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RAPID COMMUNICATION

Hippocampal Contribution to the Novel Use of Relational Information in Declarative Memory

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Text

INTRODUCTION

Declarative memory, which encompasses the acquisition, storage, and retrieval of events and facts (Cohen and Squire, 1980), can be expressed flexibly in novel situations different from the original learning environment (Eichenbaum and Cohen, 2001). Declarative memory relies on the integrity of multiple structures in the medial temporal lobe (MTL), but animal research (Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997; Honey et al., 1998) indicates that the hippocampus specifically underlies the flexible expression of declarative memories. In the present report, we demonstrate selective hippocampal activation in humans during recognition of pairs of items whose relationship was not explicitly learned but could be mediated through an overlapping relation with an explicitly learned common item. This result suggests a specific role for the human hippocampus in the novel expression of declarative memories.

The MTL comprises several structures, including the hippocampal formation (dentate gyrus, CA fields, and subiculum), and surrounding entorhinal, perirhinal, and parahippocampal cortices. These structures are likely to contribute differently to declarative memory, but the unique contribution of each structure remains a subject of debate. An emerging hypothesis, supported by evidence from studies of rats (Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997; Honey et al., 1998) and monkeys (Gaffan and Parker, 1996; Brasted et al., 2003), proposes that the hippocampus plays an essential role in the flexible expression of declarative memories. According to this view, experiences yield memories that are learned directly from the environment (rote associations). Flexibility is needed when elements of individual experiences must be related or conjoined in new ways to deal with novel situations. This flexibility is thought to be a powerful characteristic of declarative memory because it allows for the generative use of the elements of experience to address new questions posed by the environment (Eichenbaum and Cohen, 2001).

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In rats, damage to the hippocampal system, either by lesion to the hippocampus proper (Bunsey and Eichenbaum, 1996) or through disconnection of the hippocampus from its cortical and subcortical output pathways (Dusek and Eichenbaum, 1997), impairs the flexibility of declarative memories without disrupting the ability to learn explicitly trained memories (rote associations). However, it is unknown in any mammalian species, including in humans, whether the hippocampus plays a unique role in the flexible expression of declarative memories. Neuroimaging studies of humans have suggested hippocampal contributions to encoding (Davachi and Wagner, 2002; Davachi et al., 2003) and retrieval (Eldridge et al., 2000; Cansino et al., 2002) of declarative information, but none has specifically addressed questions regarding flexible expression of relational information as in previous rat studies. In the present investigation, we modeled a study with rats (Bunsey and Eichenbaum, 1996) and used functional magnetic resonance imaging (fMRI) to examine whether the human hippocampus plays a specific and unique role in the flexible expression of declarative memory.

Prior to scanning, participants received explicit training on three sets of paired associates (Fig. 1A). Participants first learned to associate specific faces (stimuli A) with specific houses (stimuli B). Then, participants learned to associate another set of faces (stimuli C) with the same specific houses (stimuli B). In both training phases, each face-house pair was presented four times. Thus, each house was associated with two different faces in the two successive learning phases. The A and C faces were not shown as being related explicitly, but each A and C face could be flexibly related to one another through their overlapping associations with the same house (B). Participants also received training on another set of face-face paired associates consisting of two novel faces (stimuli D and E) not previously seen. Each DE pair was presented once so that memory would be below the ceiling performance for the face-house pairs (AB and BC).

During two blocked retrieval scans, participants made two-alternative forced-choice judgments on learned face-house pairs (AB and BC) and learned face-face pairs (DE) (Fig. 1B). In addition, participants made recognition judgments regarding the relation between A and C faces. For all trials, the incorrect item (foil) was a stimulus

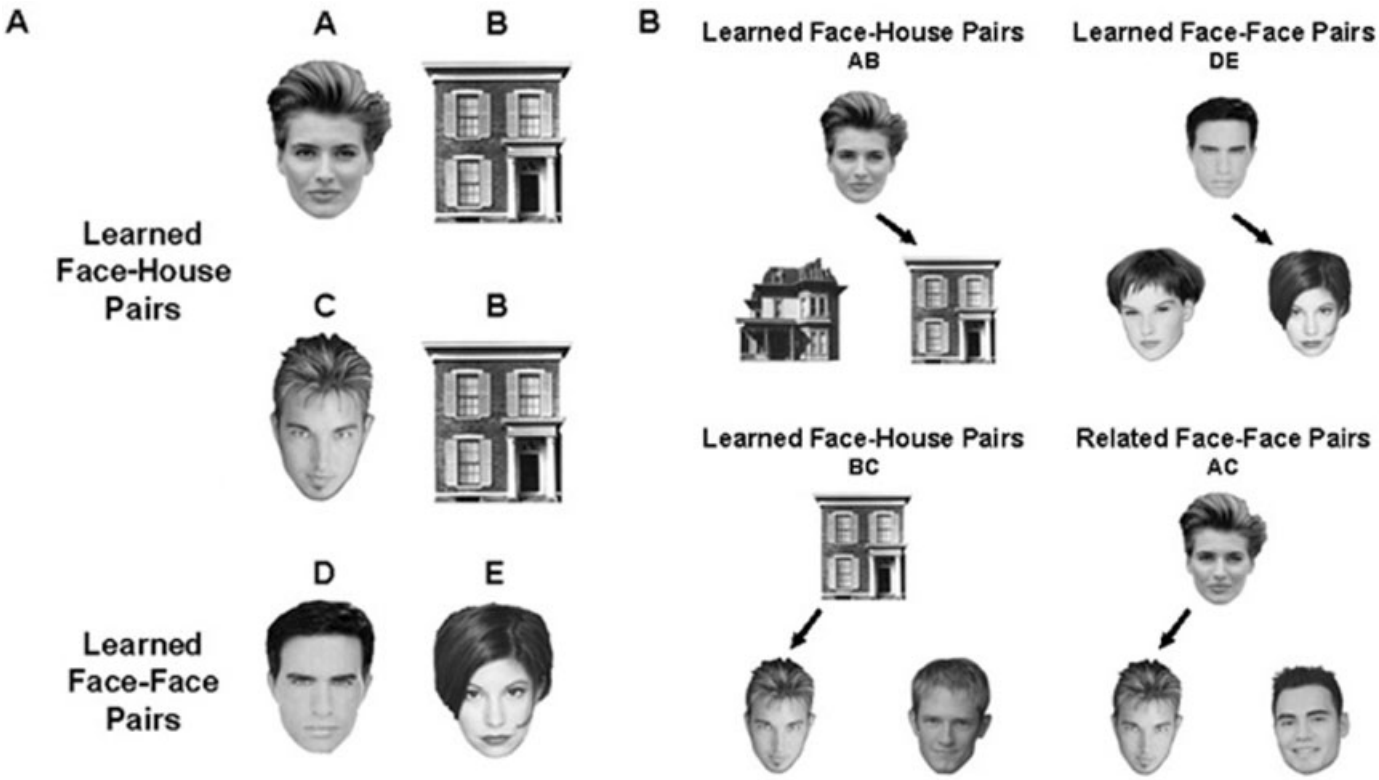

FIGURE 1. Behavioral methods. A: Participants received explicit training on three sets of 30 paired associates: an initial set of face-house pairs consisting of pictures of faces (A) and houses (B), a second set of face-house pairs consisting of the same houses (B) paired with new faces (C), and a set of face-face pairs consisting of novel faces (DE). B: During scanned retrieval, participants made two-alternative forced-choice judgments of four types; learned face-house pairs (AB and BC), learned face-face pairs (DE), and related face-face pairs (AC).

shown in another pairing so that all individual stimuli were familiar. Thus, memory judgments for trained pairs (AB, BC, DE) had to be based on learned associations. For face-face pairs (AC) whose relationship was not explicitly learned, participants could recognize a relation between specific faces through overlapping associations with the same house (B). Imaging data were acquired on a 3.0-tesla (T) Signa MRI system (GE Medical Systems, Milwaukee, WI), and image preprocessing and statistical analyses were performed using SPM99 (see Methods and Materials).

Memory for the learned face-house pairs was near perfect (AB, mean percentage accuracy ±SE, 97.7 ± 1.3; BC, 96.0 ± 1.3), and significantly better ($P < 0.01$) than related but never learned face-face pairs (AC, 89.2 ± 2.0), which, in turn, was significantly better ($P < 0.001$) than the once-trained face-face pairs (DE, 74.3 ± 2.4). Response latencies were faster for the learned face-house pairs (AB, mean RT (ms) ±SE, 1719.6 ± 142.3; BC, 1875.6 ± 103.5) than for the related or learned face pairs ($P < 0.001$), which did not differ from one another (DE, 2696.1 ± 74.4; AC, 2566.7 ± 166.3; $P = 0.349$).

To investigate how the MTL, and in particular the hippocampus, contributes to novel use of learned information, we compared activation during recognition of related face-face pairs (AC) with activation associated with recognition of explicitly learned face-face pairs (DE). This contrast provided the critical comparison because it controlled for stimulus materials (only faces) and response times (equal for these pairs). Regions in both left and right hippocampus (MNI coordinates: −28, −28, −16 and 30, −22, −22) demonstrated greater activation for related face-face pairs (AC) than learned face-face pairs (DE) (Fig. 2). In addition, these hippocampal regions demonstrated activation for related face-face pairs (AC) that was greater than for explicitly learned face-house pairs (AB and BC; $P < 0.001$). The hippocampal activation, therefore, could not be driven by face stimuli per se (present in both AC and DE stimuli), retrieval success (greatest for learned face-house pairs AB and BC), or retrieval effort (greatest for the worst-remembered DE stimuli). Thus, this hippocampal activation was selective for memory retrieval requiring a flexible relation between elements of previously memorized associations. Hippocampal activation was associated with retrieval of learned face-house pairs (AB and BC) in a novel situation (related face-face pairs, AC), but it may also reflect encoding of new face-face associations (AC). A pure encoding interpretation, however, would predict that the worst-known information (DE pairs) should yield the strongest encoding activation in a region that was involved exclusively in encoding.

Another, more posterior, hippocampal region was activated by all retrieval conditions. This region in left posterior hippocampus (−18, −30, −8) demonstrated equivalent activation across all pair types (Fig. 2), the pattern of which was significantly different from the more anterior hippocampal region (region × pair interaction, $P < 0.001$). The two kinds of hippocampal activations suggest that different parts of the hippocampus may play roles in different

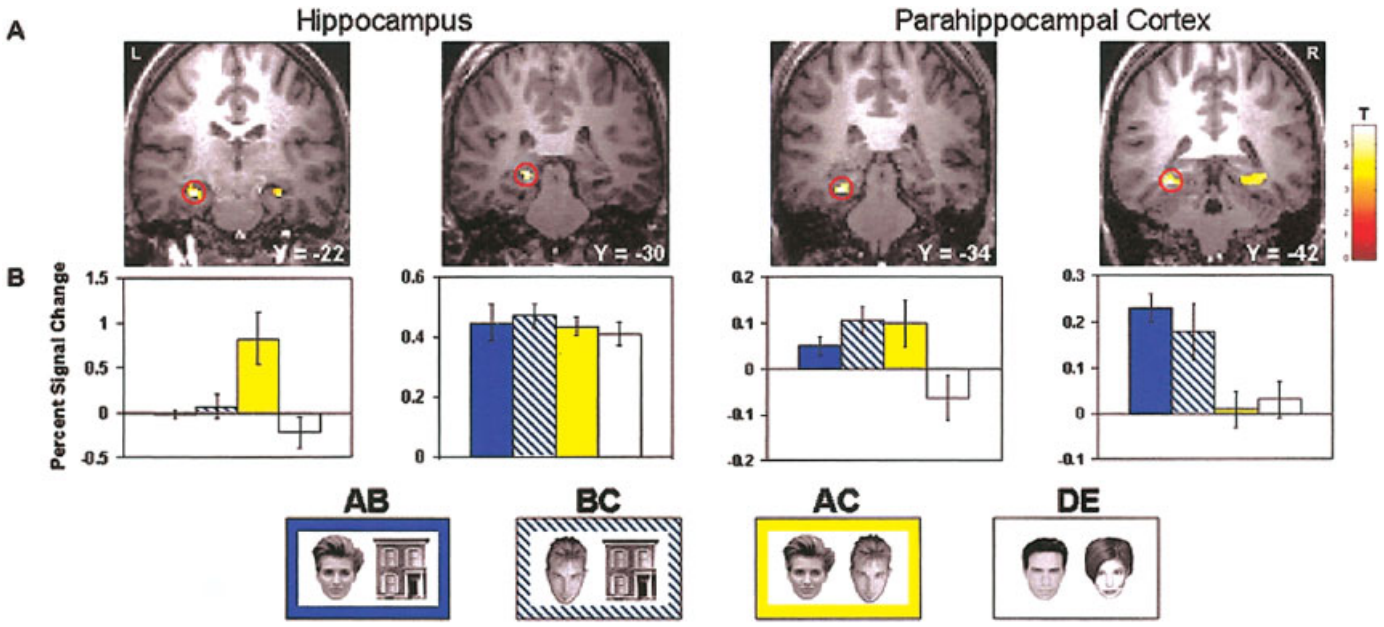

FIGURE 2. Medial temporal lobe activations during recognition. Mean signal change during recognition memory revealed different activation patterns in hippocampus and parahippocampal cortex. A: MTL regions active during recognition memory ($P < 0.001$, cluster size = 5 voxels). B: Mean percentage signal change relative to baseline as a function of pair type averaged across subjects for each MTL region designated by red oval. Error bars represent standard error of mean for each pair type.

declarative memory processes (Stark and Squire, 2000, 2003; Stark et al., 2002).

Bilateral regions in anterior parahippocampal cortex (−28, −34, −18 and 30, −24, −28) also demonstrated greater activation for related face-face pairs (AC) compared with learned face-face pairs (DE). In contrast to hippocampus, however, these parahippocampal regions demonstrated equivalent activation for related face-face pairs (AC) and learned face-house pairs (AB and BC), which was significantly different from the hippocampal activation (region × pair interaction, $P < 0.001$) (Fig. 2). This pattern of activation may reflect item familiarity (individual items in the learned face-house and related face-face pairs were seen more frequently during encoding than the learned face-face pairs), successful recognition memory (better in all three conditions than the learned face-face pairs), or the strong response of parahippocampal regions to spatial stimuli such as houses (Epstein and Kanwisher, 1998). In the latter case, the activation associated with related face-face pairs (in which no house was presented) would reflect the retrieval of memory for the house that associated the two faces. A more posterior region of parahippocampal cortex (−30, −42, −14 and 28, −48, −6) (Fig. 2) demonstrated greater activation for the learned face-house pairs (AB and BC) than either face-face pair (AC and DE). This activation could reflect retrieval success or the presence of a house in the face-house pairs. Importantly, whereas many MTL regions were associated with recognition, only the hippocampus yielded activation that was specific to flexible use of elements of previous experience.

Animal studies indicate a role for the hippocampus in the flexible expression of declarative memories (Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997; Honey et al., 1998). In the present report, we demonstrate a selective hippocampal response in the human brain associated with the recognition of information not explicitly learned. These results are consistent with the finding that hippocampal atrophy in nondemented elderly impairs performance on a memory task that requires novel use of learned information (Myers et al., 2003). The present findings go beyond animal and patient studies by indicating that activation associated with the flexible expression of declarative memory may be unique to the hippocampus because no other MTL region demonstrated a similar activation. Activations displayed in the more posterior hippocampal region and in parahippocampal cortex during retrieval of explicitly learned associations may serve as representations necessary for hippocampal processes that can conjoin novel relations between elements of learned associations. The current results are restricted to retrieval, but it has been suggested that the hippocampus may also contribute to the encoding of associations that allow for the later flexible use of that information in novel ways (O'Reilly and Rudy, 2001). However, the present findings indicate that the hippocampus makes a unique contribution that allows lessons from the past to be applied flexibly to the future.

METHODS AND MATERIALS

Behavioral Methods

Participants

Ten healthy, right-handed volunteers (age 18–23, mean 20.2 ± 0.57 years; six males, four females) participated in the experiment

for payment after giving informed consent in accordance with a protocol approved by the Stanford Institutional Review Board.

Stimulus materials

Stimulus materials consisted of black and white photographs of 120 faces (60 male, 60 female) and 30 houses. These photographs were used to construct three sets of paired associates; two sets of face-house pairs and one set of face-face pairs. The first set of face-house pairs (AB) pairs consisted of 30 faces (stimuli A) and 30 houses (stimuli B). The second set of face-house pairs (BC) consisted of the same 30 houses (stimuli B) and a different set of 30 faces (stimuli C). Thus, these face-house pairs were constructed such that two faces (one man and one woman) shared an association with the same house (B). The face-face pairs (DE) consisted of 30 male faces paired with 30 female faces. The presentation of different stimuli was counterbalanced across pair types.

Task procedure

Prior to scanning, participants received explicit training on each set of face-house pairs (AB and BC). Participants were first given four study-test epochs on the 30 AB pairs. During the study portion of training, each house-face pair was presented for 4 s, and participants were given intentional study instructions. After studying all 30 AB pairs, participants performed a forced-choice memory test to assess their learning of the pairs. Following AB training, participants received an additional set of four study-test epochs on the BC paired associates. The procedure for BC training was identical to that of AB training. Multiple exposures to the face-house pairs ensured that participants' recognition memory performance exceeded a criterion of 85% correct on each set of pairs. Additional training on the 30 face-face pairs (DE) was identical to that for face-house pairs except participants received only one study-test exposure.

During scanning, stimuli were generated by a Macintosh G3 (Apple, Cupertino, CA) computer and back-projected via a magnet-compatible projector onto a screen that could be viewed through a mirror mounted above the participant's head. Participants responded with an optical button held in their right hand, and responses were recorded by a computer interfaced with the optical switch using the PsyScope button box (Cohen et al., 1993). During two blocked retrieval scans, participants performed forced-choice recognition memory judgments on learned face-house pairs (AB and BC), learned face-face pairs (DE), and related face-face pairs (AC). Participants received six blocks of each pair type in a pseudo-random order during which blocks of related face-face pairs (AC) always appeared before the corresponding blocks of learned face-house pairs (AB and BC). This was done so that no learning during scanning could contribute to AC recognition performance. Each block lasted 30 s and contained five forced-choice trials in which each set of stimuli was presented for 5 s followed by a 1-s intertrial interval. Six additional blocks of a low-level baseline task were intermixed with the memory blocks where participants indicated the direction of presented arrows (left or right).

Imaging Methods

Whole-brain imaging data were acquired on a 3.0 T Signa MRI system (GE Medical Systems). Prior to functional imaging, T2-weighted flow-compensated spin-echo anatomical images [repetition time (TR) = 4,500 ms; echo time (TE) = 85 ms] were acquired in 30 contiguous 6-mm coronal slices. Functional images were acquired with the same slice locations as the anatomical images using a T2*-weighted 2D gradient echo spiral pulse sequence (Glover and Lai, 1998; TR = 2,000 ms; TE = 30 ms; 1 interleave; flip angle = 75°; FOV = 24 cm; 64 × 64 voxels). A total of 384 functional volumes were acquired for each participant over two scan sessions. Six discarded volumes (a total of 12 s) were collected at the beginning of each scan session to allow for T1 stabilization.

Imaging Analysis

Image preprocessing and statistical analyses were performed using SPM99 (Wellcome Department of Cognitive Neurology). Functional volumes were realigned to the first volume in the time series to correct for motion. A mean T2*-weighted volume was computed during realignment, and the T2-weighted anatomical volume was co-registered to this mean functional volume. The T2-weighted anatomical volume was then spatially normalized into common stereotaxic space (Talairach and Tournoux, 1988) using a standard template brain from the MNI series. The spatial transformations calculated during the normalization of the anatomical volume were then used to normalize the functional volumes. After normalization, the functional volumes were resampled to 2-mm^3 voxels and smoothed with an 8-mm isotropic Gaussian kernel.

For individual participants, differences between different pair types were assessed using the general linear model (Friston et al., 1995). Regressor functions were constructed by modeling stimulus-related activation as a delayed boxcar function convolved with a synthetic hemodynamic response function. Individual participant data were then analyzed using a fixed effects model (Friston et al., 1994), and linear contrasts were performed to generate a SPM{t} map representing differences in brain activation between conditions. Contrast images generated in the individual participant analysis were then analyzed across participants using a mixed effects general linear model, treating participants as a random effect allowing for population inference (Holmes and Friston, 1998).

We focused on the contrast between related face-face pairs (AC) and learned face-face pairs (DE), since this comparison controlled for stimulus materials (faces) and reaction times. A threshold of $P < 0.001$ uncorrected for multiple comparisons with an extent threshold of five voxels was used to identify MTL regions which demonstrated greater activation during related face-face pairs (AC) compared with learned face-face (DE) pairs. Activation identified by this group contrast was localized to different MTL subregions according to standard criteria (Amaral and Insausti, 1990). Mean signal change during each block type relative to baseline was then extracted from each MTL region of interest to investigate regional responses to the learned face-house pairs (AB and AC) relative to both types of face-face pairs (AC and DE). Within each MTL

region, repeated-measures analysis of variance (ANOVA) was used to assess differences in mean responses for each pair type. The interaction between MTL region and pair type was used to assess response differences across regions. Additional contrast and region of interest analyses were performed to isolate MTL regions that demonstrated activation for all pair types (AB, BC, AC, and DE) and regions that demonstrated greater response to learned face-house pairs (AB and BC) relative to face-face pairs (AC and DE).

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