Behavioral/Systems/Cognitive

Past Experience Modulates the Neural Mechanisms of Episodic Memory Formation

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Neuroscientists have observed the "birth" of memories, but have not explored how an organism's past experience with materials interacts with the neural mechanisms of episodic memory formation. Using functional neuroimaging, we searched for such an interaction by examining brain activity during memory encoding that predicted participants' subsequent episodic memory for novel and repeated scenes. Memory for both scene types was predicted by a common posterior network in occipital and parietal cortices. Medial temporal memory predictors were modulated by scene repetition: the right anterior hippocampus and right amygdala predicted memory for novel scenes only, whereas posterior hippocampi predicted memory for repeated scenes only. There was also greater functional connectivity between the temporal pole and anterior versus posterior hippocampus, and this link predicted memory for novel but not repeated scenes. In contrast, there was greater functional connectivity between the precuneus and posterior versus anterior hippocampus, and this link predicted memory for repeated but not novel scenes. Together, these results reveal a functional specialization within the hippocampus for the encoding of novel and previously experienced materials, and suggest that the topography of this specialization might be related to local variations in connectivity. Because episodic memory for repeated scenes was superior, our results also support traditional views of encoding emphasizing the role of prior representations, and illuminate one way in which humans use existing memories to help form new ones. In so doing, our results challenge recent novelty-encoding hypotheses.

Introduction

Observing the "birth" of new memories by comparing the neural correlates of remembered and forgotten experiences has allowed researchers to explore the neurocognitive processes underpinning memory formation (Brewer et al., 1998; Wagner et al., 1998). In studies of this kind, memories are typically acquired through exposure to materials that are novel in their experimental context to prevent memory retrieval from contaminating memory-encoding processes. While this approach has been useful for investigating how novel information is encoded into memory, events unconnected with one's past are truly exceptional in daily experience, which is dominated by familiar people, places and things. Accordingly, understanding how the neural mechanisms of encoding are modulated by recent experiences with such stimuli is likely to advance our understanding of how memory functions under everyday circumstances.

Detailed study of the encoding of novel materials has been encouraged by current theoretical proposals that encoding is enhanced by—or even dependent upon—the novelty of the information to be encoded (Tulving and Kroll, 1995). Several biological mechanisms involving a hippocampal "novelty signal" have been proposed that could support this selectivity (Tulving et al., 1996; Lisman and Grace, 2005). These proposals are based on reports that recognition accuracy for novel stimuli is considerably higher than that for repeated stimuli (Tulving and Kroll, 1995; Kormi-Nouri et al., 2005). However, the experimental paradigm used to compare encoding of novel and repeated information has been subject to criticism regarding an uneven comparison of memory for repeated and novel items: distinguishing targets from recently presented lures requires information about the source of items, whereas distinguishing targets from novel lures does not (Kinsbourne and George, 1974; Dobbins et al., 1998; Poppenk et al., 2010b). Because the evidence available to support novelty-encoding proposals is not a stable foundation for growing multidisciplinary interest in this area, one goal of the current work is to test the cognitive and neural predictions of these proposals.

Here, we report a first look at how memories are formed when they involve previously repeated materials and compare the functional magnetic resonance imaging (fMRI) correlates of encoding for truly novel experiences. To address recent proposals that novelty is better encoded than familiarity, we also present a new measure of memory performance designed to allow a level comparison of how well novel and repeated materials are encoded. Behaviorally, we predicted that the memory advantage often seen for novel items would not be upheld once a controlled memory comparison was established. At the brain level, we hypothesized that the hippocampus would be more sensitive to novel than repeated materials and would also predict later memory for novel

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materials. As no past study has evaluated subsequent memory predictors for repeated materials, our assessment of memory predictors for these materials was exploratory.

Materials and Methods

Overview. The study was conducted in three phases (see Fig. 1): (1) a prescanning repetition phase, in which participants viewed various indoor and outdoor scenes three times; (2) an encoding phase, during which participants encoded repeated and novel scenes by viewing them under either "action" or "intention" instructions while being scanned using functional magnetic resonance imaging (fMRI); and (3) a postscanning phase, in which memory was tested outside the scanner. Phase 1 allowed us to familiarize participants with a number of items before their presentation during scanning in phase 2. Data from the phase 3 memory test were used to assess memory for novel and repeated items behaviorally, then to retrospectively categorize events from the phase 2 encoding task as subsequent memory "hits" or "misses" (Brewer et al., 1998; Wagner et al., 1998).

Participants. Sixteen right-handed volunteers from the Greater Toronto Area, all fluent in English with normal or corrected-to-normal vision and hearing, participated in the experiment (9 female; aged 22–35 years, mean age 25.8). Participants were screened for the absence of neurological and psychiatric conditions and received financial remuneration for their participation. Of these 16, two were excluded for chance-level performance on behavioral tasks, and a third due to excess imaging artifact. The protocol for this experiment was approved by the Research Ethics Board at Baycrest Hospital in Toronto.

Figure 1. Schematic of experimental design. During the repetition phase (***a***), which took place immediately before fMRI scanning in a mock fMRI scanner, participants were exposed to one set of scenes three times. During the encoding phase (***b***), which took place in the fMRI scanner, participants viewed the repeated scenes and a novel set while imagining themselves performing an action in the scene or imagining a possible intention associated with the scene. In a subsequent memory test outside of the scanner (***c***), participants were presented with all of the scenes from the encoding phase along with additional lures, some of which had been presented in phase 1 but not during scanning (repeated lures), and some of which had not previously been presented (novel lures). They were asked to determine whether each scene was presented during scanning and, if so, whether it was associated with action or intention instructions.

Stimuli. A collection of 384 scenes was prepared (320 × 240 pixels). Images were selected from a set of photographs depicting emotionally neutral object configurations, rooms and landscapes. No human subjects, animal subjects, or any well known landmarks were depicted in the images. For each participant, this collection of scenes was randomly split into two sets of 192 images: a "repetition" set and a "novelty" set.

Procedure. Participants were informed that the study consisted of three phases that together would take ~2.5 h to complete, and that their memory would be tested at the end of the experiment (Fig. 1). In the phase 1 prescanning repetition task, participants viewed the repetition set of scenes in a mock fMRI scanner. This setting was used to maximize the contextual match between phase 1 and a later memory-encoding phase. Participants were informed that their memory for the scenes presented would not be tested, but that they were to view each of the scenes to familiarize themselves with the stimulus set. Each image was presented for 2.2 s and was followed by a 0.8 s presentation of a fixation cross. The full set of repetition scenes was presented in random sequence three times. To ensure that participants were alert for this task, they were prompted at several intervals to press a button to continue. During fMRI scanning in phase 2, participants encoded scenes into memory while completing several tasks. Data were collected over four functional runs, each containing eight study blocks of eight images. Each block was preceded by 2 s of instruction and 2 s of fixation and was followed by 12 s of fixation. Each image was presented for 4 s and followed by 2 s of fixation. Half of the blocks contained repetition scenes (previously seen three times in phase 1) and the other half contained novel scenes (seen for the first time in phase 2). For each block, participants processed the scenes in accordance with instructions presented before each block and above each image. For blocks associated with "action" instructions, participants imagined themselves performing an action in the scene; for blocks associated with "intention" instructions, participants associated a future intention with the scene. Because we wished to relate any novelty and subsequent memory effects to findings reported by other investigators, and these effects are not typically assessed in the context of prospective memory, we did not include any data from the intention encoding condition in the current study [our findings on prospective memory are described by Poppenk et al. (2010a)]. Following the presentation of each stimulus, participants pressed a key on an MR-compatible keypad to indicate successful generation of an action or intention. Participants practiced both encoding tasks before scanning. In total, 256 pictures were presented, 64 in each of four block types: novel scenes with action instructions, repeated scenes with action instructions, novel scenes with intention instructions and repeated scenes with intention instructions. A different random allocation of scenes to these conditions was arranged for each participant. Each run contained two blocks of each type presented in a random sequence. In a memory test in phase 3, participants viewed on a computer the 128 novel and 128 repeated "target" scenes encountered during scanning, as well as 64 "repeated lure" scenes repeated three times in phase I but not presented during scanning and 64 "novel lure" scenes not presented at all during the experiment. Each scene was presented for a maximum of 4 s and was followed by 1 s of fixation. Participants indicated whether each scene was studied as an intention, studied as an action, or not studied during scanning.

MRI scanning and data analysis. All imaging was performed on a 3 tesla whole-body MRI system (Siemens). Twenty-eight contiguous 5-mm-thick axial oblique slices were obtained, capturing the entire brain volume of each participant. The field of view was 200 by 200 mm (64 × 64 matrix) providing an in-plane resolution of 3 mm. T2-weighted EPI image acquisition was used for all functional scans (TE = 30 ms; TR = 2000 ms; flip angle = 70°). Each run involved the acquisition of eight initial stabilization volumes that were discarded and 264 task volumes (33 volumes per block with eight blocks). An additional T1-weighted

high-resolution MRI volume was obtained for the display of neuroanatomy during the same experimental session using a three-dimensional (3D) MPRAGE (magnetization-prepared rapid-acquisition gradient echo) pulse sequence in the same orientation as the functional scans (160 slices; 1 mm thick; FOV = 256 × 256 mm; 192 × 256 matrix; 1 mm in-plane resolution).

Initial image preprocessing was performed using FSL (FMRIB Software Library version 4; Smith et al., 2004). Following motion correction of the T2-weighted functional images, probabilistic independent component analysis was conducted on a run-by-run basis to identify and remove high-amplitude time course spikes as well as residual motion artifacts, high-frequency scanner noise and artifacts related to gradient timing errors. This step was performed using MELODIC (Beckmann and Smith, 2004) and detailed inspection of independent components by two raters. Timing differences between slices in the same volume were corrected using SPM software (Statistical Parametric Mapping version 5). Functional data were then transformed into MNI (Montreal Neurological Institute) space (Cocosco et al., 1997), resampled into isotropic voxels (3 × 3 × 3 mm), and smoothed using a 3D Gaussian kernel with a full-width at half maximum value of 6 mm.

In all analyses, intensity units were converted to a percentage signal change score based upon the intensity of each image relative to a reference scan. In our blocked analysis, this scan was taken following a 16 s interblock interval and in the same TR in which block instructions were presented. In our event-related analysis, we examined the percentage signal change in each event from 2 to 10 s following each stimulus onset relative to onset of a reference scan, as taken 2 s after trial onset, to allow for a hemodynamic return to baseline from the preceding trial. We determined that this window was optimal for response detection on the basis of hemodynamic response function modeling as well as inspection of global intensity data.

All functional neuroimaging analyses were conducted using nonparametric resampling statistics (non-rotated partial least squares in PLS-GUI; McIntosh and Lobaugh, 2004). Unlike rotated PLS, non-rotated PLS is a hypothesis-driven approach. It is suitable for testing network-level effects, in which case permutation testing is used to evaluate network stability, or for assessment of effects that are local in nature, in which case a bootstrap resampling procedure is used to evaluate the stability of signal differences in individual voxels. For each analysis, we created a singular profile containing a contrast matrix and a singular image describing the relationship of all voxels to the singular profile. In cases where a test of the stability of the singular profile was required, permutation testing was performed using 500 samples. In cases where local differences in signal were of focal interest, bootstrap resampling was conducted using 100 samples. Maps were created expressing the ratio of voxel salience over the estimated SE (i.e., bootstrap ratio; BSR) for the purpose of identifying statistically reliable relationships between individual brain voxels and the singular profile. To characterize voxel responses in terms of a specific spatial distribution, we inspected BSR maps from the peak hemodynamic response at 4–6 s following stimulus onset for clusters of reliably differentiated voxels, defined as any set of at least 12 contiguous cortical or subcortical voxels above a BSR of 2.81 and a peak of 3.5 (approximately corresponding to a minimum spatial extent of 324 mm^3, a 99.95% peak confidence interval and a 99% extent confidence interval) that was no closer than 12 mm to another cluster. This corresponds to a more conservative threshold than is often used in full-brain neuroimaging analyses, which are typically thresholded at an uncorrected $p < 0.001$ and frequently include no restriction of minimum spatial extent. Labels for identified clusters were obtained by transforming peak MNI coordinates into Talairach coordinates using a best-fit icbm2tal transform (Lancaster et al., 2007) and localizing these coordinates in a Talairach brain atlas (Mai et al., 2004).

All fMRI analyses in our study pertained to fMRI data collected during phase 2 (encoding), as no neuroimaging data were collected during any other phase. As a preliminary manipulation check, we attempted to replicate previous findings of novelty effects in the brain by contrasting neural activity associated with blocks of novel and repeated scenes. To evaluate whether novel and repeated scenes are encoded in similar or different ways, we assessed the interaction between novelty and subsequent memory success. Phase 2 encoding trials were classified as successful or unsuccessful for each participant based on source judgments in the phase 3 memory test. Source hits were "action" items identified as such, whereas miss items were "action" items identified as intention items or lures. For descriptive purposes, memory for the categorized scenes was also entered into two event-related contrasts exploring subsequent memory effects for novel and repeated stimuli.

To identify regions that were associated with subsequent memory regardless of stimulus type, we ran a conjunction analysis. First, to create a mask limiting our analysis to voxels in which group subsequent memory effects were found for both novel and familiar items, each the two BSR maps associated with novel and repeated stimuli were thresholded at 1.96 (approximately corresponding to a 95% confidence interval) with suprathreshold voxels set to a value of one and subthreshold voxels set to a value of zero. The product was taken of the two maps, yielding a binary mask occluding voxels failing to surpass threshold in both group contrasts (Friston et al., 2005). Next, using bootstrap resampling, we evaluated whether voxels located within the mask were reliably associated with a positive scaled singular-image product (i.e., were associated with positive subsequent memory effects in both novelty and familiarity conditions at the within-subjects level). First, the singular value-scaled singular image was taken from the contrast of hits and misses for both the novel and familiar conditions in each subject. The product of these scaled images was calculated and averaged across subjects to establish a group mean for each conjunction voxel. This procedure was repeated 100 times with bootstrap resampling to establish a 95% confidence interval about the mean. All voxels that included zero within this interval were exclusively masked. The surviving voxels were entered into a cluster analysis of the kind described for other group analyses above.

Finally, we compared the overall functional connectivity of anterior and posterior aspects of the hippocampus. Seeds for this analysis were selected from the peak anterior and posterior hippocampal voxels in the interaction analysis. To obtain within-subject voxelwise correlation values, a spatiotemporal stack of all events described in terms of percentage signal change was assembled for each subject (as in above analyses) and used to generate a mean and SD image for each time point of each event. Seed voxel SD values were extracted and multiplied with their full SD images to create a series of SD product images for each event. Next, the difference was assessed between the mean event images and corresponding images for each event in the stack. Seed voxel difference values were extracted and multiplied with their full difference images to create a series of difference product images for each event. Finally, the difference product images were averaged at each time point and divided by the SD product image to generate a within-subject correlation image for each time point and subject. This procedure was conducted separately for the anterior and posterior hippocampal seeds. The difference between the resulting correlation images was compared using non-rotated contrasts (as above). The resulting overall connectivity map was inspected for clusters using the same method as in earlier analyses.

In a follow-up analysis, we repeated our within-subject correlation computations, this time calculating functional connectivity separately for each of the "novel hit", "novel miss", "repeated hit" and "repeated miss" conditions. Separate maps for these conditions were created based on functional connectivity with each hippocampal seed. To avoid high type I error rates associated with inspecting multiple whole-brain maps, we performed two tightly constrained analyses in place of further full-brain contrasts. First, we conducted a region-of-interest (ROI) analysis assessing whether hippocampal functional connectivity with the anterior temporal lobes or precuneus, regions of theoretical interest identified in the above overall connectivity analysis, predicted subsequent memory. These ROIs were delineated by the bounds of the original identified clusters. We searched for voxel subclusters falling within the ROIs of at least four voxels (64 mm^3) with anterior or posterior hippocampal connectivity that reliably predicted subsequent memory for novel or familiar items (i.e., surpassed a threshold of BSR 1.96). Second, we performed permutation tests to evaluate whether large-scale functional connectivity networks were present that distinguished between hits and misses, while also exploring for possible subsequent memory interactions with novelty.

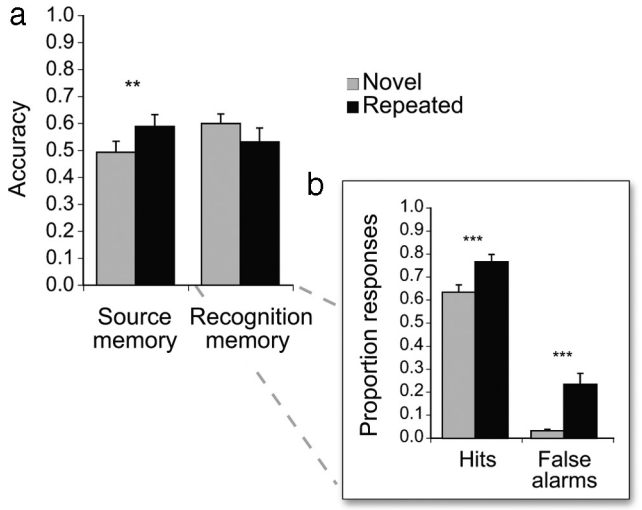

Figure 2. Behavioral measures of memory performance. We observed a trend toward the typical advantage for novel materials in recognition memory accuracy, the measure that has been used to compare memory for novel and familiar materials in all previous novelty studies (***a***). However, recognition memory is confounded here and in other studies investigating novelty and memory: while we wish to compare memory strength for novel and repeated targets, repeated lures are more difficult to reject than novel ones. Inset (***b***) is a plot illustrating how a higher false-alarm rate in the repeated relative to novel condition (***$p < 0.001$) deflated recognition accuracy scores in the repeated condition. Our new approach was to measure source memory accuracy for novel and repeated items, a measure that does not suffer from this confound. We observed the opposite pattern to that observed when using the recognition memory measure: memory was superior for repeated materials (**$p < 0.005$). Chance recognition memory accuracy was 0.00; chance source memory accuracy was 0.33. Error bars in all plots depict +1 SEM.

Results

Behavioral results

We first explored whether recognition memory performance was improved by repetition of scenes three times (phase 1) before the scanned memory encoding task in phase 2. In cognitive investigations on memory for novel and repeated materials, performance is typically assessed by asking participants to identify studied novel and repeated targets among novel and repeated lures. Similarly, in our memory test, we asked participants whether scenes were part of one of the scanning tasks or were not seen during scanning. Because "intention" data were not analyzed, recognition memory hits were specifically those novel or repeated phase 2 "action" items that participants correctly identified as being part of any scanning task (i.e., either as an "action" or "intention" item). Recognition misses were those phase 2 action items that participants incorrectly rejected as lures. Novel lures were items that were not presented at all before testing in phase 3, whereas repeated lures were items presented three times during the repetition phase (phase 1) but not at all during phase 2. False alarms were lures that participants identified as either "action" or "intention" items, whereas correct rejections were lures that were successfully identified as lures. Participants recognized more of the repeated target scenes as having been presented during scanning than target scenes that were novel as of the study phase, two-tailed $t_{(12)} = 4.44$, $p < 0.001$ (Fig. 2). However, participants also made more false alarms to repeated lures than novel ones, two-tailed $t_{(12)} = 3.80$, $p < 0.005$. As a result, a trend toward higher overall recognition accuracy for novel items was observed, two-tailed $t_{(12)} = 1.84$, $p < 0.1$.

This pattern of high false alarms reducing accuracy in the repeated condition is typical of cognitive investigations of novelty (e.g., Tulving and Kroll, 1995). However, better discrimination is required to reject repeated lures than novel ones, since participants must decide whether familiar lures were seen during fMRI scanning or the prescanning repetition phase. In contrast, novel lures may be rejected by the absence of recognition alone, since they were never previously encountered. Regardless of whether recognition memory is measured using the difference between hits minus false alarms or d', its calculation involves using the rate of false alarms to lures. Because better discrimination is required for repeated lures, it may not be fair to use recognition accuracy as a measure for comparing episodic memory for novel and repeated items (Kinsbourne and George, 1974; Dobbins et al., 1998; Poppenk et al., 2010b). To illustrate this discrepancy, it would not be appropriate to evaluate memory for friends and strangers based on one's ability to determine whether a particular friend and stranger attended a birthday party. Whereas it would be simple to recall that no stranger attended, it would be more difficult to rule out a friend who had attended past birthday parties. Just as this does not indicate that episodic memory for strangers is superior, so it is not fair to say episodic memory for novel items is superior based on comparable evidence.

Our innovative approach was to circumvent this confound by directly evaluating memory for source, an important attribute of episodic memory (Tulving, 1983), in addition to evaluating recognition memory itself. During our memory test, participants indicated whether the scene was presented in the scanner (recognition memory) and if so, which of two tasks encountered during scanning was associated with each scene (source memory). Source memory hits were "action" items specifically identified as such, whereas source misses were "action" items that were not identified correctly. Whereas the recognition memory decision required participants to discriminate using information acquired both before and during scanning, the source memory decision required them to discriminate exclusively on the basis of information acquired during scanning. When comparing source memory for the scenes that were novel or that had been repeated three times before the study phase, we observed an advantage of repetition, in contrast to the novelty advantage obtained using the confounded recognition memory measure. Participants correctly identified the source of repeated scenes more frequently than they correctly identified the source of novel ones, two-tailed $t_{(12)} = 4.28$, $p < 0.005$ (Fig. 2). When source memory accuracy was assessed together with recognition memory accuracy in a repeated-measures ANOVA, an interaction was observed between the measures, with better recognition memory accuracy for novel scenes and better source memory accuracy for repeated ones, $F_{(1,12)} = 16.97$, $p < 0.005$ (Fig. 2). All behavioral effects were the same whether or not excluded participants were included in the analyses.

Functional neuroimaging results

While our behavioral evidence favors the position that past experience in the form of repetitions, rather than novelty, benefits memory once confounding factors are removed, neuroimaging has consistently revealed greater medial temporal lobe (MTL) responses to novel relative to repeated materials (Tulving et al., 1996; Kirchhoff et al., 2000; Kumaran and Maguire, 2006; Poppenk et al., 2008). Because the MTL is known to be important for memory in general (Scoville and Milner, 1957), and because novelty and subsequent memory effects have been observed in the same hippocampal region (Kirchhoff et al., 2000), many researchers have linked MTL novelty responses to memory encoding. Along these lines, various MTL memory-encoding mechanisms

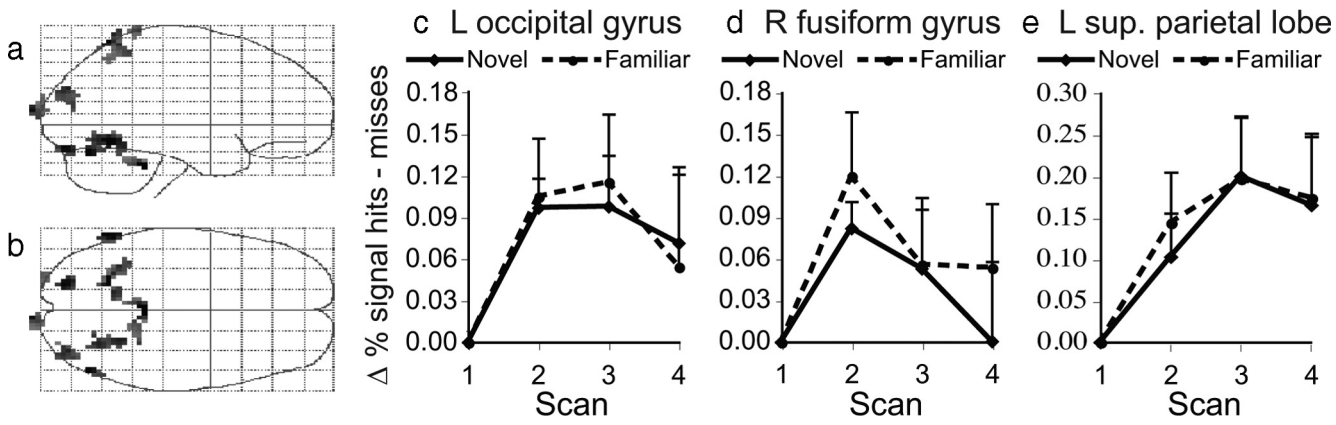

Figure 3. Stable subsequent memory regions. A transparent brain depicts those regions in which brain activity at encoding predicted subsequent source memory for both novel scenes viewed for the first time during the study phase and repeated scenes viewed three times before the study phase. The regions are shown in a sagittal view (***a***; anterior = right) and a transverse view (***b***; left = up). Response plots for specific regions of interest are depicted separately on the right for novel and repeated scenes (***c–e***; +1 SE). To identify the common network, activation maps were combined from source memory hit > source memory miss contrasts for novel and repeated scenes. Depicted regions surpassed a threshold of $p < 0.05$ in both contrasts, then survived a bootstrap resampling procedure designed to evaluate whether conjoint effects could be observed at the within-subject level.

Table 1. Voxel clusters that predicted subsequent memory for both novel and familiar scenes (conjunction analysis: source memory hits − source memory misses)

Region	BA	Hemi.	Peak MNI coordinate			95% CI of scaled SI product × 10^2			Spatial extent (mm^3)
			x	*y*	*z*	LL	M	UL	
Temporal lobe									
Inferior temporal g.	37	L	−63	−60	−15	0.5	16.9	20.7	729
Parietal lobe									
Superior parietal l.	7	R	27	−42	78	0.1	5.1	14.8	648
		L	−24	−60	69	0.2	18.0	20.9	1863
Parietoccipital transition zone	19	R	33	−84	30	0.1	7.5	9.8	1215
Occipital lobe									
Fusiform g.	19	R	24	−54	−15	0.6	7.8	12.6	1080
	19/37	R	48	−72	−24	0.8	14.0	17.8	378
Occipital g.	18/19	L	−21	−87	−18	1.5	11.8	18.5	648
	18	L	−30	−99	15	0.2	2.4	4.4	405
		R	6	−105	12	1.0	9.6	10.2	810
Sublobar									
Pons	—	L/R	0	−39	−36	1.2	18.9	36.4	567

Regions were defined as any cluster of 12 or more voxels surviving a threshold of BSR 1.96 ($p < 0.05$) in both of the subsequent memory contrasts. Voxels were also required to survive bootstrap testing with 95% confidence prior to inclusion in a region. Coordinates are displayed in MNI space (Cocoso et al., 1997). BA, Brodmann's area; Hemi., hemisphere; L, left; R, right; 95% CI, 95% confidence interval; SI, singular image; LL, lower limit; M, mean; UL, upper limit; g., gyrus; l., lobe.

have been proposed that require novelty for efficacious encoding (Tulving et al., 1996; Borisyuk et al., 2001; Lisman and Grace, 2005). Accordingly, MTL responses are of particular interest here.

To confirm that our novelty manipulation exerted comparable effects on brain activity to those observed in previous investigations, we first contrasted the fMRI signal associated with novel and repeated scenes (see supplemental Table 1, available at www.jneurosci.org as supplemental material online). We identified more activity in the right anterior hippocampus, fusiform gyrus, right visual cortex and left prefrontal cortex (PFC) in response to novel scenes, an effect often seen in neural priming studies comparing brain responses to novel and repeated stimuli (Schacter et al., 2007). In contrast, we found more activity in the right posterior hippocampus, motor cortex and bilateral PFC in response to repeated relative to novel scenes. Novelty/repetition dissociations in anterior/posterior hippocampus and left/right PFC have been observed in numerous neuroimaging investigations of novelty (Lepage et al., 1998; Habib et al., 2003) and were interpreted often as encoding/retrieval dissociations.

A new departure in our fMRI analysis was to assess how subsequent memory predictors in the brain interact with novelty. We first back-sorted novel and repeated scenes that appeared in the scanned encoding task using source memory data from the memory test (Brewer et al., 1998; Wagner et al., 1998). It is typical for recognition memory-based sorting to be used in such analyses, but just as our behavioral evidence indicates that source confusion prevents a fair comparison of recognition memory for novel and repeated items, this same evidence illustrates that misses do not have a consistent meaning across novel and familiar items in an fMRI study. Interactions between novelty and recognition memory-based subsequent memory observed using brain measures would be influenced by the same source confusion confound identified in our behavioral data. Whereas novel hits and misses would differ in terms of whether novel items were encoded, familiar hits and misses would differ in terms of whether source information was encoded. As a result of this issue, and because source information is considered an important attribute of episodic memory (Tulving, 1983), our source memory-based approach is fully consistent with the goal of our current investigation: to measure the neural underpinnings of successful episodic memory formation associated with novel versus familiar information.

We first conducted a conjunction analysis to identify regions that predicted memory independently of our novelty manipula-

tion (Fig. 3, Table 1). The regions matching this profile were primarily located in posterior neocortex and included bilateral occipital gyri, the right parietoccipital transition zone and bilateral parietal cortex. However, no MTL region predicted memory for both novel and repeated scenes.

We next computed an interaction contrast and searched for MTL regions in which novelty interacted with subsequent memory. We identified a greater subsequent memory effect for novel scenes in the right anterior hippocampus and right amygdala, and a greater subsequent memory effect for familiar scenes in bilateral posterior hippocampal regions (Fig. 4, Table 2). An ROI analysis of the subsequent memory effects in these regions revealed that the anterior hippocampus peak predicted memory for novel scenes (BSR = 2.33, $p < 0.05$), but did not predict memory for repeated ones (BSR = −1.11, $p > 0.25$). In contrast, while memory for repeated scenes was predicted by both the left posterior hippocampus (BSR = 3.70, $p < 0.001$) and right posterior hippocampus (BSR = 4.02, $p < 0.001$), memory for novel scenes was not predicted by either region (left BSR = −0.76, $p > 0.4$; right BSR = −1.365, $p > 0.15$). A *post hoc* test for a three-way interaction of region, novelty and subsequent memory revealed an effect between the right anterior and left posterior hippocampus, $F_{(1,12)} = 8.07$, $p < 0.05$, and a weak effect between the right anterior and right posterior hippocampus, $F_{(1,12)} = 4.48$, $p = 0.056$, but no effect between the left and right posterior hippocampus, $F_{(1,12)} = 0.37$, $p > 0.35$. No additional region predicted memory in the MTL. For descriptive purposes, full-brain subsequent memory effects for novel and repeated scenes are provided in supplemental Tables 2, 3, available at www.jneurosci.org as supplemental material.

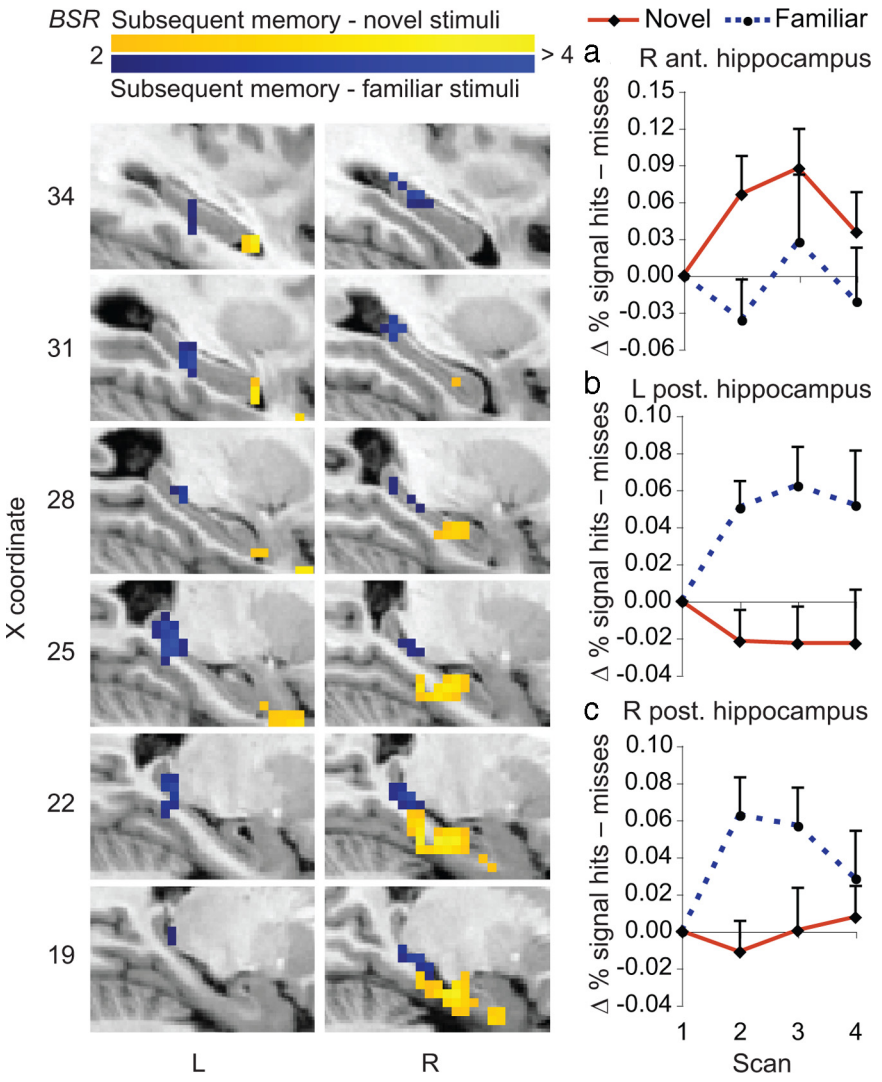

Figure 4. MTL subsequent memory interactions. A slice series is depicted moving medially in progression from top to bottom (both hemispheres; anterior = right), with functional activations overlaid on an MNI template brain. MTL regions predicting subsequent source memory for novel items seen for the first time during the study phase and repeated items seen three times before the study phase are plotted in yellow and blue, respectively. Activity during encoding in the right anterior hippocampus (***a***) predicted subsequent source memory (hits minus misses) for novel scenes only, whereas activity in the posterior hippocampi (***b*** and ***c***) predicted subsequent source memory for repeated scenes only (plots are shown +1 SEM).

Different connectivity of the anterior and posterior hippocampus could underlie this hippocampal double dissociation: the anterior hippocampus has been shown to have higher functional connectivity with the anterior and lateral temporal lobes, whereas the body and posterior aspects of the hippocampus has been shown to have higher functional connectivity with parietal cortex, posterior cingulate cortex and ventral PFC (Kahn et al., 2008). To confirm whether this same distinction in functional connectivity was observable in our data and related to the location of the hippocampal subsequent memory effects, we conducted a functional connectivity analysis seeded from anterior and posterior hippocampal subsequent memory regions. In this analysis, we calculated the within-subject correlation between activity in each seed and activity in the rest of the brain, then compared the correlations of the two seeds using a within-subject contrast. The pattern we observed was consistent with earlier findings: the anterior hippocampal novelty-encoding region preferentially correlated with anterior and lateral temporal lobe regions, as well as regions along the central sulcus, whereas the posterior hippocampal encoding regions correlated with inferior parietal cortex, visual cortex, posterior cingulate cortex as well as ventral and dorsolateral PFC (Fig. 5; supplemental Table 4, available at www.jneurosci.org as supplemental material online).

To determine how these differences in functional connectivity might contribute to memory encoding, we performed several ROI analyses, searching the precuneus and anterior temporal regions identified in the overall connectivity analysis described above for any small cluster of four or more voxels (64 mm^3) in which greater anterior or posterior hippocampal connectivity predicted subsequent memory success for novel or familiar items (at a threshold of BSR 1.96, approximately corresponding to a 95% confidence interval). Greater connectivity between the anterior hippocampal seed and a cluster in the right anterior temporal lobe predicted successful memory for novel scenes but not repeated ones, whereas greater connectivity between the posterior hippocampus and voxels in the left pre-

Table 2. Activated clusters in the interaction contrast of subsequent memory with novel and familiar pictures

Region	BA	Side	Peak MNI coordinates			Peak BSR	Spatial extent (mm^3)
			x	*Y*	*z*		
Novel subsequent memory > familiar subsequent memory							
Frontal lobe							
Inferior frontal g.	11/47	R	33	39	−9	5.74	459
Dorsolateral prefrontal ctx.	9	L	−39	36	33	4.73	648
Precentral g.	6	L	−45	6	42	6.80	1323
Temporal lobe							
Inferior temporal g.	20	R	36	−15	−36	3.50	1053
Parahippocampal g.	28/36	R					
Anterior hippocampus	—	R					
Inferior temporal g.	37	L	−48	−60	−27	4.95	729
Middle temporal g.	39	L	−36	−63	21	5.66	486
			−57	−75	21	3.97	486
Parietal lobe							
Parietoccipital transition zone	19	L	−39	−87	33	3.70	405
Occipital lobe							
Occipital g.	19	L	−45	−90	15	4.60	540
Familiar subsequent memory > novel subsequent memory							
Parietal lobe							
Postcentral g.	1	R	57	−21	54	−3.60	351
Temporal lobe							
Temporal pole	38	L	−39	21	−27	−6.73	1215
Posterior hippocampus	—	L	−24	−33	−3	−4.00	567
	—	R	33	−27	−6	−4.88	459
Limbic lobe							
Cingulate g.	24/32	R	15	18	36	−4.51	378

Regions were defined as any cluster with a minimum peak BSR of 3.5 ($p < 0.0005$) and an extent of at least 12 voxels (extent threshold was BSR 2.81 or $p < 0.005$). Peak coordinates are displayed in MNI space (Cocoso et al., 1997). BA, Brodmann's area; L, left; R, right; g., gyrus.

cuneus predicted successful memory for repeated scenes but not novel ones.

A different approach to evaluating the significance of the observed subsequent memory differences is to test the ability of large-scale functional connectivity networks to predict subsequent memory as a whole. To this end, we performed a series of *post hoc* non-rotated PLS contrasts, focusing on whether reliable differences in brain scores could be obtained for each contrast. We found no evidence of a shared anterior and posterior functional connectivity predicting subsequent memory, $p > 0.5$, nor did anterior hippocampal functional connectivity predict subsequent memory on its own, $p > 0.5$. Functional connectivity with the posterior hippocampus did predict memory, $p < 0.05$. In addition, a functional connectivity interaction between subsequent memory and novelty was found in the posterior hippocampus, $p < 0.05$, although no corresponding interaction was observed with anterior hippocampus functional connectivity, $p > 0.5$.

Returning to our signal intensity data, as a final step, we searched the interaction contrast map for stand-alone regions predicting memory outside of the MTL. At the cortical level, a majority of regions were found to have greater subsequent memory effects for novel scenes than for repeated ones (Fig. 6, Table 2). Regions that preferentially predicted memory for novel scenes included bilateral prefrontal and temporal regions as well as left posterior parietal cortex and the left occipital lobe. Regions that preferentially predicted memory for repeated scenes included right postcentral gyrus, the left temporal pole and the right cingulate gyrus.

Discussion

Our results support the view that recent past experiences in the form of repeated stimulus exposures can enhance the formation of new episodic memories, and also reveal regional specialization of novelty and familiarity encoding within the hippocampus. In so doing, our results do not support recent novelty-encoding proposals predicting encoding benefits to the extent that incoming information is novel (Tulving and Kroll, 1995; Borisyuk et al., 2001; Lisman and Grace, 2005). This prediction is clearly incongruent with superior source memory for repeated relative to novel scenes. While a novelty effect was replicated in recognition memory, this measure was likely confounded by source confusion (Kinsbourne and George, 1974; Dobbins et al., 1998).

With respect to our neuroimaging evidence, investigators have proposed that neural mechanisms filter out redundant information before it reaches encoding structures, allowing only novel information to pass (Tulving et al., 1996). Whereas such a process would entail a core encoding network that responds to information in a graded manner to the extent the information is novel, we observed large-scale interactions in the networks predicting encoding of novel and repeated scenes, involving constellations of MTL, temporal and frontal regions. Critically, in our exploration of encoding interactions, we noted a double dissociation of subsequent memory predictors for novel and repeated materials along the longitudinal axis of the hippocampus. While previous studies have implicated the hippocampus in both novelty detection and subsequent memory for novel items, no studies have tested for an interaction of the type we observed between novelty, hippocampal region and subsequent memory effects.

Behaviorally, memory was superior for repeated scenes once an important confound was addressed. Participants were more likely to recognize repeated scenes, but were also poorer at rejecting repeated lures presented during the encoding phase than novel lures, and recognition accuracy scores were superior for novel scenes as a result. This pattern has been observed numerous times and forms the basis for theoretical claims regarding superior memory for novel items (Tulving and Kroll, 1995; Kormi-

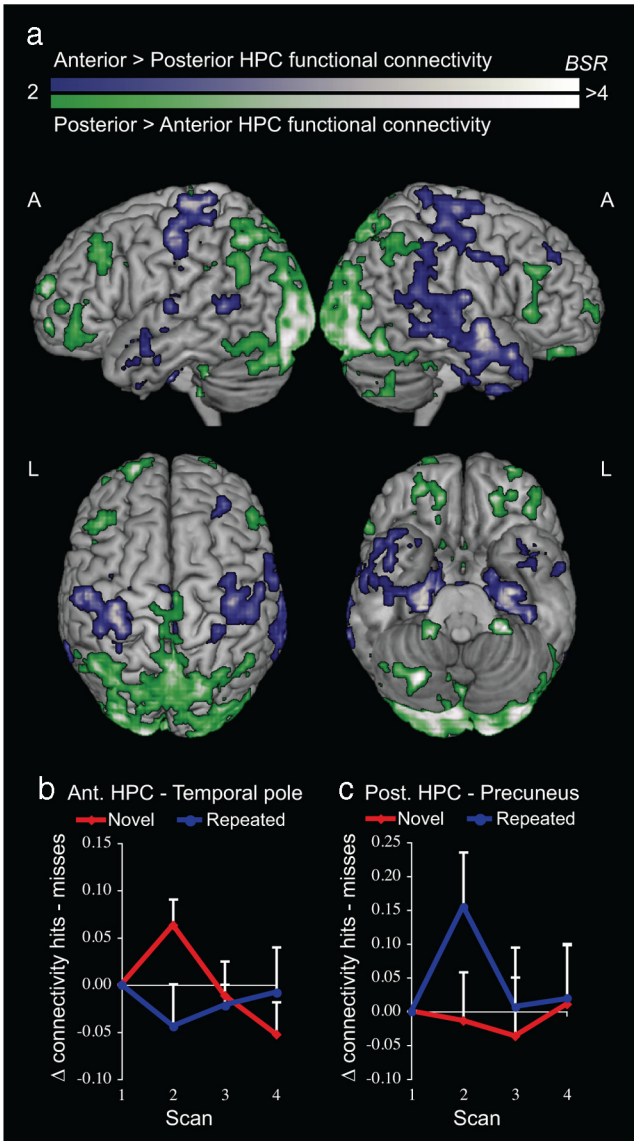

Figure 5. Anterior versus posterior hippocampal functional connectivity. Left, right, superior and inferior views of a 3D rendering comparing the functional connectivity associated with the anterior and posterior hippocampus (***a***). Regions more functionally connected to the anterior hippocampus are shown in violet; those more functionally connected to the posterior hippocampus are shown in green. The contrast is displayed on an MNI template brain. In the top row, middle is posterior; in the bottom row, middle is right. All clusters of 12 or more contiguous voxels surpassing a threshold of BSR 2.0 (approximately corresponding to a threshold of $p <$ 0.05) are displayed. Functional connectivity was greater between the right temporal pole and anterior versus posterior hippocampus, predicting source memory for novel but not repeated scenes (***b***). Functional connectivity was greater between the left precuneus and posterior versus anterior hippocampus, predicting source memory for repeated but not novel scenes (***c***).

Nouri et al., 2005). However, whereas a truly novel lure may be rejected by the absence of familiarity, it is only possible to reject a lure seen in multiple contexts on the basis of source information. As a result, recognition memory for novel and repeated items involves different memory constructs that are not appropriate to compare directly. When, instead, we measured source memory, thus requiring the same information for responses in the novel and repeated conditions, memory was superior for repeated scenes relative to novel ones. The fact that source memory showed this pattern, and recognition memory, the reverse, suggests earlier findings of novelty advantages based on recognition memory are related to the issue discussed here.

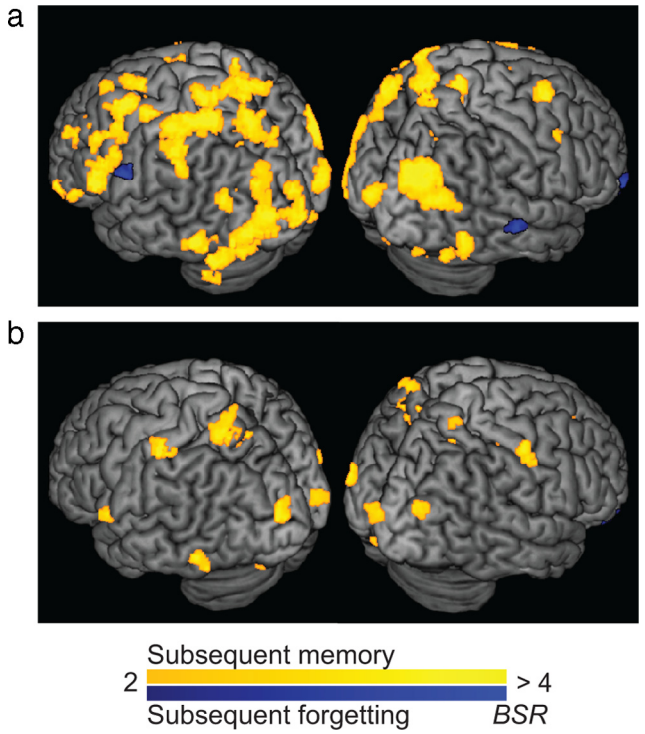

Figure 6. Subsequent source memory networks for novel and repeated scenes. Renderings depict brain activity during encoding that predicted subsequent source memory for novel scenes seen for the first time at encoding (***a***), and repeated scenes seen three times before encoding (***b***). Activations predicting later memory success are in yellow and activations predicting later memory failure are in blue. Regions supporting memory for novel scenes were greater in number and extent than those supporting memory for repeated scenes. All activations are displayed on an MNI template brain (posterior = middle). All clusters of 12 or more contiguous voxels surpassing a threshold of BSR 2.0 (approximately corresponding to a threshold of $p <$ 0.05) are displayed.

At the brain level, an overall contrast of novel and repeated scenes revealed regions similar to those reported in other neuroimaging investigations of repetition and novelty (Schacter et al., 2007), serving as a manipulation check. Of particular note, we observed a greater response to novel scenes in the right anterior hippocampus and a greater response to repeated scenes in posterior hippocampi. This general pattern has been observed in a meta-analysis of similar studies (Lepage et al., 1998).

Our unique approach was to search for interactions in encoding mechanisms for novel and repeated materials. Researchers have previously identified novelty-sensitive hippocampal regions that also predict memory for novel materials (Kirchhoff et al., 2000). Similarly, in the current study, we found that the right anterior hippocampus was both sensitive to novelty and predictive of subsequent source memory for novel scenes. However, activity in the region did not distinguish hits from misses in the repeated condition, suggesting that the right anterior hippocampus contributed to memory encoding only when materials were novel. We also observed posterior hippocampal regions that showed the opposite pattern of activity, responding more to repeated scenes than novel ones, and predicting subsequent memory for repeated scenes only. This new evidence suggests that while some hippocampal regions do appear to be specialized in processing novel materials, this sensitivity is not a general feature of the MTL encoding system, which also includes other hippocampal regions specialized in working with information that is familiar.

Concerning the specific topography of the observed hippocampal responses, our evidence appears to complement an emerging understanding of functional organization along the long axis of the hippocampus. Numerous studies have linked the anterior hippocampus with acquisition and assimilation of new memories, and the posterior hippocampus with the retrieval of old ones (Lepage et al., 1998; Maguire et al., 2006; Berlingeri et al., 2008), with remote memories engaging more posterior aspects than relatively recent ones (Gilboa et al., 2004). In an apparent contradiction of this pattern, encoding-specific activation has been shown to occur along the entire hippocampal axis (Schacter and Wagner, 1999), much as activity in both anterior and posterior hippocampus predicted encoding success under different conditions in the current study. However, the encoding of repeated materials likely involves an element of retrieval resulting from previous exposures to the materials. Along these lines, the current results suggest that encoding operations that involve episodic retrieval fall more posteriorly in the hippocampus than those that do not.

Functional connectivity differences between anterior and posterior hippocampus could help explain this difference in organization. We found that activity in the posterior hippocampal encoding regions was more correlated with inferior parietal cortex, precuneus, ventral PFC and dorsolateral PFC than was activity in the anterior region. Similar configurations have attracted interest as a "default network" that has been linked with autobiographical memory retrieval (Svoboda et al., 2006; Buckner et al., 2008). In contrast, anterior hippocampus activity primarily correlated with anterior and lateral temporal lobes, which are better known for their central role in semantic processing (Vandenberghe et al., 2002; Rogers et al., 2006). These connectivity findings confirm earlier observations regarding intrinsic functional connectivity differences between anterior and posterior hippocampus (Kahn et al., 2008) and directly link these differences to the hippocampal memory-encoding regions observed in the current study. Our findings also hint at a possible functional role for these local variations in functional connectivity, since posterior hippocampal connectivity with the precuneus predicted memory for repeated, but not novel, scenes, whereas anterior hippocampal connectivity with the right anterior temporal lobe predicted memory for novel, but not repeated scenes.

Some overlap in the networks predicting successful memory formation for novel and repeated scenes was observed. This overlap occurred primarily in posterior neocortex and included bilateral occipital gyri, the right parietoccipital transition zone and bilateral parietal cortex. These regions have been associated with the integration of visual and motor information in the dorsal visual pathway (Goodale and Westwood, 2004) and their contribution to memory could be related to our requirement that participants imagine actions in visually presented scenes during encoding. Interestingly, many cortical subsequent memory responses were attenuated for repeated scenes relative to novel ones, despite our finding that source memory is superior for repeated items. However, greater brain responses do not always predict better memory (Daselaar et al., 2004; Miller et al., 2008). One possible explanation for the link between signal attenuation and better memory for repeated scenes is that repetition increased cortical processing efficiency—and subsequent memory—by reducing the requirement for a basic parsing of the scenes.

It is interesting to consider what differences in novelty and familiarity processing led to the observed familiarity memory advantage and double dissociation of hippocampal subsequent memory responses. The current study was not ideally suited for answering such a question, as our main objective was to determine whether there exist any novelty-based differences in the brain basis of subsequent memory. Laboratory testing with a group of 14 undergraduate students revealed no hint of novelty-based differences in the vividness of mental imagery generated during our encoding task, but other candidate mechanisms remain, such as possible differences in levels of item memory associated with novel and familiar items. That said, the current findings are not undermined by want of a deeper, underlying cause. Regardless of the underlying cause of the novelty-based dissociations observed in the current study, the reported phenomena are of intrinsic interest and pose a challenge for existing notions of the role of novelty in memory formation. Efforts directed at exploring underlying causes will be a worthwhile goal for future research.

To summarize, when controlling for confounds that often emerge in memory tests for novel and repeated materials, we observed superior memory for repeated, relative to novel, scenes. At the brain level, this memory benefit was associated with unique predictors of memory formation for repeated scenes. In the MTL, right anterior hippocampus predicted memory for novel scenes only, whereas posterior hippocampi predicted memory for repeated scenes only. Importantly, we found that the anterior region was functionally connected with the lateral and anterior temporal lobes, whereas the posterior regions were functionally connected with regions comprising the "default network". As these differences in connectivity were linked with novelty and familiarity-specific encoding effects, they could help explain the location of novelty- and repetition-sensitive regions of the hippocampus. We conclude that memory representations established though past exposures to materials are not used to filter out information, as has been suggested in recent proposals (e.g., Tulving et al., 1996), but are instead used to support new encoding, in line with influential views of memory encoding emphasizing the role of prior representations in memory formation (Ebbinghaus, 1913; Nadel and Moscovitch, 1997). More generally, our findings suggest that human memory as it typically operates—in environments with which both novel and familiar people, places and things abound—can be better understood by investigating, at a behavioral and neural level, how new and old memories interact.

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