *t*-maps are color-coded, refer to color scale on right; L, left; R, right.

A follow-up conjunction analysis confirmed that the activation pattern that we observed in the MTL was indeed present for both encoding and maintenance [(encoding – Novel > Familiar) ∩ (maintenance - Novel > Familiar)]. The conjunction analysis demonstrated that the same MTL regions showed sustained activity (starting at encoding and persisting throughout the delay-period – maintenance). Observed peaks within the MTL included the left hippocampus ($[x\ y\ z] = [-30\ -18\ -15]$, $Z = 2.90$, $P_{UNCOR} < 0.0001$) and bilateral PHC (right $[x\ y\ z] = [24\ -24\ -15]$, $Z = 2.79$, $P_{UNCOR} < 0.0001$; left $[x\ y\ z] = [-24\ -33\ -18]$, $Z = 2.84$, $P_{UNCOR} < 0.0001$).

At retrieval, the contrast Novel > Familiar demonstrated activity in the right PHC ($[x\ y\ z] = [33\ -33\ -18]$, $Z = 3.34$, $P_{COR} < 0.01$; not depicted). The reverse contrast (Familiar > Novel) did not show any differential activity in the MTL during encoding, maintenance or retrieval.

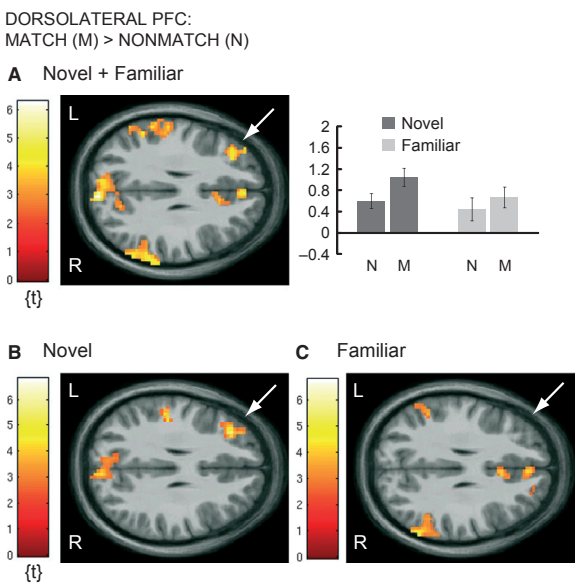

FIG. 4. Greater left dlPFC activity for correct Match trials than for correct Non match trials during retrieval (retrieval success effect). (A) Statistical parametric *t*-map (left panel) shows left dlPFC activity across novel and familiar trials (arrow). Bar graph (right panel) depicts parameter estimates (beta-weights) as a function of novelty and retrieval type (Match, M; Non-match, N). (B) Statistical parametric *t*-map shows left dlPFC activity for novel trials only (arrow). (C) Statistical parametric *t*-map shows absence of left dlPFC activity for familiar trials (arrow). Statistical parametric *t*-maps are color-coded, refer to color scale on left; L, left; R, right.

To assess whether the MTL are activated regardless of stimulus Novelty/Familiarity, we contrasted encoding, maintenance and retrieval with the ITI (fixation) across both conditions (Novel and Familiar). The contrast encoding > ITI showed bilateral activity in the hippocampus ([*x y z*] = [−27 −21 −18], $t = 4.70$, $P_{COR} < 0.01$ and [*x y z*] = [21 −30 −9], $t = 6.13$, $P_{COR} < 0.01$; left and right hippocampus, respectively; not shown) and in the PHC ([−27 −54 −9], $Z = 4.79$, $P_{COR} < 0.01$ and [*x y z*] = [33 −54 −6], $Z = 4.91$, $P_{COR} < 0.01$, left and right PHC, respectively), consistent with the findings reported above. The contrast maintenance > ITI did not result in any MTL activity. The contrast retrieval > ITI showed bilateral activity in the PHC ([*x y z*] = [−24 −54 −9], $Z = 6.15$, $P_{COR} < 0.01$ and [*x y z*] = [33 −36 −15], $Z = 5.81$, $P_{COR} < 0.01$, left and right PHC, respectively; not shown).

dlPFC activity is modulated by familiarity during encoding and retrieval, but not during maintenance

We investigated whether mid-dlPFC activity was modulated by: (i) whether the scenes were from the novel or the familiar stimulus set (Familiar > Novel); and (ii) by whether the scenes seen at retrieval were correctly identified as matching one of the four sample scenes vs. not matching any of the four sample scenes seen during encoding [correct Match (hit) > correct Non match (correct rejection); retrieval success]. Across both conditions (Novel and Familiar), we observed retrieval success-related activity in the left mid-dlPFC during retrieval, i.e. activity was greater for matching scenes (correct Match or hits) than for non-matching (new) scenes (correct Non-match or correct rejections). The activation peak was focused on the left middle frontal gyrus ([*x y z*] = [−33 36 27], $Z = 3.49$, $P_{COR} < 0.01$; Fig. 4A), corresponding to mid-dlPFC [approximately Brodmann area (BA) 46]. When the same analysis was repeated separately for the Novel and Familiar conditions, it became evident that this effect was driven by the Novel condition ([*x y z*] = [−33 36 27], $Z = 4.08$, $P_{COR} < 0.01$; Fig. 4B), and was not present for the Familiar condition (Fig. 4C). This was confirmed by a conjunction analysis that showed only a small area of conjunction within the left mid-dlPFC that did not reach statistical significance ([*x y z*] = [−30 −39 24], $Z = 2.60$, $P_{UNCOR} < 0.01$). We did not observe any retrieval success-related activity in the MTL. In addition, for the contrast retrieval of familiar scenes greater than retrieval of novel scenes (Familiar > Novel), there was no significant activity in the PFC.

Other brain areas activated for the retrieval success analysis (correct Match/hit) > (correct Non match/correct rejection) across Novel and Familiar conditions included the cuneus (bilateral), the right supramarginal gyrus, the anterior cingulate gyrus extending into the pre-SMA, the left postcentral gyrus extending in the supramarginal gyrus, the right vertical ramus of the lateral fissure (anterior insula), the left precentral gyrus and the right anterior inferior frontal sulcus extending into the anterior middle frontal gyrus. Of these activation clusters, the cuneus, the anterior insula and postcentral gyrus were specific to the Novel condition, while the supramarginal gyrus and the anterior cingulate/pre-SMA were specific to the Familiar condition.

To assess whether the observed mid-dlPFC activity was activated during retrieval regardless of familiarity and retrieval type, we contrasted retrieval with the ITI (fixation) across both Familiarity (Novel and Familiar) and retrieval type (Match and Non match) conditions. This contrast showed only a peak in the right mid-dlPFC (approximately BA 46), located in the inferior frontal gyrus (IFG; approximately corresponding to BA 46) ([*x y z*] = [48 33 15], $Z = 3.76$, $P_{COR} < 0.01$, not shown), demonstrating that the observed left mid-dlPFC activity was specific to the Match > Non match contrast, i.e. retrieval success.

We also contrasted activity during encoding of familiar scenes (Familiar condition) with activity during encoding of novel scenes (Novel condition). This contrast (Familiar encoding > Novel encoding) showed activity in the right mid-dlPFC (approximately corresponding to BA 9). The activation peak was focused in the middle frontal gyrus ([*x y z*] = [33 21 39], $Z = 4.48$, $P_{COR} < 0.01$; not depicted). In contrast to the observed activity in the MTL for novel trials, mid-dlPFC activity did not persist during maintenance, that is, there was no differential activity in the PFC for this contrast for maintenance.

To assess whether the mid-dlPFC was activated during encoding regardless of familiarity and retrieval type, we contrasted encoding with the ITI (fixation) across both familiarity (Novel and Familiar) and retrieval type (Match and Non match) conditions. This contrast did not show any activation within the PFC. Therefore, the observed activation in the right mid-dlPFC was most likely specific to encoding of familiar stimuli.

Discussion

Consistent with our prediction, we found that MTL activity was greater when novel trial-unique scenes rather than familiar trial-unique scenes needed to be encoded into a WM buffer and maintained during a brief delay-period. This activation pattern was not related to the trial-uniqueness of the scenes, but to whether or not they were previously learned (i.e. whether they were novel or familiar). Consistent with our previous work, the observed activation in the left hippocampus and in the PHC during encoding and maintenance suggests that these areas are recruited during WM when the stimulus is novel and no prior representation of the stimulus input exists (Hasselmo & Stern, 2006). The activation pattern within the mid-dlPFC did not simply exhibit the reverse pattern, that is, greater activity when trial-unique familiar scenes needed to be encoded and maintained in WM compared with novel scenes. Instead, activity in the left mid-dlPFC was related to retrieval success, and was driven by trials with novel scenes. In addition, while encoding of familiar scenes compared with novel scenes recruited the right mid-dlPFC, this activity was not sustained during the delay-period. The observed activation in the mid-dlPFC suggests that this activity may be related to monitoring of scene familiarity during both encoding and retrieval during WM.

MTL activity is related to encoding and maintenance of novel information

Previous work in our laboratory and others have demonstrated that the hippocampus and parahippocampal areas are recruited during WM for trial-unique novel visual input, but not for WM with repeated stimuli (Stern *et al.*, 2001; see also Ranganath & D'Esposito, 2001), and subsequent research has demonstrated that the delay-period activity in the MTL promotes long-term encoding (Schon *et al.*, 2004; Ranganath *et al.*, 2005). The findings reported here extend these previous results by demonstrating it is not the trial-uniqueness of the novel stimuli that recruits MTL areas, but instead suggest the MTL may be recruited when visual input (i.e. novel information) has no existing memory trace in the brain. Computational modeling work and slice recording studies have shown that parahippocampal neurons have intrinsic mechanisms that could maintain activity in the absence of existing patterns of modified

recurrent synapses within medial temporal cell networks (Klink & Alonso, 1997; Fransén *et al.*, 2002; Hasselmo & Stern, 2006). The modeling work has also shown how this persistent activity in parahippocampal regions during the WM delay provides the appropriate mechanism for long-term encoding (Atkinson & Shiffrin, 1968; Jensen & Lisman, 1996; Hasselmo *et al.*, 2002; Howard & Kahana, 2002), a prediction that we tested previously with fMRI (Schon *et al.*, 2004, 2005). In these studies, sustained delay-period activity predicted subsequent memory for complex visual scenes. Based on this previous work on delay-period activity and on the computational modeling and slice recording studies, the greater delay-period activity that we observed in the MTL for trials with novel scenes compared with trials with familiar trial-unique scenes may be due to mechanisms related to long-term or episodic encoding during the WM delay. The finding that delay-period activity in the hippocampus and parahippocampal regions predicts subsequent memory in the absence of stimulus input in the context of a WM task fits with work demonstrating a role for the hippocampus in immediate post-stimulus processing of brief movie episodes (Ben-Yakov & Dudai, 2011), and with reverse replay of spatiotemporal sequences during stopping (non-running) periods in dorsal hippocampal neurons of awake rats (Foster & Wilson, 2006).

Mid-dlPFC recruitment during encoding and retrieval in WM and familiarity monitoring

The results presented here suggest a retrieval success effect in the left mid-dlPFC that was specific to novel stimuli. That is, only for stimuli from the novel stimulus set was activity greater in this region when the stimulus seen during retrieval was identical to one of the four sample scenes seen during the preceding encoding phase (Match) than when it was not seen during the preceding encoding phase (Non match). In episodic memory studies, retrieval success is evaluated by comparing hits vs. correct rejections (hits > correct rejections). In our analysis, only correct trials were included, thus our Match vs. Non-match comparison was the WM equivalent of a retrieval success evaluation, with the exception that both the time interval between encoding and retrieval and the list length at encoding were much shorter than in episodic retrieval tasks. The retrieval success effect was only present for the Novel condition. This is consistent with previous work on retrieval success in episodic memory, because in the Novel condition, as in episodic memory studies, all stimuli were unfamiliar (i.e. novel), unless they were seen again during retrieval as a match in the context of WM or as an old item in the context of episodic retrieval. During encoding of familiar scenes we observed greater activity in the right mid-dlPFC than during encoding of novel scenes. Both findings in the left and right mid-dlPFC suggest a role for the mid-dlPFC in monitoring of scene familiarity.

Monitoring is an executive or cognitive (top-down) control process that is fundamental to WM. The role of the mid-dlPFC in monitoring is widely accepted (Petrides & Milner, 1982; Petrides, 1991, 1995, 2000; MacDonald *et al.*, 2000; Rowe *et al.*, 2000; Stern *et al.*, 2000; Wagner *et al.*, 2001). In particular, the left mid-dlPFC may play a role in match enhancement (Druzgal & D'Esposito, 2001), also suggesting top-down control, but our behavioral data are not consistent with this idea. A match enhancement account would predict slower reaction times for Non match decisions than for Match decisions. However, our data showed the opposite pattern with faster reaction times for Non match decisions than for Match decisions, which was not modulated by stimulus familiarity. Studies that showed mid-dlPFC activity or impaired performance in animals with mid-dlPFC lesions for WM with familiar stimuli used stimuli that were drawn repeatedly from the same small stimulus pool (Petrides, 1995, 2000; Owen *et al.*, 1996, 1998; Stern *et al.*, 2001; Schon *et al.*, 2008). In these studies, proactive interference among the current and past trial-relevant stimuli would increase with time. In contrast, in the present study proactive interference was minimized because all familiar stimuli were trial-unique. Furthermore, the dlPFC does not simply support active maintenance *per se* (Petrides, 2000; Rowe *et al.*, 2000).

Previous functional neuroimaging work has demonstrated that the left IFG (BA 45) supports familiarity-based proactive interference resolution (for review, see Jonides & Nee, 2006). These results suggest that this area is active during retrieval from WM when a non-matching probe is identical to a stimulus encountered on a recent trial (recent negative condition), but not when a non-matching probe is identical to a stimulus seen on a much earlier trial (non-recent negative condition; e.g. D'Esposito *et al.*, 1999; Badre & Wagner, 2005; Öztekin *et al.*, 2009). In the current study, proactive interference was minimal because all stimuli were trial-unique within the Sternberg task. It is possible, however, that there may have been some degree of non-recent interference from the retrieval 4 session during which the participants were tested on the familiar stimulus set shortly before the start of the Sternberg task. This could introduce a degree of non-recent interference in the case of the Familiar condition, and suggest an alternative explanation for the retrieval-related dlPFC activation related to interference monitoring. We believe it is unlikely, because our participants did not differ in accuracy or reaction times on novel and familiar trials.

Together, these findings could explain the absence of greater delay-period activity in the dlPFC and of greater retrieval-related activity in the left IFG for the Familiar condition than for the Novel condition. While minimal interference among the familiar stimuli in our study could perhaps explain the absence of dlPFC activity during the WM delay, it does not explain the effects observed in the mid-dlPFC during encoding and retrieval. The observed retrieval success effect is consistent with previous studies that have associated the dlPFC with familiarity monitoring in episodic memory tasks (Henson *et al.*, 2000; Bunge *et al.*, 2004; Dobbins *et al.*, 2004), with the caveat that dlPFC activity for retrieval success during episodic memory was right-lateralized, not left-lateralized as in our study. While these studies investigated the role of the dlPFC in episodic retrieval, there is evidence that this region is also involved in retrieval from WM (Druzgal & D'Esposito, 2001; Sakai *et al.*, 2002; Ranganath *et al.*, 2003). Specifically, consistent with our results, Druzgal & D'Esposito (2001) reported greater left dlPFC activation for Match decisions compared with Non match decisions during a delayed recognition task, supporting the idea that this region may signal a short-term retrieval success effect (Match/hit > Non match/correct rejection). Similarly, the familiarity effect that we observed in the right mid-dlPFC during encoding (i.e. Familiar > Novel) was specific to familiar stimuli, and is also consistent with the idea that the mid-dlPFC supports familiarity monitoring. In this case, executive control-related processes in the mid-dlPFC may be needed during encoding of familiar complex or contextual/associative information (Blumenfeld & Ranganath, 2006; Qin *et al.*, 2007), especially when cognitive set shifting is required to keep track of the task rule (White & Wise, 1999; Monchi *et al.*, 2001; Mansouri *et al.*, 2006; Hales *et al.*, 2009; Moore *et al.*, 2009). This may be so, because without close monitoring of the current task rule, the familiarity of the stimuli may trigger a retrieval response when encoding is required. This idea is consistent with a role of the mid-dlPFC in executive or cognitive control as keeping

track of the behavioral goal by initiating the appropriate response and inhibiting task-inappropriate responses is required for accurate task performance.

While one might argue that the mid-dlPFC is recruited in our task for novelty/familiarity discrimination rather than monitoring of stimulus familiarity, this alternative interpretation is unlikely based on lesion studies in monkeys showing that animals with lesions in the mid-dlPFC are unimpaired in discriminating novel from familiar stimuli (Bachevalier & Mishkin, 1986; Petrides, 1991; Meunier *et al.*, 1997). Thus, the observed retrieval success and familiarity effects in the left mid-dlPFC are most likely related to familiarity monitoring rather than to novelty/familiarity discrimination *per se*.

Although the current study was focused on MTL and prefrontal contributions to WM for trial-unique information, the posterior parietal cortex also plays a role in WM and episodic retrieval. We did not observe differential delay-period or retrieval-related activity as a function of scene familiarity, or a retrieval success effect in the posterior parietal cortex, except for a retrieval success-related activation in the postcentral gyrus that extended into the supramarginal gyrus for the Familiar condition. Previous studies reporting retrieval success effects in the inferior parietal sulcus used episodic retrieval tasks (Dobbins *et al.*, 2003; Shannon & Buckner, 2004; Iidaka *et al.*, 2006; Vilberg & Rugg, 2008, 2009; Spaniol *et al.*, 2009; Nelson *et al.*, 2010; see Wagner *et al.*, 2005; for review). It is possible that because we used a WM task with a much shorter time interval between encoding and retrieval and a shorter list-length during encoding than is used for a typical episodic retrieval task, that posterior parietal regions show a retrieval success effect only in the context of episodic memory, but not in the context of WM. Perhaps, in the context of WM the mid-dlPFC is sufficient for monitoring retrieval success. The mid-dlPFC is functionally connected to the inferior parietal sulcus region involved in retrieval success (Nelson *et al.*, 2010). Future studies are needed to investigate whether a dissociation between episodic retrieval and retrieval during WM exists within the posterior parietal cortex.

Complementary roles of the PFC and the MTL during WM?

Our data show greater MTL activity for encoding and maintenance of trial-unique novel scenes than trial-unique familiar scenes, and greater right mid-dlPFC activity for encoding, but not maintenance, of trial-unique familiar scenes than novel scenes. Thus, our findings suggest that the mid-dlPFC and MTL may play complementary roles only during WM encoding. A complementary relationship between the MTL and the PFC may be particularly evident when WM demands are high, for example, when there is a high WM load as in our study or under high interference conditions. Recent work has suggested that MTL activity is modulated by WM load (Axmacher *et al.*, 2009; Schon *et al.*, 2009). In our previous study (Schon *et al.*, 2009), we observed a WM load effect at encoding (and retrieval) of novel, complex visual scenes in both the MTL (encoding and retrieval) and the dlPFC (encoding only). However, in that study we did not assess whether subsequent memory-related activity in these brain areas was modulated by WM load. Axmacher *et al.* (2009) investigated subsequent memory-related activity in the MTL as a function of WM load. Their data showed that the parahippocampal gyrus was the locus of interaction between WM load and LTM encoding, but reported no dlPFC activity. During WM, the PFC and MTL may either play complementary roles in that a greater WM load could impair LTM encoding as suggested by Axmacher *et al.* (2009), or in that high WM demands could enhance LTM encoding as suggested by Blumenfeld & Ranganath (2006) and Qin *et al.* (2007). It may be possible that PFC-mediated WM mechanisms can support MTL-mediated LTM mechanisms for LTM encoding during WM if both memory systems act on the same stimuli (Blumenfeld & Ranganath, 2006; Qin *et al.*, 2007; Axmacher *et al.*, 2008) due to PFC–MTL cooperation. This is consistent with the idea that the PFC may exert top-down control on the MTL during episodic memory encoding (e.g. Blumenfeld & Ranganath, 2006). Conversely, if PFC-mediated and MTL-mediated mechanisms act on different stimuli as in a dual-task paradigm, incidental LTM encoding during WM may be impaired due to PFC–MTL competition. Future studies are needed to disentangle conditions of PFC and MTL cooperation and competition during WM task performance.

Conclusions

Our findings demonstrate: (i) that the observed novelty effect in parahippocampal areas and in the hippocampus is not driven by the trial-uniqueness of the stimuli *per se*, a confound in previous WM studies; and (ii) that the mid-dlPFC is recruited for monitoring of scene familiarity during encoding and retrieval in the context of a WM task. Our results extend previous work on the role of the hippocampus and PHC in long-term encoding during WM by showing that the novelty of the stimuli, not their trial-uniqueness, accounts for the encoding and maintenance-related activation during WM. In addition, our results demonstrate that the mid-dlPFC is recruited for monitoring of scene familiarity and retrieval success. This finding extends previous work on monitoring of retrieval success during episodic memory tasks to WM tasks.

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Abbreviations

BA, Brodmann area; BOLD, blood oxygen level-dependent; *d'*, discriminability; DARTEL, Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra; dlPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; FWHM, full-width at half-maximum; IFG, inferior frontal gyrus; ITI, inter-trial interval; LTM, long-term memory; MTL, medial temporal lobes; PFC, prefrontal cortex; PHC, parahippocampal cortex; SMA, supplementary motor area; WM, working memory.

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