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Hippocampal Contributions to Episodic Encoding: Insights From Relational and Item-Based Learning

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Davachi, Lila and Anthony D. Wagner. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. *J Neurophysiol* 88: 982–990, 2002; 10.1152/jn.00046.2002. The integrity of the hippocampus and surrounding medial-temporal cortices is critical for episodic memory, with the hippocampus being posited to support relational or configural associative learning. The present event-related functional magnetic resonance imaging (fMRI) study investigated the role of specific medial-temporal lobe structures in learning during relational and item-based processing, as well as the extent to which these structures are engaged during item-based maintenance of stimuli in working memory. fMRI indexed involvement of the hippocampus and underlying cortical regions during performance of two verbal encoding conditions, one that required item-based maintenance of word triplets in working memory and the other that entailed the formation of inter-item associations across the words in each triplet. Sixteen subjects were scanned using a rapid event-related fMRI design while they encountered the item-based and relational processing trials. To examine the correlation between fMRI signal in medial-temporal structures during learning and the subject's subsequent ability to remember the stimuli (a measure of effective memory formation), subjects were administered a yes-no recognition memory test following completion of the encoding scans. Results revealed that the hippocampus proper was engaged during both relational and item-based processing, with relational processing resulting in a greater hippocampal response. By contrast, entorhinal and parahippocampal gyri were differentially engaged during item-based processing, providing strong evidence for a functional neuroanatomic distinction between hippocampal and parahippocampal structures. Analysis of the neural correlates of subsequent memory revealed that activation in the bilateral hippocampus was reliably correlated with behavioral measures of effective memory formation only for those stimuli that were encoded in a relational manner. Taken together, these data provide evidence that the hippocampus, while engaged during item-based working memory maintenance, differentially subserves the relational binding of items into an integrated memory trace so that the experience can be later remembered.

INTRODUCTION

It is well established that the integrity of the hippocampus, a component of the medial-temporal lobe (MTL) memory system, is important for declarative or explicit memory, but it does not appear necessary for working memory (Cohen et al. 1997; Gabrieli 1998; Scoville and Milner 1957; Squire 1992). Animal and human lesion evidence suggests that the hippocampus subserves relational (Cohen and Eichenbaum 1993; Eichenbaum 2000; Squire 1994) or configural (O'Reilly and Rudy 2001) learning mechanisms that are important for binding the array of features associated with an event into an integrated trace. Consistent with this interpretation, functional neuroimaging investigations in humans have revealed MTL activation during episodic encoding—the transformation of an experience into a durable memory that can be subsequently consciously remembered following a filled delay (reviewed in Lepage et al. 1998; Paller and Wagner 2002; Wagner et al. 1999). However, given the extant imaging literature, the precise contexts under which hippocampal responses are observed during episodic encoding remain poorly understood.

Initial blocked-design positron emission tomography (PET) studies of episodic memory suggest that hippocampal activation increases during encoding, with more anterior hippocampal regions often being engaged during conditions that foster relational processing of two or more stimuli (e.g., Dolan and Fletcher 1997; Henke et al. 1997, 1999; for reviews see Lepage et al. 1998; Schacter and Wagner 1999). By contrast, blocked-design and event-related functional magnetic resonance imaging (fMRI) investigations have often failed to observe hippocampal activity during episodic learning (e.g., Brewer et al. 1998; Ranganath and D'Esposito 2001; Wagner et al. 1998; for a review see Schacter and Wagner 1999), with such studies often observing activation in the posterior parahippocampal gyrus. Schacter and Wagner (1999) suggested that initial fMRI failures to observe hippocampal responses might reflect the relative absence of relational processing demands during the encoding conditions of these studies.

One recently adopted event-related fMRI approach to delineating the neural correlates of episodic encoding is to assess how event-by-event differences in neural activation during encoding correlate with later memory ability. This *subsequent memory paradigm*—where later memory performance is used to back-sort neural encoding signals into events later remembered and those later forgotten (Fabiani and Donchin 1995; Halgren and Smith 1987; Paller et al. 1987; Rugg 1995; Sandquist et al. 1980)—is a powerful approach for exploring the neural bases of encoding. This is because it provides a

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direct correlation between a behavioral measure of effective learning (subsequent remembering) and a measure of neural processing (fMRI signal intensity). Importantly, extant fMRI data from subsequent memory studies have more often failed to observe hippocampal correlates of effective encoding (Baker et al. 2001; Brewer et al. 1998; Otten and Rugg 2001a; Wagner et al. 1998), although reports of hippocampal effects have recently emerged (Casasanto et al. 2002; Kirchhoff et al. 2000; Otten et al. 2001; Strange et al. 2002). One suggestion is that, at least with respect to the hippocampus, failures to observe correlates of subsequent memory may reflect poor signal-to-noise due to susceptibility-induced signal loss in this region (Strange et al. 2002; but see Schacter and Wagner 1999). Although this remains a possibility, in this study, we explored whether hippocampal subsequent memory effects may particularly emerge when relational processing of two or more stimuli is fostered during learning (Killgore et al. 2000; Rombouts et al. 1997; Sperling et al. 2001).

A second fundamental issue that has arisen regarding hippocampal function is whether the hippocampal formation may contribute to the maintenance of information in working memory (Ranganath and D'Esposito 2001; Stern et al. 2001). Although considerable data indicate that working memory is intact in amnesic patients with bilateral MTL insult (Gabrieli 1998), Ranganath and D'Esposito (2001) have recently suggested that the binding mechanisms subserved by the hippocampus may also play an important role in working memory maintenance. This hypothesis is based on their fMRI observations of hippocampal activation during the delay period of a face working memory task. However, as these authors noted, it was not possible to rule out an encoding interpretation of their findings. Given the centrality of this question to understanding the functional contributions of hippocampal computations, we explored whether hippocampal activation during working memory may generalize to a rote verbal rehearsal paradigm, and if so, whether the magnitude of activation correlates with effective encoding as indexed by subsequent memory performance.

In this event-related fMRI study, scanning was conducted while participants performed relational or item-based processing of word triplets, after which memory for the words was indexed off-line. This approach permitted *1*) an assessment of the relative magnitude of hippocampal activation during relational and item-based processing, *2*) determination of whether hippocampal activation was observed during verbal working memory maintenance, and *3*) exploration of whether MTL subsequent memory effects were associated with each of these conditions.

METHODS

During each scanning trial, healthy adults (ages 18–35 yr; $n = 16$), who gave informed consent in a manner approved by the Committee on the Use of Humans as Experimental Subjects at the Massachusetts Institute of Technology (MIT) and the Human Studies Committee of the Massachusetts General Hospital (MGH), performed one of two incidental encoding tasks (Rote and Elab). Stimuli consisted of a column of visually presented triplets of nouns printed in uppercase letters (Fig. 1). On rote rehearsal trials (Rote), the cue "REPEAT" indicated that subjects should covertly rehearse the word triplet in the order presented throughout the duration of the trial. Importantly, and in contrast to many prior investigations of working memory, there was no probe or decision phase at the end of the trial; that is, participants were not required to compare a test probe against the contents of working memory. Thus this task primarily necessitated recruitment of item-based phonological access and maintenance of these phonological representations for the duration of the trial. During elaborative rehearsal trials (Elab), the cue "ORDER" indicated that subjects should covertly reorder the words in the triplet along the subjective dimension of "desirability," going from least to most desirable. To ensure that the task elicited between-item relational processing, all members of a word triplet had a similar desirability rating, indexed by normative behavioral pilot data. The instructions further emphasized that subjects should settle on their order only after considering the desirability of each item *in relation to* the other items in the triplet.

Prior to fMRI scanning, participants received extensive practice on the experimental tasks, both outside and inside the magnet, to ensure that they understood the instructions and could perform the tasks in the time allotted. Over the course of eight event-related fMRI scans, 112 8-s trials from each of the two trial types (Rote and Elab) were intermixed with variable-duration visual fixation null events. The order of the conditions within each scan was determined using an optimal sequencing program designed to maximize the efficiency of

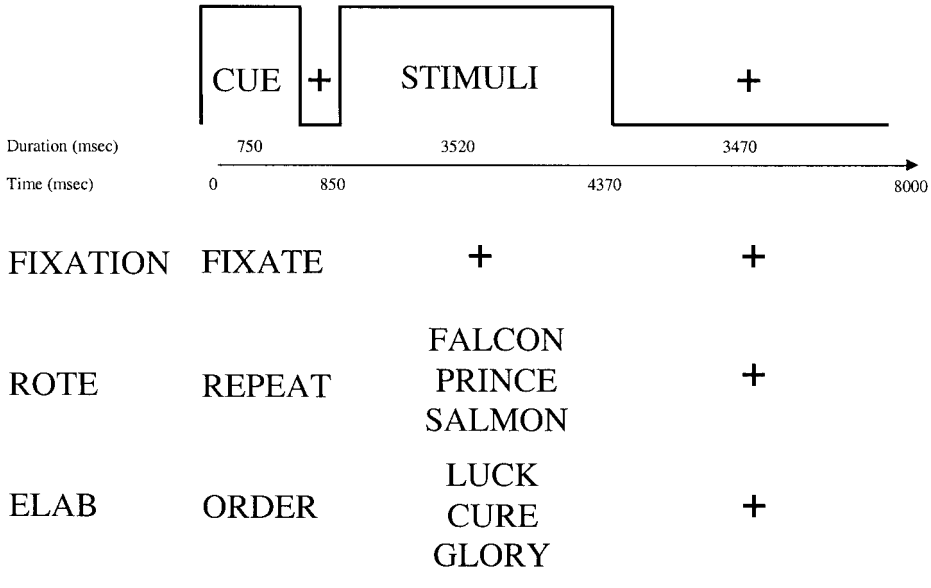


FIG. 1. Trial structure and examples from each of the 3 trial types (Fixation, Rote, and Elab) are presented. For each trial, a cue (i.e., FIXATE, REPEAT, and ORDER) was followed by a triplet of words or a + sign. Duration of each event within a trial and cumulative trial time are noted on timeline. All experimental trials were 8 s, while the length of Fixation trials was varied (see METHODS).

recovery of the BOLD response, based on the assumption of a linear time invariant system (Dale 1999; Dale and Buckner 1997). The periods of visual fixation, which cumulatively accounted for one-third of the total scan time, lasted between 2 and 22 s and "jittered" in increments of 2 s, which was determined by the optimization algorithm. During fixation null events (Fix), the cue "FIXATE" indicated that subjects should fixate on a + sign throughout the duration of its appearance on the screen.

The extent to which the processes recruited during the item-based and relational processing paradigms contributed to episodic encoding was assessed using a (nonscanned) recognition memory test administered approximately 20 min after the last fMRI scan. During this test, all previously encountered words and a set of unstudied distractors were presented individually, and subjects indicated whether they remembered having studied the item and designated their confidence (either "high" or "low") when responding "studied." These behavioral measures of subsequent remembering were used to conduct a subsequent memory analysis on the fMRI encoding data.

The fMRI data were collected on a 1.5T Siemens Sonata system using a gradient-echo echo-planar pulse sequence (TR = 2 s, TE = 40 ms, 21 axial slices, 3.125 × 3.125 × 5 mm, 0.2 mm inter-slice gap, 168 volume acquisitions per run). Head motion was restricted using a bite-bar apparatus. The data were processed using standard preprocessing and analysis procedures within SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Images were corrected for differences in slice acquisition timing by resampling all slices in time to match the first slice, followed by motion correction across all runs (using sinc interpolation). Structural and functional data were spatially normalized to an echo planar image (EPI) template based on the MNI305 stereotactic space (Cocosco et al. 1997)—an approximation of Talairach space (Talairach and Tournoux 1988)—using a 12-parameter affine transformation along with a nonlinear transformation using cosine basis functions. Images were resampled into 3-mm cubic voxels and spatially smoothed with an 8-mm full width half maximum (FWHM) isotropic Gaussian kernel.

To assess MTL activation during both item-based and relational processing, all experimental trials (collapsed across task and separately for each task) were contrasted with baseline (fixation trials). To assess the differential response during the two processing tasks, Rote and Elab trials were directly contrasted. Effects were estimated using a subject-specific fixed-effects model, with session-specific effects and low-frequency signal components treated as confounds. The subject-specific estimates derived from each of these contrasts were entered into a second-level group analysis treating subjects as a random effect, using a one-sample *t*-test against a contrast value of zero at each voxel. For comparisons to the fixation baseline, regions were considered reliable to the extent that they consisted of ≥5 contiguous voxels that exceeded an uncorrected threshold of $P < 0.001$. Following Strange et al. (2002) for the direct contrasts between tasks, a slightly more liberal threshold of $P < 0.005$ was adopted, given the lower signal-to-noise often observed in anterior MTL (Ojemann et al. 1997).

The correlates of item-based and relational processing were further explored within the hippocampus proper and within surrounding MTL cortices using region-of-interest (ROI) analyses. Spherical ROIs were defined by including all significant voxels within a 6-mm radius of each maximum identified within the MTL from the group functional contrasts. Signal within each ROI was calculated for each subject by selectively averaging the data with respect to peristimulus time for trials in each condition. The resultant hemodynamic response reflects percent signal change relative to baseline from 0–14 s peristimulus time. These data were subjected to mixed-effects analysis of variance (ANOVA), treating Task (Rote/Elab) and Time (0–14 s) as repeated measures and subjects as a random effect. These analyses were conducted to determine whether there was a main effect of Task or a Task × Time interaction. For regions demonstrating a significant Task × Time interaction, planned contrasts further compared the percent signal change associated with the Rote and the Elab trials at the time point corresponding to the peak response (defined from the mean of the 2 trial types).

To examine *within-task* differences in the hemodynamic response correlated with subsequent memory, trials were divided into those in which subjects later remembered zero, one, two, or three items from a triplet. This analysis was conducted collapsing across confidence because there were insufficient trials to permit analysis restricted only to the high confidence and forgotten trials. Moreover, owing to the small number of trials in which subjects remembered all three items from a triplet that was rote rehearsed and zero items from a triplet that was elaboratively rehearsed, these bins were not included in the respective subsequent memory analysis. For each task, the ROI analysis examined whether there was a reliable main effect of Memory (0/1/2 or 1/2/3 items remembered) or a reliable Memory × Time (0–14 s) interaction; planned contrasts further explored whether the peak magnitude of the response differed by subsequent memory.

RESULTS

Behavioral performance on the subsequent recognition test revealed that the probability of responding "old" (collapsed across confidence) differed across trial type [Elab/Rote/New; $F(2,30) = 77.03$]; the hit rate was superior following relational (Elab) relative to item-based (Rote) processing, with the hit rate for the Rote task being superior to the false alarm rate (Fig. 2*A*). Response latencies also reliably differed across trial type [$F(2,30) = 11.14$], with latencies to New items (1,688 ms) being significantly longer than those to Rote (1,507 ms) and Elab (1,474 ms) studied items; the studied conditions did not reliably differ. To explore recognition by triplet, analyses revealed a significant Task × Memory interaction [$F(3,45) = 27.33$]. Subjects were more likely to remember all three items from a triplet following Elab relative to Rote processing; conversely, subjects were more likely to remember zero or one of the items following Rote relative to Elab processing (Fig. 2*B*). These data replicate the well-established result that subsequent memory is superior following relational/elaborative processing relative to item-based/rote rehearsal (Craik and Lockhart 1972; Wagner et al. 2001; Woodward et al. 1973).

Performance on the subsequent memory test was further assessed to test the assumption that subsequent remembering following elaborative processing is at least partially due to relational memory, whereas relational memory in minimal following rote rehearsal. To do so, we calculated the expected

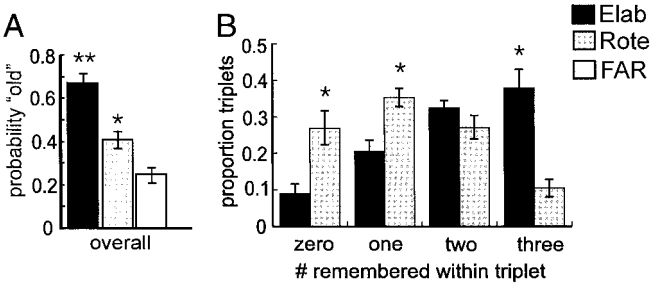


FIG. 2. Displayed are the probability of recognition and proportion of studied trials in which a set number of words from the triple were remembered. *A*: probability of recognizing an item as "old" for Elab- and Rote-studied items as well as the false alarm rate (FAR) to new items. (*significantly different from FAR at $P < 0.05$; **significantly different from Rote and FAR conditions at $P < 0.0001$). *B*: proportion of triplets from which either 0, 1, 2, or 3 items were later remembered from the Elab and Rote conditions. (*Significantly different from other condition at $P < 0.001$.)

frequency of recognizing all three items in a triplet based on item memory alone (hit rate^3) and compared this to the observed frequency of recognized triplets. This analysis yielded an observed-expected measure for each condition for each subject. A sign test on these data revealed that the frequency with which subjects recognized all three items in a triplet was greater than that expected from item memory alone following elaborative processing ($\chi^2 = 11.27$, $P < 0.001$) but not following rote processing ($\chi^2 = 1.67$, $P > 0.2$). This outcome suggests that subsequent memory for rote-rehearsed trials primarily reflects the encoding of item information, whereas subsequent memory for elaboratively-rehearsed trials includes a relational component.

Voxel-based statistical analyses revealed that performance of the incidental encoding tasks (collapsed across task) elicited activation in occipital, parietal, cerebellar, frontal, and bilateral medial-temporal regions. Here we focus on the MTL responses (results beyond the MTL have been reported in Davachi et al., 2001a). Consideration of the task effects, irrespective of subsequent memory, revealed that performance of both the Elab and Rote tasks yielded reliable bilateral hippocampal activation, including anterior and posterior hippocampal foci, compared with fixation (Fig. 3*A*). Direct comparison of Elab to Rote trials revealed that activation was greater in the right entorhinal cortex and bilateral parahippocampal gyri during Rote trials, whereas activation was greater in the hippocampus during Elab trials (Fig. 3*B*). These results indicate that *1*) the bilateral hippocampal regions were engaged during both relational processing and item-based rote rehearsal and *2*) the hippocampal and parahippocampal regions were differentially sensitive to relational and item-based processing. The former results extend the observation of hippocampal activation during visual working (Ranganath and D'Esposito 2001) to a verbal working memory context. The latter speak to current theories regarding functional distinctions within the MTL (e.g., Brown and Aggleton 2001; Eldridge et al. 2000).

To further explore the relative magnitude of hippocampal activation during relational and item-based processing, ROI within the right and left hippocampus were obtained from the comparison of both tasks (i.e., all trials) to baseline (Fig. 4, *A* and *B*). ROI analyses revealed greater activation during Elab trials compared with Rote trials in the right hippocampus [$F(1,15) = 5.36$, $P < 0.05$] but not in the left hippocampus [$F(1,15) = 1.89$; although there was a trend for a Task × Time interaction, $F(6,90) = 1.88$, $P < 0.10$, that hinted at a greater response during the relational task]. Thus these ROI analyses, in conjunction with the voxel-based direct contrast, provide support for our prediction that relational processing would elicit greater hippocampal engagement relative to item-based processing.

Subsequent memory analyses on the above two ROIs revealed that activation in the right hippocampus *during Elab trials* differed according to subsequent memory performance [main effect of Memory, $F(2,12) = 3.48$, $P < 0.05$]; activation was greater for trials after which subjects remembered three items versus two items ($P < 0.02$; Fig. 4*A*). For the left hippocampal ROI, the subsequent memory effect was marginal [Memory × Time interaction: $F(12,144) = 1.66$, $P = 0.08$]; planned comparisons revealed that peak activation was greater for trials after which subjects remembered three items versus two items ($P < 0.005$) and versus one item ($P < 0.005$; Fig. 4*B*). Neither region showed a subsequent Memory effect or a Memory × Time interaction following Rote item maintenance (all $F < 1.16$, $P > 0.33$).

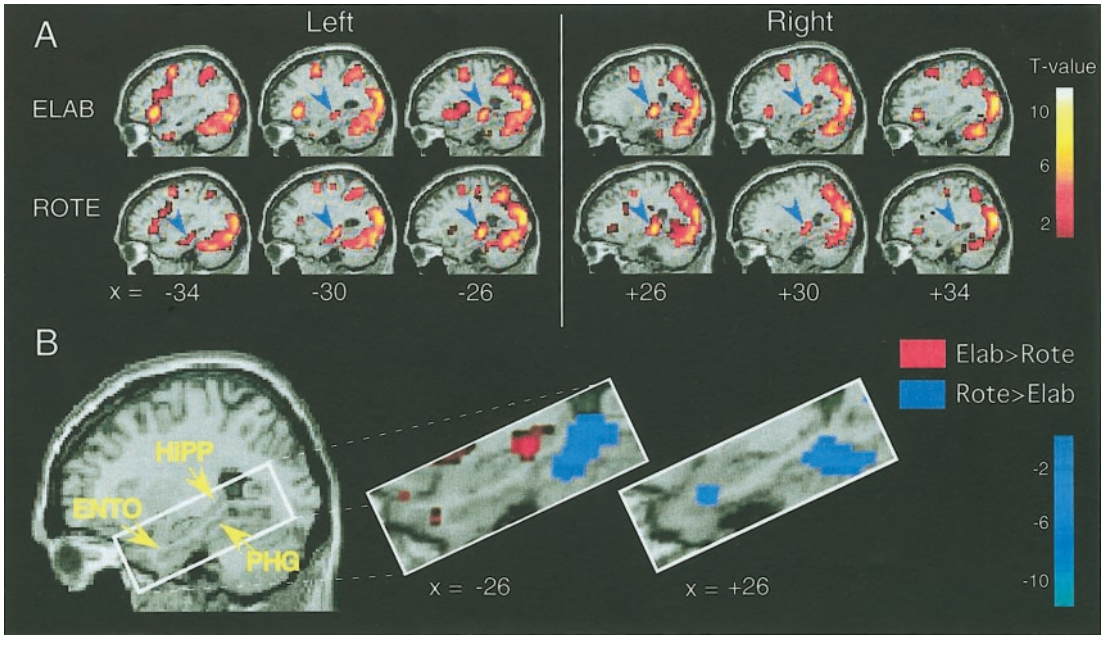
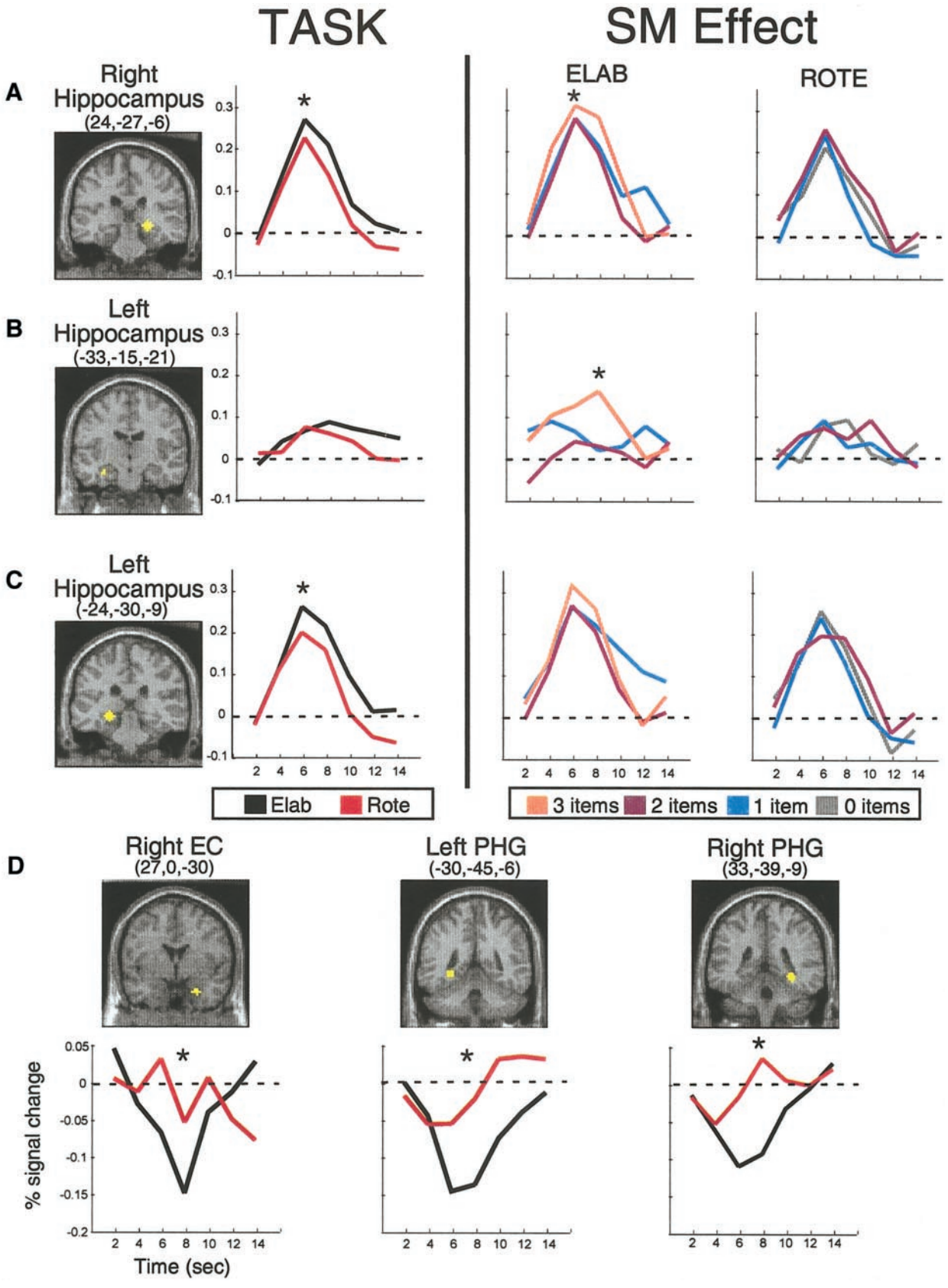


FIG. 3. Statistical maps revealed multiple medial temporal regions associated with Elab and Rote processing. *A*: midsagittal sections through left and right medial temporal regions displaying activations during the Elab and the Rote tasks compared with the fixation baseline. Montreal Neurological Institute (MNI) *x* coordinates are presented below the sections. *B*: direct contrasts of Elab and Rote tasks revealed differential task effects in hippocampal, parahippocampal, and entorhinal regions. The anatomical section (*left*) shows the medial-temporal lobe (MTL) location rendered at *right*. The left hippocampus (HIPP) revealed greater activation during Elab vs. Rote processing (red), whereas bilateral parahippocampal (PHG) and right entorhinal (EC) regions demonstrated the reverse pattern (blue).


TASK
SM Effect
A
Right Hippocampus (24,-27,-6)
ELAB
ROTE
B
Left Hippocampus (-33,-15,-21)
C
Left Hippocampus (-24,-30,-9)
Elab
Rote
3 items
2 items
1 item
0 items
D
Right EC (27,0,-30)
Left PHG (-30,-45,-6)
Right PHG (33,-39,-9)
% signal change
Time (sec)

An additional left hippocampal focus was observed in the contrast of Rote > Fixation; this region was explored for task and subsequent memory effects (Fig. 4*C*). This ROI, which corresponds to the left hippocampal region displayed in Fig. 3*B*, showed greater activation during performance of the Elab task compared with the Rote task [$F(1,15) = 6.73$, $P < 0.05$]. This was the case even though the region was identified from a contrast of Rote trials relative to baseline and thus might be biased in favor of this working memory condition. Subsequent memory analyses further revealed a trend for a subsequent memory effect for the Elab trials [main effect of Memory, $F(2,12) = 2.68$, $P < 0.09$]. However, the planned comparisons failed to reveal a reliable effect when directly comparing memory levels ($F < 1.0$), indicating that interpretation of this marginal subsequent memory trend warrants caution. Again, there was no subsequent memory effect in the Rote condition ($F < 1.0$).

To further characterize the response of the entorhinal (EC) and parahippocampal (PHG) regions that demonstrated greater activation during item-based (Rote) compared with relational (Elab) processing in the voxel-based analysis (Fig. 3*B*), averaged hemodynamic responses were obtained for each condition from the right entorhinal and bilateral parahippocampal ROIs. These ROIs were defined based on this contrast (i.e., Rote > Elab) because no regions in the parahippocampal gyrus (including EC) were observed relative to baseline when collapsing across task. Not surprisingly, ROI analyses confirmed the greater activation in these regions during Rote compared with Elab trials [right EC, Task × Time, $F(6,90) = 3.06$, $P < 0.01$; bilateral PHG, $F(1,15) > 15.54$, $P < 0.002$; Fig. 4*D*]. The right PHG and right EC ROIs failed to show a reliable subsequent memory effect for Rote trials ($F < 1.40$, $P > 0.20$). By contrast, there was a significant subsequent *forgetting* effect for Elab trials in the posterior right PHG region (Memory × Time: $F(12,144) = 2.06$, $P < 0.03$). Planned contrasts revealed an *inverse* correlation between memory and activation such that activation during trials after which only one item was remembered was greater than during trials yielding recognition of two ($P = 0.054$) or three ($P < 0.01$) items. Such subsequent forgetting effects have been noted elsewhere, but not within the MTL (Otten and Rugg 2001b; Wagner and Davachi 2001; Wagner et al. 1998 but see Taylor et al. 2001). Subsequent memory analyses of the left PHG region revealed no reliable effects for either the Rote [$F(12,132) = 1.46$, $P > 0.14$] or the Elab [$F(12,144) = 1.72$, $P < 0.07$] tasks, although there was a trend in the latter contrast for a similar subsequent forgetting effect.

In all of the above analyses, reliable subsequent memory effects within MTL were observed following elaborative, but not following item-based, encoding. One possible concern is that the absence of such an effect in the rote condition may simply be due to the necessary exclusion of trials for which three items were later remembered following rote encoding (owing to small bin size; see METHODS). To explore whether this might be the case, we conducted an additional analysis on the data from the seven subjects in our sample who yielded at least eight trials in this bin. These Memory (1/2/3 items remembered) × Time ANOVAs revealed a similar outcome; there was no main effect of Memory in any of the hippocampal ROIs (all $F < 1$, $P > 0.51$) nor was there an interaction (all $F < 1$, $P > 0.68$). While interpretative caution is warranted, given the low number of subjects and the low number of trials contributing to these analyses, it is important to note that in no case was the percent signal change greater during trials in which three items were subsequently remembered relative to trials in which two items were subsequently remembered. Thus the null outcomes in these additional analyses of the rote condition do not simply reflect low power due to analyzing a subset of the subjects.

DISCUSSION

This study revealed four important insights into the nature of medial-temporal contributions to encoding. First, relative to item-based processing, relational processing was associated with greater activation of the bilateral hippocampus, including anterior and posterior hippocampal regions. Second, hippocampal activation during relational processing was correlated with later memory. Third, hippocampal activation was observed during an item-based verbal working memory condition, extending the contexts in which hippocampal processing has been associated with working memory, however, no MTL region was correlated with subsequent memory following rote rehearsal. Finally, relative to relational processing, item-based processing was associated with greater EC and posterior PHG activation, pointing to a functional dissociation between these structures and the hippocampus.

The bilateral hippocampus was engaged to a greater extent during relational processing of multiple stimuli compared with item-based rote rehearsal. This result provides support for theories of hippocampal function that stress its role in relational or configural processing, whereby multiple features or components of an experience are bound together into an integrated memory (Cohen et al. 1997; Eichenbaum 2000; O'Reilly and Rudy 2001). Prior studies have shown that damage to the hippocampus results in deficits in relational memory in both rats (Honey et al. 1998) and monkeys (Gaffan and Parker 1996), with these deficits putatively revealing the contributions of the auto-associative properties of CA3 neurons to associative learning (Marr 1971). Recent fMRI studies of episodic retrieval suggest that the hippocampus is differentially involved in the recollection of episodic details relative to nonrecollective memory (Eldridge et al. 2000; for reviews see Brown and Aggleton 2001; Yonelinas 2001). The present data extend the differential role of the hippocampus in relational memory to encoding.

Our results also provide strong evidence that prior PET (Dolan and Fletcher 1997; Henke et al. 1999; Rombouts et al. 1997) and recent fMRI (Killgore et al. 2000; Sperling et al. 2001) observations of hippocampal activation during associa-

FIG. 4. BOLD percent signal changes over time within 3 hippocampal (*A–C*) and 3 medial-temporal cortical (*D*) regions. *A* and *B*: task and subsequent memory (SM) effects are plotted for the right and left hippocampal regions-of-interest (ROIs), defined from a contrast of both Elab and Rote tasks compared with baseline. *C*: condition effects are displayed for the left hippocampal ROI observed when contrasting Rote trials to baseline. *D*: task effects are rendered for the right entorhinal cortex (EC) and left and right parahippocampal regions (PHG) observed in contrast of Rote compared with Elab trials. MNI peak coordinates presented for each ROI. All significant effects are marked with an asterisk ($P < 0.05$) and are detailed in RESULTS.

tive encoding conditions reflect learning mechanisms important for later remembering. Specifically, the subsequent memory analysis revealed that the level of engagement of the hippocampus during relational encoding was correlated with behavioral measures of effective memory formation. When greater hippocampal responses co-occurred with the relational processing of a word triplet, the words were more likely to be later remembered compared with events accompanied by a more modest hippocampal response. Although the memory probe consisted of a single item, analysis of the probability that subjects would remember all three items in a triplet suggested that processes above and beyond item memory were present following performance of the relational, but not the item-based, encoding task. Collectively these data suggest that hippocampal computations may facilitate subsequent recognition by linking studied items and thus providing an increased probability of being able to later recollect details of the episode. This interpretation makes the prediction that hippocampal activation during encoding should differentially correlate with later source recollection and associative recognition compared with later item recognition in the absence of recollection. Recent results from a study of source encoding suggest that this prediction may hold (Davachi et al. 2001b).

The present data also extend the recent observation of hippocampal activation during visual working memory in humans (Ranganath and D'Esposito 2001) and in animal models (Friedman and Goldman-Rakic 1988; Sybirska et al. 2002) to a verbal maintenance context. Although the hippocampus was engaged to a greater extent by the relational encoding task, nevertheless bilateral hippocampal activation was observed during performance of the rote rehearsal task. One interpretation of this hippocampal activation is that hippocampal binding processes are not only important for episodic memory formation, but also play a central role in the maintenance of representations within working memory (Ranganath and D'Esposito 2001). The present, and somewhat unexpected absence of a subsequent memory effect during our verbal working memory condition, does not permit rejection of this perspective. Nevertheless, as noted by Ranganath and D'Esposito (2001), it remains possible that episodic encoding co-occurs with effective working memory maintenance such that these hippocampal activations reflect the role of the hippocampus in declarative memory formation. Given the extensive neuropsychological data on the preservation of working memory maintenance abilities in individuals with global amnesia (Cave and Squire 1992), this latter interpretation would appear more likely. The observation of hippocampal activation during an item-based, working memory condition could reflect incidental relational processing that may have co-occurred during rote rehearsal of the word triplet, albeit to a lesser extent than during the elaborative task. Such processing does not appear to have fostered the formation of inter-item associations—at least not to the degree that associative memory was expressed in behavior; nevertheless, relational processes may support the binding of item and contextual representations. Future investigations of the relation between hippocampal activation during verbal working memory maintenance and subsequent source recognition may serve to further clarify the functional significance of hippocampal activation during working memory maintenance.

In contrast to the hippocampus, the present study revealed that the EC and PHG were engaged to a greater extent during item-based processing. As can be seen in Fig. 4, activation during item-based encoding did not markedly differ from the fixation baseline, whereas the response during the relational trials fell below baseline. One might be concerned about this pattern, as, theoretically, it could reflect "deactivation" of these regions during the relational trials rather than "activation" during the item-based trials. However, recent fMRI data suggest that the directionality (i.e., above or below baseline) of MTL activation can vary depending on the type of baseline task employed (Stark and Squire 2001). For example, Stark and Squire (2001) have argued that the commonly adopted fixation baseline, which we used in the current study, may itself result in active engagement of the MTL, perhaps reflecting mnemonic operations associated with self-generated episodic remembering and memory formation during these null periods. Importantly, these authors demonstrated that memory conditions that appear to yield a "deactivation" of MTL when compared with null baselines may well yield an "activation" when compared with baselines that require a simple motor response. Given such observations, we believe it is reasonably likely that the PHG and EC may have been engaged by both encoding tasks, with the item-based condition differentially eliciting the processes subserves by these structures.

The differential pattern of activation across tasks and levels of subsequent memory between the hippocampus and these underlying cortical structures provide strong evidence for functional heterogeneity within the MTL. From one theoretical perspective, engagement of PHG, in contrast to the hippocampus, may differentially subserve item memory (Aggleton and Shaw 1996; Brown and Aggleton 2001; Vargha-Khadem et al. 1997). Electrophysiological recordings in rats and monkeys have shown that the neuronal responses in parahippocampal regions signal information about items and their prior occurrence (Brown et al. 1987; Li et al. 1993), while hippocampal neurons show no such modulation and are more likely coding the relations between objects in an environment (Eichenbaum 2000; Parkinson et al. 1988; Rolls et al. 1989; Wan et al. 1999). The present dissociative pattern between the PHG and the hippocampus provides support for this theoretical perspective. Although this perspective might further predict that parahippocampal activation during item-based processing should correlate with later memory ability, this was not the case in the present study. It is unclear whether the null subsequent memory effects observed within MTL following item-based processing reflect a consequence of low power due to moderate levels of later successful remembering in this condition (Fig. 2) that are exacerbated by potentially lower signal-to-noise. Previous findings have demonstrated a role for parahippocampal computations in successful encoding of individual words (Baker et al. 2001; Kirchhoff et al. 2000; Otten et al. 2001; Wagner et al. 1998) and pictures (Brewer et al. 1998; Kirchhoff et al. 2000), although these earlier studies do not clarify whether parahippocampal processes support later item or relational memory. Moreover, although in this study no region within MTL correlated with subsequent memory performance following rote rehearsal, such correlations were observed in prefrontal, supplementary motor, posterior parietal, and cerebellar regions (Davachi et al. 2001a). Thus it would appear unlikely that the recognition memory test indexed event features (e.g., semantic codes) that may not have been attended in the rote condition, because if this were the case, then no

correlates of subsequent memory would have been expected in this condition. Of central interest for future investigation will be to determine whether these cortical and cerebellar structures interact with parahippocampal and/or hippocampal regions during the encoding of item-based information into long-term memory.

Intriguingly, although parahippocampal activation did not correlate with later memory following item-based processing, an inverse parahippocampal subsequent memory effect was observed following relational processing. That is, the magnitude of parahippocampal activation demonstrated the opposite relation to later memory performance to that observed in the hippocampus. Greater recruitment of parahippocampal mechanisms during the relational task may be indicative of a failure to successfully recruit the appropriate relational processes during those trials, with the subject instead perhaps recruiting item-based mechanisms that lead to poorer memory formation.

A striking aspect of the present hippocampal subsequent memory effects that were associated with relational processing is their anatomical similarity to the few prior reports of hippocampal correlates of later recognition (Kirchhoff et al. 2000; Otten et al. 2001) or recall (Strange et al. 2002). The anatomical localization of our right hippocampal focus during relational processing [Talairach coordinates: (24, −26, −4)][1] converges well with the posterior hippocampal focus that Kirchhoff et al. (2000) observed to correlate with subsequent recognition of studied pictures [Talairach coordinates: (28, −30, −6)]. Otten et al. (2001) reported that activity within the anterior left hippocampus [Montreal Neurological Institute (MNI) coordinates: (−27,-15,-12)], a focus that is similar to the anterior hippocampal region revealed in the present study [MNI coordinates: (−33,-15,-21)], correlated with memory for words that were either processed semantically (animacy judgment) or superficially (alphabetical judgment). Strange et al. (2002) found that activation of a left hippocampal region [MNI coordinates: (−22,-26,-16)] correlated with subsequent recall of words and this region is in close proximity to the posterior left hippocampal region reported in this study [MNI coordinates (−24, −30, −9)]. Moreover, although across-method direct comparisons are difficult, Fernandez and colleagues have reported correlates of subsequent recall within a similar anterior hippocampal region using intracranial electrophysiological measures in humans (Fell et al. 2001; Fernandez et al. 1999, 2002). Finally, the hippocampal activations observed during working memory maintenance by Ranganath and D'Esposito (2001) [MNI coordinates: right (30, −22, −15); left (−30, −15, −20)] were situated near those seen in the present study during verbal maintenance of stimuli. These consistent, across-study observations of multiple hippocampal foci that correlate with measures of effective encoding and working memory suggest that there may be sub-regions within the hippocampus proper that, due to their precise patterns of connections with cortical regions, may be more or less engaged during episodic encoding based on differences in stimulus domain, processing, or both (see also Small et al. 2001).

In summary, the present data provide strong evidence that the hippocampus is differentially engaged during relational processing and that event-by-event differences in recruitment of these computations impact whether the event will be later remembered or forgotten. These results from the intact human brain suggest that the well-established neuropsychological observation that patients with hippocampal insult exhibit a profound inability to remember new experiences at least partially emerges due to failures to form or encode new memories. Importantly, the present data further indicate that the subcomponents of the medial-temporal circuit are not functionally homogeneous, because parahippocampal regions were differentially sensitive to item-based processing. Further research promises to clarify the relation between MTL computations and the ability to keep information in mind and bring information back to mind.

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[1] Coordinates were transformed from MNI to Talairach stereotactic space for purposes of comparison across studies using the method described at: http://www.mrc-cbu.cam.ac.uk/Imaging/.

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