



# Activity in the hippocampus and neocortical working memory regions predicts successful associative memory for temporally discontinuous events

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## ARTICLE INFO

### Article history:

Received 19 March 2010  
Received in revised form 5 June 2010  
Accepted 20 July 2010  
Available online 1 August 2010

### Keywords:

fMRI  
Human  
Medial temporal lobe  
Prefrontal  
Encoding

## ABSTRACT

Models of mnemonic function suggest that the hippocampus binds temporally discontinuous events in memory (Wallenstein, Eichenbaum, & Hasselmo, 1998), 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 discontinuous 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.

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## 1. 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 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 discontinuous 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

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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 border 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.

## 2. Materials and methods

### 2.1. Subjects

Twenty-six healthy volunteers (mean age = 23.23 ± 1 years, 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.

### 2.2. 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.).

### 2.3. Experimental procedure

During the scan, subjects were shown individual images, each presented for 2.5 s with jittered interstimulus intervals (ISIs) ranging between 0.5 and 1.1 s (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 s 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

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