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Activation of human hippocampal formation reflects success in both encoding and cued recall of paired associates

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Contemporary theories of hippocampal function suggest that both encoding and retrieval of episodic memories may be accomplished by neural circuitry embedded within the same anatomical structures, but neuroimaging support for this hypothesis has been ambiguous. Recent studies suggest that the best available indicators of hippocampal encoding and retrieval operations are selective activations due to novelty, encoding success, and recall success in a paired associate learning paradigm. In the current study, both encoding and cued recall of paired associate words were conducted during a single session of fMRI scanning. Bilateral activation in the medial temporal lobe was detected for encoding word pairs vs. a fixation baseline and for encoding novel word pairs vs. repeated word pairs. These activations were stronger in subjects who successfully memorized more word pairs. In cued recall, greater responses were seen in higher performing subjects. In lower performing subjects, responses were greater to cue words whose paired associate was correctly recalled than to cue words whose correct associate had been forgotten (or not encoded). The difference between correct and incorrect trials was more pronounced on repeated presentations of the same cue words, but not apparent on their first presentation alone. Overlap of encoding and retrieval effects was maximal in the middle of the longitudinal extent of the right hippocampus, with one additional locus of overlap outside the MTL, in left occipitotemporal cortex. The conjunction of these effects suggests that it is correct to view both encoding and recall of associative memories as functions of an integrated hippocampal system.

Keywords: Hippocampus; Medial temporal lobe; Episodic memory; Encoding; Retrieval; fMRI

Introduction

Although the structures of the medial temporal lobe (MTL) are undisputedly essential for the formation of long-lasting declarative memories, the specific nature of the neuronal processing that occurs there is a subject of ongoing debate. Many theorists now agree that the contents of an individual's long-term memory ultimately reside in the cerebral cortex (Hoffman and McNaughton, 2002; Treves and Rolls, 1994), while the MTL is necessary for the formation of an initial memory trace when new information is encoded. Other functions attributed to the MTL according to such a theoretical perspective include the retrieval of recently encoded information, when the situation demands it, maintenance of recent memories for a considerable period of time, and the consolidation of the information in the cortex through a slower process of hippocampal–cortical interaction (Gluck and Myers, 2001; McClelland et al., 1995).

The concepts of "encoding" and "retrieval" may or may not correspond to basic mechanisms of MTL function. Rather, they are conventional terms arising from the pragmatic need to study human memory function through the presentation of discrete items, such as words and pictures. The MTL is a multimodal structure receiving highly processed input from a wide variety of association cortices (Lavenex and Amaral, 2000), and therefore it is more difficult to predict what kinds of task paradigms will cause detectable BOLD signal changes in the MTL than in unimodal sensory and motor areas. Several early studies of episodic memory encoding, particularly those involving verbal material, did not demonstrate selective activation in the MTL in comparisons across different task conditions (Buckner et al., 1995; Shallice et al., 1994), while a recent study suggests that the MTL may have a comparatively high level of activity during tasks commonly used as "baselines" in fMRI experiments (Stark and Squire, 2001). Nonetheless, several studies have demonstrated significantly greater activation in MTL in a number of comparison conditions. These include: novel vs. repeated stimuli (Constable et al., 2000; Stern et al., 1996), meaningful vs. meaningless stimuli, (Kelley et al., 1998; Martin et al., 1997), deep vs. shallow processing (Henke et al., 1997; Wagner et al., 1998), and subsequent successful recognition of individual items (Brewer et al., 1998; Wagner et al., 1998).

Taken together, these effects suggest a general hypothesis that enhanced neural activity in the MTL is indicative of encoding information into long-term memory, and that such activation is driven primarily by factors other than the deliberate effort of

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subjects to memorize information. Such a conclusion is supported by the results of Reber et al. (2002), who demonstrate that deliberate effort predicts activation in prefrontal regions, whereas success in encoding (as indexed by subsequent recognition) predicts activation in the MTL independently of effort. Other studies have attempted to distinguish the roles of individual substructures within the MTL with respect to the encoding of information. Animal models of episodic memory (Brown and Aggleton, 2001; Eichenbaum et al., 1994; Rudy and Sutherland, 1995) had suggested that familiarity with single-item stimuli may depend on parahippocampal structures (entorhinal, perirhinal, and parahippocampal cortices), whereas the hippocampal formation (including Ammon's Horn, dentate gyrus, and subiculum) is necessary for the formation of flexible, relational, and contextual memories. Human neuroimaging research has been largely consistent with this viewpoint. Selective activation in the hippocampus, as opposed to the parahippocampal region, has been reported in encoding multiple items in a relational manner (Davachi and Wagner, 2002; Sperling et al., 2001), and for establishing memories leading to the successful recall of the context in which an item was encountered (Davachi et al., 2003), to successful free recall (Fernandez et al., 1998), and associative recognition of word pairs (Jackson and Schacter, 2004).

As a selective role of the hippocampus in encoding has been elucidated, questions have arisen as to the relationship between encoding and retrieval of episodic and/or associative memories. Specifically, do the same structures carry out both operations, of forming lasting memory traces and recalling them into active memory, or are these processes anatomically dissociable? Associative memory tasks offer a valuable means of investigating this relationship because they do not suffer from an ambiguity present in studies that have revealed selective MTL activation for successful recognition memory of single items, compared to unrecognized or novel stimuli (Daselaar et al., 2001; Gabrieli et al., 1997; Grasby et al., 1993; Nyberg et al., 1996). If selective activation to novelty is a hallmark of encoding, and selective activation to successful recognition a hallmark of retrieval, these effects may cancel out: an unrecognized old stimulus may trigger further encoding activity to a greater extent than a recognized one.

Recent studies have indicated that successful recall of episodic details of prior experience with a stimuli, compared with mere familiarity, corresponds with a selective increase in activation within the hippocampus (Dobbins et al., 2003; Eldridge et al., 2000), whereas successful recognition memory may only be indicated by a reduced response compared to novel stimuli (Henson et al., 2003; Rugg and Yonelinas, 2003). Therefore, the question of whether or not signal increases in the same region may reflect neural processes underlying both encoding and retrieval may best be answered by an experimental design that takes advantage of these established effects: episodic encoding is best isolated by novelty and success effects, while retrieval is identifiable with selective activation to presentation of cue stimuli that engender successful recall of associative details, compared with cues that do not.

Two our knowledge, there have been two fMRI studies that investigated both encoding and recall of paired associates. Small et al. (2001) reported similar overlapping activation patterns during training with face/name pairs and cued recall of associative pairs. These activations, however, consisted of increased signal relative to a baseline, not specific effects of success. Zeineh et al. (2003) reported a dissociation between encoding and cued recall on a similar task, with encoding effects localized to a hippocampal subregion comprising the dentate gyrus and CA2/3, while retrieval effects were more posterior and centered in the subiculum. Both the encoding effect and the retrieval effect in this study consisted of a temporal decline in activity compared to a baseline, as performance improved. Although these effects are easily interpretable as a decline in the encoding of novel associations as the same pairs become increasingly learned, temporal decline as an indicator of retrieval activity is questionable. Given the apparently contradictory findings of Small et al. and Zeineh et al., the question of whether or not the same hippocampal circuitry may both form associations and recall them remains unanswered. Resolution of this issue is important for understanding the function of the hippocampus, as many existing computational modeling studies have proposed mechanisms by which a recurrent associative network may perform two tasks with seemingly contradictory demands: (1) classifying an input as novel and encoding a new representation for it, and (2) identifying an input as a retrieval cue for a previously experienced episodic memory, thus recalling further details (O'Reilly and Norman, 2002; Treves and Rolls, 1992).

To assess the degree to which the same structures may participate in both of these processes, we conducted a two-part experiment, consisting of separate encoding and retrieval scans. In the first part, subjects were shown word pairs under instruction to memorize the response word that went with each cue word. Analysis of this phase allowed us to test for effects of novelty and relative success (between subjects), both of which are theorized to reflect encoding processes. In the second part of the experiment, subjects were shown single cue words under instructions to covertly generate the correct paired associate. A written test immediately following the fMRI scanning was used to assess the overall performance of each subject, and also to classify individual cued recall trials as successful or unsuccessful. In this way, both encoding and retrieval were indicated by specific comparison effects established by previous studies, rather than the more ambiguous method of comparing signal level during different task conditions within a run. The results of each specific comparison, as well as conjunction analyses of the effects, are presented here to elucidate the degree to which associative encoding and retrieval operations may have overlapping anatomical distributions.

Methods

Subjects

MRI scanning was performed on 12 healthy volunteer subjects, (age range 21–30, 4 female, 2 left handed), all of whom were students or employees of Yale University. All subjects were neurologically and psychologically normal, native speakers of English. Each gave informed consent for the study, and was paid for his or her participation. Visual stimuli were generated using an Apple Power Macintosh computer running the program Psyscope (Cohen et al., 1993), and projected to a screen visible to subjects in the scanner using an LCD projector.

Encoding task

Thirty word pairs were generated, for a total of 60 words. All words were common, monosyllabic concrete nouns in English, and only words without common semantic associations between them

were selected as members of a pair (Postman and Keppel, 1970). The pairs were divided arbitrarily into three sets of 10. For each subject, one set of 10 pairs was designated as the "easy" set, to be presented 12 times over four imaging runs. The other two sets were designated as "hard" sets, each to be presented only twice. Each run consisted of an initial 27.5 s baseline of fixation on a central cross, followed by four 27.5-s periods of word pair presentation, each comprising one set, alternating with four periods of fixation. Each run included three presentations of the easy set, and one presentation of one of the two hard sets. The hard sets were interspersed in a fixed order for all subjects. As the encoding task was intended to be a block-design study, the order of individual word pairs within a set was randomized at the time of set presentation and not recorded.

Each word pair presentation consisted of one second of fixation, followed by one second of display of the first word of the pair ("cue word"), followed by 750 ms of display of the cue word together with the second, or "response," word below it. Subjects were instructed simply to memorize the associations as best they could, using any strategy they desired.

Retrieval task

After four imaging runs of encoding arbitrary word pair associations, subjects underwent four imaging runs of retrieval testing. This portion of the experiment used an event-related fMRI design. Each run consisted of 15 presentations of single cue words. Each presentation comprised a display of a cue word for 2 s, followed by a 14-s fixation period. In total, "easy" words were presented 30 times across the four runs (each word three times). "Hard" words were also presented 30 times, each one appearing once or twice, because there were twice as many hard words as there were easy words. Subjects were instructed to attempt to generate the correct response word using covert speech. After imaging, subjects were given a written test consisting of the 30 cue words to evaluate which associates they successfully retained. This written test was used to generate overall performance scores for each subject on easy and hard words, and was also used to identify individual retrieval trials as "correct" and "incorrect" based on whether or not they remembered the specific associates for those trials immediately after the retrieval scans.

fMRI imaging parameters

Functional MR imaging was performed on a 1.5-T MRI system with standard quadrature head coil. First, a T1-weighted sagittal localizer scan was performed to locate the hippocampal formation in each subject. Using a sagittal T1-weighted slice through the left MTL in which the hippocampus was clearly observed, 16 coronal oblique slices were defined perpendicular to the long axis of the hippocampus. The seventh slice was centered on the anterior end of the hippocampus, such that the area imaged included the entire temporal lobe and frontal cortex except for the most anterior regions, extending back to the posterior end of the corpus callosum (Fig. 1). Both T1-weighted anatomical images and EPI BOLD images were acquired in this coronal oblique orientation. Imaging parameters for EPI-BOLD images were as follows: TE = 50, TR = 1500, FOV = 20 cm, flip angle = 77°, matrix size = 64 × 64. The first four images of each run were discarded to assure that magnetization had reached steady-state levels for images used in statistical analysis.

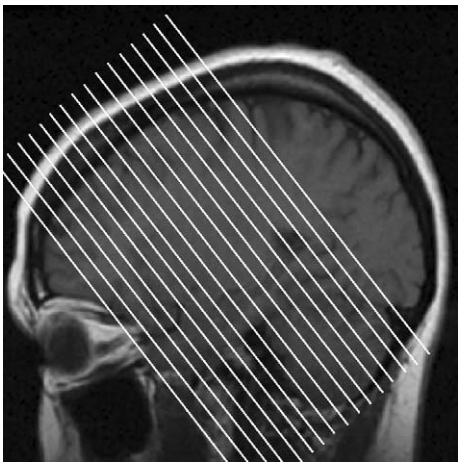

Fig. 1. A: Illustration of the coronal-oblique slice acquisition paradigm. 16 slices were defined perpendicular to the long axis of the hippocampus, with the anterior end of the hippocampus at the eighth slice.

Image analysis

The following preprocessing steps were applied to all functional images prior to statistical analysis: masking of non-brain voxels using Brain Extraction Tool (Smith, 2002), motion-correction using the AFNI program 3dvolreg (http://afni.nimh.nih.gov), temporal smoothing (3-point linear filter with weights 0.15–0.70–0.15), and normalization of each voxel's time course to a mean of 100, which facilitates comparisons between runs and subjects by making regression coefficients interpretable as percent signal change.

Within-subject statistical analysis was conducted using a multiple-regression approach, commonly referred to as the general linear model. For encoding runs, this took the form of a boxcar block design. The time-course of word-pair presentation versus fixation was convolved with a gamma density function model of the hemodynamic response (Cohen, 1997) to create regressors of interest. Separate regressors were used for the first presentation of a given set of 10 word-pairs ("novel blocks") and subsequent presentations of the same words in the first two runs ("repeat blocks"). All presentations of word pairs in the last two encoding runs were modeled with a third regressor ("late blocks"). To examine the effect of viewing word-pair presentations versus fixation, a linear contrast combining all three regressors was used. To examine effects of word-pair novelty, a linear contrast of novel blocks versus repeat blocks was used.

In analysis of the cued recall runs, comprising the second half of the experiment, an event-related design was used to examine the magnitude of response to each single word presentation. Preliminary analyses of the timecourses of voxels in the hippocampal region were conducted to select a hemodynamic response model appropriate for this region of the brain. A gamma density function was used as the basic model, as in Cohen, 1997. The parameters of the gamma density function (tau = 1.25, n = 5) were selected by fitting the average response, time-locked to stimulus presentation, in hippocampal ROIs across all subjects, as a slightly more sensitive approach than selecting default values from the literature, which have mainly been derived from visual cortex. A delta function representing times of cue word presentation was convolved with this hemodynamic response function, using separate regressors for word presentations of different conditions

(see Results for the comparisons that were examined). The regression coefficient of the hemodynamic response function was used as the "summary statistic" for linear contrasts and second-level across-subjects analyses.

To combine results across subjects, we used a conventional random-effects analysis. For most comparisons, this involved, at each voxel, entering the regression contrast coefficients from each subject (expressed as percent-signal change) into a one-sample *t* test. For analysis of between-subject effects related to performance, coefficients were entered into a nonparametric two-sample Mann–Whitney *U* test (see Results). Because we had directional hypotheses derived from theory for most contrasts tested, one-tailed significance tests were used except where indicated. Transformations of single-subject coefficient maps into a common space were conducted as follows using FLIRT software (Jenkinson and Smith, 2001): a linear 6-parameter rigid transform was computed between each subject's raw EPI image and high-resolution coronal-oblique anatomical image, followed by an affine 12-parameter transform between the subjects anatomical image and the MNI-152 standard brain template, providing an isotropic resolution of 2 mm for the interpolated statistical images. Transformed images were spatially smoothed with an 8-mm FWHM Gaussian filter in order to facilitate comparison across differences in individual anatomy. Additionally, an average anatomical template of coronal-oblique slices was constructed by coregistering the high-resolution anatomical images of each subject to one representative subject and then averaging. Solely for purposes of display, some final thresholded statistical parametric maps were projected back onto this coronal-oblique template, so that the spatial extent of activations in the medial temporal lobe may be better evaluated by the reader through viewing multi-slice montages.

In order to investigate the overlap between observable effects that relate to the theoretical processes of encoding and retrieval, we employed conjunction analyses to combine activation maps resulting from different comparisons. Conjunction analyses were performed as follows. First, statistical values for each contrast were converted to equivalent *z* scores via their probability density function. Next, the minimum *z* score across the contrasts of interest was taken as each voxel's conjunction value. Note that this approach tests only the hypothesis that a given voxel was activated in all contrasts of interest, and not that the amount of activation in each contrast was equivalent, as done in another common approach to conjunction analysis (Price and Friston, 1997). Thus, the *P* value corresponding to the minimum *z* score constitutes evidence against the null hypothesis that a voxel is not activated in both contrasts of interest, although it may very well be active in one.

Correction for multiple comparisons across voxels within the scanned brain space was performed via a spatial-extent thresholding procedure (Forman et al., 1995). Monte Carlo simulations were used to estimate the number of adjacent voxels that must be jointly activated at a given voxel-wise threshold so that the probability of a single false-positive cluster under the null hypothesis was less than 0.05. In primary comparisons, the search volume included the entire scanned portion of the brain. In conjunction analyses, search space was confined to the larger of two activation maps, masked at the voxel-wise threshold.

Although voxel-based hypothesis testing was the primary means of statistical analysis for this study, we also conducted analyses on hippocampal ROIs defined within each subject individually. This was done in order to derive representative averaged timecourses for the hippocampus during encoding and retrieval. ROIs were manually drawn on each subject's representative EPI image, using a coregistered T1-weighted anatomical scan as a guide to identify voxels clearly located in the left and right hippocampi over three slices, thus covering a longitudinal extent of approximately 21 mm. Timecourses of voxels within each ROI were averaged and normalized to a mean of 100. The four encoding runs of each subject were separately averaged together to produce a grand mean timecourse for the block-design encoding experiment. To compute event-related timecourses from the cued recall experiment, we averaged together trials in each condition, timelocked to the presentation of cue words.

Results

Behavioral

Immediately after completing the functional imaging portion of this study, subjects completed a written test, on which they were asked to write the paired associate word corresponding to each of the 30 cue words presented during the imaging runs. From these tests, each subject was assigned a total score out of 30, and separate sub-scores for the 10 "easy" word pairs (presented 12 times for encoding) and the 20 "hard" word pairs (presented two times each.) Mean scores were 8.42/10 (84%, $n = 12$, SD = 2.1) on easy pairs and 8.8/20 (44%, $n = 12$, SD = 7.4) on hard pairs. Total score out of 30 was used as a measure of performance for each subject in across-subjects analyses of activation related to performance. Four subjects exhibited almost perfect performance, with scores ranging from 27 to 29. The remaining eight subjects performed more modestly, with scores ranging from 3 to 19. Therefore, we separated the subjects into a "good performance" group and a "fair performance" group, to facilitate comparisons of fMRI activation related to relative success in encoding and retrieval. Additionally, the written tests were used to classify each retrieval trial in the event-related imaging runs as "correct" or "incorrect," depending on whether or not the subject had successfully learned each particular word pair association.

Encoding

To identify areas involved in the associative encoding of word pairs, we tested a direct contrast of signal level during the encoding runs between all blocks of word-pair presentation and all blocks of fixation (Fig. 2). This exploratory analysis used a voxel-wise threshold of $P < 0.01$ (2-tailed, so as to reveal task-induced deactivations) and a spatial extent threshold of 244 voxels, to correct for multiple comparisons throughout the brain. Unsurprisingly, performance of the encoding task relative to a fixation baseline resulted in extensive activation throughout lateral prefrontal and medial temporal regions. Deactivations relative to fixation were seen in ventromedial prefrontal cortex, bilateral insula, and in a bilateral posterior medial temporal region straddling the borders of the parahippocampal, lingual and fusiform gyri. (Talairach coordinates are available upon request from the authors). The relevance of this contrast to encoding is questionable, however, as it involved averaging together multiple presentations of the same word pairs, even after many associations had already become well learned. As discussed in Introduction, novelty and relative success effects may be a better index of encoding activity than simple comparison of signal levels across

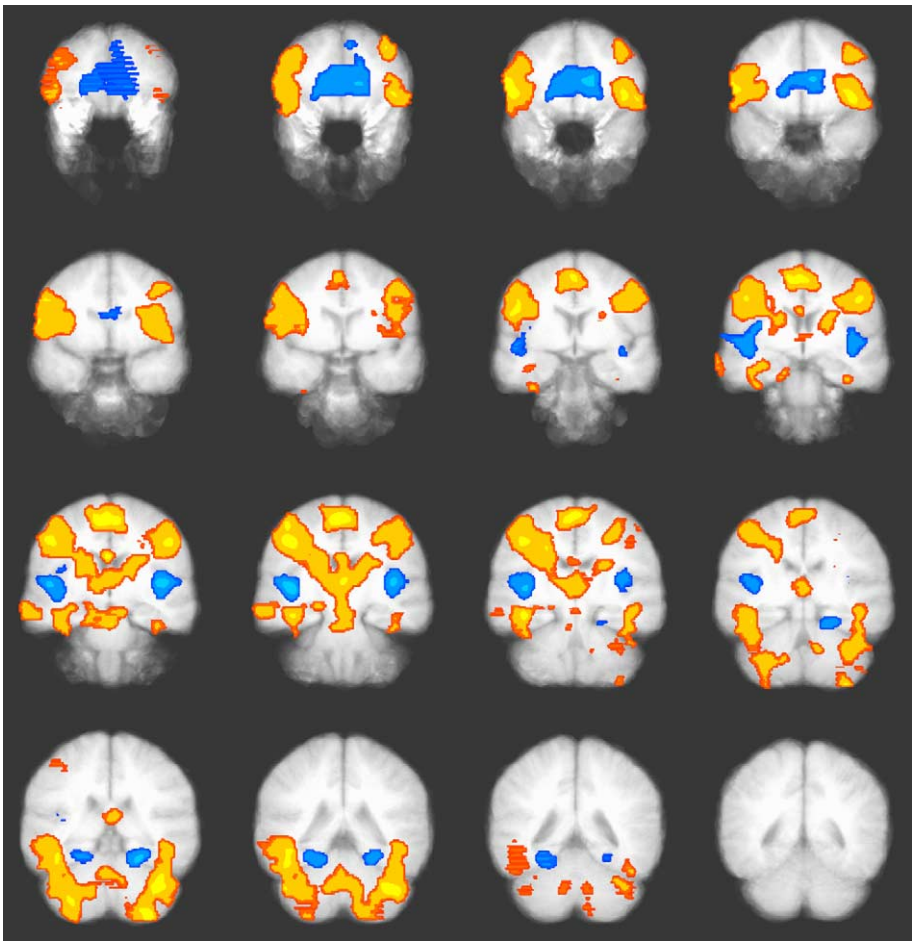

Fig. 2. Activation during encoding of word pairs compared with a fixation baseline. This contrast includes all encoding blocks over four runs. Thresholded at $P < 0.01$ (two-tailed), spatial extent of 244 voxels. Positive activations in red/yellow, negative in blue/purple.

different task conditions. Therefore, we conducted more specialized tests on the encoding data to explore these effects.

To examine effects related to encoding novel word pairs, we tested a linear contrast of encoding blocks within the first two runs alone, since the latter two runs contained only repetitions. As there were three sets of word pairs, each encoding block within the first two runs was classified as either novel ($n = 3$) or repetition ($n = 5$). The activation map of this contrast was thresholded in an identical manner as the encoding vs. fixation comparison, and is displayed in Fig. 3. Extensive activation to novel word pairs, relative to repeated pairs, is evident in bilateral medial temporal areas, as well as in superior and medial prefrontal cortex.

To further characterize the activity of the hippocampus during the encoding of novel and repeated word pairs, we extracted average timecourses of the anatomically defined hippocampal ROIs. The timecourse of hippocampal signal during the first two runs, averaged across voxels and subjects, is presented as the dashed line in Fig. 4, low-pass filtered (5th order Butterworth, cutoff = 0.033 Hz) to emphasize the variability on the time-scale of the experimental design. The fitted general linear model, similarly averaged but unfiltered, is displayed as the solid line. This figure demonstrates that the hemodynamic response to repeated presentation of word pairs is much reduced relative to the novel word pairs presented in the first two blocks, but is restored upon presentation of another novel set in the eighth block.

As selective neural activity to novel stimuli is a common indicator of encoding, we hypothesized that the magnitude of the effect may also predict subsequent memory performance for cued recall of the paired associate words, as subsequent memory success effects are another correlate of brain activity related to memory formation. To test this, we compared the magnitude of activation in the novelty contrast in the two groups of subjects: the four with near perfect recall, and the eight with more mediocre performance. A nonparametric Mann–Whitney U test, robust to small sample size, was used to compare the novelty contrast coefficients in the good group and the fair group. As we were only interested in the voxels showing a significant effect of novelty, the results of this test were combined with the novelty comparison using the minimum z score conjunction procedure described above. A voxel-wise threshold of $P < 0.05$, one-tailed, was employed, requiring a spatial extent threshold of 314 voxels to maintain a family-wise error rate of 0.05. The resulting SPM (Fig. 5) shows that novelty-specific activity in the right hippocampus is indeed higher in subjects who successfully encoded more word pairs.

Cued recall

In the cued recall portion of the experiment, we wished to test the hypothesis that the hippocampal BOLD response to cue words

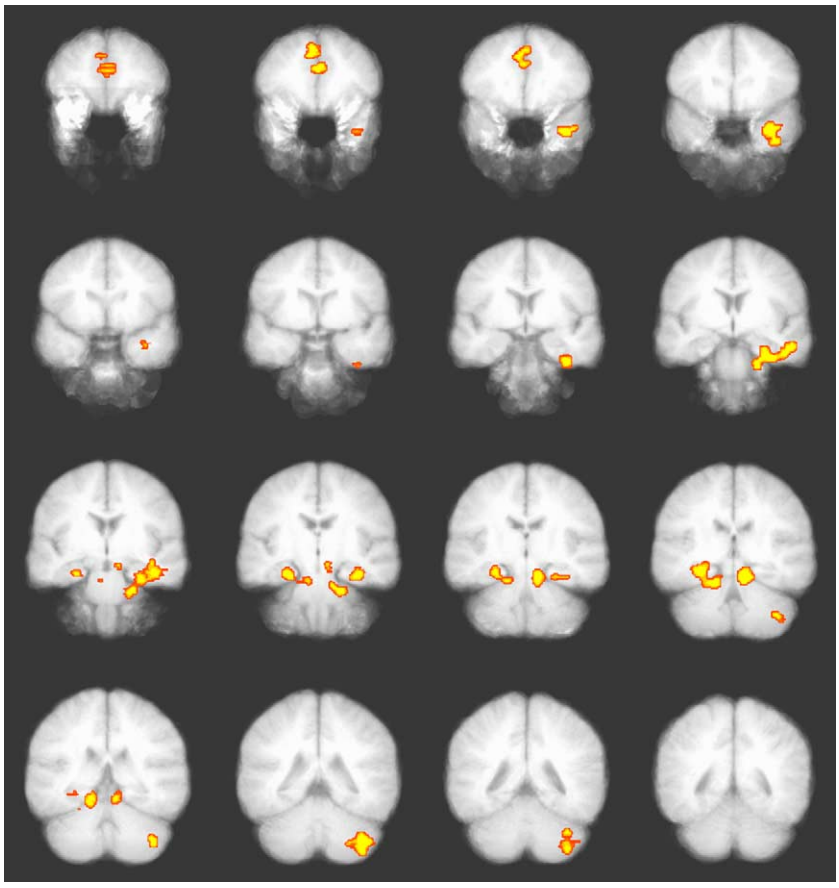

Fig. 3. Areas exhibiting greater activation during encoding of novel word pairs, compared to viewing word pairs that were previously presented, during the first two runs alone. Thresholded at $P < 0.01$ (two-tailed), spatial extent of 244 voxels. No negative activations are present.

was higher for words to which the subject knew the correct paired associate, than for those cue words whose correct response words had been forgotten (or not encoded). The conventional method would have been to estimate the response separately for correct and incorrect trials in each subject, compute a linear contrast, and enter the contrast coefficients into a one-sample t test, treating subjects as a random effect. However, for the four subjects in the "good group," there were insufficient incorrect trials ($n < 5$) to yield a reliable estimate of the hemodynamic response. Therefore, we used two different tests for effects of success in cued recall. The first was to proceed exactly as just described, but limiting the analysis to the eight subjects with poorer performance. Applied to the anatomically defined hippocampal ROI timecourses, this contrast was highly significant on the right [$t(7) = 3.23$, $P < 0.01$], but not quite on the left [$t(7) = 1.64$, $P = 0.073$], although there was no significant difference in the effect size between the two sides [paired $t(7) = -0.383$]. As another test of recall success effects, we collapsed all recall trials into a single condition and calculated one regression coefficient for the response to cue words. The Mann–Whitney procedure was then used to test whether the response was greater in the higher-performance group. On the ROI data, the Mann–Whitney U test was again significant on the right [$W = 27$, $p = .036$] but not on the left [$W = 22$, $p = .184$]. Parametric t tests gave a similar result. The voxel-wise results of these two tests were combined using conjunction analysis and are displayed in Fig. 6. Again, a voxel-wise threshold of $P < 0.05$ was used, with a spatial extent threshold of 346 voxels.

To make sure that these effects were due specifically to recall success and not confounded by other factors, we subdivided trials into different conditions. First, using all 12 subjects, we divided the 60 cue trials into 30 "easy" words, whose pairings had been viewed 12 times during the encoding scans, and 30 "hard" words, whose pairings had been viewed only twice. No significant MTL activation was detected for this contrast. On the ROI data, two-tailed t test results were [$t(11) = -.0451$] on the right and [$t(11) = -1.15$] on the left. Next, we tested for effects of cue word novelty. We re-divided the 60 trials into 30 "novel" trials, in which a given cue word was presented for the first time in the context of cued recall, and 30 "repeat" trials, in which a cue word was seen for the second or third time. Once again, no significant activation related to this distinction was observed. Two-tailed t tests applied to ROI data were [$t(11) = -1.13$] on the right and [$t(11) = 1.46$] on the left. Finally, using the eight subjects with fair performance, we divided trials into four conditions—"correct novel," "correct repeat," "incorrect novel," and "incorrect repeat." This allowed us to test for main effects of success and novelty, an interaction effect between the factors, and for simple effects. Because hippocampal activation is known to be sensitive to stimulus novelty, we wished to see whether the success effects were limited to the first presentation of a given cue word. In fact, the opposite appeared to be true. As before, the main effect of success was significant on the right in ROI data, and just under significance on the left. Although no significant main effect of novelty or interaction effect was detected, the simple effect of "correct repeat" vs. "incorrect repeat" was highly significant on both sides [right:

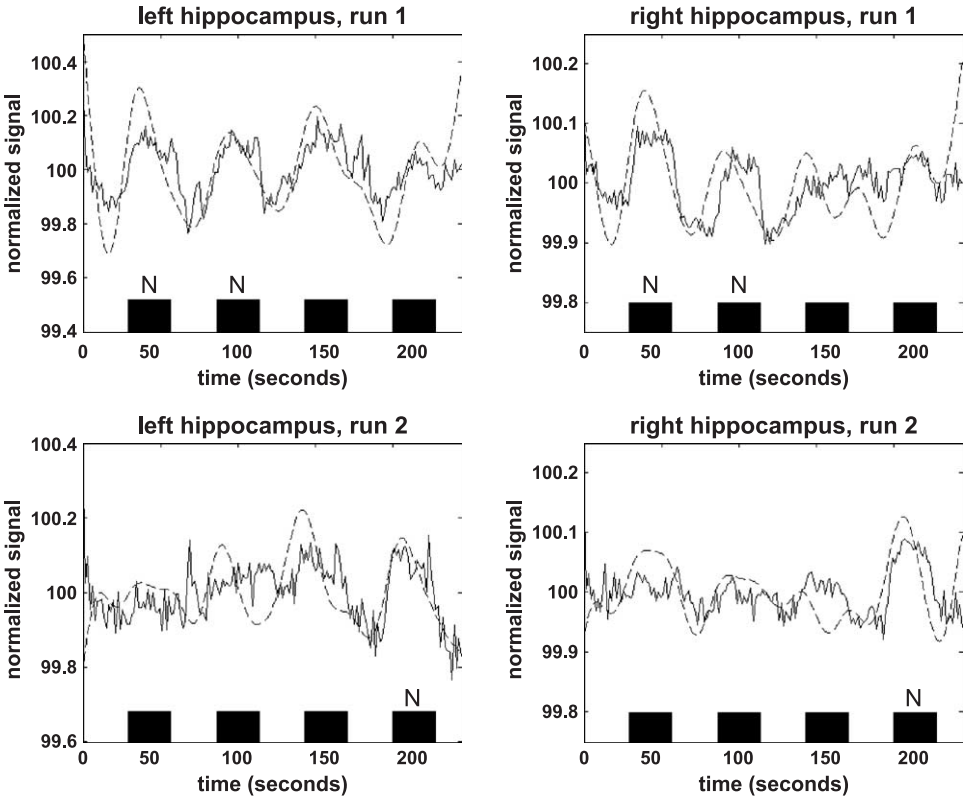

Fig. 4. Dashed line: fMRI timecourse in the left and right hippocampi during the first two encoding runs, averaged across voxels, low-pass filtered, and averaged across subjects. Solid line: fit timecourse from the general linear model used in statistical analysis, unfiltered, and averaged across subjects. Blocks indicate time periods of word pair presentation, while intervening time periods were occupied by a fixation condition. Periods when a set of word pairs was presented for the first time are marked with an "N", for novel.

$t(7) = 2.60$, $P = 0.018$; left: $t(7) = 2.43$, $P = 0.022$], while the simple effect of "correct novel" vs. "incorrect novel" was not significant [right: $t(7) = .218$, $P = 0.417$; left: $t(7) = 0.033$, $P = 0.488$]. This suggests that the success effects may be present primarily on repeated presentations of cue words, rather than on the first presentation. Such a difference would be expected to manifest itself as a significant interaction effect, calculated as a linear contrast of correct novel and incorrect repeated trials vs. correct repeated and incorrect novel trials. In fact, such a trend is apparent on both sides (right: $t(7) = -1.76$, $P = 0.123$, left: $t(7) = -2.05$, $P = 0.080$), but not significant. These trends reflect the fact that the strongest responses in the group with poorer performance are those to correct repeated trials. In the four subjects with near perfect performance, however, responses to novel trials are greater than those to repeated trials, though not significantly so. In order to fully tease apart interactions between novelty and success effects in cued recall, a different experiment optimized to examine this distinction would be desirable. As this question is not central to the hypotheses of interest in the current experiment, we will not discuss it further.

As an additional illustration of the effects of success on hippocampal timecourses in cued recall, we averaged together all correct trials ($n = 403$) and incorrect trials ($n = 257$) across 11 subjects. One subject's data (from the high-performance group) were inadvertently acquired with slightly different timing with respect to stimulus presentation, so she was excluded from this analysis. Because stimulus timing was staggered with respect to image acquisition, timepoints at intervals of 0.5 s were averaged and then resampled to the TR of 1.5 s, to produce left and right hippocampal timecourses for correct and incorrect trials. Fig. 7 presents these averaged timecourses, along with estimated gamma density function responses fitted to the timepoints using the same parameters used in the statistical analyses. These plots demonstrate that there is very little response to incorrect trials. However, they represent a collapsing of within-subjects and across-subjects effects, and so it is important to refer to the random effects analyses discussed above in order to make statistical inferences on the differences.

Overlap of encoding and retrieval effects

The primary goal of this experiment was to test the hypothesis that both encoding and retrieval of associative memories may engage specific neuronal processing in the same regions of the hippocampus, under the premise that novelty and subsequent memory effects index encoding, while recall success effects index retrieval processes. The conjunction of novelty and subsequent memory effects in encoding is represented by the activation map presented in Fig. 5, while effects of retrieval success, both within and between subjects, are represented by the map in Fig. 6. Having obtained these maps, we then conducted further analyses to determine the extent to which activations related to encoding and retrieval overlap in the MTL and other areas. In Fig. 8, we present a series of coronal slices in MNI space, on which are superimposed activation maps for the novelty and subsequent memory conjunction analysis (green color), and the retrieval success conjunction analysis (orange color). Voxels jointly activated in both analyses are colored in red. Encoding-related activity in the right MTL comprises a

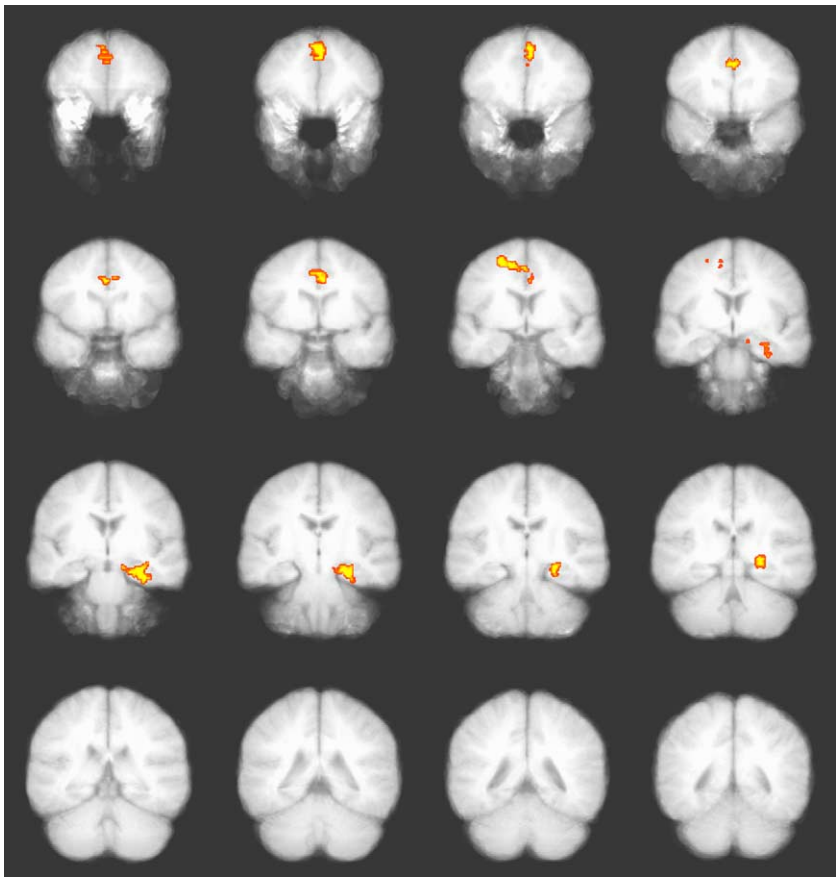

Fig. 5. Areas in which the amount of activation for novel vs. repeated word pairs was greater in the high-performance group than in the other subjects, conjoined with activation map for novel vs. repeated word pairs overall. Conjunction map, thresholded at $P < 0.05$ (one-tailed) for both contrasts, spatial extent of 314 voxels.

spatially continuous cluster of 329 voxels, with a center-of-mass located within the hippocampal formation (Talairach coordinates $x = 25.7$, $y = -24.8$, $z = -13.9$). Retrieval-related activity in the right MTL comprises a spatially continuous cluster of 489 voxels, with a center-of-mass also located in the hippocampal formation (Talairach coordinates $x = 16.6$, $y = -27.4$, $z = -7.2$), but extending somewhat more posteriorly. Overlap between the two clusters comprises 80 voxels, with a center-of-mass in the hippocampal formation (Talairach coordinates $x = 23.6$, $y = -29.6$, $z = -8.2$).

As an additional test of overlap between activity related to encoding and retrieval, we conducted one grand conjunction analysis involving all five contrasts previously enumerated:

(1) encoding vs. fixation (Fig. 2),
(2) novel vs. repeated word pairs (Fig. 3),
(3) good performers novelty vs. fair performers novelty (conjoined with contrast #2 in Fig. 5)
(4) correct vs. incorrect recall within fair-performing subjects (conjoined with contrast #5 in Fig. 6),
(5) good performers recall vs. fair performers recall (conjoined with contrast #4 Fig. 6).

As before, conjunction maps were constructed by assigning the minimum z score across all five contrasts to each voxel. In each contrast, tests were one-tailed, based on directional hypotheses. This analysis produces results similar to those obtained by simply assessing the overlap between the encoding and retrieval related clusters in the MTL, as displayed in Fig. 8. However, it also allows us to examine whether any other locations in the brain demonstrated a conjunction of all of these effects. Furthermore, the inclusion of the first contrast, encoding vs. fixation, allows for the exclusion of areas that are not positively activated during the encoding task compared with fixation. This facilitates interpretation of the data, as significant task-induced deactivation was observed in both medial temporal and prefrontal regions in the two-tailed comparison presented in Fig. 2. The map resulting from the minimum z score conjunction of all five contrasts was thresholded at $P < 0.05$, with a spatial extent threshold of 24 voxels. As expected, a region in the right hippocampus (Figs. 9A–B) was detected, representing maximal overlap between encoding and retrieval related activity in the medial temporal lobe. This activation was located approximately in the middle of the longitudinal extent of the hippocampus, with Talairach coordinates $x = 23.7$, $y = -30.0$, $z = -8.2$. One other significant cluster was detected, at the left occipitotemporal junction (Figs. 9C–D), with Talairach coordinates $x = -51.0$, $y = -50.6$, $z = -16.7$. As two of the five conjoined contrasts involve comparisons across subjects at different performance levels, we present in Fig. 10 scatter plots of the individual subjects' percent signal change values at the centroid voxels of the two regions highlighted in Fig. 9. These plots demonstrate the range of individual variability in encoding

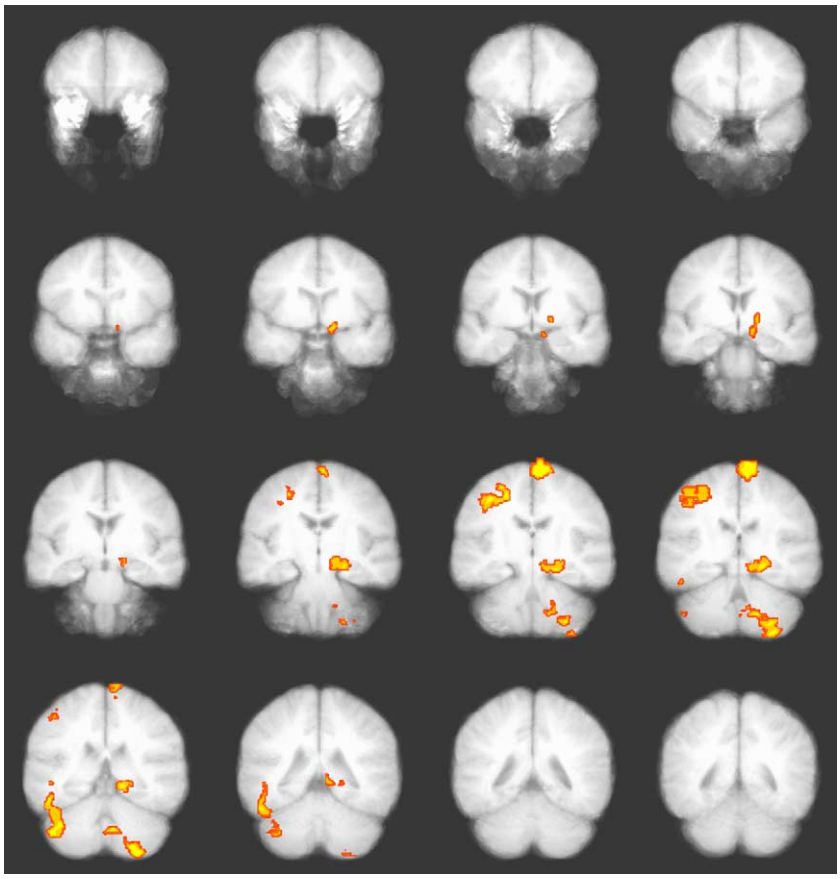

Fig. 6. Conjunction of two contrasts testing for selective activation related to success in cued recall: (1) areas exhibiting greater evoked responses to cue words for which the correct paired associate was known, compared to those for which it was not known. Analysis restricted to the eight subjects with poorer performance, as the other four subjects had too few incorrect trials to analyze. (2) Areas exhibiting greater averaged evoked responses to all cue words in the four-subject high-performance group compared to the other eight subjects by a nonparametric Mann–Whitney *U* test. Conjunction map, thresholded at $P < 0.05$ (one-tailed) for both contrasts, spatial extent of 346 voxels.

novel vs. repeated word pairs and in cued recall, and also the extent to which the subjects with near-perfect performance tended to exhibit stronger activation in these contrasts.

In order to verify that the timecourses derived from anatomically specified hippocampal ROIs were representative of the region surviving the five-way conjunction analysis, we warped the

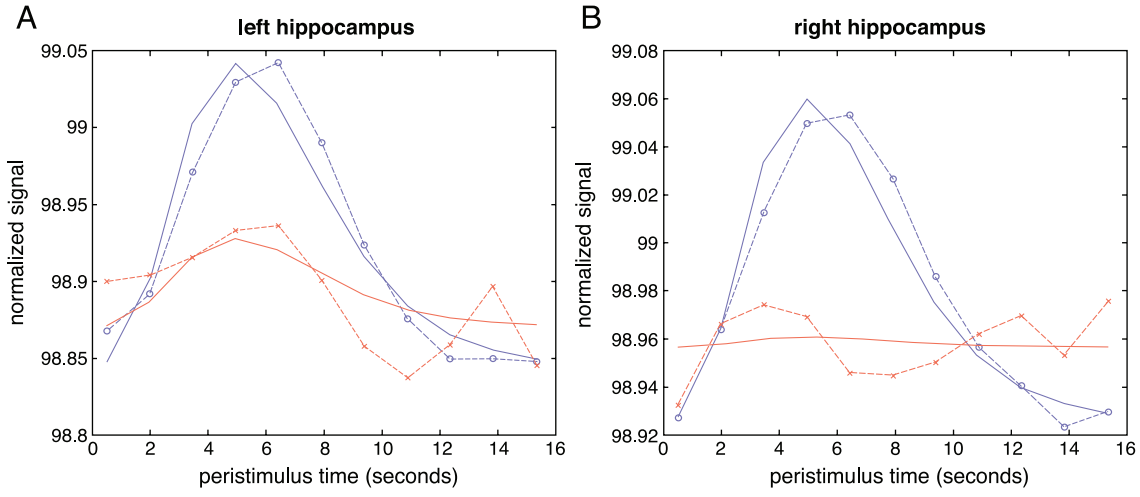

Fig. 7. Composite timecourses of right and left hippocampal evoked responses to cue words, time-locked to stimulus presentation, averaged across voxels and across 11 subjects, and resampled to the TR of 1.5 s. Blue circles are averaged timepoints from all correct trials ($n = 403$) in all subjects, while the solid blue line is the gamma density function regression of this timecourse, using the same parameters as in the voxel-wise analysis. Red X's are averaged timepoints from all incorrect trials ($n = 257$), while the solid red line is the regression of the incorrect timecourse.

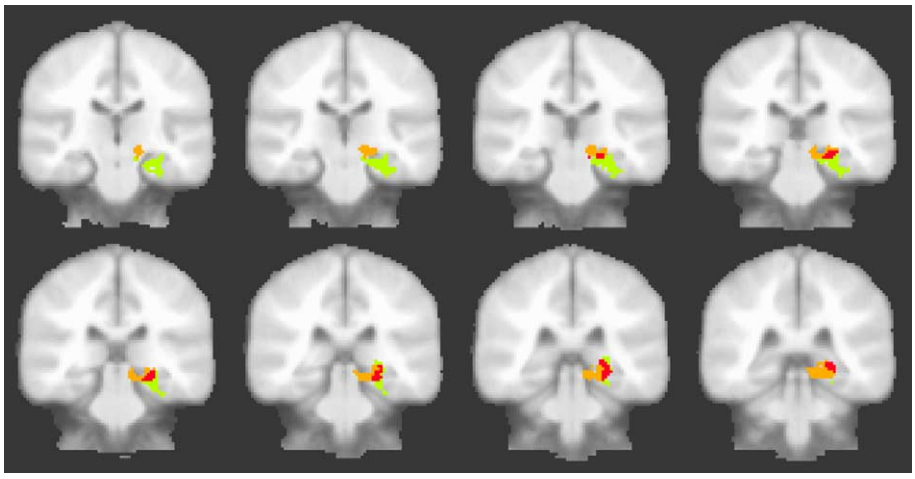

Fig. 8. Eight 2-mm-thick coronal slices in MNI space illustrating the overlap of encoding and retrieval related activations in the right hippocampus. Slices range from 21 mm posterior to 35 mm posterior in the MNI coordinate system. Green color: activations resulting from the novelty and encoding success conjunction analysis (Fig. 5). Orange color : activations resulting from the cued recall success conjunction analysis (Fig. 6). Red color : overlap between the two.

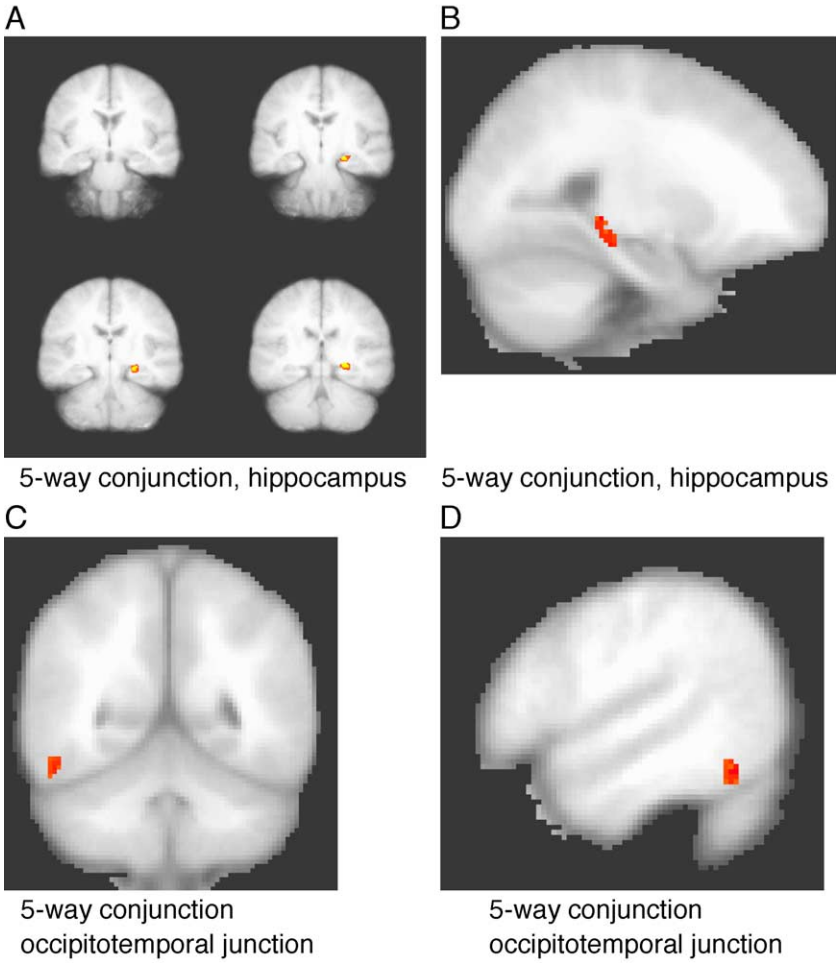

Fig. 9. Conjunction analysis of voxels significantly activated in five different comparisons: (1) encoding vs. fixation, (2) encoding of novel word pairs vs. repeated word pairs, (3) greater novelty-related activation in the high-performance subjects, (4) greater response to correct cued recall trials than to incorrect trials in the poorer-performing eight subjects, and (5) greater cued recall activation across all trials in the high-performance group relative to the other eight subjects. (A) Coronal view of the right hippocampal activation, in averaged anatomical space from 12 participants, slices perpendicular to long axis of hippocampus. (B) Sagittal view of the right hippocampal activation, in MNI space. (C) Coronal view of the left occipitotemporal activation, in MNI space. (D) Sagittal view of the left occipitotemporal activation, in MNI space.

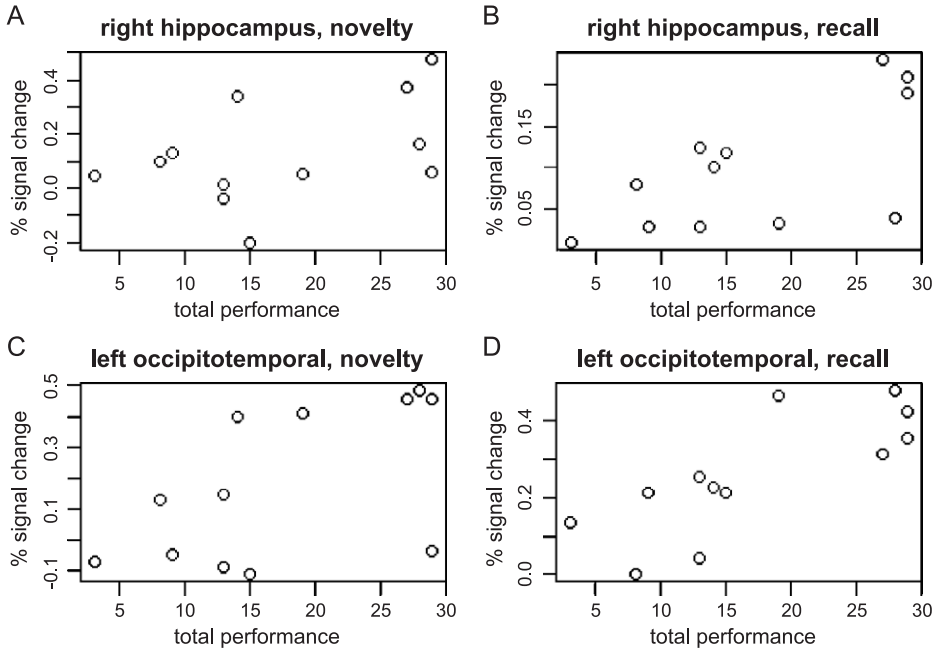

Fig. 10. Individual subject beta weights in centroid voxels of clusters surviving 5-way conjunction analysis: relationship with memory performance. (A) Novel vs. repeated word pairs during encoding, in right hippocampus. (B) Total average response to cue word presentation during cued recall, in right hippocampus. (A) Novel vs. repeated word pairs during encoding, in left occipitotemporal cortex. (B) Total average response to cue word presentation during cued recall, in left occipitotemporal cortex.

statistical map of the conjunction analysis back into the anatomical space of each individual subject, and visually evaluated the overlap between the activated region and the anatomically defined right hippocampal ROI. In every case, the activated region was contained almost completely within the anatomically defined ROI (data not shown), such that the ROI timecourses represent a superset of the activated voxels on the right, and of their homologous counterpart on the left.

Discussion

We have reported here a study of both encoding and cued recall of paired associate words. We have shown positive effects of both novelty and subsequent memory success on hippocampal fMRI signal levels during viewing of word pairs, indicative of the encoding of associative information into memory. We have also shown positive effects of success in cued recall of the same word pairs, indicative of the retrieval of these associations from hippocampal storage. Furthermore, we have demonstrated that associative encoding and retrieval effects overlap considerably in the main body of the hippocampus. Elsewhere (Meltzer and Constable, 2004), we have presented a much more extensive review of the large body of evidence, from neuroimaging and other sources, in support of our assertion that novelty and success effects are the best available indices of encoding and retrieval of episodic memories. The current results suggest that the formation of an associative memory trace in the hippocampus and the retrieval of such a trace from a cue are both operations that may result in an increase in local metabolic demand and/or blood flow. Although these results are hardly surprising given the critical role of the hippocampus in the neuropsychology of memory, the demonstration that both operations result in a BOLD increase in the same region has important implications for a theoretical understanding of how the hippocampus supports episodic memory.

A number of computational models of hippocampal function in episodic memory have been proposed. For example, an extensive body of work using parallel distributed processing models (reviewed in McClelland et al., 1995; O'Reilly and Norman, 2002) has explored the complementary roles of neocortex and hippocampus in memory. This work has suggested that the neocortex learns slowly and extracts generalizations (i.e., semantic memory) from a multitude of experiences, whereas hippocampal structures learn quickly and maintain separate memories of distinct experiences (i.e., episodic memory), which are used to gradually update neocortical representations. In order to function well in this role, the hippocampal formation must be able to perform two operations that have conflicting demands. In *pattern separation*, a novel stimulus must be recognized as novel and encoded into memory with its own distinct representation. In *pattern completion*, an input must be interpreted as a retrieval cue, initiating a restoration of neural activity related to a previous experience. The challenge is to allow pattern separation to proceed without recall processes interfering with them, and vice-versa. Simulations have indicated that both processes are indeed feasibly implemented by a single network.

In lower-level neuronal modeling work, based on biophysical and computational constraints imposed by hippocampal cytoarchitecture, Treves and Rolls (1992,1994) have proposed that encoding of novel patterns and retrieval of stored ones are accomplished by an autoassociative network in the hippocampal subregion CA3, although the two processes may reflect differential engagement of input mechanisms from surrounding subregions. Although the resolution of EPI-based fMRI is not able to easily localize neuronal activity within individual substructures of the hippocampus (e.g., CA1, CA3, dentate gyrus), due to their small

volume and shared blood supply, the present results are at least consistent with the models mentioned above. As seen in the conjunction analyses of Figs. 8 and 9, activations related to novelty and success in encoding and in retrieval occupy closely neighboring regions of the medial temporal lobe, with overlap maximal at a medial superior part of the MTL, corresponding to the approximate location of the dentate gyrus and hippocampus proper. Therefore, the present results provide empirical evidence in humans that an autoassociative network located in the hippocampus proper may participate in both pattern separation and pattern completion.

A primary role of the hippocampus (as opposed to surrounding MTL structures) in the formation and recall of associative memories is amply supported by other recent neuroimaging studies. A number of studies have reported specific hippocampal activations related to overtly associative encoding demands (Davachi and Wagner, 2002; Sperling et al., 2001) and subsequent associative memory success (Davachi et al., 2003; Jackson and Schacter, 2004). On the retrieval side, hippocampal-specific activation has been linked to correctly recalling episodic details of a previous exposure to an item, beyond mere familiarity (Dobbins et al., 2003; Eldridge et al., 2000). The proposal that familiarity and recall are dissociable processes, with the latter relying more on the hippocampus, is discussed at length in Rugg and Yonelinas (2003) and in Brown and Aggleton (2001).

Finally, a few studies have examined both encoding and cued recall of face–name pairs. Small et al. (2001) found overlapping activation along the long axis of the hippocampus during both encoding and cued recall of face–name pairs, in a pattern that was not a simple summation of activation seen to faces and names in isolation. Zeineh et al. (2003) found a novelty encoding effect localized to hippocampal area CA2/CA3 and/or dentate gyrus (DG), similar to the novelty effect seen in the present study. Zeineh et al. also report an effect of cued recall centered on the subiculum, in the form of a temporal decline in activation as more associations are correctly recalled, analogous to the decline in encoding activity in CA2/CA3/DG. To date, however, there is no precedent for interpreting a temporal *decline* in activity with greater retrieval success as indicative of retrieval operations, whereas increased activity in the MTL under conditions of greater retrieval success is a common finding (Daselaar et al., 2001; Dobbins et al., 2003; Gabrieli et al., 1997; Nyberg et al., 1995). The authors did not sort individual trials as correct and incorrect as was done in the present study. Thus, it is possible that the results of the two studies may agree more closely if such a contrast were examined. The location of maximal overlap between associative encoding and recall identified in our study corresponds closely with the CA2/CA3/DG ROI in Zeineh's study. Additional differences between the two studies are that we used word pairs instead of face–name pairs, and that retrieval activations were based on evoked responses to stimulus presentation, rather than a comparison of signal levels over a longer period of time.

As this study focused on the hippocampal formation, we have not discussed the extensive body of neuroimaging findings of selective activation related to encoding and retrieval in the prefrontal cortex. Although retrieval success (as opposed to effort/search) does not appear to correlate with prefrontal activity (Buckner et al., 1998a,b), numerous studies have reported prefrontal activity during encoding correlated with subsequent item memory (Brewer et al., 1998; Wagner et al., 1998), recollection as opposed to familiarity (Henson et al., 1999), and source memory (Ranganath et al., 2000). Nonetheless, the mnemonic functions of the MTL and prefrontal cortex have been at least partially dissociated by an elegant experiment by Reber et al. (2002), in which single words were presented along with a cue instructing subjects to either attempt to remember or to forget the word. Although subsequent memory effects were found in both MTL and prefrontal cortex, the prefrontal effects were accounted for by the nature of the cue, suggesting that deliberate effort was involved, whereas the MTL effects were independent of the cue, suggesting that the mnemonic functions of the MTL are more automatic, in some sense independent of conscious effort, even though factors such as attention, arousal, and elaborative processing may certainly influence subsequent memory (Grady et al., 1998). This hypothesis is of course consistent with the nature of the human amnesic syndrome, in which a patient's cognitive abilities may appear to be perfectly normal if the patient is examined for only a short time, within the range of their short-term memory. Furthermore, prefrontal areas activated in encoding and retrieval phases of LTM tasks are also activated in working memory tasks (Ranganath et al., 2003). These results, as well as those of the present study, support the hypothesis that increased neural activity in the hippocampus during associative and episodic encoding (indexed by novelty and subsequent memory effects) and during cued recall, reflect mnemonic processes that are beyond the direct conscious control of subjects.

Finally, we shall briefly discuss the one other brain region found in this study to exhibit differential activation related to novelty, encoding success, and retrieval success for paired-associate words: the left occipitotemporal junction. Numerous neuroimaging studies have implicated this region as being especially involved in reading, to the extent that it has been called the "visual word form area" (Jobard et al., 2003). Although a specialization of this region for reading above all is questionable (Price and Devlin, 2003), its heavy involvement in the process of recognizing words is undisputed. In this light, it is not surprising that memory-related effects were seen in this region, as our task was based purely on words, as opposed to many other memory studies that have used pictures or a combination of words and pictures. The finding of significant effects during both encoding and retrieval of paired associate words in the hippocampus and in a cortical area partially responsible for recognition of words reinforces the popular idea that hippocampal function in memory is a product of specific interactions between multimodal hippocampal circuitry, which incorporates a general mechanism for forming and retrieving associative memories, and neocortical circuitry, which is characterized by greater domain specificity.

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