Published in final edited form as:

Neuropsychologia. 2010 September ; 48(11): 3351–3359. doi:10.1016/j.neuropsychologia.2010.07.025.

Activity in the hippocampus and neocortical working memory regions predicts successful associative memory for temporally-discontiguous events

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Abstract

Models of mnemonic function suggest that the hippocampus binds temporally-discontiguous events in memory (Wallenstein, G.V., Eichenbaum, H., & Hasselmo, M.E., (1998). The hippocampus as an associator of discontiguous events. *Trends Neurosci*, 21 (8), 317–323), which has been supported by recent studies in humans. Less is known, however, about the involvement of working memory in bridging the temporal gap between to-be-associated events. In this study, subsequent memory for associations between temporally-discontiguous stimuli was examined using functional magnetic resonance imaging. In the scanner, subjects were instructed to remember sequentially-presented images. Occasionally, a plus-sign was presented during the interstimulus-interval between two images, instructing subjects to associate the two images as a pair. Following the scan, subjects identified remembered images and their pairs. Images following the plus-sign were separated into trials in which items were later recognized and the pair remembered, recognized and the pair forgotten, or not recognized. Blood-oxygen-level-dependent responses were measured to identify regions where response amplitude predicted subsequent associative- or item-memory. Distinct neocortical regions were involved in each memory condition, where activity in bilateral frontal and parietal regions predicted memory for associative-information and bilateral occipital and medial frontal regions for item-information. While activity in posterior regions of the medial temporal lobe showed an intermediate response predicting memory for both conditions, bilateral hippocampal activity only predicted associative memory.

Keywords

fMRI; human; medial temporal lobe; prefrontal; encoding

Introduction

The human brain has remarkable capacity for forming associations between items, yet given the constant stream of stimuli that one encounters and attends to each day, some experiences

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will be later remembered and some will not. Even if elements of an experience are remembered, particular associations between those elements may be forgotten. While many studies have examined the formation of associative memory for concurrently presented items, few have considered the more natural experience of encoding stimuli across time (Hales, Israel, Swann, & Brewer, 2009; Konkel, Warren, Duff, Tranel, & Cohen, 2008; Murray & Ranganath, 2007; Qin, et al., 2007; Qin, et al., 2009; Sommer, Rose, Glascher, Wolbers, & Buchel, 2005; Sommer, Rose, Weiller, & Buchel, 2005; Staresina & Davachi, 2009; Takeda, Naya, Fujimichi, Takeuchi, & Miyashita, 2005).

Forming lasting associative memories for items presented over time involves cooperation of working memory and long-term memory (LTM). Information pertaining to an initial item must be held in mind until information regarding a subsequent item can be added to the memory. Cortical regions, including prefrontal cortex (PFC) and parietal cortex, are commonly activated during working memory tasks where active maintenance of information over time is needed (Cabeza & Nyberg, 2000; D'Esposito, 2007; Kim, et al., 2009; Mottaghy, 2006; Passingham & Sakai, 2004). In order for the association to be formed and stored into memory, additional brain regions important for LTM encoding must be recruited. This cooperation between brain systems might allow for more flexibility in encoding wide-ranging experiences into LTM. Encoding of experiences across time is fundamental to episodic memory, and so it is important to explore the involvement and coordination between brain regions involved in working memory and LTM during the formation of associative memories for temporally-discontiguous stimuli. Such research may provide wider understanding of episodic memory and whether encoding relies on distributed brain regions whose participation depends on task demands.

Although associative memory research has focused primarily on activity in the MTL, involvement of certain neocortical regions in associative and/or item encoding has been reported for concurrently presented stimuli or associations made without temporal discontiguity. PFC involvement in item and associative memory formation has been described in several neuroimaging, neuropsychological, and electrophysiological studies (Achim & Lepage, 2005; Blumenfeld, Parks, Yonelinas, & Ranganath, 2010; Blumenfeld & Ranganath, 2006, 2007; Chua, Schacter, Rand-Giovannetti, & Sperling, 2007; Davachi & Wagner, 2002; Dolan & Fletcher, 1997; Fletcher, Shallice, & Dolan, 2000; Geuze, Vermetten, Ruf, de Kloet, & Westenberg, 2008; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Jackson & Schacter, 2004; Kapur, et al., 1996; Montaldi, et al., 1998; Park & Rugg, 2008; Peters, Daum, Gizewski, Forsting, & Suchan, 2009; Pihlajamaki, et al., 2003; Prince, Daselaar, & Cabeza, 2005; Ranganath, Cohen, Dam, & D'Esposito, 2004; Ranganath, et al., 2003; Rauchs, et al., 2008; Sperling, et al., 2003; Staresina & Davachi, 2006; Tendolkar, et al., 2007; Uncapher, Otten, & Rugg, 2006; Wagner, et al., 1998; Weyerts, Tendolkar, Smid, & Heinze, 1997). These studies commonly report greater activity in frontal regions during the encoding of subsequently remembered associations. Additional cortical regions have also been identified as engaged in associative encoding, including parietal (Achim & Lepage, 2005; Chua, et al., 2007; Fletcher, et al., 2000; Park & Rugg, 2008; Peters, et al., 2009; Pihlajamaki, et al., 2003; Rauchs, et al., 2008; Tendolkar, et al., 2007; Uncapher, et al., 2006; Uncapher & Wagner, 2009), temporal (Qin, et al., 2007; Rauchs, et al., 2008; Uncapher, et al., 2006), and occipital (Fletcher, et al., 2000; Ranganath, et al., 2004; Tendolkar, et al., 2007) regions.

Animal studies, primarily using lesions or electrophysiological recordings, have also examined MTL and cortical contributions to associative memory formation. Lesions of the hippocampus result in associative learning impairments in monkeys performing a spatial relational learning task (Lavenex, Amaral, & Lavenex, 2006) and a concurrent discrimination task (Mahut, Zola-Morgan, & Moss, 1982). Electrophysiological studies have also shown hippocampal involvement in forming associative memories (Cahusac, Rolls, Miyashita, & Niki, 1993; Wirth, et al., 2009; Wirth, et al., 2003). Cortical involvement in associative learning has also

been assigned to prefrontal (Asaad, Rainer, & Miller, 1998; Friedman & Goldman-Rakic, 1994; Inase, Li, Takashima, & Iijima, 2006), parietal (Friedman & Goldman-Rakic, 1994), and temporal (Takeda, et al., 2005) regions in monkeys, and in parietal and temporal regions in rats (Davis & McDaniel, 1993).

How are items that are separated by time or space associated into LTM? In addition to the engagement of brain regions involved in working memory, areas involved in LTM encoding, such as the medial temporal lobe (MTL; Squire, 1992), play an important role in the formation of associative memories. A recent study has examined how the hippocampus is specifically involved in associative encoding when relational gaps, either spatial or spatiotemporal, are present (Staresina & Davachi, 2009). Items and colors were presented 'combined' (e.g. a blue shirt), 'spatially discontinuous' (e.g. grey-scale grapes, with a green boarder around the image), or 'spatiotemporally discontinuous' (e.g. a red border followed by a grey-scale cup). With increasing relational separation ('combined' to 'spatial' to 'spatiotemporal'), they found increased hippocampal activity. The researchers concluded that the hippocampus is uniquely involved in forming associations across relational gaps (spatial and temporal). Although they found increased hippocampal activity in the spatiotemporal condition relative to the purely spatial condition, both types of trials included a spatial transformation; no trials examined purely temporal discontinuity. Also, the study examined intra-item associations, which were established between an item and its color. What remains unclear is whether the hippocampus is similarly recruited when spatial components are held constant and only temporal discontinuity exists between items to be associated. Further, their study focused primarily on hippocampal participation in encoding discontinuous events, and the involvement of wider cortical regions during such encoding requires further exploration.

Another recent study used sequential presentation of two visual items in a pair to examine regional brain responses for successful individual item encoding and successful associative item-item encoding (Qin, et al., 2009). Every item was included in a pair and a delay period separated the two paired items. A functional dissociation was measured in the MTL and adjacent cortical regions, where posterior parahippocampal, perirhinal, and inferior temporal cortices were more active for remembered items regardless of subsequent associative memory, whereas the hippocampus and inferior prefrontal cortex were more active only when associative information was remembered. While this study shed light on the differential involvement of hippocampal and MTL cortical regions during encoding of temporally-discontinuous events, wider examination of frontal and parietal working memory circuitry was not presented. In addition, the study explored activation differences between the first and second presented stimulus of associated pairs rather than holding stimulus order constant. Thus, no study that we know of has yet isolated neural activity in humans that predicts successful memory for associations across time.

The present study examines brain activity related to successful item- and association-based encoding of discrete events, allowing the BOLD response amplitude to be examined for items based on the success of subsequent memory for the item and association. Items were presented sequentially to assure that each item was individually processed and to examine regions involved in the associative encoding of discrete events presented across time. Rapid-event-related functional magnetic resonance imaging (fMRI) was used to examine MTL and cortical activity during an associative encoding task, and a post-scan recognition test was used to determine the subsequent associative- and item-memory for each visual stimulus. Activity in these regions was then examined relative to the subsequent memory for items and their associative properties. Given previous findings, the hypotheses were that frontal and medial temporal regions, particularly dorsolateral prefrontal cortex (DLPFC) and hippocampus, would show subsequent memory effects in regards to association-based encoding for temporally-

discrete events. Posterior cortical and medial temporal regions were predicted to show subsequent memory effects for the individual items.

Materials and Methods

Subjects

Twenty-six healthy volunteers (mean age = 23.23 ± 1 year, seven males) were recruited from the University of California, San Diego (UCSD) community and the surrounding area. All subjects had normal or corrected vision and gave informed consent approved by the UCSD Institutional Review Board.

Stimuli

Stimuli in this experiment consisted of 296 color images of everyday objects. Two-hundred, fifty-six of the images were presented sequentially while the subject was in the scanner, and a plus-sign appeared between some of the stimuli. An additional forty novel stimuli were included in the post-scan recognition test as foils for the item memory test. Images were acquired from Rossion and Pourtois color Snodgrass images (Rossion & Pourtois, 2004) and Hemera object library (Hemera Technologies Inc).

Experimental Procedure

During the scan, subjects were shown individual images, each presented for 2.5 seconds with jittered interstimulus intervals (ISIs) ranging between 0.5 and 11 seconds (Fig. 1A). The ISIs were calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale & Buckner, 1997). Subjects were told to remember all individual images. A plus-sign was presented in the center of the screen for 0.5 seconds immediately following some of the images; during these trials, subjects were instructed to associate the image that preceded the plus-sign (1P) with the image that followed the plus-sign (2P) and to remember the items as a pair. To ensure that the 'plus-sign' contained meaningful information to subjects as an instruction to associate items, unpaired items were also presented (1U and 2U). These items were also presented as pairs, but without an intervening 'plus-sign.' This design allowed assessment of the effects of explicit instruction to associate on associative memory performance and brain activity (Hales, et al., 2009). Unpaired stimuli are not considered further in the present study. To ensure that subjects saw each image, they were given a button box and asked to press a left or right button if the image represented a living or non-living object, respectively. Two hundred and fifty-six images were presented over four 362 second runs. Each image was presented once; 130 images were included in associated pairs, and 126 were unpaired. Image presentation pseudorandomly varied between paired and unpaired stimuli. Objects in each pair were unrelated. Inclusion of unpaired items prevented subjects from predicting before the time of the plus-sign which items would be associated.

Subjects completed a self-paced post-scan recognition test in which they were shown all stimuli previously viewed during the encoding task as well as novel stimuli used as foils for the item-memory question. When each stimulus was presented, subjects were asked to rate how well they remembered that image from the scanner presentation, from "1, Poorly," meaning they believe the item is new, to "5, Very Well," meaning they believe the item is old (Fig. 1B). For trials in which the object was previously viewed during encoding, subjects were given an immediate follow up question in which they were shown two choice images (both of which were previously shown during encoding) and were told to identify which of the two images was the pair of the original image or to respond that the original image was unpaired. For analyses, scores of 4 and 5 were considered to be "remembered." All 256 images were judged in this manner; the 40 novel items were also judged in the same manner, but without a follow-up question. This recognition test lasted approximately 30 minutes.

Functional MRI Parameters

Subjects were scanned at the Keck Center for Functional MRI at the University of California, San Diego using a 3T GE scanner. Functional images were acquired using gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 1.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). The brain was covered using 22 slices obtained perpendicular to the long axis of the hippocampus with $4 \times 4 \times 7$ mm voxels. The largest dimension of the functional voxels was along the length of the hippocampus allowing for the inclusion of more tissue within each voxel and smoothing within the direction of the hippocampus. This technique also takes advantage of the linear structure of the hippocampus and parahippocampal gyrus to maximize signal. Field maps were acquired to measure and correct for static field inhomogeneities (Smith, et al., 2004). A T1-weighted structural scan was acquired in the same plane and with the same voxel size as the functional scans. A high resolution structural scan was also acquired sagittally using a T1-weighted ($1 \times 1 \times 1$ mm) magnetization-prepared rapid gradient echo sequence or an inversion recovery prepared fast spoiled gradient recalled sequence.

Data Analysis

Functional data from each run were field-map corrected (Smith, et al., 2004). Using the AFNI suite of programs (Cox, 1996), slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm, voxels outside the brain were eliminated using a threshold mask of the functional data, and functional runs were corrected for motion and concatenated. A general linear model was constructed using multiple regression analysis; six motion regressors obtained from the registration process were included along with regressors for correctly and incorrectly encoded paired and unpaired images.

Standard landmarks, including the anterior and posterior commissures, were defined manually on the anatomical scans and used to transform the structural and functional data into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation (Cox, 1996). No spatial smoothing was performed because our functional voxel size allowed for smoothing while maintaining anatomical specificity. For all conditions, hemodynamic response functions were derived from the fMRI data using signal deconvolution with delta basis functions and a defined time window of 15 seconds following the onset of each stimulus (AFNI Software; Cox, 1996). Multiple linear regression analyses were used to examine relative activity during the encoding of items that followed a plus-sign (2P items) when they were later recognized and associative properties were remembered (“associative”), when they were later recognized and associative properties were forgotten (“item-only”), or when they were not later recognized (“forgotten”). Whole brain voxel-wise *t*-tests (two-tailed) carried out across all 26 subjects were conducted to examine which brain regions showed more activity under the following contrasts: (1) associative minus item-only, (2) item-only minus forgotten. Associative and item-only trials were performed under the same instructions allowing for better isolation of associative subsequent memory effects. Comparing associative trials to unpaired trials would result in higher trial numbers, but the contrast would be less controlled given the difference in instructions for paired and unpaired trials. In order to correct for multiple comparisons and yield a whole brain significance value of $p < 0.05$ corrected for all comparisons (based on Monte Carlo simulations), functional clusters of least 5 contiguous voxels were identified in conditions (1) and (2). Statistical activation maps were displayed using SUMA- AFNI Surface Mapper (Saad, Reynolds, Argall, Japee, & Cox, 2004) on the smooth white matter surface of the Talairach and Tournoux N27 average brain (from Freesurfer). The average hemodynamic response function was extracted for each cluster of interest.

In order to improve MTL alignment between subjects, the region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique (Miller, Beg, Ceritoglu, & Stark, 2005) was applied. Bilateral hippocampus and subregions of parahippocampal gyrus (PHG), including perirhinal (PRC), entorhinal (ERC), and parahippocampal (PHC) cortices, were defined for each subject on Talairach transformed images. Previously described landmarks were used to define PRC and ERC (Insausti, et al., 1998) and PHC (Stark & Okado, 2003). These defined anatomical regions of interest for each subject were normalized using ROI-LDDMM to a modified model of a previously created template segmentation (Kirwan, Jones, Miller, & Stark, 2007). Functional imaging data, after being corrected for spatial distortions using field maps acquired during each subject's scanning session (Smith, et al., 2004) underwent the same ROI-LDDMM transformation as was applied to the anatomical data. Hippocampal voxels active in the associative minus item-only condition, the item-only minus forgotten condition, or both were identified using a conjunction analysis of these two conditions masked by the anatomically defined left and right hippocampus.

Results

Behavioral Analysis

Analyses were focused on responses to 2P stimuli, those that followed the associative instruction (plus-sign). Seventy-seven percent ($\pm 2\%$ SEM; range of 49–94%) of 2P stimuli were subsequently recognized with confidence level 4 or 5 out of the 5-point scale (chance level of 40%). Following the recognition of a stimulus, subjects were presented with three options: (1) the stimulus was paired with item 'A,' (2) the stimulus was paired with item 'B,' or (3) the stimulus was 'unpaired.' Of the recognized 2P stimuli, the correct associative pair was identified at a rate of 63% ($\pm 3\%$ SEM; range of 21–90%). Of these stimuli, 25% were not included in the analyzed group of "associative" trials because the correct pair (2P) was not identified when the 1P item was the cue. The exclusion of trials in which associative information was remembered in only one direction resulted in lower trial numbers in each condition, but allowed for purer samples of associative and item-only conditions. Each subject's performance yielded a bin size for each trial category that was within two standard deviations from the category's mean bin size, and, therefore, all subjects were included in the analysis. Subjects had an average of 24.8 associative memory trials, 14.0 item-only memory trials, and 15.3 forgotten trials with no significant pattern of distribution across ISI length.

fMRI Analysis

"Associative memory" (i.e., 2P associative relative to 2P item-only) brain regions were identified where the size of the BOLD response predicted memory for associative information. Regions identified by this contrast with an alpha value of 0.05, corrected, are listed in Table 1. Bilateral frontal and parietal neocortical regions as well as posterior regions of the MTL showed increased activity during the encoding of associative trials relative to item-only trials ($p < 0.05$). Specific regions responding in an "associative memory" fashion include bilateral prefrontal cortex, left lateral parietal cortex, occipital cortex, and right precuneus (Fig. 2A–D). Although these regions showed a response to both item-only and forgotten trials, the activation did not differ between them, and the responses were significantly smaller than the response to associative trials. Increased activity during associative trials relative to item-only trials was also seen in bilateral posterior regions of the MTL, including posterior PHC, fusiform, and ventral occipital regions (Fig. 2E–F). These regions, however, exhibited a graded effect, where the response during associative trials was greater than during item-only trials, and the response during item-only trials appeared greater than during forgotten trials. Whole-brain analysis of item-only trials relative to forgotten trials, however, was used to confirm an "item memory" effect in these regions.

“Item memory” (i.e., 2P item-only relative to 2P forgotten) brain regions were identified where the size of the BOLD response predicted memory for items without memory for the pair. Regions identified by this contrast with an alpha value of 0.05, corrected, are listed in Table 2. Bilateral occipital and right medial frontal neocortical regions as well as posterior regions of the MTL, including posterior PHC and fusiform, showed increased activity during the encoding of item-only trials relative to forgotten trials ($p < 0.05$; Fig. 3A–D). In these regions, the response to forgotten trials was significantly smaller than the responses to associative and item-only trials. These regions were not identified in the above analysis of regions important for associative memory. Posterior MTL regions functionally defined in this contrast were near those defined in the previous contrast (Fig. 2E–F). The only region of overlap, however, between the “associative memory” and “item memory” contrasts was in left fusiform (Fig. 4). Accordingly, activity in this region showed a step-wise activation increase over the three trial types, as these voxels satisfied the statistical threshold for significant activation when associative trials were compared to item-only trials and also when item-only trials were compared to forgotten trials.

The functionally defined posterior MTL regions identified in both contrasts included voxels extending into different anatomical regions, including hippocampus, parahippocampus, fusiform, and occipital lobe. In order to examine the specific contribution of the hippocampus to associative and item memory formation, active voxels for both conditions overlapping with the anatomically defined hippocampus were isolated (peak locations: $-26, -28, -8; 31, -29, -4$), and impulse response curves in these overlapping voxels were analyzed. Despite wider posterior MTL involvement in both “associative memory” and “item memory,” bilateral hippocampus showed an “associative memory” response, with increased activity only predicting memory for temporally-discontiguous associative pairs (Fig. 5).

Discussion

The present study examined the successful formation of associative and item memory for sequentially presented visual stimuli. Distinct neocortical regions were involved in binding temporally-discontiguous items into memory (bilateral frontal and parietal regions) and item encoding (bilateral occipital and medial frontal regions). Overlapping effects were seen in posterior regions of the MTL and adjacent cortex, including fusiform cortex, while bilateral hippocampal activity predicted associative memory for temporally-discontiguous stimuli.

Working memory regions involved in long-term memory associative encoding

Increased response in bilateral frontal and parietal cortex was found in the present study for the successful encoding of item and associative information relative to item-only information. These regions have often been described as playing a role in working memory maintenance in human imaging studies, using techniques such as positron emission tomography, fMRI, electroencephalography, and transcranial magnetic stimulation, as well as animal electrophysiological studies (see Cabeza & Nyberg, 2000; D'Esposito, 2007; Kim, et al., 2009; Mottaghy, 2006; Passingham & Sakai, 2004 for review).

The current results extend these findings to include the involvement of frontal and parietal regions in the formation of associative memory across discrete events. In order to succeed in this task that involves encoding the association between items across time, working memory structures might maintain the first item in mind through the delay in order for it to be bound with the second item into a long-term associative memory. During the binding of the two items, coordinated involvement of working memory and LTM structures would be expected. The results of the present study support this model, as successful associative encoding engaged regions involved in working memory (bilateral frontal and parietal regions) as well as LTM (bilateral hippocampus and posterior PHC). Blumenfeld and Ranganath (2006) examined

working memory and LTM interactions focusing on the contribution of DLPFC. In their study, subjects performed two working memory tasks, i.e. three noun rehearsal and three noun reordering based on the weights of the objects described by each noun, followed by a post-scan LTM test in which they reported the strength of their memory for each word. Activity in DLPFC was correlated with subsequent memory performance for words encoded in the reorder condition but not in the rehearsal condition. Their results support DLPFC involvement in both working memory, through the organization of information, and in associative LTM encoding.

Additional support for this model of working memory and LTM coordination comes from a previous study that found increased delay period activity in PFC between associated relative to non-associated discontiguous items, whereas increased MTL activity was not seen until the two events could be bound into memory (Hales, et al., 2009). However, delay period subsequent memory effects for different trial types (associative, item-only, and forgotten) have not been examined, which might further explain how these different memory processes cooperate to associate events across time. The current findings also support a model discussed by D'Esposito (2007) in which multimodal cortical areas, such as lateral PFC and parietal cortex, are involved in working memory processing, and via their connections to primary, unimodal sensory areas, together work to maintain representations over a delay. Given this model, DLPFC and parietal activity would be expected to be accompanied by an increased response in occipital and left lateral inferior frontal regions for nameable, visual object stimuli, such as those used in the current study.

Posterior cortical involvement in visual item memory

Studies examining item-memory encoding in relation to associative-memory encoding usually focus on MTL substructure involvement and with less attention to neocortical contributions. A few studies have reported certain cortical regions showing an increased response during the encoding of subsequently remembered items, including ventrolateral prefrontal (Blumenfeld, et al., 2010; Murray & Ranganath, 2007), posterior inferior temporal (Qin, et al., 2009; Uncapher, et al., 2006), retrosplenial (Chua, et al., 2007), and fusiform (Sperling, et al., 2003) cortices. In one of the earliest fMRI studies to report signal changes in the hippocampus, the authors reported an interaction between ventral cortical regions and MTL structures for novel picture encoding (Stern, et al., 1996). They found response changes for novel picture encoding in bilateral hippocampus as well as in lingual and fusiform areas, regions known to be important for visual object recognition and discrimination. A recent study demonstrated repetition effects in posterior regions of the inferior temporal lobe that were sensitive only to visual features of stimuli and not to conceptual features (Wig, Buckner, & Schacter, 2009). The present findings extend prior results by showing a network of posterior cortical areas, including bilateral occipital and fusiform cortex, that exhibit increased response for the successful encoding of items, but where the response is not enhanced by additional encoding of associative information.

Subsequent memory effects in the MTL and adjacent cortex

The established role of the MTL in successful memory encoding motivated the additional analysis of this region. With debate surrounding the specific involvement of MTL substructures, a number of studies and reviews have examined the specific involvement of the PHG versus the hippocampus proper in successful versus unsuccessful associative- and item-encoding (Cohen, Poldrack, & Eichenbaum, 1997; Davachi, 2006; Diana, Yonelinas, & Ranganath, 2007; Mayes, Montaldi, & Migo, 2007; Ranganath & D'Esposito, 2001; Rauchs, et al., 2008; Staeresina & Davachi, 2008; Tendolkar, et al., 2007).

The role of posterior PHC in memory formation is debated. Some studies have ascribed associative memory functions to posterior PHC for its involvement in encoding source

(Davachi, Mitchell, & Wagner, 2003), associative (Kirwan & Stark, 2004; Sommer, Rose, Glascher, et al., 2005), and contextual (Davachi, 2006) information. Kirwan and Stark (2004), for instance, reported increased activity in the hippocampus and PHC during successful associative encoding of face-name pairs. Meanwhile, other studies have emphasized the importance of posterior PHC in item encoding (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Fernandez, et al., 1998; George, Horel, & Cirillo, 1989; Kirchhoff, Wagner, Maril, & Stern, 2000; Rauchs, et al., 2008; Stern, et al., 1996; Wagner, et al., 1998). One such study conducted a temporary lesion experiment in monkeys where cooling probes placed over PHG caused deficits in a visual memory task (George, et al., 1989). In the present study, posterior regions of PHC, and adjacent fusiform cortex, exhibited subsequent memory effects for both item and associative information, with maximal overlap between contrasts in left fusiform (Fig. 4). Therefore, these findings do not distinguish between these two possibilities, but support a third possibility, that the PHG is involved in both item- and associative-encoding, and the graded response may represent simple memory strength. Gold, et al. (2006) reported a similar finding in posterior PHC / fusiform gyrus. Subjects learned a series of adjectives in the scanner and were asked to create a mental image of either an indoor or outdoor scene that fits with the word they were shown. Following the scan, subjects were tested on their item and source memory. The researchers found that different MTL regions, including posterior PHC / fusiform gyrus, showed both a subsequent item-memory and source-memory effect. The current findings complement these results for this area of the MTL.

Hippocampal involvement in successful item and associative encoding has also been reported and debated. The hippocampus has a well-established critical role in declarative memory formation (see Squire, 2009 for review). Numerous lesion studies in humans and animals have supported the need for an intact functional hippocampus for encoding declarative information into LTM (Cohen & Squire, 1980; Manns & Eichenbaum, 2006; Mishkin, 1978; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991). More recent human fMRI studies have examined the specific role of the hippocampus, relative to other subregions of the MTL, in the encoding of associated items. Functional MRI studies have found increased activity in the hippocampus during the encoding of associated names and faces for pairs that are later remembered compared to those later forgotten (Chua, et al., 2007; Sperling, et al., 2003). Studies examining other types of associative encoding, between pairs of visual pictures or words or between an object and a location, have reported similar results with greater hippocampal activity for subsequently remembered associations relative to forgotten associations (Achim & Lepage, 2005; Jackson & Schacter, 2004; Qin, et al., 2007; Qin, et al., 2009; Ranganath, et al., 2004; Staresina & Davachi, 2006).

Unlike previous associative encoding studies which have commonly presented two items concurrently, some recent studies have examined the formation of associations across spatial and/or temporal gaps (Hales, et al., 2009; Konkel, et al., 2008; Murray & Ranganath, 2007; Qin, et al., 2007; Qin, et al., 2009; Staresina & Davachi, 2009). As a strategy for examining temporal relational gaps, using sequential presentation of items forces subjects to create associations between the items across time (Hales, et al., 2009; Qin, et al., 2009). Hales et al. (2009) examined differential MTL and PFC responses for paired versus unpaired items and found distinct temporal contributions of these two regions towards associative encoding. While PFC was active in response to the cue to associate and during the delay between paired stimuli, the MTL did not increase in response until the presentation of the second item. Focusing on paired items and activity within and around the MTL, Qin et al. (2009) conducted a task to examine MTL subregional involvement in forming successful associative and item memories. In accordance with previous studies and those mentioned above, they found an increased response in the hippocampus, as well as inferior PFC, for successful associative encoding and in posterior PHC for successful item encoding. Working memory circuitry may have been less salient in their analysis because items following the temporal gap were not used for identifying

item-memory regions and were not used as cues for testing associative memory. In the present study, associations were tested in each direction, which assures that the association was strong and less likely contaminated by guesses in a forced-choice recognition test.

Another recent study examined the formation of associations across spatial and temporal relational gaps (Staresina & Davachi, 2009). They reported increased hippocampal response for encoding spatially discontinuous associations relative to spatially contiguous associations with even greater response to the successful formation of spatiotemporally-discontinuous associations. Both types of discontinuous associations, however, involved spatial relational gaps. The present study extends these findings by addressing and supporting the selective involvement of the human hippocampus in forming associations across temporal gaps without the need for spatial manipulations. In addition, this study examines the involvement of cortical working memory regions, including frontal and parietal cortices, along with LTM regions in encoding temporally-discontinuous associations.

The current study provides evidence for a functional dissociation between frontoparietal and posterior cortical regions for associative encoding, where frontoparietal regions are more active for binding associative information across time and posterior cortical regions are more active for forming individual memories of visual objects. This study uniquely examines subsequent memory effects in both the MTL and neocortex for items associated across time and the process of linking new information to a previously encoded item. These findings support the following model for associating temporally-discontinuous events: neocortical working memory regions maintain neural representation of an item across a delay, allowing concurrence between that active representation and later ones for hippocampal binding. Further investigation is needed regarding cortical and MTL regional activity during the time delay between stimuli being associatively encoded into LTM. The present findings suggest coordination between working memory and LTM structures in the fundamental ability of organisms to associate information across discrete events into memory and to form relational episodic memory for ongoing experience.

Acknowledgments

This work was supported by the National Institute of Neurological Disorders and Stroke K23 NS050305 and the University of California, San Diego Departments of Neurosciences and Radiology. JBH is supported by the National Science Foundation through the Graduate Research Fellowship Program.

Grant sponsor: National Institute of Neurological Disorders and Stroke; Grant number: K23 NS050305; JBH supported by the NSF GRFP.

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Figure 1.

Experimental design. *A*, Example of the encoding task used in the scanner illustrating the presentation of two paired and two unpaired stimuli. A plus-sign, cuing the association of the preceding stimulus (1P) with the one to follow (2P), is presented for the first 0.5s of a 0.5–11 second ISI only between paired images and not between unpaired images (1U and 2U). Each stimulus is presented for 2.5 seconds. *B*, Example of the post-scan recognition test. Subjects were shown stimuli previously viewed during the encoding task as well as novel stimuli, and they were asked if they remember seeing the image in the scanner, responding “1” (poorly) through “5” (very well). If the object was included in the encoding task, a follow up question was provided where subjects were shown two choice stimuli (both of which had been previously viewed) and were asked which object (1 or 2) was the associated pair (if paired) or to respond 3 if the target was unpaired.

Figure 2.

Activity in bilateral frontal and parietal neocortical regions predicts memory for associative information only. Activity in bilateral regions of posterior MTL, extending into lateral temporal and occipital cortices, predicts memory for associative information, but also is influenced by memory for items. Yellow arrows indicate left prefrontal (extending both lateral and medial) (A), right prefrontal (B), left lateral parietal and occipital (C), right precuneus (D), and bilateral posterior MTL (E,F) clusters used for time-course analyses. Statistical activation maps for regions showing significantly increased activity ($p < 0.05$, corrected for multiple comparisons) for associative trials compared to item-only trials are overlaid on the smooth white matter surface of the Talairach and Tournoux N27 average brain. Graphs depicting the time course of percent signal change in these regions for each condition beginning with the onset of stimuli following a plus-sign, 2P. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

Figure 3.

Activity in bilateral occipital and right medial frontal neocortical regions predicts memory for items, regardless of additional memory for associative information. Activity in bilateral regions of posterior MTL, regions similar to those defined functionally in the previous contrast, predicts memory for items, but also is influenced by additional associative memory. Yellow arrows indicate left occipital (A), right medial frontal (B), and bilateral posterior MTL (C,D) clusters used for time-course analyses. Statistical activation maps for regions showing significantly increased activity ($p < 0.05$, corrected for multiple comparisons) for item-only trials compared to forgotten trials are overlaid on the smooth white matter surface of the Talairach and Tournoux N27 average brain. Graphs depicting the time course of percent signal change in these regions for each condition beginning with the onset of stimuli following a plus-sign, 2P. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

Figure 4.

Left, Left fusiform cortex predicts memory for items and is influenced by additional memory for associative information. White circles indicate the left fusiform cluster, the only region of overlap between the “associative memory” and “item memory” contrasts; this region was then used for time-course analysis. Statistical activation maps for regions showing significantly increased activity ($p < 0.05$) for associative compared to item-only trials, “associative memory,” and for item-only compared to forgotten trials, “item memory,” are overlaid on the left hemisphere ventral smooth white matter surface of the Talairach and Tournoux N27 average brain. *Right*, Graph depicting the time course of percent signal change in the identified cluster in each condition beginning with the onset of stimuli following a plus-sign, 2P. Activity in left fusiform shows a stepwise increase from forgotten to item-only to associative trials. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

Figure 5.

Bilateral hippocampus predicts memory for associative information. Graphs depict the time course of percent signal change in left and right hippocampus for each condition beginning with the onset of stimuli following a plus-sign, 2P. Voxels functionally defined in posterior MTL from the “associative memory” and “item memory” conditions extended into multiple anatomical brain regions; therefore, time courses of activity were extracted from those voxels that overlapped with anatomically defined bilateral hippocampus. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

Table 1

Significantly active brain regions for associative versus item-only trials.*

$p < 0.05^{**}$	#Volume	X	Y	Z	t-values
L Precuneus (BA 7)	35904	-26	-65	28	5.2375
L Precentral Gyrus (BA 6)	31424	-26	-9	52	5.0144
R Cerebellum	11392	30	-69	-24	4.4381
L Striatum	6848	-18	7	8	4.4458
R Lingual Gyrus (BA 18)	5760	10	-77	4	4.4084
R Precuneus (BA 31)	3264	22	-69	20	4.3196
L Cerebellum	1408	-14	-53	-40	3.4985
R Cerebellum	1344	18	-41	-28	3.245
L Cuneus (BA 17)	1280	-10	-81	12	3.4166
R Precentral Gyrus (BA 6)	1152	22	-13	52	3.9336
R Middle Frontal Gyrus (BA 10)	1088	34	35	20	3.2486
L Precentral Gyrus (BA 4)	1088	-26	-25	60	3.4927
L Midbrain	1024	-6	-21	-8	3.8523
R Striatum	960	22	-5	16	4.089
L Cerebellum	832	-10	-57	-4	3.4716
L Cerebellum	704	-6	-41	-24	2.5972
L Cerebellum	704	-14	-61	-16	4.1222
L Inferior Frontal Gyrus (BA 47)	640	-50	39	-8	3.4677
L Thalamus	640	-18	-13	4	3.2927
R Superior Frontal Gyrus (BA 8)	640	18	27	48	-2.9286
R Hippocampus	576	30	-33	-8	3.4074
L Lingual Gyrus (BA 18)	576	-18	-81	-4	2.8385
L Parahippocampal Gyrus (BA 19)	576	-22	-53	0	3.4153
L Putamen	512	-30	3	4	2.858
R Precuneus (BA 7)	512	6	-61	44	2.6297

* coordinates correspond to the voxel of maximum intensity for each cluster

** corrected for multiple comparisons

Table 2

Significantly active brain regions for item-only versus forgotten trials.*

$p < 0.05^{**}$	#Volume	X	Y	Z	t-values
R Parahippocampal Gyrus (BA 36)	9728	26	-37	-12	3.6068
L Fusiform Gyrus (BA 37)	5184	-42	-49	-12	3.795
R Insula (BA 13)	4224	26	-29	20	3.9061
L Posterior Cingulate (BA 30)	2816	-26	-49	20	3.1384
L Inferior Occipital Gyrus (BA 18)	1408	-30	-89	-4	3.9172
L Cingulate Gyrus (BA 31)	960	-26	-25	36	3.5273
L Cingulate Gyrus (BA 31)	896	-18	-33	32	3.4189
Brainstem	832	6	-13	-28	3.1858
R Posterior Cingulate (BA 23)	768	2	-33	16	2.8386
L Thalamus	576	-22	-25	4	2.7505
R Cingulate Gyrus (BA 32)	576	18	15	36	2.8948
R Precuneus (BA 31)	576	18	-53	32	2.8237
L Cerebellum	512	-2	-41	-12	3.3703
L Fusiform Gyrus (BA 20)	384	-38	-1	-20	3.3649
L Cerebellum	384	-22	-45	-16	2.5557
R Thalamus	320	22	-25	4	2.6238
R Superior Temporal (BA 41)	320	34	-41	12	3.5759
R Cuneus (BA 19)	320	22	-85	36	2.6615
L Precuneus (BA 19)	320	-18	-85	44	3.1007
R Medial Frontal Gyrus (BA 6)	320	2	-5	48	2.9164

* coordinates correspond to the voxel of maximum intensity for each cluster

** corrected for multiple comparisons