HIPPOCAMPUS 19:265–272 (2009)

The Neural Correlates of Recollection: Hippocampal Activation Declines as Episodic Memory Fades

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ABSTRACT: Memories for certain events tend to linger in rich, vivid detail, and retrieval of these memories includes a sense of re-experiencing the details of the event. Most events, however, are not retained in any detailed way for more than a few days. According to one theory, the hippocampus plays a specific role in supporting episodic retrieval, that is, the re-experiencing of an event as part of one's personal past. This theory predicts that as episodic memories fade over time and are reduced to feelings of familiarity, activity in the hippocampus should no longer be associated with retrieval. We used high-resolution functional imaging to explore neural activity in medial temporal lobe subregions while participants performed a recognition task at both a short (10-min) and long (1-week) study-test delay. For each recognized item, subjects made "Remember/Know" judgments, allowing us to distinguish between items that were consistently episodic across the two tests and items that were initially episodic, but later became merely familiar. Our results demonstrate that activity in the subiculum is specifically associated with episodic recollection. Overall, recollected items were associated with higher activity in the subiculum than other items. For transiently recollected items, there was a decrease in subicular activity across the 1-week delay as memory faded from recollection to familiarity, whereas consistently recollected items were associated with enhanced subicular activity at both delays. These results provide evidence of a link between subicular activation and recollective experience. © **2008 Wiley-Liss, Inc.**

KEY WORDS: fMRI; subiculum; parahippocampal cortex; remember/know; forgetting

INTRODUCTION

Memories may be recollected as events from one's personal past, accompanied by contextual information and incidental details from the learning episode. Alternatively, recognition may be based on feelings of familiarity, with no accompanying recollection of the episode in which the memory was formed (Tulving, 1985). Several lines of evidence suggest that these different types of memory retrieval depend on different substrates in the medial temporal lobe (MTL).

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Grant sponsors: NIH (to B.J.K.); Sigma Xi (to I.V.V.); Natural Sciences and Engineering Research Council of Canada (Julie-Payette Research Scholarship to I.V.V.).
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Accepted for publication 12 August 2008
DOI 10.1002/hipo.20503
Published online 1 October 2008 in Wiley InterScience (www.interscience.wiley.com).

Patients with selective hippocampal damage have been reported to exhibit deficits in episodic memory, with familiarity-based recognition largely intact (Vargha-Khadem et al., 1997; Yonelinas et al., 2002; Holdstock et al., 2005). Functional magnetic resonance imaging (fMRI) data have also shown that hippocampal activity is associated with the retrieval of episodic memories but not feelings of familiarity (Eldridge et al., 2000; Yonelinas et al., 2005; Daselaar et al., 2006; Suchan et al., 2008), and that subicular activity in particular is associated with episodic retrieval (Eldridge et al., 2005).

Support for a selective role of the hippocampus in episodic recollection is not unequivocal, however. Deficits in recognition based on familiarity have also been reported in patients with hippocampal lesions, suggesting that the hippocampus may support both episodic and familiarity-based recognition (Wixted and Squire, 2004; Wais et al., 2006). One difficulty in interpreting these data is that the hippocampus appears to play a role in both memory encoding and retrieval. Thus, recognition deficits in these patients may be due to impairments in learning as well as retrieval.

Here, we test the relationship between episodic recollection and hippocampal activity by examining activation in the MTL when subjects perform a recognition test after a short and long delay. Previous work has shown that many items recollected at a short delay are merely familiar after 1 week (Knowlton and Squire, 1995). If activity in the hippocampus selectively supports episodic recollection, then this activation should decline as episodic memories fade. Those items that are consistently recollected should be accompanied by hippocampal activation at both the short and long delays. Items that are initially recollected but later become familiar should be accompanied by hippocampal activity only at the short delay; at the long delay, these items should show low levels of activation equivalent to that of forgotten items. Alternatively, if hippocampal activation for these items remains elevated, this would argue against the idea that the hippocampus plays a specific role in episodic memory, and instead may support both recollection and familiarity. In addition to providing a strong test of the hypothesis that hippocampal activation is associated with episodic recollection, our use of high-resolution neuroimaging techniques allows us to measure

activity in all of the hippocampal subregions during recognition, providing further clarification of the involvement of these regions in declarative memory processes. It should be noted, however, that use of these techniques limits our ability to measure activity in regions outside the MTL, such as the prefrontal and parietal cortices, which have also been shown to be involved in episodic recollection (Dobbins and Wagner, 2005; Cabeza, 2008).

MATERIALS AND METHODS

Participants

Twelve healthy individuals (six females) participated in this study. All but one were right-handed. Participants were fluent English speakers and between 25 and 30 years old (mean = 27.9 ± 2.15). The study was approved by the UCLA Office for Protection of Research Participants.

Materials

Encoding stimuli consisted of 150 unrelated object pairs (Snodgrass and Vanderwart, 1980) with corresponding object names printed below. Pairs were presented either horizontally or vertically, and the first or "cue" object was presented in one of four colors: blue, yellow, pink, or green, while the other was always black and white. Pairs were counterbalanced such that each orientation and color appeared with the same frequency (Fig. 1).

Two retrieval tests were performed—one 10 min after encoding and another 1 week later. Retrieval test stimuli consisted of 150 words corresponding to cue items from the encoding session, and 78 lure words. Unique lures were used for each retrieval session. Cues and lures were counterbalanced across subjects such that 50 of the lures presented to half the subjects served as study items for the other half.

Procedure

During the encoding phase, participants viewed each object pair for 6 s and were instructed to imagine the objects interacting and to remember the details of each display. During the two recognition tests, participants indicated whether memories were episodic using a two-step "Remember/Know" procedure. Subjects first indicated whether an item was previously studied or new (3 s) and were then asked to make a Remember/Know judgment (3 s). If subjects remembered the moment during which they had studied the item, they gave it an "R" response. If, however, they confidently recognized an item in the absence of recollection, they gave it a "K" response. Prior to the experiment, participants were asked to define "Remember" and "Know" in their own words and to offer an example of each.

Following the second retrieval session, participants completed a post-test evaluating their memories for details of the encoding episode. Participants were presented with all 150 cue words, and were prompted to indicate the relative position of the picture pairs during encoding, the color of the cue object, and the object with which each cue item was paired.

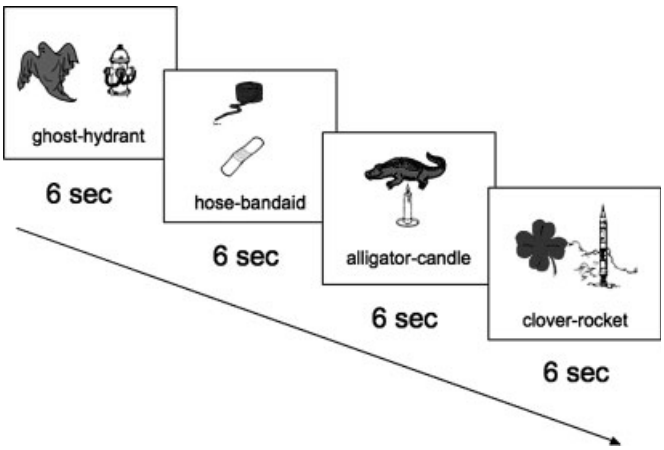

FIGURE 1. Encoding paradigm. Object pairs differed in color and orientation on screen, and subjects were instructed to imagine items within a pair interacting with one another.

Trial Distribution and Baseline Task

Each retrieval session included six runs consisting of 25 target trials, 13 lure trials, and 12 baseline trials each. Trial order was determined using a genetic algorithm (Wager and Nichols, 2003) to maximize the detection of amplitude differences across conditions.

Because the MTL is particularly active during passive rest trials, there is often more activity associated with fixation than with a non-mnemonic baseline task. This spontaneous activity can reduce or eliminate the ability to detect changes in hippocampal activity that correlate with the task of interest. To reduce this interfering effect of spontaneous thought, the baseline task used in the present study was the odd/even digit task, which minimizes hippocampal activity in comparison to fixation (Stark and Squire, 2001). In this task, participants saw a series of single digits presented for 600 msec each (total trial length 6 s) and were asked to make an odd/even judgment.

Data Acquisition and Preprocessing

Structural and functional imaging were performed with a 3T Siemens Allegra scanner using an event-related, rapid presentation design. Structural images included (1) sagittal localizer images to identify the long axis of the hippocampus, (2) high-resolution T2 hippocampal images perpendicular to the long axis of the hippocampus (TR = 4 s, TE = 105 msec, 18 slices, voxel size $0.4 \times 0.4 \times 3$ mm^3, 20 cm FOV), (3) high-resolution gradient echo EPI sequences coplanar with the functional images (TR = 5 s, TE = 66 msec, 18 slices, voxel size $1.6 \times 1.6 \times 3$ mm^3, 20 cm FOV), to aid in alignment of the high resolution structural and functional images, and (4) an MP-RAGE (TR = 2.3 s, TE = 2.93 msec) for future volumetric analyses. For functional imaging of the MTL, high-resolution gradient echo EPI sequences

TABLE 1.

Response Conditions Across the Short and Long Delay

Ten-minute	One-week	Response condition	Percentage of trials
R	R	RR: consistently episodic	18.06 ± 2.09
R	K	RK: initially episodic, later familiar	20.67 ± 1.82
K	K	KK: consistently familiar	12.22 ± 2.09
M	M	MM: consistently missed	10.61 ± 2.38

Percentage of each response condition comprising the total number of trials ± the standard error of the mean.
R: remember; K: know; M: miss.

were used, consisting of 18 slices perpendicular to the long axis of the hippocampus (TR = 3 s, TE = 39 msec, voxel size 1.6 × 1.6 × 3 mm^3, 20 cm FOV).

Preprocessing was performed using the FSL toolbox (www.fmrib.ox.ac.uk/fsl). Skulls were stripped using the Brain Extraction Tool (Smith, 2002), and functional images were realigned using McFLIRT to compensate for small head movement (Jenkinson et al., 2002). For participants with translational motion over 1 mm, images were denoised using MELODIC (Beckmann and Smith, 2004); however, no subjects showed motion greater than 2 mm. Data were filtered with a high-pass cutoff of 75 s, and were not smoothed given the small size of MTL subregions.

Response Classification

Participants' responses from each of the two retrieval tests were classified as either remember (R), know (K), miss (M), correct rejection (CR), or false alarm. Because the same cue items were used for both retrieval sessions, we were able to track participants' memory for the same item at the 10-min and 1-week retrieval tests. This enabled us to compare activity related to item memories in the following response conditions: those that were consistently episodic (RR), those that were initially episodic but later faded to familiarity (RK), those that were consistently familiar (KK), those that were consistently unrecognized (missed; MM), and correctly rejected items (Table 1). Participant responses led to several other conditions, which were not included in our analyses due to very low trial numbers (RM, KR, KM, MR, MK); false alarms were not included for the same reason.

Regions of Interest and Timecourse Analyses

Regions of interest (ROIs) were created for each individual participant (Fig. 2). Anatomical landmarks that were visible on each participant's high-resolution structural scan were used to delineate subregional boundaries. In the hippocampal formation, ROIs were created for the CA1 field, the CA2/3 fields and dentate gyrus (DG), and the subiculum. The CA2/3 fields and the DG were not separable and therefore were collapsed into a single ROI. Cortical ROIs surrounding the hippocampus included the entorhinal cortex (EC) and a combined parahippocampal–perirhinal ROI. All boundaries were defined using an anatomical atlas in the coronal plane (Duvernoy, 1998) and specifications as delineated by Amaral and Insausti (1990). Furthermore, because susceptibility artifacts may be seen in the anterior regions of the MTL during EPI sequences, areas that were not visible in the functional scans were not included in the ROI analysis (Zeineh et al., 2000). All ROIs were prepared by the same observer (I.V.V.) to maintain consistency.

Group timecourses were created using the summary statistics approach to the mixed effects model. First, timecourses for each condition were extracted from each ROI in each participant using a finite impulse response model. The design matrix in this model contained entries for each response condition such that the duration of experimental trials lasted from stimulus onset until participant response for the R/K judgment; the remaining time from response until removal of the stimulus from the screen was left unmodeled. The design matrix also contained entries for baseline task trials. We estimated the underlying hemodynamic response for each trial type by averaging the signal at 3-s bins beginning 3 s prior to stimulus onset and ending 12 s after stimulus onset. For a given condition and subject, weighted least squares was used to combine activation across the six runs in each retrieval session. The timecourses generated by the baseline task were subtracted from all trial types, yielding a "difference from baseline" timecourse. Finally, timecourses across all participants were averaged for each ROI.

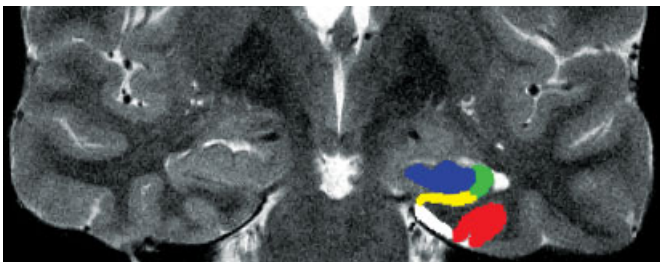

FIGURE 2. Regions of interest in a sample slice (anterior). Regions delineated in the left hemisphere only so as to allow viewing of underlying anatomy. Red: combined parahippocampal–perirhinal cortices; white: EC; yellow: subiculum; green: CA1; blue: combined areas CA 2, 3, and the denate gyrus.

Statistical analyses were based on the amplitude of each response type during the peak of the timecourse in each ROI. Within the 15-s timecourse, the specific time point used for statistical analysis was selected as the 3-s bin that contained the greatest positive deviation from baseline in the group data, regardless of response type. Because the hemodynamic response may vary over testing sessions, peaks were determined separately for each of the two retrieval sessions. In this way, we were able to avoid scenarios in which changes in hippocampal activity across the 1-week delay were due to shifts in hemodynamic response shape, rather than changes in response amplitude.

Amplitude data for each subject were normalized by dividing the amplitude of all responses by the amplitude of the response type with the greatest amplitude; this rescaled the maximum response to a value of one. The normalization decreased intersubject variability, establishing the reliability of some trends in the non-normalized data, but did not change the overall pattern of results.

Amplitude data from each retrieval session for each ROI were analyzed using a repeated measures analysis of variance (ANOVA) to compare activity associated with nonbaseline response types. Planned comparisons were conducted using paired, two-tailed *t* tests (uncorrected). Finally, to directly test the hypothesis that loss of episodic content across the delay would result in decreased hippocampal activation, we evaluated the interaction of response type (RR vs. RK) and delay length (short vs. long) using a two-way ANOVA for each ROI.

RESULTS

Behavioral Results

Participants accurately identified studied items during both retrieval tests. The hit rate for the 10-min test was 76.83 ± 2.76% (standard error of the mean), with a false alarm rate of 16.45 ± 3.88%. Overall hit rate for the 1-week test was 65.44 ± 2.97%, with a false alarm rate of 28.74 ± 4.19%. As intended, the 1-week delay caused some memories to fade; sorting hits into R and K responses, results show that participants' R rates decreased over the week delay, whereas K rates increased (Fig. 3). In both tests, R responses were more accurate than K responses. False alarm rates were lower for R than for K items [10-min: $t(11) = 4.179$, $P = 0.0015$; 1-week: $t(11) = 6.527$, $P < 0.0001$]. False alarm rates for K items were significantly higher after the long delay than after the short delay ($P < 0.01$), but were not different across delays for R items.

The post-test revealed differences in the number of episodic details retrieved depending on response condition. KK items were more likely to co-occur with the retrieval of zero correct details than RR items [$t(11) = 2.479$, $P = 0.032$]. KK items also showed fewer average details recalled than RR items [$t(11) = 2.363$, $P = 0.038$], while the number of details accompanying RK items did not differ either from RR ($P > 0.2$) or KK ($P > 0.1$). Finally, the number of KK items accompanied by 0, 1, or 2+ details was not different from the number expected by guessing alone (Ps > 0.4).

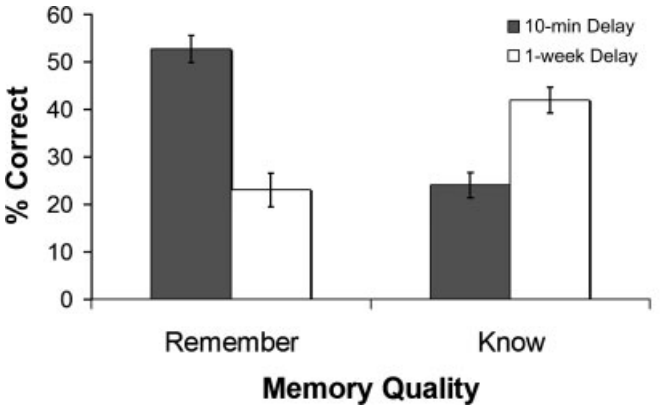

FIGURE 3. Behavioral results from the short (10-min) and long (1-week) delay recognition tests. Over the 1-week delay, the proportion of Remember responses decreased, whereas Know responses increased.

fMRI Results

For the 10-min retrieval session, a 2 (hemisphere) × 5 (response condition) repeated measures ANOVA for peak amplitude in each ROI revealed no significant main effects of hemisphere (Ps > 0.1), as well as no significant interactions between hemisphere and response type (Ps > 0.2). For the 1-week retrieval session, these analyses revealed no significant main effects of hemisphere ($P > 0.3$ in all cases) in all but one ROI [parahippocampal–perirhinal cortices, $F(1, 11) = 16.391$, $P < 0.002$]. However, no significant interactions between hemisphere and response type were found for any ROI ($P > 0.08$ in all cases). Thus, peak amplitude data in subsequent analyses were collapsed across hemispheres.

Short-Delay Retrieval Session

Hippocampal formation

Consistent with prior work, responses in the subiculum were greatest for recollected items (Fig. 4). In this region, only RR [$t(11) = 3.306$, $P = 0.007$] and RK trials [$t(11) = 2.272$, $P = 0.044$] were associated with greater peak amplitude than baseline trials. An ANOVA revealed a significant main effect of response type [$F(4, 44) = 3.504$, $P = 0.014$], and planned two-tailed paired *t* tests showed that this effect was due to greater R responses. RR items exhibited greater peak amplitude than both KK items [$t(11) = 3.753$, $P = 0.003$] and MM items [$t(11) = 3.066$, $P = 0.011$]. For RK items, there was a strong trend toward greater peak amplitude than KK items [$t(11) = 2.182$, $P = 0.052$]. There was also a trend for RK peak amplitude to be greater than that associated with MM items [$t(11) = 1.978$, $P = 0.074$]. No significant differences were found between RR and RK items ($P > 0.45$), or between KK and MM items ($P > 0.66$). In sum, in the subiculum, only the items associated with recollection (RR and RK) showed activation above a non-mnemonic baseline at the short delay. Activation levels associated with forgotten and merely familiar items

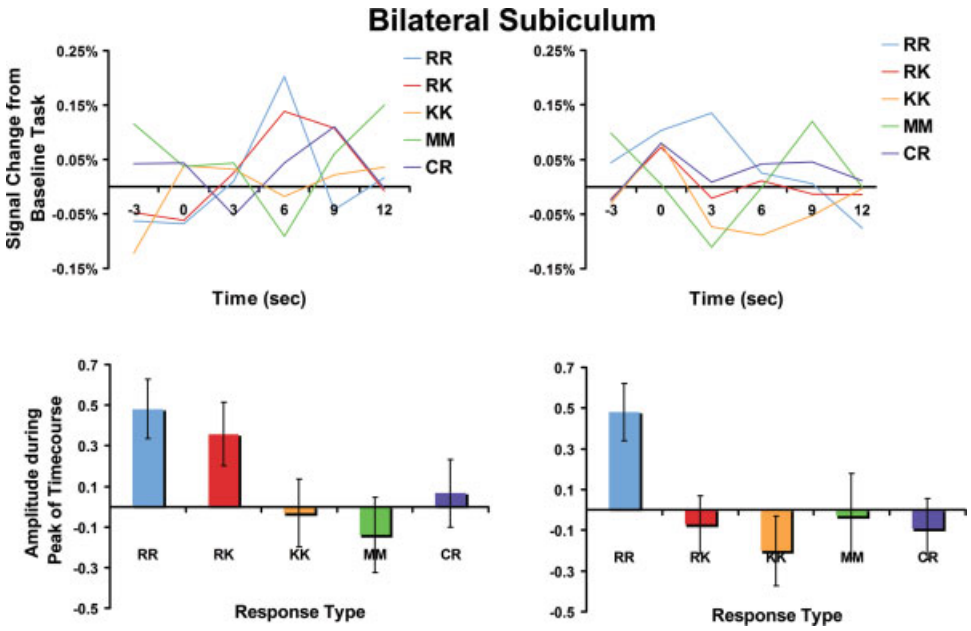

FIGURE 4. Short- and long-delay activation in the subiculum. Timecourses represent percent signal change from baseline, and bar graphs represent the normalized peak amplitude of each timecourse.

(MM and KK) were lower than that associated with recollection and were not reliably distinguishable from baseline levels.

The CA fields and DG showed a different pattern of results, with greatest peak amplitude associated with novel or missed items. In CA1, only CR items showed greater activation than baseline [$t(11) = 3.565$, $P = 0.004$]. An ANOVA revealed a trend toward significance for main effect of trial type in this area [$F(4, 44) = 2.496$, $P = 0.056$], such that CR items were associated with significantly greater activity than KK items [$t(11) = 2.219$, $P = 0.048$]. MM items also showed a strong trend toward displaying greater activity than KK items [$t(11) = 2.102$, $P = 0.059$]. In CA23/DG, both CR and MM items

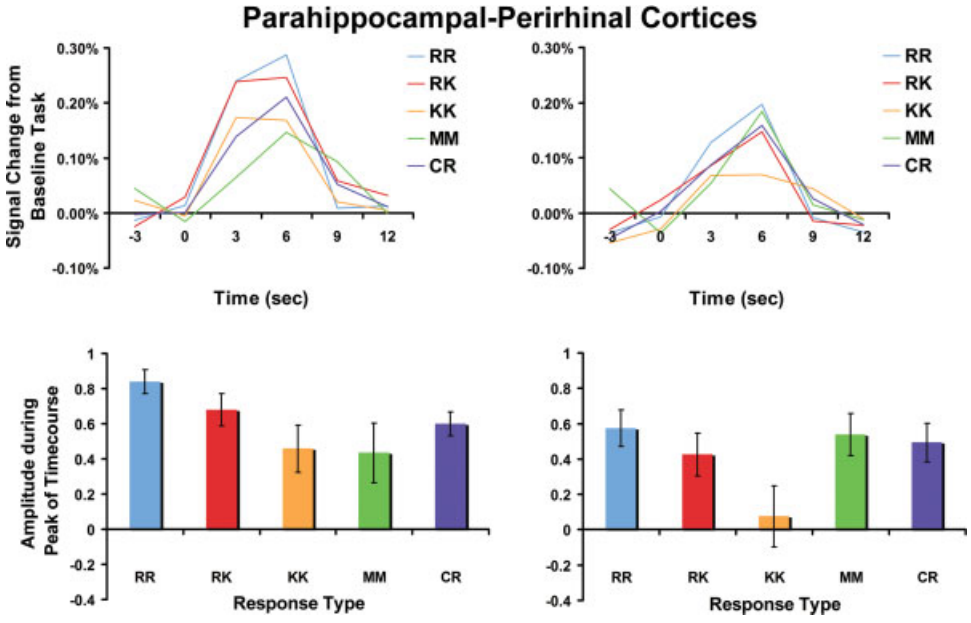

FIGURE 5. Short- and long-delay activation in the parahippocampal-perirhinal cortices. Timecourses represent percent signal change from baseline, and bar graphs represent the normalized peak amplitude of each timecourse.

showed greater activation than baseline [CR: $t(11) = 3.563$, $P = 0.004$; MM: $t(11) = 4.118$, $P = 0.002$], but an ANOVA revealed no main effect of trial type ($P > 0.33$).

MTL cortex

The parahippocampal–perirhinal cortices showed greatest activity for RR trials (Fig. 5). In this ROI, all response types were significantly above baseline levels of activation [RR, $t(11) = 12.325$, $P < 0.0001$; RK, $t(11) = 7.381$, $P < 0.0001$; KK, $t(11) = 3.375$, $P = 0.006$; MM, $t(11) = 2.559$, $P = 0.027$; CR, $t(11) = 8.783$, $P < 0.0001$]. An ANOVA revealed a strong trend toward significance for main effect of response condition [$F(4, 44) = 2.464$, $P = 0.059$]. Planned comparisons showed that RR items were associated with greater activation than both KK [$t(11) = 2.540$, $P = 0.027$] and CR items [$t(11) = 2.353$, $P = 0.038$], with a trend toward greater activation than MM items [$t(11) = 2.144$, $P = 0.055$].

In contrast, in the EC, no response types showed activation significantly different from baseline ($P > 0.1$ in all cases), and an ANOVA revealed no main effect of trial type ($P > 0.45$).

Long-Delay Retrieval Session

When calculating peak amplitudes for the long-delay session, we noted that these peaks occurred earlier in two subregions than in the short-delay session. In the subiculum, the peak at the short delay occurred within the 6 s bin, while at the long delay, the peak shifted to the 3 s bin. Area CA1 exhibited a similar shift from the 9 s bin to the 6 s bin. It is possible that neural activation during a repeated test is faster than that in the initial test due to retrieval practice. Alternatively, it is possible that these shifts simply resulted from coarse temporal sampling combined with a low signal-to-noise (S/N) ratio, common in MTL fMRI activation.

Hippocampal formation

In the subiculum, only RR items were associated with peak amplitude above baseline [$t(11) = 3.395$, $P = 0.006$] (Fig. 4). An ANOVA revealed a significant main effect of trial type [$F(4, 44) = 3.013$, $P = 0.028$], which the planned comparisons showed was due to greater activity in RR trials. These items showed greater peak amplitude than RK [$t(11) = 2.908$, $P = 0.014$], KK [$t(11) = 3.472$, $P = 0.005$], MM [$t(11) = 2.773$, $P = 0.018$], and CR items [$t(11) = 2.997$, $P = 0.012$]. No significant differences were found between RK and KK items ($P > 0.48$), RK and MM items ($P > 0.87$), or KK and MM items ($P > 0.56$). Thus, at the long delay, above-baseline activation in the subiculum was only obtained during recollection. Items that had been previously recollected but were now merely familiar were associated with reliable reduced activation that fell to levels similar to that associated with forgotten items and baseline levels of activation. Given that RR items were associated with activity elevated above baseline at −3 and 0 s, we conducted a simple linear regression, which controlled for repeated measures and found that the BOLD signal for RR items showed a linear trend by increasing in amplitude from −3 to 0 to 3 s ($P < 0.05$). Thus, it is unlikely that the differences found between RR, KK, and MM items were simply due to noise at 3 s.

In CA1, no response condition showed activity significantly above baseline. However, an ANOVA revealed a main effect of condition [$F(4, 44) = 3.510$, $P = 0.014$]. Planned comparisons showed that MM items were associated with greater activity than both RK [$t(11) = 2.63$, $P = 0.023$] and KK items [$t(11) = 2.7$, $P = 0.021$]. Additionally, RR items were associated with greater activation than KK items [$t(11) = 2.344$, $P = 0.039$]. In area CA23/DG, both CR [$t(11) = 3.754$, $P = 0.003$] and MM items [$t(11) = 2.347$, $P = 0.039$] showed activation significantly above baseline. An ANOVA for CA23/DG revealed no main effect of trial type ($P > 0.29$).

MTL cortex

In the parahippocampal–perirhinal cortices, RR [$t(11) = 5.611$, $P < 0.0001$], RK [$t(11) = 3.495$, $P = 0.005$], MM [$t(11) = 4.518$, $P < 0.001$], and CR items [$t(11) = 4.557$, $P < 0.001$] were each associated with peak amplitude significantly above baseline (Fig. 5). An ANOVA revealed a main effect of response condition [$F(4, 44) = 2.914$, $P = 0.032$]. Planned comparisons showed that RR items were associated with greater activation than KK items [$t(11) = 3.396$, $P = 0.006$], with RK items showing a trend toward greater activity than KK items [$t(11) = 2.048$, $P = 0.065$]. Additionally, CR items showed greater activity than KK items [$t(11) = 2.22$, $P = 0.048$]. In the EC, no response conditions showed activation different from baseline (Ps > 0.1), and an ANOVA revealed no main effect of response condition ($P > 0.62$).

Short versus long delay

To directly test the hypothesis that the loss of episodic content is associated with a corresponding loss of hippocampal activity, we examined the interaction between delay length (short vs. long) and response type (RR vs. RK) within each MTL subregion. An ANOVA for subiculum revealed a significant interaction between delay and response type [$F(1, 11) = 9.056$, $P = 0.012$], such that activity associated with RR items remained stable over the delay, whereas that associated with RK items decreased (Fig. 6). There were no other significant interactions between delay and response type in any other MTL region, suggesting that the pattern of activation for the different response types was similar in all other regions at the two retrieval tests.

DISCUSSION

These data support the view that neural activation in the hippocampus plays a role in the experience of recollection. Our study confirms prior research showing that successful retrieval of episodic memories results in significantly greater activation in the hippocampus—in particular the subiculum—than did recognition accompanied by feelings of familiarity. Familiarity-

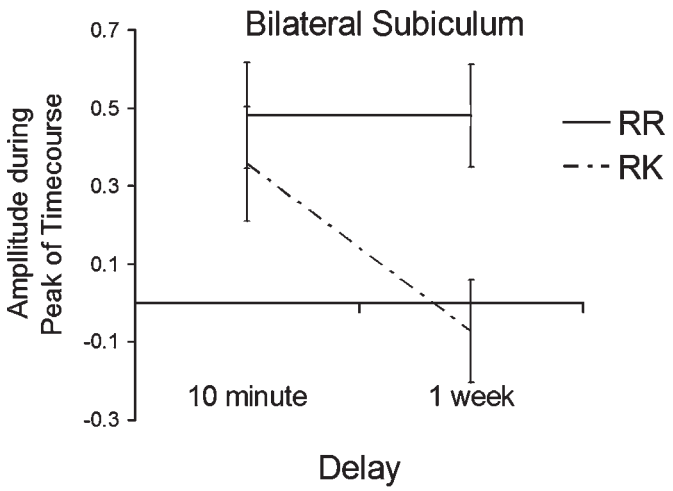

FIGURE 6. Interaction between delay-length and response type in the subiculum. Over the 1-week delay, activity associated with RR items remained elevated, whereas activity associated with RK items was initially equivalent to that of RR items, but later declined to baseline levels of activation.

based recognition did not result in hippocampal activation above that associated with missed items.

More critically, our results show that as a memory loses its episodic quality over time, retrieval-related activity in the hippocampus is lost. For RK items, there was elevated activity in the subiculum at the short delay as items were recollected, but later, when these same items were merely familiar, activity in the subiculum was similar to that associated with consistently familiar (KK) and missed items (MM). These results provide compelling evidence that neural activity in the subiculum is specifically associated with episodic retrieval, since the shift from episodic to familiarity-based memory over time is accompanied by a loss of retrieval activity in the subiculum.

In other hippocampal subregions, we found that the greatest activity was often associated with novel or missed items. One possibility is that this activity reflects pattern separation (Treves and Rolls, 1994), whereby new representations are formed in memory. In our study, activity in CA23/DG was most consistent with pattern separation, a finding that is consistent with data from single-unit studies (Leutgeb et al., 2007).

Several theoretical models (Aggleton and Brown, 1999; Norman and O'Reilly, 2003) suggest that MTL cortex alone can support familiarity, while the hippocampus is necessary for recollection, and a growing body of neuroimaging and neuropsychological studies now supports this idea (Gilboa et al., 2006; Diana et al., 2007). In a recent fMRI study, significant hippocampal activity during recollection compared to correctly rejected items was seen at all delays tested, including 6 weeks, while no significant hippocampal activity was found comparing familiarity responses with correct rejections (Suchan et al., 2008). The present study is consistent with these findings in that hippocampal activity was associated with recollection at both the immediate and the delayed test. The use of high-resolution fMRI in the present study allowed us to specifically localize the signal to the subiculum.

Furthermore, our design allowed us to assess the change in BOLD signal in the subiculum for those items initially recollected and later merely familiar. Activation associated with these items at the long delay was similar to that of missed items. Results showing that subicular activation tracked whether or not the same items were accompanied by episodic memory demonstrate that characteristics of the items per se were not driving the response. Rather, the response in the subiculum appears to be strongly associated with subjects' recollective experience.

The present results showed a pattern of activation in the parahippocampal–perirhinal cortices that differed from that seen in the subiculum. fMRI studies of MTL cortex have identified regions in the parahippocampal cortex that show both parametric decreases and increases in activation with increasing familiarity (Daselaar et al., 2006; Montaldi et al., 2006; Suchan et al., 2008). In the present results, the parahippocampal–perirhinal cortices exhibited activity greater than baseline for recollected, familiar, missed, and correctly rejected items, suggesting that these areas may play a role in recollection, familiarity, and memory encoding. In contrast, in the subiculum, only episodic retrieval generated activity that was significantly greater than the non-mnemonic baseline at both short and long delays. This pattern may reflect a role for the hippocampus in qualitative distinctions in memorial experience, while the parahippocampal and perirhinal cortices play a more general role in encoding and retrieving declarative memory.

A possible limitation of the present results is that the R/K task used here may not reflect episodic versus familiarity-based memory, but rather memory strength (Wais et al., 2006). It is definitely the case that R/K judgments may be operationalized by subjects as an assessment of memory strength under some conditions (Eldridge et al., 2002). In the present study, we used a two-step procedure, where subjects first decide if they confidently recognize an item and then evaluate whether the item is accompanied by episodic recollection. Using this method, when subjects are asked about episodic details at the time of each R/K judgment, only Remember judgments are accompanied by significant memory for these details (Dudukovic and Knowlton, 2006). In the present study, assessment of memory for episodic details occurred outside the scanner after the completion of the second retrieval test. Nevertheless, similar results were obtained. For consistently familiar items, there was no evidence of memory for episodic memory for the study phase. In contrast, consistently recollected items were accompanied by significant memory for these details. The results of the post-test indicate that Remember responses in the present study were valid indicators of the presence of episodic memory. For items that had been initially recollected, but were later familiar, the level of detail memory was variable and not different from either of the other conditions. Given that the post-test was self-paced, it is possible that for some of these items, episodic details could be recovered that were not available to the subject during the R/K test in the scanner, which required a response within a 3-s deadline.

Another possible limitation is the fact that a lack of a significant difference in BOLD signal between conditions in a given

region does not necessarily demonstrate that the region does not support cognitive processes specific to one of the conditions. In the present study, a lack of a difference between BOLD signal in the hippocampus associated with familiar (KK) and missed (MM) items may not demonstrate that the hippocampus plays no role in familiarity processing. It may be that the relationship between memory processing in the hippocampus and BOLD signal is nonlinear such that moderate levels of hippocampal processing, as might be expected with recognition based on familiarity, would result in similar levels of BOLD as that associated with a non-mnemonic baseline task (Squire et al., 2007). Nevertheless, the present results are consistent with a specific role for the hippocampus in recollection, and add to a growing body of evidence that recollection and familiarity are neurally dissociable (Skinner and Fernandes, 2007).

In summary, the present study has shown that neural activity in the subicular region of the hippocampus tracks the successful retrieval of episodic memories. These data provide a link between activation in a specific hippocampal subregion and episodic recollection.

Acknowledgments

We thank the participants for their participation in our study. We also thank Russell Poldrack, Jeanette Mumford, Don Kalar, Seth Bouvier, and Florence Roussotte for technical assistance.

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