HIPPOCAMPUS 15:997–1005 (2005)

RAPID COMMUNICATION

Functional Connectivity With the Hippocampus During Successful Memory Formation

Charan Ranganath,[1]* Aaron Heller,[1] Michael X. Cohen,[1]
Craig J. Brozinsky,[1] and Jesse Rissman[2]

ABSTRACT: Although it is well established that the hippocampus is critical for episodic memory, little is known about how the hippocampus interacts with cortical regions during successful memory formation. Here, we used event-related functional magnetic resonance imaging (fMRI) to identify areas that exhibited differential functional connectivity with the hippocampus during processing of novel objects that were subsequently remembered or forgotten on a postscan test. Functional connectivity with the hippocampus was enhanced during successful, as compared with unsuccessful, memory formation, in a distributed network of limbic cortical areas—including perirhinal, orbitofrontal, and retrosplenial/posterior cingulate cortex—that are anatomically connected with the hippocampal formation. Increased connectivity was also observed in lateral temporal, medial parietal, and medial occipital cortex. These findings demonstrate that successful memory formation is associated with transient increases in cortico-hippocampal interaction.

KEY WORDS: encoding; perirhinal; retrosplenial; prefrontal; fMRI

A large body of evidence from humans and nonhuman primates suggests that the medial temporal lobe region plays a critical role in forming new declarative memories (Eichenbaum and Cohen, 2001; Squire et al., 2004). Most theories of hippocampal function suggest that the hippocampus is critical for declarative memory precisely because of the unique convergence of cortical regions that project to this region. For example, one influential idea is that, during encoding, various aspects of an event are processed in diverse neocortical association areas, and that the hippocampus "binds" these neocortical memory representations in a manner that can support expressions of relational/declarative memory (Eichenbaum and Cohen, 2001; O'Reilly and Rudy, 2001; Howard et al., 2005). Implicit in this, and other hypotheses of hippocampal function, is the idea that interactions between the hippocampus and neocortex are critical for normal declarative memory formation.

At present, little is known about how the human hippocampus interacts with neocortical regions during successful and unsuccessful memory formation. Some previous neuroimaging studies have addressed this question by examining changes in functional coupling with the hippocampus that correlated with individual differences in memory performance (Grady et al., 2003) or correlated with task manipulations that differentially engaged episodic encoding processes (Rajah et al., 1999; Habib et al., 2003). For example, Grady and colleagues used positron emission tomography (PET) to scan older and younger subjects, during encoding of objects and words. They next used seed-based partial least squares (PLS) analysis to examine networks in which coupling with the hippocampus correlated with individual differences in memory performance. In another study, Habib and colleagues used seed-based PLS to identify networks that differentially coupled with the hippocampus during processing of novel relative to familiar words (Habib et al., 2003), based on the assumption that situationally novel stimuli are more likely to be successfully encoded (Stern et al., 1996; Tulving et al., 1996; Ranganath and Rainer, 2003). Finally, Rajah and colleagues used structural equation modeling of PET data to investigate differences in functional connectivity between a medial temporal region and other cortical regions during encoding and retrieval tasks with face stimuli (Rajah et al., 1999). Results from these blocked-trial PET studies generally revealed increased functional connectivity between the medial temporal lobes and prefrontal and extrastriate visual areas during memory encoding. However, it is not clear whether transient changes in coupling between the hippocampus and these cortical regions are specifically related to successful encoding of a given item.

Here, we used functional magnetic resonance imaging (fMRI) to examine the extent to which successful item encoding is associated with transient changes in cortico-hippocampal interaction. In this experiment, subjects were scanned while performing a working memory (WM) task with trial-unique line drawings of complex objects (Fig. 1). Immediately after the scan session, subjects were given a surprise long-term memory (LTM) test on objects presented during the scan. We previously showed that activity in the left hippocampus during the early delay period of each WM trial was significantly correlated with subsequent LTM

[1] **Department of Psychology and Center for Neuroscience, University of California at Davis, Davis, California;** [2] **Department of Psychology, University of California at Berkeley, Berkeley, California**
Grant sponsor: NIH; Grant numbers: R01 MH68721, PO1 NS40813; Grant sponsor: UC Davis Alzheimer's Disease Center.
*Correspondence to: Charan Ranganath, Ph.D., Center for Neuroscience, 1544 Newton Ct., University of California at Davis, Davis, CA 95616.
E-mail: cranganath@ucdavis.edu
Accepted for publication 16 September 2005
DOI 10.1002/hipo.20141
Published online 9 November 2005 in Wiley InterScience (www.interscience.wiley.com).

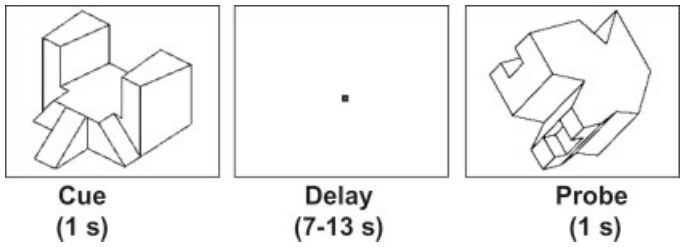

FIGURE 1. Experimental task. Schematic depiction of example stimuli and timing for trials of the visual working memory task. Following the scan session, subjects completed a surprise long-term memory task for each cue object, and activity was separately examined for trials on which the object was subsequently remembered or forgotten.

performance (Ranganath et al., 2005). In the present study, we sought to identify cortical regions that showed enhanced coupling with this left hippocampal region during processing of objects that were subsequently remembered relative to processing of objects that were subsequently forgotten.

We used the "beta series correlation" method (Rissman et al., 2004) to examine event-related changes in functional connectivity with the hippocampus. The beta series method uses a standard general linear model (GLM) approach for estimating activity during specific components of each WM trial (Courtney et al., 1997; Zarahn et al., 1997; Postle et al., 2000; Ranganath and D'Esposito, 2001; Ranganath et al., 2003, 2004a,b), but adapts the model such that separate beta values are computed to estimate activation changes for each component of each individual trial. With this approach, a series of beta values can be extracted from a seed region, indexing trial-to-trial activity fluctuations within that region. The beta series can then be used as dependent data in a voxel-based correlation analysis, in which, for a given task component or trial type, activity changes are correlated between the seed region and voxels across the brain.

The beta series correlation analysis method allowed us to separately identify patterns of functional coupling with the left hippocampal seed region during the cue, early delay, and late delay phases of each WM trial. (Connectivity effects were not analyzed during the probe period because there were insufficient numbers of trials to separately examine connectivity effects for matching vs. nonmatching probes.) We were specifically interested in identifying areas where functional coupling with the hippocampal seed was greater on trials with subsequently remembered objects than on trials with subsequently forgotten objects. Results of our previous behavioral analyses suggested that processing early in the memory delay was critical for successful LTM formation (Ranganath et al., 2005), and that the left hippocampal region showed activity during this time period that differentiated between subsequently remembered and forgotten objects. We therefore predicted that neocortical areas should show differential connectivity with the hippocampus during the early delay.

Results from the contrast between subsequently remembered and forgotten trial types are summarized in Table 1, and scatterplots are shown for a subset of these regions in Figure 2. Consistent with our initial hypothesis, the majority of the identified areas exhibited differential connectivity with the hippocampus during the early delay phase. During the cue period, differential connectivity effects were observed in precuneus (Brodmann's area [BA] 18), superior parietal cortex (BA 7), and left middle temporal gyrus (BA 37). During the early delay period, differential connectivity effects were observed in limbic cortical regions, including bilateral regions in the anterior collateral sulcus (lying in perirhinal, anterior inferior temporal, and/or temporopolar cortex (Insausti et al., 1998)), medial orbitofrontal cortex (at or near BA 11; (Ongur et al., 2003)), ventral frontopolar cortex (BA 10, Ongur et al., 2003), insula, and caudal ventromedial cortical areas spanning the posterior cingulate and retrosplenial cortices (BA 23/29/30/31; (Vogt et al., 2001). Other areas showing differential connectivity during the early delay included the superior and middle temporal, supramarginal, and angular gyri, precuneus, and several early visual cortical areas. Finally, regions in the right superior frontal (BA 10), angular (BA 19/39), and middle temporal (BA 19) gyri showed greater connectivity with the hippocampus during the late delay period of the remembered trials as compared with the forgotten trials.

To our knowledge, no prior fMRI study has directly compared functional connectivity with the hippocampus during successful and unsuccessful episodic memory formation. Our results showed that the hippocampus exhibits functional connectivity with a wide network of neocortical areas that is predictive of successful visual LTM formation. Additionally, the locations of areas identified in these analyses converge remarkably with the known neuroanatomy of the primate hippocampal formation. For example, it is well known that the entorhinal cortex (EC) (the primary point of cortical connectivity in the hippocampal formation) receives direct projections from the perirhinal, parahippocampal, posterior cingulate, retrosplenial, insular, orbitofrontal, and superior temporal cortices (Insausti et al., 1987). In addition to these bidirectional connections, the subiculum and the CA1 are known to have direct projections to the orbitofrontal cortex (Barbas and Blatt, 1995; Carmichael and Price, 1995), and CA1 receives direct projections from parietal areas 7a and 7b, and area TE (Rockland and Van Hoesen, 1999; Zhong and Rockland, 2004). The present results suggest that each of these neocortical regions is not only anatomically linked with the hippocampal formation, but that their activity is functionally linked with the hippocampus during successful memory formation. Accordingly, our results implicate these areas as a true network for visual memory encoding.

Results from previous studies have shown that analyses of functional connectivity are not simply redundant with analyses of activation changes (Gazzaley et al., 2004; Rissman et al., 2004). The present results were consistent with this idea. Many of the regions identified as showing subsequent memory effects in our previous report (Ranganath et al., 2005), such as the lateral prefrontal cortex, did not exhibit memory-correlated changes in connectivity with the hippocampus. Conversely, some areas that showed changes in connectivity, such as the retrosplenial/posterior cingulate cortex, did not show subsequent memory effects in

TABLE 1.

Local Maxima of Regions Exhibiting Differential Connectivity With the Hippocampus, During Processing of Subsequently Remembered Items As Compared With Subsequently Forgotten Items

Region	BA	Z-value	x	y	z	$r_{\text{remembered}}$	$r_{\text{forgotten}}$
Cue							
Precuneus (L)	18	4.32	−21	−66	28	0.35 (0.05)	0.12 (0.08)
Superior parietal gyrus (L)	7	3.59	−24	−70	70	0.32 (0.09)	0.14 (0.11)
Middle temporal gyrus (L)	37	3.46	−70	−60	10	0.27 (0.04)	0.06 (0.10)
Early delay							
Retrosplenial/posterior cingulate cortex	23/31	4.49	4	−63	14	0.51 (0.06)	0.13 (0.09)
Cuneus	18	4.46	0	−74	18	0.48 (0.06)	0.24 (0.09)
Retrosplenial/posterior cingulate cortex	23/29/30	4.41	10	−63	7	0.46 (0.07)	0.05 (0.10)
Middle temporal gyrus (R)	21/37	4.24	60	−56	0	0.44 (0.07)	0.20 (0.09)
Middle temporal gyrus (L)	39	4.00	−60	−70	21	0.45 (0.06)	0.25 (0.09)
Middle temporal gyrus (L)	21/37	4.00	−60	−66	7	0.42 (0.07)	0.25 (0.12)
Supramarginal gyrus (R)	39/40	3.97	56	−49	32	0.41 (0.06)	0.25 (0.08)
Postcentral gyrus (L)	42	3.85	−70	−28	14	0.46 (0.07)	0.22 (0.07)
Lateral orbital gyrus (R)	47	3.84	32	63	−18	0.26 (0.06)	0.03 (0.08)
Anterior collateral sulcus (L)	3	3.73	−46	−7	−46	0.40 (0.06)	0.11 (0.12)
Postcentral sulcus (R)	2	3.68	42	−38	63	0.50 (0.04)	0.17 (0.06)
Superior temporal gyrus (L)	42/22	3.66	−56	−46	18	0.45 (0.07)	0.19 (0.11)
Middle temporal gyrus (R)	21/37	3.65	66	−52	4	0.41 (0.06)	0.18 (0.11)
Middle temporal gyrus (L)	21	3.64	−63	−24	−4	0.46 (0.06)	0.15 (0.12)
Insula (L)		3.62	−38	4	4	0.44 (0.05)	0.14 (0.08)
Middle occipital gyrus (L)		3.59	−32	−102	21	0.36 (0.08)	0.01 (0.11)
Superior frontal gyrus (L)	6	3.5	−32	14	60	0.45 (0.06)	0.13 (0.11)
Postcentral gyrus (R)	48	3.5	66	0	7	0.46 (0.07)	0.24 (0.10)
Cuneus (L)	17	3.48	−7	−102	4	0.29 (0.08)	0.01 (0.11)
Fusiform gyrus (L)	20	3.45	−46	7	−46	0.37 (0.07)	0.19 (0.10)
Gyrus rectus (R)	11	3.42	4	42	−28	0.14 (0.09)	−0.03 (0.08)
Cuneus (R)	17	3.42	4	−94	7	0.44 (0.06)	0.23 (0.12)
Cerebellum (R)		3.38	7	−56	−21	0.33 (0.06)	0.26 (0.10)
Superior temporal gyrus (R)	21	3.36	63	−4	−4	0.47 (0.06)	0.31 (0.10)
Middle temporal gyrus (L)	39	3.34	−66	−66	14	0.28 (0.07)	0.12 (0.10)
Cuneus (L)	18	3.31	−18	−105	10	0.40 (0.07)	0.16 (0.10)
Superior temporal gyrus (L)	48	3.3	−52	−14	7	0.40 (0.06)	0.13 (0.08)
Middle occipital gyrus (L)	21/37	3.29	−70	−63	4	0.32 (0.07)	0.03 (0.10)
Angular gyrus (R)	19/39	3.29	42	−84	32	0.23 (0.07)	−0.06 (0.11)
Superior temporal gyrus (R)	21/22	3.28	−63	7	−4	0.40 (0.08)	0.20 (0.12)
Gyrus rectus (R)	11	3.26	7	49	−24	0.18 (0.11)	−0.12 (0.1)
Cuneus (L)	18	3.25	−10	−88	−4	0.48 (0.08)	0.30 (0.11)
Cuneus (R)	17	3.23	14	−84	7	0.41 (0.06)	0.15 (0.12)
Superior temporal sulcus (R)	22/42	3.22	52	−32	7	0.42 (0.07)	0.07 (0.13)
Anterior collateral sulcus (R)	20/36	3.21	38	−4	−46	0.34 (0.07)	0.16 (0.09)
Cuneus (L)	19	3.19	−7	−10	28	0.25 (0.04)	−0.06 (0.07)
Anterior collateral sulcus (L)	20	3.18	−32	7	−42	0.34 (0.07)	0.03 (0.10)
Middle occipital gyrus (L)	19	3.18	−38	−80	14	0.43 (0.05)	0.30 (0.09)
Fusiform gyrus (L)	6	3.18	−46	−28	−32	0.37 (0.09)	0.12 (0.11)
Superior temporal gyrus (L)	12/38	3.14	−63	14	−10	0.43 (0.08)	0.12 (0.11)
Middle occipital gyrus (L)	19	3.12	−42	−91	21	0.28 (0.06)	0.02 (0.13)
Middle occipital gyrus (R)	21/37	3.11	60	−63	−7	0.41 (0.07)	0.19 (0.12)
Cerebellum (R)		3.07	10	−63	−24	0.46 (0.05)	0.26 (0.09)
Supramarginal gyrus (L)	40	3.02	−63	−42	38	0.42 (0.07)	0.15 (0.09)
Central sulcus (R)	4	3.01	49	−14	63	0.36 (0.09)	0.26 (0.09)
Precentral gyrus (R)	6	2.95	46	−7	60	0.46 (0.07)	0.31 (0.07)
Superior temporal gyrus (L)	21/38	2.93	−66	4	−14	0.36 (0.08)	0.15 (0.11)
Superior temporal gyrus (R)	42	2.88	66	−21	7	0.43 (0.06)	0.16 (0.12)

Continued

TABLE 1. (Continued)

Region	BA	Z-value	x	y	z	$r_{remembered}$	$r_{forgotten}$
Late delay							
Angular gyrus (R)	19/39	3.57	35	−74	35	0.39 (0.07)	0.13 (0.10)
Middle temporal gyrus (R)	19	3.27	38	−84	28	0.35 (0.08)	−0.08 (0.13)
Superior frontal gyrus (R)	10	3.48	24	56	−18	0.34 (0.07)	0.03 (0.12)

R = right; L = left; BA = Brodmann's area; *x*, *y*, *z* = MNI coordinates (mm); *Z*-values reflect transformed statistics resulting from the paired *t*-tests contrasting Fisher-transformed correlations between remembered and forgotten trials. $r_{remembered}$ and $r_{forgotten}$ are mean raw Pearson's correlation coefficient values during the designated task period between activity in the hippocampal seed and the voxel at the local maxima for subsequently remembered and forgotten items, respectively (SEM values in parentheses). The raw *r*-values are included for illustrative purposes, but the Fisher-transformed values were used in all significance tests.

our previous report. These findings suggest that analyses of functional connectivity can provide a valuable complement to standard analyses of subsequent memory effects.

Our connectivity analyses identified bilateral regions in the anterior collateral sulcus that likely extended into the perirhinal cortex. These results are consistent with findings from a study that used intracranial EEG recordings to examine functional interactions between the hippocampus and perirhinal cortex during successful and unsuccessful memory formation (Fernandez et al., 1999; Fell et al., 2001). In this study, EEG was recorded from depth electrode contacts in the hippocampus proper and in the anterior collateral sulcus (likely corresponding to the ento- and perirhinal cortex) during encoding of words that were successfully recalled and words that were not recalled on a subsequent memory test. Interestingly, frequency oscillations in the gamma band (36–40 Hz) in these two regions showed heightened phase synchronization—a measure of functional coupling—during trials with subsequently remembered items, relative to trials with forgotten items (Fell et al., 2001). It is unclear whether the γ-band synchronization measured by Fell and colleagues might represent a neural mechanism for the correlations in BOLD signal changes observed here. Nonetheless, our results converge with theirs in demonstrating that successful memory formation is associated with enhanced coupling between the hippocampus and perirhinal cortex. These results also converge with results from rats (Muir and Bilkey, 2001) and monkeys (Gaffan and Parker, 1996) demonstrating functional interactions between the hippocampus and the perirhinal cortex.

In addition to the anterior collateral sulcus, the retrosplenial and posterior cingulate cortices also showed increased functional connectivity with the hippocampus during successful memory formation. These areas have been reported to show increased activity during retrieval of items that are recollected (Wagner et al., 2005), but they have not been implicated in neuroimaging studies of successful encoding. Indeed, our previous analyses did not reveal overall activity differences between subsequently remembered and forgotten items in these regions (Ranganath et al., 2005). The present results suggest that retrosplenial and posterior cingulate regions might still contribute to memory encoding through changes in functional connectivity with the hippocampus. Results from lesion studies are consistent with this possibility. For instance, there have been a number of case reports of human amnesia resulting from retrosplenial cortex lesions (Valenstein et al., 1987; Bowers et al., 1988; Yasuda et al., 1997; Masuo et al., 1999; Aggleton and Pearce, 2001; McDonald et al., 2001). Consistent with these reports, lesions (Vann and Aggleton, 2002; Vann et al., 2003) or temporary inactivation (Cooper and Mizumori, 1999, 2001; Cooper et al., 2001) of the retrosplenial cortex in rats have been shown to impair spatial memory. Critically, hippocampal disruption (through fornix lesions) has been shown to reduce retrosplenial activity levels (Vann et al., 2000), and retrosplenial inactivation has been shown to disrupt hippocampal place cell coding (Cooper and Mizumori, 2001). These findings in rodents converge with the present human neuroimaging data to suggest that retrosplenial and posterior cingulate cortices exhibit tight functional coupling with the hippocampus in the service of memory.

One neocortical area that has been consistently implicated in neuroimaging studies of successful memory formation is the lateral prefrontal cortex (Buckner et al., 1999; Fernandez and Tendolkar, 2001; Paller and Wagner, 2002; Ranganath and Knight, 2003). As noted earlier, we also observed subsequent memory effects in dorsolateral (BA 9) and ventrolateral (BA 44, 45, and 47) prefrontal cortex in this dataset (Ranganath et al., 2005). On the basis of such findings, a number of researchers have suggested that functional interactions between lateral prefrontal cor-

FIGURE 2. Functional connectivity with the hippocampus related to successful memory formation. At left, statistical maps overlaid on averaged T1-weighted images show regions that exhibited greater connectivity with the hippocampus for objects that were subsequently remembered relative to objects that are subsequently forgotten during the cue (A), the early delay (B), and the late delay (C) periods. Arrows point to regions of interest that were used to generate the scatterplots at right. Each scatterplot shows parameter estimates indexing activation on each trial in the hippocampal seed region (*x*-axis) and corresponding parameter estimates in each region of interest. Separate plots are shown for trials with subsequently remembered (left) and subsequently forgotten (right) items. Data from different subjects are shown in different shapes/colors. For visualization purposes, each subject's beta values were *z*-transformed, and only datapoints < 2.75 standard deviations from the mean are plotted. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

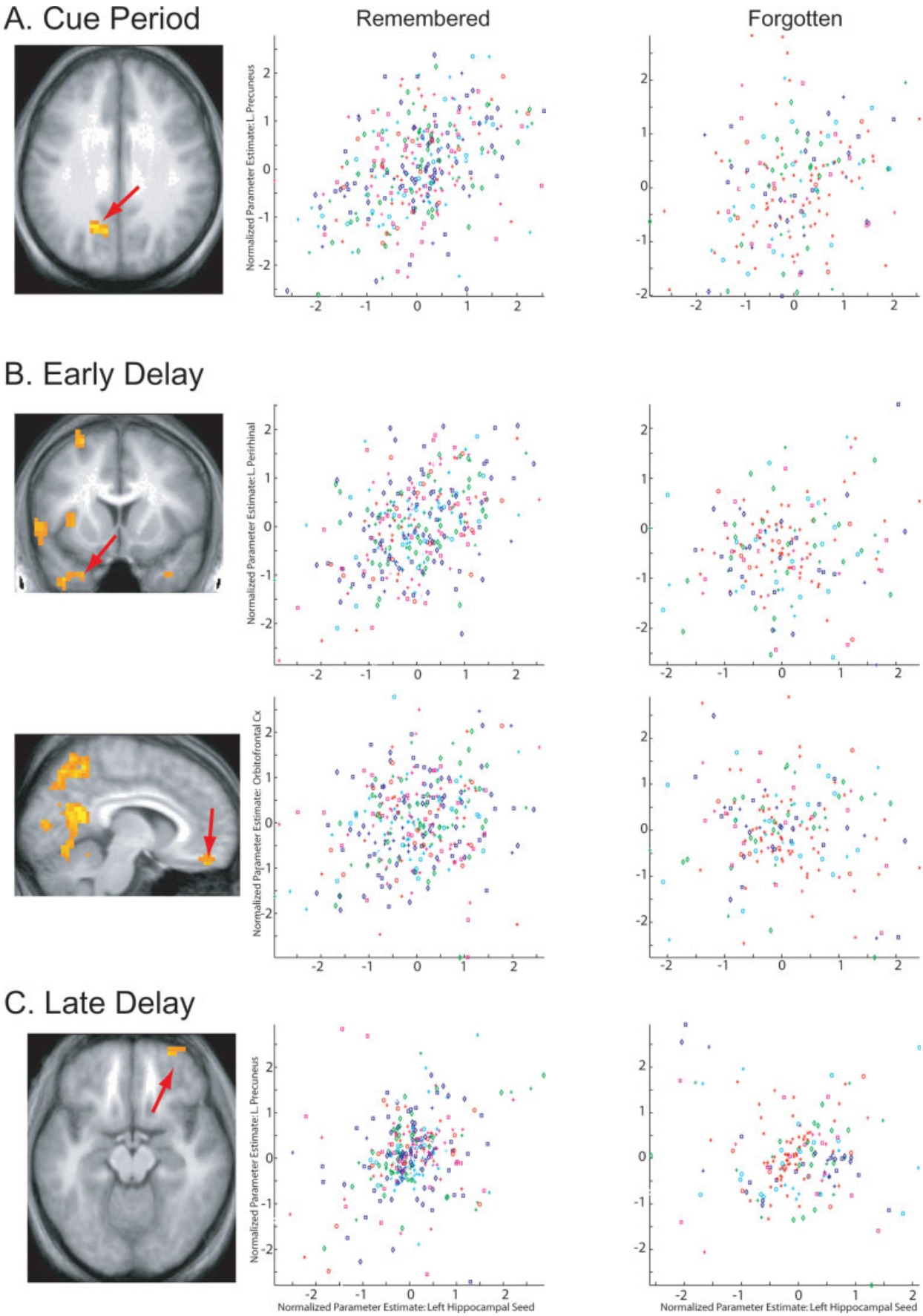
A. Cue Period
Remembered
Forgotten
B. Early Delay
C. Late Delay
Normalized Parameter Estimate: L. Precuneus
Normalized Parameter Estimate: L. Perirhinal
Normalized Parameter Estimate: Orbitofrontal Cx
Normalized Parameter Estimate: Left Hippocampal Seed

FIGURE 2

tex and the hippocampus should be critical for normal memory (Becker and Lim, 2003; Simons and Spiers, 2003). Thus, it was somewhat surprising that we did not see enhanced connectivity between lateral prefrontal cortex and hippocampus, during successful memory formation. Instead, successful memory formation was associated with enhanced coupling between the hippocampus and the orbitofrontal cortex. We note that null effects in any neuroimaging analyses should be interpreted with extreme caution. At the same time, our results suggest that functional interactions between the hippocampus and the orbitofrontal cortex—rather than the lateral prefrontal cortex—may play a significant role in memory formation. As noted earlier, the orbitofrontal cortex is heavily interconnected with the EC and the perirhinal cortex and receives a direct input from CA1 (Barbas and Blatt, 1995; Carmichael and Price, 1995; Cavada et al., 2000). In contrast, lateral prefrontal areas are indirectly connected to the hippocampal formation via the retrosplenial and parahippocampal cortices (Goldman-Rakic et al., 1984). Reasoning from the anatomy, it is possible that lateral prefrontal areas indirectly influence memory formation by modulating activity in retrosplenial, parahippocampal, and posterior cortical areas, whereas orbitofrontal cortex may directly influence memory formation through functional coupling with the hippocampal formation.

Finally, we found that several early visual cortical areas showed memory-related changes in connectivity with the hippocampus, in addition to the areas mentioned earlier. These findings, though unexpected, are consistent with those of the previous PET studies of hippocampal connectivity. For example, Grady and colleagues (Grady et al., 2003) found that activity in the inferior temporal, fusiform, and middle temporal gyri was positively correlated with medial temporal activity and recognition accuracy. Likewise, Rajah and colleagues observed increased connectivity between the medial temporal lobe and occipitotemporal visual areas during face encoding as compared with retrieval or perception tasks. These results strongly support the idea that visual memory processes rely in a strong interplay between medial temporal areas and posterior cortical areas that are traditionally linked to visual perception (Ranganath, in press; Ranganath and D'Esposito, 2005).

The present results clearly demonstrate that correlations between hippocampal and cortical activity are heightened during successful memory formation, although the underlying neural mechanisms for these effects are not clear. The simplest interpretation is that such correlations reflect direct functional interactions between the hippocampus and cortex. This interaction could reflect feedforward information transfer, as suggested by some researchers (Fell et al., 2001; Fernandez et al., 2002), feedback from the hippocampus to the cortex (Ranganath and D'Esposito, 2005), or both. The "direct interaction" hypothesis is consistent with the idea that many of the connectivity effects were observed in regions that are closely or directly connected with the hippocampal formation. Another possibility is that changes in activity correlations between the hippocampus and any given cortical region might be driven by a third region. For example, memory-related changes in neuromodulatory influences could alter correlations between activity in the hippocampus and a wide range of limbic cortical regions (Ranganath and Rainer, 2003; Schott et al., 2004; Wittmann et al., 2005). The neuromodulatory hypothesis is consistent with a variety of findings implicating the dopaminergic (Lisman and Otmakhova, 2001; Schott et al., 2004; Lisman and Grace, 2005; Wittmann et al., 2005) and cholinergic (Hasselmo, 1999; Ranganath and Rainer, 2003; Sherman et al., 2003) systems in successful memory formation. The current analyses cannot differentiate between these and other possible mechanisms.

In conclusion, the present results show that analyses of task-related changes in functional connectivity can provide a useful complement to standard analyses of overall BOLD signal changes. Our findings underscore the point that the contribution of any given region to declarative memory formation may be governed, in part, by its interactions with anatomically connected regions (McIntosh, 1999, 2000). As such, these results lay the groundwork for future research investigating specific roles of different cortico-hippocampal pathways in different aspects of memory encoding.

DETAILED METHODS

Eight males and seven females from the UC Davis student community participated in this experiment. Each gave informed consent prior to the experiment and was paid for the participation. The materials were line drawings of novel "possible" objects (Fig. 1) drawn from previous studies (Schacter et al., 1990, 1992; Schacter and Cooper, 1993; Williams and Tarr, 1997, 1999). During the scanning phase, participants first performed a visuomotor response task, the results of which were used to empirically estimate a subject-specific hemodynamic response function (HRF). Next, participants performed 128 trials of a delayed-recognition task. On each trial, a cue object was shown for 1 s, and the subjects were instructed to maintain a vivid mental image of the stimulus across a variable 7–13 s delay period. Following the delay, a probe object (either a matching or nonmatching object) was shown for 1 s, and participants pressed one of the two buttons on a response box to indicate whether the probe was identical to or different from the cue stimulus. Match/nonmatch decisions were made by pressing one of the two buttons on a magnet-compatible response device. A variable 9–15 s intertrial interval (ITI) preceded the start of the next trial. Half of the trials contained items seen in a prescan training session (eight presentations of each item; these trials are not discussed here) and half contained novel, trial-unique items (i.e., items that were not presented during the prescan training session). There were an equal number of match and nonmatch trials, and all trial types were presented in a pseudorandom order.

Following the scanning session, participants were given a surprise recognition memory test to assess LTM for all of the items that were shown as cue stimuli in the scanner (64 novel and 8 learned plus 37 novel foils). In this test, participants were shown each item individually on a computer screen and

were instructed to rate each item on a confidence scale that ranged from 1 ("definitely seen during scanning phase") to 6 ("definitely NOT seen during scanning phase"). Subjects were instructed to distribute their responses across the entire range of the scale when making their decisions. Responses on this subsequent LTM test were used to selectively average trials during the fMRI scanning session. Comparisons described later focused on contrasts between trials with stimuli that were subsequently remembered with high confidence (items that were endorsed with a "1" or "2" confidence rating on the postscan LTM test) and trials with stimuli that were subsequently forgotten (novel items that were endorsed with a "5" or "6" on the postscan LTM test).

MRI Acquisition and Processing

MRI data were collected on a 1.5T GE Signa scanner at the UC Davis Research Imaging Center. Functional imaging was done with a gradient echo echoplanar imaging (EPI) sequence (TR = 2,000, TE = 40, FOV = 220, 64 × 64 matrix, voxel size = 3.4375 × 3.4375 × 5 mm^3), with each volume consisting of 24 axial slices. Coplanar and high-resolution T1-weighted images were also acquired. FMRI data preprocessing was performed with Statistical Parametric Mapping (SPM99) software, for all subjects. EPI images were sinc interpolated in time to correct for between-slice timing differences in image acquisition, realigned using a six-parameter rigid-body transformation algorithm, spatially normalized to the template from the International Consortium for Brain Mapping Project (Cocosco et al., 1997), resliced into 3.5-mm isotropic voxels, and spatially smoothed with an 8-mm FWHM Gaussian filter.

MRI Data Analysis

To analyze functional connectivity with the hippocampus, we chose a seed region in the left hippocampus that was identified in a group analysis reported previously (Ranganath et al., 2005). The seed region was specifically defined by identifying all contiguous voxels in the left hippocampus that exceeded a $P < 0.001$ statistical threshold in the contrast of early delay activity between remembered and forgotten trials. This same seed region was used in each single-subject analysis.

To assess functional connectivity, activity changes during each phase of each trial were estimated by multiple regression analysis (Courtney et al., 1997; Zarahn et al., 1997; Postle et al., 2000; Rowe et al., 2000; Ranganath and D'Esposito, 2001; Munk et al., 2002; Sakai et al., 2002; Curtis et al., 2004; Ranganath et al., 2004a; Rissman et al., 2004). We performed the analyses using the implementation of the modified GLM (Worsley and Friston, 1995) in the VoxBo software package (freely available at www.voxbo.org). In these analyses, BOLD signal changes associated with the cue, early delay, late delay, and probe periods of each trial were modeled with separate covariates (see Ranganath et al., 2005, for reasoning and methods for separating activity during early and late delay periods). Each covariate was constructed by convolving vectors of expected neural activity associated with each component of each trial with a subject-specific HRF estimated from responses in the central sulcus during the visuomotor response task (Aguirre et al., 1998; Handwerker et al., 2004; Ranganath et al., 2004a). Data from the visuomotor response task were not available for one subject. For this subject, covariates were constructed by convolving the vector of expected neural activity with the "canonical" HRF included in SPM99. We have found that the SPM99 HRF corresponds closely to an average of over 50 empirically derived HRFs that we have estimated in our lab (Brozinsky and Ranganath, unpublished observations).

Each covariate of interest only modeled responses for trials that were associated with correct match/nonmatch decisions on the WM probe. Additional nuisance covariates modeled responses on trials associated with incorrect WM decisions, global signal changes that could not be accounted for by variables in the design matrix (Desjardins et al., 2001), trial-specific baseline shifts, and an intercept. The convolution matrix included a time-domain representation of the $1/f$ power structure (Zarahn et al., 1997) and filters to remove frequencies above 0.25 Hz and below 0.02 Hz.

The least-squares solution of the GLM described earlier yielded a unique parameter estimate (beta value) for each component of each WM trial. We next averaged the beta values across the nine voxels in the left hippocampal seed region and sorted them by task period (cue, early delay, late delay, probe) and trial type (confidently remembered vs. low confidence vs. confidently forgotten). We refer to these condition-specific beta values as a "beta series" (Rissman et al., 2004). Under the assumptions of beta series correlation method, the extent to which two brain regions interact during a given task condition is quantified by the extent to which their respective beta series from that condition are correlated. By computing the correlation of the seed's beta series (averaged across the voxels of the seed region) with the beta series of all other voxels in the brain, condition-specific seed correlation maps were generated. All correlation analyses were conducted using Matlab 6.5 (http://www.mathworks.com).

To allow statistical conclusions to be made on the basis of the correlation magnitudes, we applied an arc-hyperbolic tangent transform (Fisher, 1921) to the correlation coefficients of all brain voxels (Rissman et al., 2004). Because the correlation coefficient is inherently restricted to the range from -1 to $+1$, this transformation serves to make its null hypothesis sampling distribution approach that of the normal distribution. The transformed correlation coefficients were then divided by their known standard deviation ($1/\sqrt{(N-3)}$, where N is the number of data points used to compute the correlation coefficient) to yield z scores.

To assess the map-wise significance of the correlation findings at the group level, the z-transformed correlation maps of the individual subjects were spatially normalized into standard MNI atlas space, using routines from SPM99 (http://www.fil.ion.ucl.ac.uk/spm). Group-level random-effects paired t-tests were then conducted to identify voxels for which the mean of

the individual subjects' transformed correlation coefficients was reliably different between remembered and forgotten trials during the cue, early delay, and late delay task periods. These statistical maps were thresholded using a two-tailed α value of $P < 0.005$ and an extent threshold of six voxels. Although most of these results would survive more stringent statistical thresholds (Table 1), we chose to use this relatively liberal threshold in order to maximize our sensitivity to identify candidate regions showing differential connectivity with the hippocampus. Our reasoning was that little is presently known about functional connectivity with the hippocampus, and that it would therefore be preferable to identify as many candidate regions as possible. For visualization purposes, thresholded statistical parametric maps were overlaid on an averaged T1-weighted image, using MRIcro software (Rorden and Brett, 2000). Because signal dropout due to susceptibility artifact is common in the orbitofrontal and anterior medial temporal cortices, we carefully inspected the local maxima in these regions with respect to the EPI images from our subjects. These local maxima did not lie in areas with high signal dropout.

Acknowledgments

The authors thank Adam Gazzaley for helpful suggestions.

REFERENCES

Aggleton JP, Pearce JM. 2001. Neural systems underlying episodic memory: insights from animal research. Philos Trans R Soc Lond B Biol Sci 356:1467–1482.

Aguirre GK, Zarahn E, D'Esposito M. 1998. The variability of human, BOLD hemodynamic responses. Neuroimage 8:360–369.

Barbas H, Blatt GJ. 1995. Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. Hippocampus 5:511–533.

Becker S, Lim J. 2003. A computational model of prefrontal control in free recall: strategic memory use in the California Verbal Learning Task. J Cogn Neurosci 15:821–832.

Bowers D, Verfaellie M, Valenstein E, Heilman KM. 1988. Impaired acquisition of temporal information in retrosplenial amnesia. Brain Cogn 8:47–66.

Buckner RL, Kelley WM, Petersen SE. 1999. Frontal cortex contributes to human memory formation. Nat Neurosci 2:311–314.

Carmichael ST, Price JL. 1995. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 363:615–641.

Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F. 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10:220–242.

Cocosco C, Kollokian V, Kwan R, Evans A. 1997. Brainweb: online interface to a 3D MRI simulated brain database. Neuroimage 5(4 Pt 2):S425.

Cooper BG, Mizumori SJ. 1999. Retrosplenial cortex inactivation selectively impairs navigation in darkness. Neuroreport 10:625–630.

Cooper BG, Mizumori SJ. 2001. Temporary inactivation of the retrosplenial cortex causes a transient reorganization of spatial coding in the hippocampus. J Neurosci 21:3986–4001.

Cooper BG, Manka TF, Mizumori SJ. 2001. Finding your way in the dark: the retrosplenial cortex contributes to spatial memory and navigation without visual cues. Behav Neurosci 115:1012–1028.

Courtney SM, Ungerleider LG, Keil K, Haxby JV. 1997. Transient and sustained activity in a distributed neural system for human working memory. Nature 386:608–611.

Curtis CE, Rao VY, D'Esposito M. 2004. Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944–3952.

Desjardins AE, Kiehl KA, Liddle PF. 2001. Removal of confounding effects of global signal in functional MRI analyses. Neuroimage 13:751–758.

Eichenbaum H, Cohen NJ. 2001. From conditioning to conscious recollection: memory systems of the brain. New York: Oxford University Press.

Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, Fernandez G. 2001. Human memory formation is accompanied by rhinal–hippocampal coupling and decoupling. Nat Neurosci 4:1259–1264.

Fernandez G, Tendolkar I. 2001. Integrated brain activity in medial temporal and prefrontal areas predicts subsequent memory performance: human declarative memory formation at the system level. Brain Res Bull 55:1–9.

Fernandez G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dumpelmann M, Van Roost D, Elger CE. 1999. Real-time tracking of memory formation in the human rhinal cortex and hippocampus. Science 285:1582–1585.

Fernandez G, Klaver P, Fell J, Grunwald T, Elger CE. 2002. Human declarative memory formation: segregating rhinal and hippocampal contributions. Hippocampus 12:514–519.

Fisher RA. 1921. On the "probable error" of a coefficient of correlation deduced from a small sample. Metron 1:3–32.

Gaffan D, Parker A. 1996. Interaction of perirhinal cortex with the fornix-fimbria: memory for objects and object-in-place memory. J Neurosci 16:5864–5869.

Gazzaley A, Rissman J, D'Esposito M. 2004. Functional connectivity during working memory maintenance. Cogn Affect Behav Neurosci 4:580–599.

Goldman-Rakic PS, Selemon LD, Schwartz ML. 1984. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. Neuroscience 12:719–743.

Grady CL, McIntosh AR, Craik FI. 2003. Age-related differences in the functional connectivity of the hippocampus during memory encoding. Hippocampus 13:572–586.

Habib R, McIntosh AR, Wheeler MA, Tulving E. 2003. Memory encoding and hippocampally-based novelty/familiarity discrimination networks. Neuropsychologia 41:271–279.

Handwerker DA, Ollinger JM, D'Esposito M. 2004. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. Neuroimage 21:1639–1651.

Hasselmo ME. 1999. Neuromodulation: acetylcholine and memory consolidation. Trends Cogn Sci 3:351–359.

Howard MW, Fotedar MS, Datey AV, Hasselmo ME. 2005. The temporal context model in spatial navigation and relational learning: toward a common explanation of medial temporal lobe function across domains. Psychol Rev 112:75–116.

Insausti R, Amaral DG, Cowan WM. 1987. The entorhinal cortex of the monkey: II. Cortical afferents. J Comp Neurol 264:356–395.

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkanen A. 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 19:659–671.

Lisman JE, Grace AA. 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46:703–713.

Lisman JE, Otmakhova NA. 2001. Storage, recall, and novelty detection of sequences by the hippocampus: elaborating on the SOCRATIC model to account for normal and aberrant effects of dopamine. Hippocampus 11:551–568.

Masuo O, Maeshima S, Kubo K, Terada T, Nakai K, Itakura T, Komai N. 1999. A case of amnestic syndrome caused by a subcortical haematoma in the right occipital lobe. Brain Inj 13:213–216.

McDonald CR, Crosson B, Valenstein E, Bowers D. 2001. Verbal encoding deficits in a patient with a left retrosplenial lesion. Neurocase 7:407–417.
McIntosh AR. 1999. Mapping cognition to the brain through neural interactions. Memory 7:523–548.
McIntosh AR. 2000. Towards a network theory of cognition. Neural Netw 13:861–870.
Muir GM, Bilkey DK. 2001. Instability in the place field location of hippocampal place cells after lesions centered on the perirhinal cortex. J Neurosci 21:4016–4025.
Munk MH, Linden DE, Muckli L, Lanfermann H, Zanella FE, Singer W, Goebel R. 2002. Distributed cortical systems in visual short-term memory revealed by event-related functional magnetic resonance imaging. Cereb Cortex 12:866–876.
Ongur D, Ferry AT, Price JL. 2003. Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol 460:425–449.
O'Reilly RC, Rudy JW. 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychol Rev 108:311–345.
Paller KA, Wagner AD. 2002. Observing the transformation of experience into memory. Trends Cogn Sci 6:93–102.
Postle BR, Zarahn E, D'Esposito M. 2000. Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. Brain Res Brain Res Protoc 5:57–66.
Rajah MN, McIntosh AR, Grady CL. 1999. Frontotemporal interactions in face encoding and recognition. Brain Res Cogn Brain Res 8:259–269.
Ranganath C. Working memory for visual objects: complementary roles of inferior temporal, medial temporal, and prefrontal cortex. Neuroscience, in press.
Ranganath C, D'Esposito M. 2001. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31:865–873.
Ranganath C, D'Esposito M. 2005. Directing the mind's eye: prefrontal, inferior and medial temporal mechanisms for visual working memory. Curr Opin Neurobiol 15:175–182.
Ranganath C, Knight RT. 2003. Prefrontal cortex and episodic memory: integrating findings from neuropsychology and event-related functional neuroimaging. In: Parker A, Wildng E, Bussey T, editors. The cognitive neuroscience of memory encoding and retrieval. Philadelphia: Psychology Press. p 83–99.
Ranganath C, Rainer G. 2003. Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4:193–202.
Ranganath C, Johnson MK, D'Esposito M. 2003. Prefrontal activity associated with working memory and episodic long-term memory. Neuropsychologia 41:378–389.
Ranganath C, Cohen MX, Dam C, D'Esposito M. 2004a. Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. J Neurosci 24:3917–3925.
Ranganath C, DeGutis J, D'Esposito M. 2004b. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. Brain Res Cogn Brain Res 20:37–45.
Ranganath C, Cohen MX, Brozinsky CJ. 2005. Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. J Cogn Neurosci 17:994–1010.
Rissman J, Gazzaley A, D'Esposito M. 2004. Measuring functional connectivity during distinct stages of a cognitive task. Neuroimage 23:752–763.
Rockland KS, Van Hoesen GW. 1999. Some temporal and parietal cortical connections converge in CA1 of the primate hippocampus. Cereb Cortex 9:232–237.
Rorden C, Brett M. 2000. Stereotaxic display of brain lesions. Behav Neurol 12:191–200.
Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE. 2000. The prefrontal cortex: response selection or maintenance within working memory? Science 288:1656–1660.
Sakai K, Rowe JB, Passingham RE. 2002. Active maintenance in prefrontal area 46 creates distractor-resistant memory. Nat Neurosci 5: 479–484.
Schacter DL, Cooper LA. 1993. Implicit and explicit memory for novel visual objects: structure and function. J Exp Psychol Learn Mem Cogn 19:995–1009.
Schacter DL, Cooper LA, Delaney SM. 1990. Implicit memory for unfamiliar objects depends on access to structural descriptions [see comments]. J Exp Psychol Gen 119:5–24.
Schacter DL, Cooper LA, Valdiserri M. 1992. Implicit and explicit memory for novel visual objects in older and younger adults. Psychol Aging 7:299–308.
Schott BH, Sellner DB, Lauer CJ, Habib R, Frey JU, Guderian S, Heinze HJ, Duzel E. 2004. Activation of midbrain structures by associative novelty and the formation of explicit memory in humans. Learn Mem 11:383–387.
Sherman SJ, Atri A, Hasselmo ME, Stern CE, Howard MW. 2003. Scopolamine impairs human recognition memory: data and modeling. Behav Neurosci 117:526–539.
Simons JS, Spiers HJ. 2003. Prefrontal and medial temporal lobe interactions in long-term memory. Nat Rev Neurosci 4:637–648.
Squire LR, Stark CE, Clark RE. 2004. The medial temporal lobe. Annu Rev Neurosci 27:279–306.
Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci USA 93:8660–8665.
Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S. 1996. Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 6:71–79.
Valenstein E, Bowers D, Verfaellie M, Heilman K, Day A, Watson R. 1987. Retrosplenial amnesia. Brain 110:1631–1646.
Vann SD, Aggleton JP. 2002. Extensive cytotoxic lesions of the rat retrosplenial cortex reveal consistent deficits on tasks that tax allocentric spatial memory. Behav Neurosci 116:85–94.
Vann SD, Brown MW, Erichsen JT, Aggleton JP. 2000. Using fos imaging in the rat to reveal the anatomical extent of the disruptive effects of fornix lesions. J Neurosci 20:8144–8152.
Vann SD, Kristina Wilton LA, Muir JL, Aggleton JP. 2003. Testing the importance of the caudal retrosplenial cortex for spatial memory in rats. Behav Brain Res 140:107–118.
Vogt BA, Vogt LJ, Perl DP, Hof PR. 2001. Cytology of human caudomedial cingulate, retrosplenial, and caudal parahippocampal cortices. J Comp Neurol 438:353–376.
Wagner AD, Shannon BJ, Kahn I, Buckner RL. 2005. Parietal lobe contributions to episodic memory retrieval. Trends Cogn Sci 9:445–453.
Williams P, Tarr MJ. 1997. Structural processing and implicit memory for possible and impossible figures. J Exp Psychol Learn Mem Cogn 23:1344–1361.
Williams P, Tarr MJ. 1999. Orientation-specific possibility priming for novel three-dimensional objects. Percept Psychophys 61:963–976.
Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Duzel E. 2005. Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron 45:459–467.
Worsley KJ, Friston KJ. 1995. Analysis of fMRI time-series revisited—again. Neuroimage 2:173–182.
Yasuda Y, Watanabe T, Tanaka H, Tadashi I, Akiguchi I. 1997. Amnesia following infarction in the right retrosplenial region. Clin Neurol Neurosurg 99:102–105.
Zarahn E, Aguirre G, D'Esposito M. 1997. A trial-based experimental design for fMRI. Neuroimage 6:122–138.
Zhong YM, Rockland KS. 2004. Connections between the anterior inferotemporal cortex (area TE) and CA1 of the hippocampus in monkey. Exp Brain Res 155:311–319.