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Evidence for a Specific Role of the Anterior Hippocampal Region in Successful Associative Encoding

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ABSTRACT: It has been well established that the hippocampal formation plays a critical role in the formation of memories. However, functional specialization within the hippocampus remains controversial. Using functional magnetic resonance imaging (fMRI) during a face-name associative encoding task, followed by a postscan recognition test for face memory and face-name pair memory, we investigated the roles of anterior and posterior hippocampal regions in successful encoding of associations and items. Whole-brain and region of interest (ROI) analyses revealed that the anterior hippocampal formation showed increased activation for subsequently remembered face-name associations compared with pairs that were forgotten. In contrast, the posterior hippocampal formation showed activation above baseline during attempted encoding of face-name pairs, but no evidence of differential activation based on subsequent memory. Furthermore, exploratory whole-brain analyses revealed that a parahippocampal region, most likely corresponding to perirhinal cortex, showed subsequent memory effects for faces. These data provide evidence for functional specialization within the hippocampal formation based on the associative nature of the stimuli and subsequent memory. © **2007 Wiley-Liss, Inc.**

KEY WORDS: medial temporal lobe; hippocampus; fMRI; memory; relational memory

INTRODUCTION

A fundamental aspect of declarative memory function is the ability to form and retain novel associations. Recent work has suggested that there are different encoding mechanisms that support subsequent successful memory for associative versus item information (for review, see Davachi, 2006). This hypothesis has been supported by findings that show that patients with hippocampal lesions can show greater deficits in associative versus item-based memory tasks (Kroll et al., 1996; Yonelinas et al., 2002; Giovanello et al., 2003; Turriziani et al., 2004). Furthermore, several neuroimaging studies have also shown greater activity in the hippocampus for associative versus item memory (Davachi and Wagner, 2002; Giovanello et al., 2004; Jackson and Schacter, 2004; Kirwan and Stark, 2004; Ranganath et al., 2004). In contrast, some neuroimaging studies suggest that the perirhinal cortex may be especially involved in item-based encoding (Davachi and Wagner, 2002; Kirwan and Stark, 2004; Ranganath et al., 2004).

Although it has been acknowledged that the hippocampal formation is important in associative memory, it remains unclear whether the hippocampal formation functions as a single unit, or if specific regions along the longitudinal axis have different functional roles. Evidence presented in a meta-analysis of earlier functional neuroimaging studies led to a hypothesis about a more specific relationship between the anterior portions of hippocampal formation and associative or relational memory (Schacter and Wagner, 1999). Three kinds of evidence lend support to this hypothesis. First, subsequent studies have showed greater activity in anterior portions of the hippocampal formation during encoding of associative information compared to item-based encoding (Davachi and Wagner, 2002), and also to retrieval (Pihlajamaki et al., 2003). Second, comparisons of successful versus failed associative encoding have shown greater activity in the anterior hippocampal formation for a variety of stimuli, including word pairs (Giovanello et al., 2004; Jackson and Schacter, 2004), word triplets (Davachi and Wagner, 2002), and face-name pairs (Sperling et al., 2003b; Zeineh et al., 2003). Third, comparisons of novel and repeated associative stimuli have shown greater activity in anterior portions of the hippocampal formation (Sperling et al., 2001; Kohler et al., 2002, 2005).

Many functional neuroimaging studies (Small et al., 2001; Jack et al., 2002; Sperling et al., 2003b; Henson, 2005), have characterized hippocampal activation based on its location along the longitudinal axis, rather than on basis of anatomic or cytoarchitectural divisions within the hippocampal formation. This is not merely a product of the limited spatial resolution

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of standard fMRI sequences because high resolution fMRI studies, which have been able to distinguish some hippocampal subregions (Zeineh et al., 2000, 2001, 2003; Eldridge et al., 2005), report activations within anterior portions of specific subregions.

The hypothesis of functional differentiation along the longitudinal axis of the hippocampal formation shows strong support from neuroanatomical evidence. Specific cytoarchitecturally defined regions, such as the CA3 fields, are interconnected along the longitudinal axis of the hippocampal formation (Amaral and Witter, 1989), thus providing a mechanism for functional differentiation. Furthermore, different regions along the longitudinal axis have different afferent and efferent projections (Witter et al., 2000). The dorsal regions of the hippocampus receive more sensory inputs, whereas the more ventral regions receive more limbic inputs (Burwell et al., 1995; Dolorfo and Amaral, 1998; Witter et al., 2000). Furthermore, even within a cytoarchitecturally defined region, there may be differential expression of genes along the dorsal-ventral axis (Leonardo et al., 2006). Thus converging evidence from neuroanatomy and genetics indicates potential for a functional distinction based on position along the longitudinal axis of the hippocampal formation.

Despite plausible neuroanatomical mechanisms coupled with several neuroimaging findings, more recent reviews have not found a definitive case for functional specialization based on associative or relational processing, either along the longitudinal axis of the hippocampal formation, or between the hippocampal formation and surrounding medial temporal cortices (Squire et al., 2004; Henson, 2005). Some studies have shown that patients with hippocampal lesions are not selectively impaired for associative tasks, but show similar impairments on item-based tasks (Stark et al., 2002; Stark and Squire, 2003). In addition, some fMRI studies comparing subsequent memory for successful associations versus items have not shown differences in anterior regions, and instead have shown differences in activation in mid-hippocampal regions (Kirwan and Stark, 2004). Moreover, one block design study that specifically examined circuitry along the longitudinal axis showed that associative encoding activated mid-hippocampal regions (Small et al., 2001).

Despite conflicting evidence in the literature, we propose that the anterior hippocampus shows functional specialization for successful associative encoding compared with the posterior hippocampus. Our previous work has suggested that the anterior hippocampal formation shows greater activation for face-name pairs that are subsequently remembered with high confidence compared to those that are forgotten (Sperling et al., 2003b). We also found that, when comparing successfully encoded face-name pairs to visual fixation, the entire longitudinal extent of the hippocampal formation was activated. However, the middle and posterior hippocampal regions did not show statistically different activation levels based on subsequent associative memory performance; that is, in contrast to the anterior hippocampal formation, we did not observe greater activation for face-name pairs that were subsequently remembered with high confidence compared to those that were forgotten. Importantly, though, our previous study tested only subsequent associative memory, and not item memory. Thus, there are two possible alternative explanations for the pattern of activation in the middle and posterior hippocampal regions: (1) the activation was related to subsequent item memory or (2) was related to the associative processing demands of the task. If the posterior activation were related to item memory, we would expect these regions to show subsequent memory effects for faces within the face-name pair. However, if the posterior activation were related to the task demands of processing two associated stimuli, we would expect this region to be active in all conditions during an associative encoding task, regardless of subsequent memory. In the current study, we use a face-name associative encoding task with a more extensive postscan memory test to probe both associative and item memory to clarify the roles of the anterior and posterior hippocampal regions in successful encoding of face-name associations.

Supporting evidence for functional specialization along the longitudinal axis of the hippocampus would include showing a region $\times$ memory interaction. Thus far, the majority of evidence supporting a special role for the anterior hippocampus in successful associative encoding comes from studies showing greater activation in the anterior hippocampus for subsequently remembered associations than for subsequently forgotten associations (Sperling et al., 2003b; Jackson and Schacter, 2004), and conflicting evidence showed either no subsequent memory effect in the hippocampus or shows the effect in a different hippocampal region (Kirwan and Stark, 2004). However, the majority of these studies have not tested for region $\times$ memory interactions. Our hypothesis for functional specialization for successful associative encoding along the longitudinal axis has, to our knowledge, not been directly tested using interaction analyses. A block design study did test for interactions based on item or associative encoding and position along the longitudinal axis, but could not directly test subsequent memory effects (Small et al., 2001). Event-related studies that have tested for functional specialization based on subsequent associative memory have focused on differences between the hippocampus and the surrounding medial temporal cortex, but not position along the longitudinal axis (Kirwan and Stark, 2004). In the current study, we aim to help resolve conflicting reports in the literature about the hypothesized specialization of the anterior hippocampus for successful associative encoding by testing for interaction effects based on position along the longitudinal axis, subsequent item memory, and subsequent associative memory.

MATERIALS AND METHODS

Participants

Written informed consent was obtained from 20 healthy, young, right-handed adults in accordance with the Human Research Committee at Brigham and Women's Hospital, Boston, MA. All subjects were free from psychiatric or neurologic disorders, were not taking medications with central nervous sys-

tem effects, and had no contraindications for MRI. Data from 18 subjects were analyzed (14F/4M, ages 20–30), and data from two subjects were excluded due to scanner malfunction. Only partial data, approximately the first half of each functional run, from another subject was used due to stimulus presentation malfunction.

Functional Magnetic Resonance Imaging Acquisition

Subjects were scanned on a General Electric Signa 3T scanner (General Electric Medical Systems, Milwaukee, WI). Whole-brain images were collected using a gradient echo echo-planar pulse sequence (TR = 2,000, TE = 30, flip angle = 90, 3.75 × 3.75 mm^2 in-plane resolution). Twenty-eight slices (5 mm, skip 1 mm) were collected in an oblique coronal orientation perpendicular to the anterior commissure-posterior commissure line. Data from the first four time points were discarded to allow for MR stabilization. A total of 149 time points were collected for each of five functional runs.

Face-Name Associative Encoding Task

We used the identical face-name associative encoding paradigm during scanning to our previous event-related encoding studies (Sperling et al., 2003b; Chua et al., 2004), but used a different and more extensive postscan recognition test that probed both memory for the face and for the face-name pair. Stimuli consisted of unfamiliar faces presented against a black background with the name printed in white underneath. First names were assigned based on census data of popular first names obtained from the internet by decade. A total of 455 face-name pairs were presented for 1.75 s each and followed by 0.25 s of visual fixation. Fixation periods consisted of a white crosshair presented against a black background, and subjects were instructed to passively view the cross. Each face-name trial was then followed by varying periods of interstimulus fixation ranging from 0 to 10 s (mean = 2.84 s) using an optimized (Available at: http://surfer.nmr.mgh.harvard.edu/optseq) "jittered" event-related design (Dale, 1999). The stimuli were presented in five encoding runs and lasted 4 min and 50 s. Each run ended with 10 s of fixation in order to capture the hemodynamic response for the final trial of interest.

In an intentional associative encoding task, subjects were instructed to try to remember the name associated with the face for later testing. They also made a purely subjective decision about whether the name "fit" the face and indicated with a button press if "yes" the name fit the face or "no" the name did not fit the face. This task was chosen to ensure that subjects attended to both the face and the name and processed them associatively. Thus, the processing demands of our encoding task were associative.

Postscan Memory Test

We utilized a postscan recognition test outside of the scanner that tested subjects for memory of the face and then the name associated with the face. Approximately 20 min after scanning, subjects completed a self-paced recognition test that included all 455 faces seen during encoding plus 200 distracter faces across five memory test runs. The test consisted of two phases: a face recognition test and a face-name associative recognition test. First, subjects indicated whether or not each face was previously seen at study, and then whether they had high or low confidence in their decision. If the face was a foil, meaning that it was not seen during the study phase, subjects completed only the face test, and did not perform the face-name associative memory test. Subjects were not informed that they would only complete the face-name associative task for studied faces; nevertheless, this design did give subjects some feedback on their memory performance for faces. If the face was indeed viewed at study, subjects were given a forced choice recognition test with two names (one that was correct, and one that was incorrect but paired with another face at encoding) and indicated with a button press if the correct name was on the left or the right, and whether they had high or low confidence that they chose the correct name. This occurred regardless of the subjects' explicit memory for the face.

The encoding trials were then sorted based on the results of the postscan test, yielding 16 possible conditions based on both the confidence and accuracy for the face and then for the face-name pair in a hierarchical structure. Trials from the face test were first categorized as high confidence hits (HCH), low confidence hits (LCH), high confidence misses (HCM), or low confidence misses (LCM). Hits were trials in which subjects correctly responded to a previously seen face as "old" and misses were trials in which subjects responded to a previously seen face as "new." Within each of these four trial types, there were four response types based on the face-name memory test. Trials from the face-name associative test were also categorized as HCH, LCH, HCM, and LCM. Hits were trials in which subjects chose the correct name associated with the face during study, and misses were trials in which subjects chose the incorrect name that had been previously paired with a different face during encoding. The purpose of the confidence ratings was to restrict the correct responses to those made with high confidence and exclude correct "guesses" which may happen in a forced choice paradigm by chance (Sperling et al., 2003a). Thus, as several other studies have done (Wagner et al., 1998; Sperling et al., 2003a; Prince et al., 2005), we analyzed HCH responses when examining remembered stimuli and analyzed all misses (HCM + LCM) when examining forgotten stimuli. To assess memory performance for the associated name, we performed one-sample *t*-tests comparing the proportion of hits (overall and HCH) to chance using SPSS.

We were interested in comparing subsequent memory for the face alone and for the whole face-name pair and thus used specific combinations of the previously mentioned 16 response types for our analyses. Remembered faces consisted of HCH responses during the face test, whereas forgotten faces consisted of HCM and LCM on the face test. Remembered face-name pairs, which describe memory for the name associated with the face, consisted of HCH responses during the face-name test, whereas forgotten face-name pairs consisted of HCM and

LCM on the face-name memory test. "Face-Remembered/Pair-Remembered" reflects trials in which both the face and the associated name were remembered. "Face-Remembered/Pair-Forgotten" reflects trials in which the face was remembered, but the associated name was forgotten. "Face-Forgotten/Pair-Remembered" reflects trials in which the face was forgotten, but the correct associated name was chosen. "Face-Forgotten/Pair-Forgotten" reflects trials in which the face and the associated name were forgotten. Memory for the face alone was a measure of item memory, but memory for the pair alone was not considered item memory because it was cued with the face and was, therefore, associative.

During the postscan memory test, subjects viewed novel faces that were not seen during the scanned encoding phase. Unlike previously seen faces, these novel faces were not followed by a forced choice recognition test for the name. If subjects indicated that a novel face was previously seen, this was considered a false alarm (FA) and could be made with either high or low confidence. If subjects indicated that a novel face was not previously seen, this was considered a correct rejection (CR) and could be made with either high or low confidence. To characterize memory performance on the face recognition test, we then calculated the FA rates and Hit rates, overall and by high or low confidence, and used these to calculate discrimination (d′).

Functional MRI Data Analysis

Functional MRI data were preprocessed and analyzed using SPM2 (Wellcome Department of Neurology, London) for Matlab (Mathworks, Natick, MA). Data were first realigned to correct for motion using sinc interpolations. Then, to allow group averaging, data were spatially normalized to the EPI template based on the MNI1305 stereotactic space. Data were smoothed using an 8 mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed according to the General Linear Model first at the individual level using concatenated runs and then averaged together treating each subject as a random effect. Group averaged maps were thresholded at $P < 0.005$ (uncorrected) with a 20 voxel extent threshold. Using weighted contrasts, we compared each condition of interest to visual fixation. We also completed higher level comparisons examining subsequent memory effects for the face-name pair and the face alone.

Specific regions of interest (ROI) were generated by creating a 4 mm sphere around a peak coordinate from a contrast of interest. The mean beta weights were then extracted from these ROI and analyzed in SPSS using repeated measures ANOVA. Results were considered significant at $P < 0.05$, one-tailed.

RESULTS

Behavioral Results

In the face recognition portion of the memory test, subjects correctly recognized the face for 62% ± 10% of the trials seen during encoding, and 78% ± 16% of the trials in which they indicated high confidence. Within Pair-Forgotten, face recognition was 61% ± 11% for previously seen faces, and 76% ± 17% with high confidence. However, FAs to distracter faces were also high, with 43% ± 12% of novel faces identified as "old," and 52% ± 24% for high confidence trials. Thus discrimination (d′) was 0.51 ± 0.29 overall and 0.83 ± 0.48 for high confidence trials. Discrimination for high confidence trials, which we used for our analyses, was significantly different from chance ($P < 0.01$), but overall discrimination did not differ from chance. One subject had no high confidence FAs and was excluded from d′ analyses.

In the pair recognition portion of the memory test, one-sample *t*-tests showed that subjects performed better than chance (50%) and correctly identified the name associated with the face 62% ± 4% of the trials regardless of face memory [$t(17) = 13.4$, $P < 0.00001$], and 72% ± 9% of the trials in which they indicated high confidence regardless of face memory [$t(17) = 10.2$, $P < 0.00001$]. Within Face-Remembered, subjects correctly identified the name 66% ± 6% [$t(17) = 11.7$, $P < 0.00001$], and 73% ± 11% with high confidence [$t(17) = 9.0$, $P < 0.00001$].

Repeated measures ANOVA showed no significant differences after correction for multiple comparisons between reaction time (available for only 16 subjects) during the encoding task based on subsequent memory effects for faces, pairs, or their interaction (Face-Remembered/Pair-Remembered: 1.21 ± 0.14 s; Face-Remembered/Pair-Forgotten: 1.19 ± 0.13 s; Face-Forgotten/Pair-Remembered: 1.24 ± 0.17 s; Face-Forgotten/Pair-Forgotten: 1.20 ± 0.13 s).

The 16 subjects with available encoding data were more likely to indicate that the name "fit" the face than not (fits: 68.9% ± .05%, range: 42.5–100%; $P < 0.005$). This task showed a behavioral effect on memory performance; there were a greater proportion of Face-Remembered/Pair-Remembered responses that were "fits" compared to "not-fits" and a greater proportion of Face-Forgotten/Pair-Forgotten response that were "not-fits" compared to "fits" ($P < 0.01$).

Imaging Results

We generated whole-brain statistical activation maps for each of Face-Remembered/Pair-Remembered, Face-Remembered/Pair-Forgotten, Face-Forgotten/Pair-Remembered, and Face-Forgotten/Pair-Forgotten > Fixation. All of these contrasts showed activation in bilateral fusiform, lateral prefrontal, dorsal medial prefrontal, and MTL regions, which is consistent with previous findings (Sperling et al., 2003b). Within the hippocampal formation, each of the contrasts showed significant activation in bilateral posterior hippocampal regions, but only contrasts in which the associated name was remembered (Face-Remembered/Pair-Remembered and Face-Forgotten/Pair-Remembered) showed significant activation in the anterior hippocampus bilaterally (Fig. 1). As is typical of many cognitive tasks, there was greater activity during fixation trials than encoding face-name trials in lateral and medial parietal, and

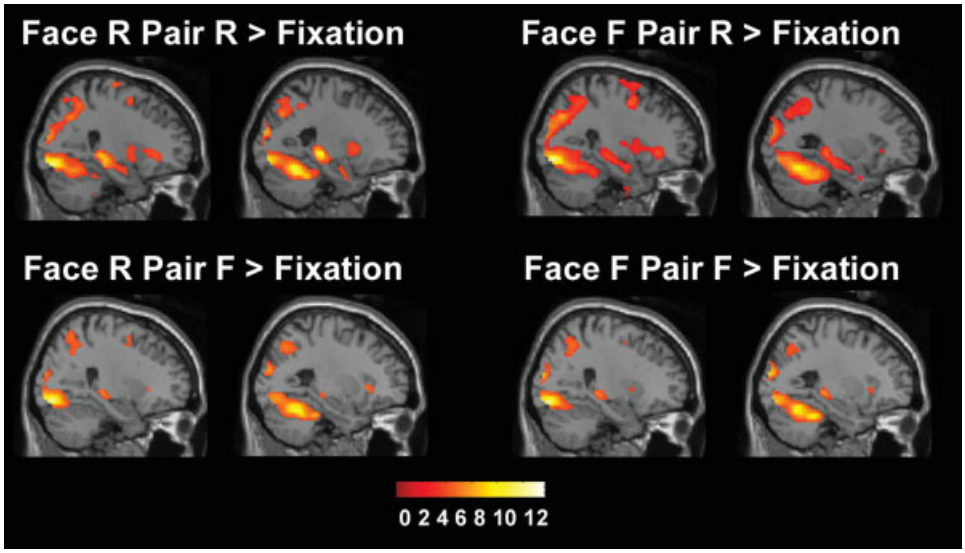

FIGURE 1. Whole-brain statistical activation maps comparing trials in which the face alone and the face-name pair were subsequently remembered (FACE R PAIR R), the face alone was subsequently remembered but the face-name pair was subsequently forgotten (FACE R PAIR F), the face was subsequently forgotten but the pair was remembered (FACE F PAIR R), and the face alone and the face-name pair were subsequently forgotten (FACE F PAIR F), to visual fixation. All comparisons showed significant posterior hippocampal activation, but only in cases when the pair was remembered did the contrasts show significant anterior hippocampal activation.

medial prefrontal regions, consistent with typical deactivation in the "default mode network" (Shulman et al., 1997).

We examined subsequent memory for the whole face-name pair and compared all trials in which the face-name pair was successfully remembered (Pair-Remembered) to trials in which it was forgotten (Pair-Forgotten). This contrast showed greater activation centered in the bilateral anterior hippocampal formation (peak coordinate on left: −22, −4, −18; right: 20, −8, −16; Fig. 2), which replicated our previous results with this paradigm on a different scanner platform (Sperling et al., 2003b). Pair-Remembered > Pair-Forgotten also showed greater activity in the left inferior prefrontal cortex and right fusiform gyrus. The reverse comparison, Pair-Forgotten > Pair-Remembered showed greater activity in bilateral medial and lateral parietal regions.

We then held memory for the face constant, and compared remembered and forgotten pairs only for trials in which the face was remembered (Face-Remembered/Pair-Remembered > Face-Remembered/Pair-Forgotten). This contrast holds subsequent face memory constant, and thus reveals activation patterns related to the face-name association. It showed greater activation centered in the left anterior hippocampal formation (peak coordinate: −28, −4, −24; Fig. 2), extending into the entorhinal cortex. This contrast also revealed greater activation in the left fusiform gyrus. The reverse contrast, Face-Remembered/Pair-Forgotten > Face-Remembered/Pair-Forgotten showed greater activity in bilateral lateral parietal regions.

We were interested in comparing activity in anterior and posterior regions of the hippocampal formation. We generated ROI from the Face-Remembered/Pair-Remembered versus fixation contrast (left anterior: −22, −4, −18; right anterior: 20, −8, −16; left posterior: −22, −32, −6; right: 24, −30, −4) and tested for significant differences in mean beta weights based on location on the longitudinal axis of the hippocampal formation (anterior vs. posterior), subsequent face memory

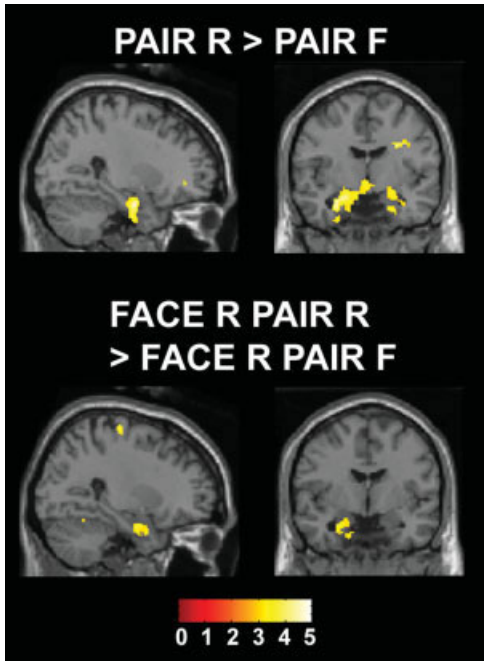

FIGURE 2. Whole-brain statistical activation maps directly comparing subsequently successfully remembered and forgotten associations regardless of face memory (PAIR R > PAIR F) and within successful face memory (FACE R PAIR R > FACE R PAIR F). Both contrasts showed significant differences in the left anterior hippocampal formation.

(remembered vs. forgotten), and subsequent pair memory (remembered vs. forgotten) in both the left and right hemispheres. In the left hemisphere, there was a significant main effect for pair memory [$F(1,17) = 4.73$, $P < 0.022$], and a significant location × subsequent pair memory interaction [$F(1,17) = 3.81$, $P < 0.034$], with greater activity in the anterior hippocampal formation for pairs that were subsequently remembered (mean ± SEM; Pair-Remembered: 1.20 ± 0.29) compared to those that were forgotten (Pair-Forgotten: 0.54 ± 0.14), but not in the posterior hippocampal formation (Pair-Remembered: 0.99 ± 0.15; Pair-Forgotten: 0.85 ± 0.23; Fig. 3). No other main effects or interactions were significant. In the right hemisphere, there were significant main effects of location [$F(1,17) = 6.88$, $P < 0.009$] and pair memory [$F(1,17) = 4.42$, $P < 0.026$]. The location × subsequent pair memory interaction [$F(1,17) = 3.04$, $P < 0.05$] was also significant (Fig. 3), with greater activity in the anterior hippocampal formation for pairs that were subsequently remembered (Pair-Remembered: 0.75 ± 0.18; Pair-Forgotten: 0.32 ± 0.17) compared with those that were forgotten, but not in the posterior hippocampal formation (Pair-Remembered: 0.90 ± 0.13; Pair-Forgotten: 0.77 ± 0.18). The location × subsequent face memory interaction was also significant [$F(1,17) = 6.23$, $P < 0.012$].

Subsequent repeated measures ANOVAs were used to determine the nature of the location × subsequent pair memory interaction and examine differences in activity within the anterior and posterior hippocampal regions separately. Within the left and right anterior hippocampal ROI, the only significant finding was that there was greater activity for pairs that were subsequently remembered compared to those that were forgotten (left: [$F(1,17) = 8.54$, $P < 0.005$], right: [$F(1,17) = 8.40$,

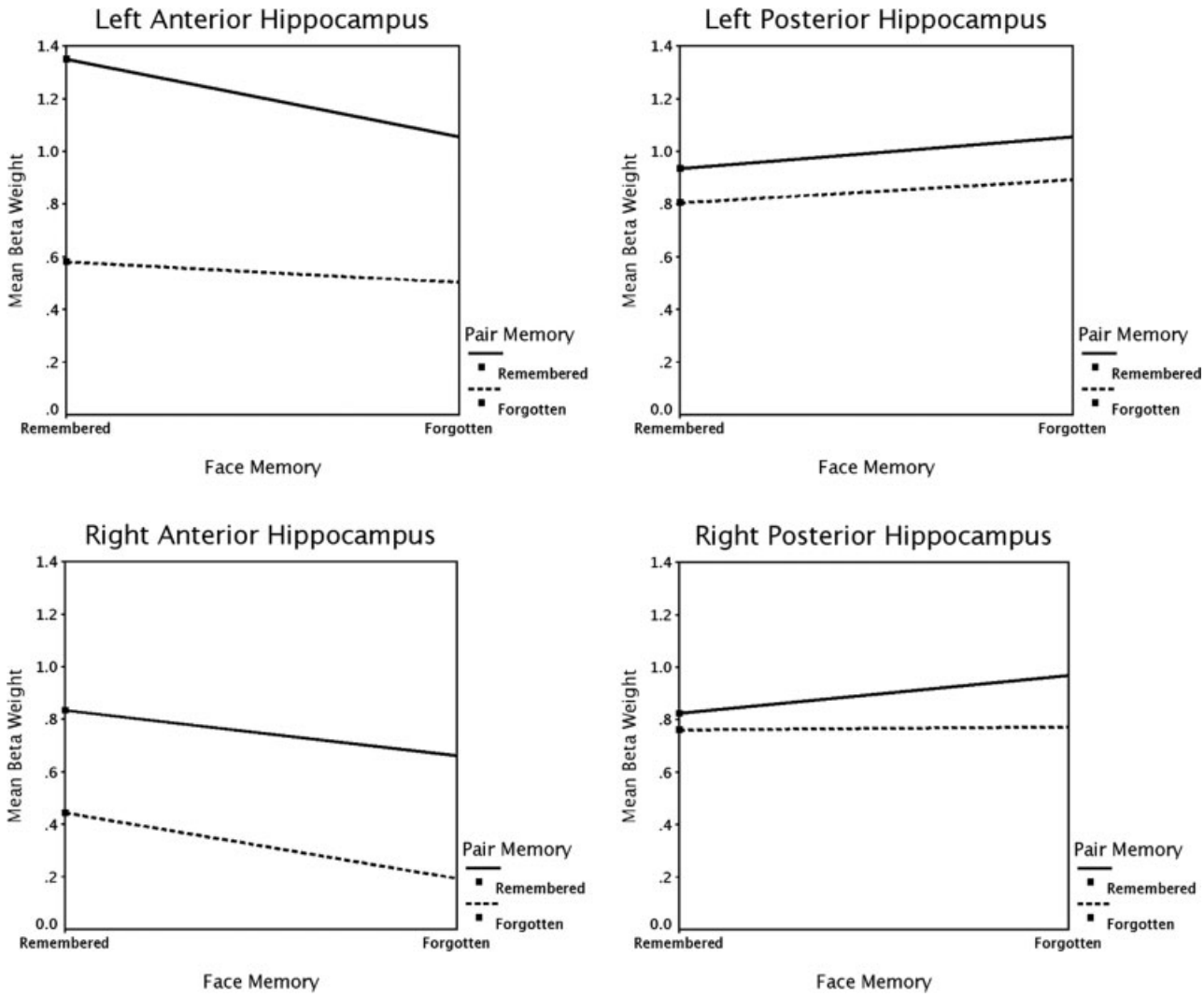

FIGURE 3. Graphs depicting the location (anterior vs. posterior hippocampus) × pair memory (remembered vs. forgotten) interaction. Anterior hippocampal regions showed significantly greater mean beta weights for remembered versus forgotten pairs whereas the posterior regions did not.

$P < 0.005$]). The posterior regions showed no other significant main effects of interactions. Although the right hippocampus showed a location × subsequent face memory interaction, neither region showed a significant effect of face memory. This interaction appears to be driven by differences in activity when faces are forgotten, with greater activity in the posterior hippocampus than the anterior hippocampus [$F(1,17) = 12.77$, $P < 0.001$].

Since neither the anterior nor the posterior hippocampal ROI showed significant effects of subsequent face memory, we completed exploratory whole-brain analyses to determine whether any MTL regions showed subsequent face memory effects. Face-Remembered > Face-Forgotten showed differences in different MTL regions than Pair-Remembered > Pair-Forgotten (Fig. 4). This region appeared to be located in the anterior parahippocampal gyrus, most likely representing perirhinal cortex (peak coordinate on left: −22, −12, −28; right: 18, −6, −28). This contrast also showed greater activation in the bilateral fusiform and right inferior prefrontal regions. The reverse contrast, Face-Forgotten > Face-Remembered showed greater activity in a right lateral parietal region.

We then examined item memory by comparing trials in which only the face was subsequently remembered and the name was forgotten (Face-Remembered/Pair-Forgotten) to trials in which both the face and the face-name pair were forgotten (Face-Forgotten/Pair-Forgotten). Similar to the comparison of all remembered faces to all forgotten faces (Face-Remembered > Face-Forgotten), specifically targeting item-only subsequent memory by using the contrast Face-Remembered/Pair-Forgotten > Face-Forgotten/Pair-Forgotten revealed activation in a left parahippocampal region (peak coordinate: −24, −14, −24). This region differed in spatial location from the one revealed in the contrast Face-Remembered/Pair-Remembered > Face-Remembered/Pair-Forgotten (Fig. 4), which demonstrates that different locations within the MTL show specific responses to successful encoding of item and associative information. Subsequent item memory effects (Face-Remembered/Pair-Forgotten > Face-Forgotten/Pair-Forgotten) also showed activation in right inferior prefrontal cortex and right retrosplenial cortex. The reverse contrast, Face-Forgotten/Pair-Forgotten > Face-Remembered/Pair-Forgotten showed greater activity in the left insula and left lateral parietal cortices.

To more specifically examine whether there were differences in brain activity between the hippocampus and surrounding medial temporal cortex, we then performed a Repeated Measures ANOVA on the mean beta weights for the anterior hippocampal region defined earlier and the left parahippocampal region from the Face-Remembered/Pair-Forgotten > Face-Forgotten/Pair-Forgotten contrast (−24, −14, −24). We tested for significant differences, in location (hippocampus vs. medial temporal cortex), subsequent face memory (remembered vs. forgotten), and subsequent pair memory (remembered vs. forgotten). There were significant main effects of location [$F(1,17) = 17.34$, $P < 0.003$], subsequent face memory [$F(1,17) = 4.58$, $P < 0.025$), and subsequent pair memory [$F(1,17) = 12.38$, $P < 0.003$]. Importantly, the location × face memory × pair memory was significant [$F(1,17) = 4.069$, $P = 0.03$] (Fig. 5).

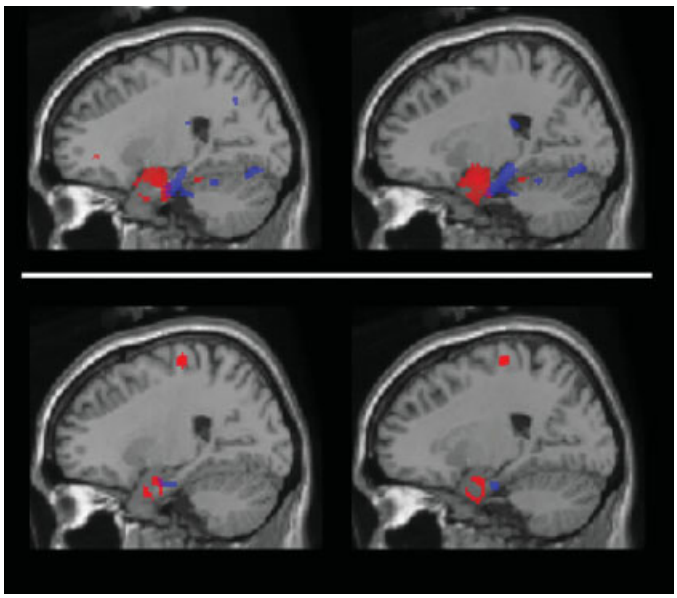

FIGURE 4. Overlays of whole-brain statistical activation maps for subsequent memory for the whole face-name pair (red) and faces alone (blue) on left sagittal slices. Main effects of pair (Pair-Remembered > Pair-Forgotten) and face (Face-Remembered > Face-Forgotten) memory are shown on top. Specific comparisons for subsequent pair (Face-Remembered/Pair-Remembered > Face-Remembered/Pair-Forgotten) and face (Face-Remembered/Pair-Forgotten > Face-Forgotten/Pair-Forgotten) memory are shown on the bottom. Both sets of comparisons show that more anterior hippocampal regions show differential activation based on pair memory, whereas a more parahippocampal region shows differential activation based on face memory.

Although there was a behavioral effect of the encoding task on memory performance, the proportion of "fit" responses did not correlate with activity in the anterior or posterior hippocampal, or parahippocampal ROI.

DISCUSSION

These data provide evidence of a specific relationship between activity in the anterior hippocampal formation and successful associative encoding. Whole-brain and ROI analyses suggested that the anterior hippocampal formation shows functional specialization for the successful formation of associations. In contrast, parahippocampal regions, likely localized to perirhinal cortices, may be specifically involved in successful item encoding. These results contribute toward our aim of resolving prior conflicting reports in the literature about the hypothesized specialization of the anterior hippocampus for successful associative encoding by testing for interaction effects based on position along the longitudinal axis, subsequent item memory, and subsequent associative memory.

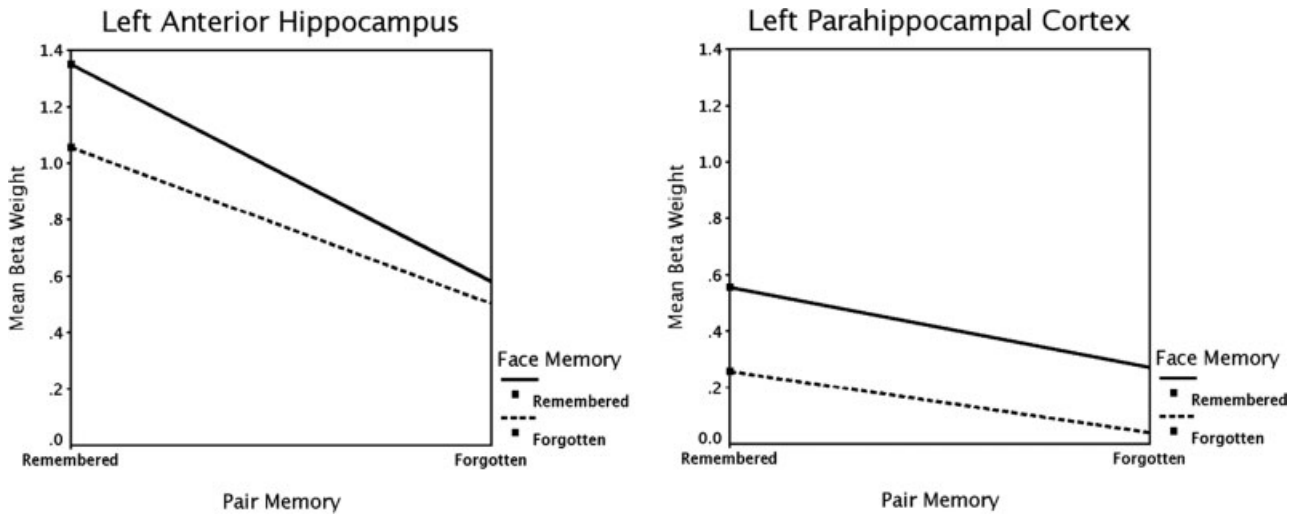

FIGURE 5. Graphs depicting the mean beta weights for the left anterior hippocampus and parahippocampal cortex that showed a significant location × face memory × pair memory interaction.

Dissociable Roles of the Anterior and Posterior Hippocampal Formation in Associative Encoding

Several pieces of evidence from whole-brain and ROI analyses in our study point to a strong relationship between the anterior hippocampal formation and successful associative encoding. A significant interaction effect between location along the longitudinal axis of the hippocampal formation and subsequent associative memory provides evidence for a functional distinction between anterior and posterior hippocampal regions based on associative encoding. These findings are consistent with several other reports in the literature that support a specific role for the anterior hippocampal formation in memory for associations between multiple items using a variety of stimuli (Davachi and Wagner, 2002; Sperling et al., 2003b; Jackson and Schacter, 2004).

Interpretation of the strength of the location × pair memory effect requires some discussion of the conditions that contributed to the interaction analysis. One particular condition in this analysis that is hard to interpret is Face-Forgotten/Pair-Remembered, representing trials in which the face was forgotten but then the correct name was chosen for the face. Although we cannot be sure what the subjects' were experiencing during the small number of Face-Forgotten/Pair-Remembered trials, one possibility is that subjects employed a 'recall-to-reject' strategy. Although the 'recall-to-reject' strategy may have been used on any trial, it seems likely that this strategy might be more prevalent in the condition when the face was forgotten but the whole pair was remembered. Unlike trials in which subjects remembered the face, subjects could not base their decision on the name associated with the target face if they had forgotten it, and would therefore have to base their decision on memory for the face associated with the incorrect name, on low familiarity of the correct name, on high familiarity of the incorrect name, or guess. Because the name choice was made with high confidence for these trials, it seems likely that the decision was based on memory for the face presented with the incorrect name during scanning. Despite the ambiguity of the Face-Forgotten/Pair-Remembered condition, which may have decreased our power to detect differences, we still showed differential effects in the anterior and posterior regions based on subsequent associative memory.

One alternative explanation for our results is that instead of being related specifically to subsequent associative memory, activity correlates strictly with the overall amount of information subsequently remembered. In all of the statistical comparisons we performed related to associative memory, the associative condition contained "more information" (i.e. both a name and a face) that was subsequently remembered compared with other conditions. However, if activity in the anterior hippocampus correlated solely with the amount of material that was subsequently remembered, we should have seen similar activation in contrasts that compared any subsequently remembered trials to those that were forgotten, but we did not. For example, comparing trials in which the face alone was subsequently remembered to when the face was forgotten did not show differences in anterior hippocampal activation. Thus, we believe that the activation in the anterior hippocampal formation is related to specificity for subsequent associative memory, not merely to the amount of information encoded.

The precise role of the posterior hippocampal formation is not as clear as the role of the anterior hippocampal formation. The posterior hippocampal formation showed activity greater than baseline for all conditions; therefore, one possible function is a more general role in associative encoding. In fact, other studies that have compared different encoding tasks that use different relational and nonrelational strategies have shown that posterior hippocampal regions show greater activation for the relational tasks (Davachi and Wagner, 2002). Although comparing several conditions to baseline must be interpreted with

some caution because the difference could also be driven by it deactivating during our passive baseline; however, a passive baseline task showed reduced percent signal change in the MTL for novel and familiar pictures compared to the active baseline condition (Stark and Squire, 2001). Thus, we would expect that an active baseline task would not change the direction of our results. Future studies could investigate the precise role of the posterior hippocampus further.

Potential Functional Specialization for Anterior Hippocampal Formation Compared to Parahippocampal Cortex

Exploratory whole-brain analyses showed a region in the parahippocampal cortex, most likely localized to perirhinal cortex, which showed a subsequent item memory effect, that is, memory for the face alone. Although this item was originally encoded using an associative task, the subsequent memory was for the item alone. Thus, this outcome represents subsequent item memory, not subsequent associative memory. It should be noted that items remembered in experiments may have some associative component because they have a contextual association of having been encountered during the study. However, this kind of association is different than the inter-item associations, such as face-name associations, that we are investigating. In fact, these kinds of contextual associations may serve as a basis for item memory (Yonelinas, 2002). Several other studies have shown subsequent memory effects for items in parahippocampal regions using a variety of stimuli (e.g., Brewer et al., 1998; Wagner et al., 1998; Otten et al., 2002; Stark and Okado, 2003; Weis et al., 2004). It seems likely that the region revealed in our study corresponds to perirhinal cortex based on its location and its known role in item-based encoding (for review, see Henson, 2005; Davachi, 2006), although we did not use high resolution imaging so the precise location should be interpreted with caution. Of particular importance, given a hypothesized division of labor between the hippocampus and medial temporal cortex, the regions showing subsequent face memory versus subsequent pair memory effects were nonoverlapping. Thus these findings also provide possible evidence for regionally specific subsequent memory effects within the MTL.

As aforementioned, a caveat to our findings overall is that our spatial resolution is somewhat limited. We performed group analyses on spatially normalized data, and thus the exact anatomic locations should be interpreted with some caution. This limitation is a concern with respect to the distinction between the hippocampus and parahippocampal cortex. Our fMRI data were acquired in oblique coronal slices and the phase encoding direction was head to foot. Thus it is likely that some distortions in the phase encoding direction of the raw data, may limit our ability to accurately distinguish the hippocampal formation and the perirhinal cortex. The spatial resolution in the longitudinal plane is also limited based on our slice thickness (5 mm, skip 1 mm). However, the distinctions between anterior and posterior regions, for which our main findings are most relevant, were based on regions that were quite distant along the longitudinal axis.

Another overall caveat is that subjects showed poor face discrimination. Face discrimination was significantly different from chance for high confidence responses, but the FAs were still high, most likely due to possible similarities between faces. This pattern means that we may have had reduced power to detect differences based on subsequent face memory, in which case there may regions other that the parahippocampal cortex that would have shown robust subsequent face memory effects with increased power. It also remains possible, although counter to our hypothesis, that the anterior hippocampus would show a face memory effect; however, this would not effect the significant location $\times$ pair memory interaction, which is our main finding.

Overall, our findings support the hypothesis that the anterior hippocampal formation is preferentially engaged in associative or relational encoding, compared with item encoding (Schacter and Wagner, 1999). Although these findings do not preclude greater anterior hippocampal activity for other kinds of comparisons, our data provide evidence for functional specialization within the hippocampal formation based on both subsequent memory and the associative nature of the stimuli. The anterior hippocampal formation showed differential activation for subsequent associative memory, but not subsequent item-only memory. We also found evidence that there may be a functional division between the anterior hippocampal formation and the parahippocampal cortex, most likely the perirhinal cortex. Both regions showed subsequent memory effects, but the anterior hippocampal formation demonstrated differential activation for associative information, whereas the parahippocampal cortex showed this for items. The issue of a functional division of labor within the medial temporal lobe is a complex, and yet unresolved issue (Aggleton and Brown, 1999; Squire et al., 2004), but our results provide additional evidence for functional specialization of anterior hippocampal regions related to associative memory.

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