

Activity in Both Hippocampus and Perirhinal Cortex Predicts the Memory Strength of Subsequently Remembered Information

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SUMMARY

It has been suggested that hippocampal activity predicts subsequent recognition success when recognition decisions are based disproportionately on recollection, whereas perirhinal activity predicts recognition success when decisions are based primarily on familiarity. Another perspective is that both hippocampal and perirhinal activity are predictive of overall memory strength. We tested the relationship between brain activity during learning and subsequent memory strength. Activity in a number of cortical regions (including regions within the “default network”) was negatively correlated with subsequent memory strength, suggesting that this activity reflects inattention or mind wandering (and, consequently, poor memory). In contrast, activity in both hippocampus and perirhinal cortex positively correlated with the subsequent memory strength of remembered items. This finding suggests that both structures cooperate during learning to determine the memory strength of what is being learned.

INTRODUCTION

Declarative memory depends on the hippocampus and adjacent medial temporal lobe structures (entorhinal, perirhinal, and parahippocampal cortices) (Squire et al., 2004). One of the most widely studied examples of declarative memory is recognition—that is, the ability to judge a recently encountered item as having been presented previously. Patients with damage to the medial temporal lobe, and even patients with damage limited to the hippocampus, have impaired recognition memory (Kopelman et al., 2007; Manns et al., 2003; Wais et al., 2006).

Functional magnetic resonance imaging (fMRI) has also been used to study recognition memory (Eichenbaum et al., 2007; Squire et al., 2007). In the subsequent memory paradigm (Paller and Wagner, 2002), participants study a list of items in the scan-

ner and later take a recognition memory test outside of the scanner. Activity associated with items that will later be remembered is then compared to activity associated with items that will later be forgotten. Because the hippocampus is necessary for recognition memory (as patients with hippocampal lesions have demonstrated), one might expect to find hippocampal activity during learning that is predictive of subsequent recognition. Yet, such hippocampal activity has been found only in some studies. The studies that have found hippocampal activity to be predictive of subsequent memory have typically involved tests of source memory or associative memory, not simple tests of recognition based on old/new judgments. For example, in studies of source memory, hippocampal activity was greater during learning when an item was later remembered together with some additional information about the study episode (e.g., the item was printed in red, not green) than when the item was later forgotten or remembered without source information (e.g., Davachi et al., 2003; Kensinger and Schacter, 2006; Ranganath et al., 2004; but see Gold et al., 2006).

A common interpretation of these findings is that hippocampal activity predicts subsequent recognition when decisions are based disproportionately on recollection and not when decisions are based primarily on familiarity (Brown and Aggleton, 2001; Eichenbaum et al., 2007; Diana et al., 2007). Recollection and familiarity are two component processes thought to underlie recognition memory (Mandler, 1980). Recollection involves remembering specific contextual details about a prior learning episode (for example, source information). Familiarity involves knowing that an item was presented without having available any additional information about the learning episode.

Recollection-based decisions and familiarity-based decisions also reflect strong memories and weak memories, respectively (Squire et al., 2007; Wixted, 2007). For example, items that are recognized and also accompanied by source information typically reflect stronger memories than items that are recognized but not accompanied by source information (Gold et al., 2006; Slotnick and Dodson, 2005). This perspective suggests that activity in hippocampus during learning, as well as activity in perirhinal cortex, should under appropriate conditions correlate positively with subsequent memory strength. This should occur

even for simple tasks of recognition memory that involve no explicit recollective component and where participants make judgments of memory strength but make no distinction between recollection-based and familiarity-based decisions.

Another expectation about the relationship between brain activity and subsequent memory strength arises from findings in cortical regions (including prefrontal cortex, medial parietal cortex [posterior cingulate/precuneus], and inferior parietal cortex) of higher activity for subsequently forgotten information than for subsequently remembered information (Daselaar et al., 2004; Otten and Rugg, 2001b; Reynolds et al., 2004; Wagner and Davachi, 2001). Some of these regions are a part of what has been termed the default network, which comprises the medial prefrontal cortex, posterior cingulate, retrosplenial cortex, and inferior parietal lobe, as well as medial temporal lobe structures (Binder et al., 1999; Buckner et al., 2008; Gusnard et al., 2001; Gusnard and Raichle, 2001; Raichle et al., 2001). It has been suggested that activity in some of these brain regions, as well as other regions, signals mind-wandering or inattention (Mason et al., 2007; Weissman et al., 2006). From these findings, one might expect that activity within a number of regions, including but not limited to regions identified with the default network, might correlate negatively with subsequent memory strength.

We tested with fMRI how brain activity relates to subsequent memory strength, first examining the whole brain and then focusing on the medial temporal lobe. Participants were scanned as they studied a list of words and then were given a test of recognition memory outside the scanner. To indicate memory strength, participants assigned confidence ratings to old and new words on a six-point scale.

RESULTS

Behavioral Performance

The distribution of responses on the recognition memory test is presented in Figure 1. Overall, participants scored $78.8\% \pm 9.6\%$ correct (hit rate, $82.4\% \pm 12.7\%$; false alarm rate, $24.9\% \pm 10.6\%$; d' , 1.79 ± 0.72). Study words were back-sorted according to the memory confidence rating subsequently assigned to each word on the recognition memory test. Despite a high overall miss rate on the recognition memory test, there were relatively few high-confidence miss trials (mean, 9.4; range, 0–31). Accordingly, we combined memory strengths 1 and 2 into a single memory strength bin for fMRI analyses. This procedure resulted in a mean of 32.0 ± 6.5 , 30.6 ± 7.1 , 37.8 ± 8.6 , 54.8 ± 10.6 , and 202.4 ± 25.1 words in memory strength bins 1&2, 3, 4, 5, and 6, respectively. Mean reaction times (RTs) during the study trials were 915 ± 52 , 956 ± 48 , 980 ± 50 , 1005 ± 49 , and 1046 ± 40 ms for memory strengths 1&2, 3, 4, 5, and 6, respectively. Longer RTs at study were associated with higher memory strengths at test (linear trend, $F_{(1,11)} = 4.93$, $p < 0.05$).

fMRI Results

First, we identified regions in which activity varied either positively or negatively during study as a function of subsequent memory strength. Specifically, we conducted a linear trend analysis on the whole-brain data with the coefficients -2 , -1 , 0 , 1 , and 2 assigned to memory strengths 1&2, 3, 4, 5, and 6,

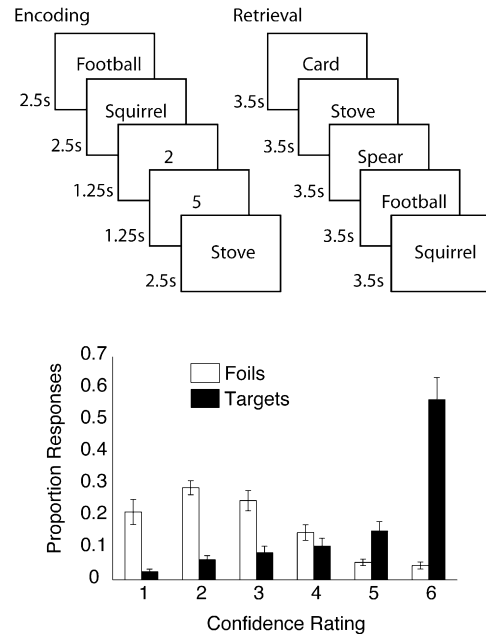


Figure 1. Recognition Memory Task and Behavioral Performance

(Top) In the scanner, participants rated (pleasant/unpleasant) 360 words (2.5 s/word). Words were intermixed with 864 1.25 s baseline trials in which participants indicated whether a digit was odd or even. At test (about 15 min later, out of the scanner), participants made confidence ratings (1–6; 1, “definitely new”; 6, “definitely old”) for the 360 studied words and 360 novel words (3.5 s/word). (Bottom) Proportion of targets (black bars) and foils (white bars) endorsed at each confidence level. Error bars indicate SEM.

respectively. The resulting statistical map was thresholded at a voxel-wise p value of $p < 0.002$ and a spatial-extent threshold of 32 contiguous voxels (256 mm^3 , $p < 0.005$). Table 1 (top section) lists regions that demonstrated a significant linear trend relating fMRI activity at study to memory strength at test. In each case, fMRI activity and memory strength were negatively correlated. That is, fMRI activity was higher in these functionally defined regions during presentation of words that would subsequently be forgotten than during presentation of words that would subsequently be remembered.

Figures 2A–2C show the five largest regions: right anterior prefrontal cortex, right posterior prefrontal cortex, bilateral inferior parietal cortex, and a posterior midline cortical region. Figure 2D shows the activity associated with each memory strength for each of these five functionally defined regions. Previous studies have also observed this inverse subsequent memory effect (i.e., greater activity during study for subsequently forgotten items than subsequently remembered items) in these same regions or closely adjacent regions: dorsolateral prefrontal cortex, posterior midline regions, and inferior parietal cortex (Daselaar et al., 2004; Otten and Rugg, 2001b; Reynolds et al., 2004; Wagner and Davachi, 2001). Some of these regions (bilateral inferior parietal cortex and the posterior midline) have been identified as belonging to the “default network,” i.e., a set of brain regions that are active during rest conditions (Gusnard et al., 2001; Gusnard and Raichle, 2001; Raichle et al., 2001). Related to this idea, activity in these and other regions has

Table 1. Regions Where Activity during Learning Correlated with Subsequent Memory Strength

Region	Peak Activation			Linear Trend	
	X	Y	Z	F Value	
Regions in the Whole Brain Where Activity during Learning Correlated Negatively with Subsequent Memory Strength (Confidence Ratings 1–6)					
R	inferior parietal cortex	57	–43	14	27.3
R	posterior prefrontal cortex	37	31	32	39.4
R	anterior prefrontal cortex	29	59	16	37.7
B	medial parietal cortex	–1	–59	42	18.5
L	inferior parietal cortex	–57	–45	38	20.5
L	superior parietal cortex	–47	–57	46	23.5
L	superior temporal gyrus	–43	–53	18	22.3
R	middle frontal gyrus	43	49	14	19.6
R	precentral gyrus	51	11	4	20.0
R	superior parietal cortex	43	–47	52	18.0
R	superior parietal cortex	35	–41	60	17.5
L	lateral temporal cortex	–47	–19	–10	17.2
R	precentral gyrus	39	–17	58	16.3
R	superior frontal gyrus	17	63	22	19.2
Regions in the Medial Temporal Lobe Where Activity during Learning Correlated Positively with the Memory Strength of Subsequently Remembered Items (Confidence Ratings 4–6)					
L	temporopolar cortex	–33	8	–30	11.9
L	perirhinal cortex	–31	–9	–26	9.8
L	hippocampus	–25	–21	–8	12.0
R	hippocampus	26	–11	–14	8.6

Note: whole brain regions; all df for the linear trend = (1,65). All p values < 0.001.

Note: medial temporal regions; all df for the linear trend = (1,39). All p values < 0.01.

also been found to correlate with mind wandering (Mason et al., 2007) and lapses of attention (Weissman et al., 2006). Thus, the increased fMRI activity associated with subsequently forgotten words may represent task-irrelevant mental activity that leads to encoding failures.

Also in the whole brain, several regions exhibited activity that was higher for the study task than for the baseline task and also varied positively with subsequent memory strength (thresholded at a voxel-wise p value of 0.005 and a spatial-extent threshold of 38 continuous voxels; 304 mm³, p < 0.005, see Table S1 available online). Among these regions was the left inferior frontal gyrus. This finding is consistent with previous reports that the left inferior frontal gyrus exhibits higher activity during orienting tasks that predict subsequent memory success and that activity is also higher in this region for subsequently remembered items than for subsequently forgotten items (e.g., Reynolds et al., 2004; Wagner et al., 1998).

Next, we inclusively masked (Cabeza et al., 2004; Weissman et al., 2006) regions in the medial temporal lobe where there was activity associated with the experimental task (study words minus baseline) with regions where activity during word presentation predicted subsequent memory. Initially, we looked for regions where activity varied across all memory strengths but did not find any regions where the relationship was positive. We then reasoned that participants might not have been fully engaged in the study task in the case of items that were subsequently forgotten (items with memory strengths 1&2 or 3) and

were instead engaged in task-irrelevant activity. Indeed, this reasoning was consistent with the finding that activity in a number of regions, including regions where activity has been related to inattention and mind wandering, was high for the subsequently forgotten items. Accordingly, we restricted our analysis to subsequently remembered items (items with memory strengths of 4, 5, or 6). Specifically, we conducted a linear trend analysis on the medial temporal lobe data for the subsequently remembered items. The resulting statistical map was thresholded at a voxel-wise p value of p < 0.005 and a spatial-extent threshold of 10 contiguous voxels (80 mm³, p < 0.005).

Table 1 lists the four regions within the medial temporal lobe that were identified by this analysis: left temporopolar cortex, left perirhinal cortex, right anterior hippocampus, and left hippocampus (Figures 3A–3C). These functionally defined regions exhibited activity during learning that was positively correlated with subsequent memory strength (Figure 3D). An ANOVA revealed no Region × Memory Strength interaction [$F_{(6,78)} = 1.3$, p > 0.2], indicating that the relationship between memory strength and activity was similar across regions. Two additional ANOVAs, comparing the left or right hippocampus with left perirhinal cortex, also revealed no difference in the relationship between activity and memory strength [F values < 1.5, p values > 0.2]. Time courses of the activity in each of the four regions are presented in Figure S1.

To explore further the relationship between brain activity and memory strength in these four medial temporal lobe regions,

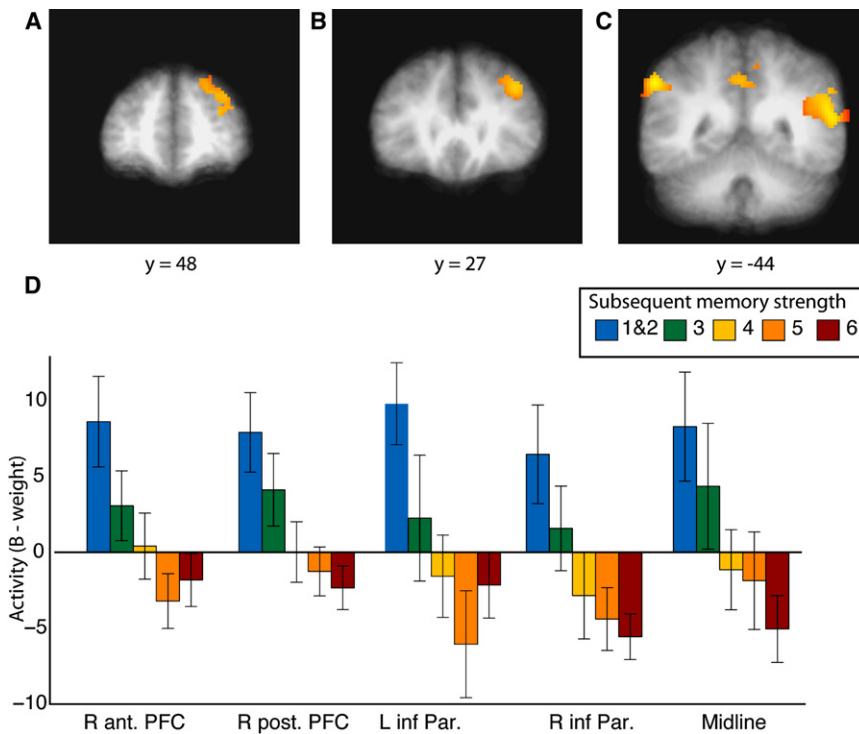


Figure 2. Regions Where Activity Correlated Negatively with Subsequent Memory Strength

A linear trend in fMRI activation that predicted subsequent memory strength was observed in (A) right anterior prefrontal cortex (R ant. PFC), (B) right posterior prefrontal cortex (R post. PFC), (C) bilateral inferior parietal cortex (L inf. Par. and R inf. Par.), and medial parietal cortex (midline). Regions of activation are shown superimposed on the averaged T1-weighted scans of all 14 participants. (D) Activation in each of the five regions as a function of the subsequent strength of recognition memory. Error bars indicate SEM.

we also extracted for each region the signal for subsequent memory strengths 1&2 and 3 in order to illustrate activity in these regions across all five memory strengths (Figure S2).

DISCUSSION

We measured brain activity with fMRI during an incidental learning task and later collected confidence judgments during a post-scan recognition memory test. There were two main findings. First, in regions within what has been termed the default network, as well as in other regions, activity negatively correlated with subsequent memory strength. Second, in the medial temporal lobe, activity in both the hippocampus and perirhinal cortex positively correlated with the subsequent memory strength of remembered items.

The finding that activity in prefrontal cortex, inferior parietal cortex, and the posterior midline (which include regions of the default network) decreased with increasing subsequent memory strength (Figure 2) is consistent with previous fMRI reports. Thus, in earlier studies, activity in these structures for items that were subsequently forgotten was greater than for items that were subsequently remembered with high confidence (Daseelaar et al., 2004; Otten and Rugg, 2001b). We extended these results by showing that activity was negatively associated with subsequent memory across five levels of memory strength. The default network was originally identified as consisting of areas that were more active during resting states than during cognitive tasks of interest (Gusnard et al., 2001; Gusnard and Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997). Interestingly, activity within these regions, as well as other regions, was subsequently linked to momentary

lapses in attention and mind wandering (Mason et al., 2007; Weissman et al., 2006). Our finding of a negative association between subsequent memory strength and activity in default network structures as well as other regions is consistent with these ideas. Participants likely varied from trial to trial in how attentive they were to the words being presented, and this variation affected how successful they later were at recognizing the words.

The second finding was that activity in hippocampus, perirhinal cortex, and temporopolar cortex increased with the subsequent memory strength of remembered items (i.e., items with memory strengths of 4, 5, or 6) (Figure 3). Interestingly, even though activity in these structures did increase during learning in relation to the memory strength of subsequently remembered items, this activity was no higher than activity associated with subsequently forgotten items (i.e., items with memory strengths of 1&2 and 3). That is, a conventional comparison of activity associated with subsequently remembered and forgotten items did not reveal medial temporal lobe activity. In fact, the activity across all five memory strengths tended toward a U-shaped function (Figure S2). Some previous studies also did not report a difference in medial temporal lobe activity between subsequently remembered items and subsequently forgotten items (Baker et al., 2001; Buckner et al., 2001; Otten and Rugg, 2001a). One possible explanation for such an outcome is that, for items that were subsequently forgotten, there was substantial mnemonic activity unrelated to the task and that an analysis restricted to the relative strength of subsequently remembered items might have revealed predictive activity in the medial temporal lobe.

We suggest that the U-shaped pattern of activity in medial temporal lobe structures reflects variation in attention to the study words at the time of word presentation. Thus, on trials where the study words were later least well remembered (i.e., study words later given ratings of 1&2), high activity in the medial temporal lobe may indicate that participants gave strong attention to, and subsequently would have had good memory for, mental activity unrelated to the word task and/or that participants were retrieving task-irrelevant information from memory.

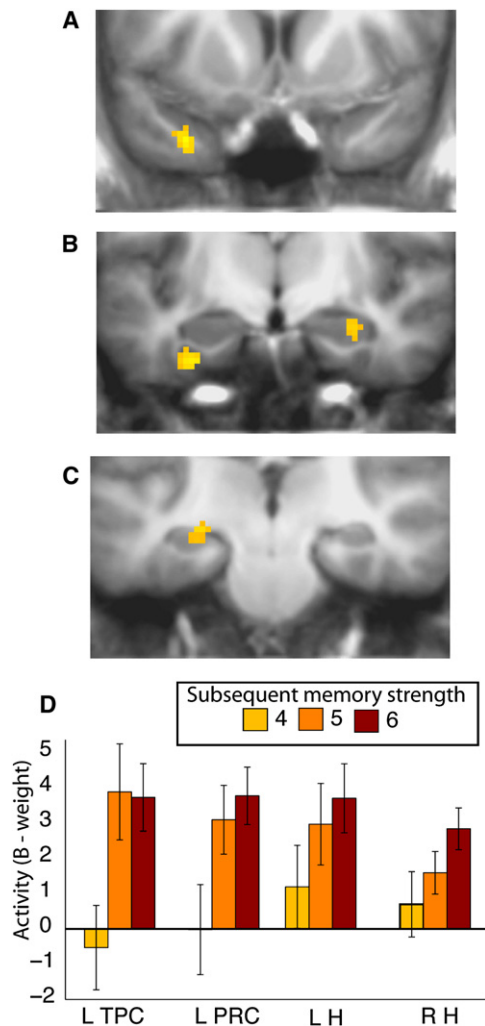


Figure 3. fMRI Activation in the Medial Temporal Lobe as a Function of Subsequent Memory Strength

Activation in (A) left temporopolar cortex (L TPC), (B) left perirhinal cortex (L PRC), right hippocampus (R H), and (C) left hippocampus (L H) varied as a function of the subsequent strength of remembered items (4, 5, or 6). Regions of activation are shown superimposed on the averaged T1-weighted scans of all 14 participants. (D) Activation in each of the four regions as a function of the subsequent strength of remembered items. Error bars indicate SEM.

Thus, one might expect activity in the medial temporal lobe for subsequently forgotten words to correlate with activity in other brain regions where activity was inversely related to subsequent memory strength. Furthermore, on trials where the study words were later best remembered (i.e., study words later given a rating of 6), high activity in the medial temporal lobe may indicate that participants gave strong attention to, and subsequently had good memory for, the study words themselves. Thus, in this case, one might expect activity in the medial temporal lobe for subsequently remembered words to correlate with activity in other brain regions where activity was positively related to subsequent memory strength. The results of a functional connectivity analysis between medial temporal lobe activity and activity in other brain regions were consistent with this idea (Figure S3).

It is worth mentioning that reaction times during study varied positively with subsequent memory strength. It is important to note that this pattern was qualitatively different from the U-shaped relationship between activity and subsequent memory strength in the medial temporal lobe. Thus, our findings in the medial temporal lobe cannot be attributed to the effect of reaction times during study.

Another issue raised by our findings concerns possible functional differentiation within the medial temporal lobe. One suggestion is that the hippocampus and perirhinal cortex differ in their contributions to recognition memory decisions. Specifically, the hippocampus has been suggested to disproportionately support recollection-based decisions, and the perirhinal cortex has been suggested to disproportionately support familiarity-based decisions (Brown and Aggleton, 2001; Eichenbaum et al., 2007). The results of some fMRI studies have been taken in support of this distinction (e.g., Davachi et al., 2003; Davachi and Wagner, 2002; Kensinger and Schacter, 2006; Ranganath et al., 2004; Uncapher et al., 2006; Uncapher and Rugg, 2005).

We tested whether activity in the hippocampus and perirhinal cortex would correlate with subsequent memory strength, and we found that activity in both these structures exhibited a similar linear relationship with the subsequent memory strength of remembered items. Our study did not distinguish explicitly between the effects of memory strength and the effects of recollection and familiarity, so it is possible that perirhinal and hippocampal activity reflect familiarity-based and recollection-based decisions, respectively. Nevertheless, given that the relationship between activity and subsequent memory strength was similar in hippocampus and perirhinal cortex, it seems parsimonious to interpret the finding in each structure in similar ways. Thus, if increasing activity in hippocampus is thought to predict increasing numbers of recollection-based decisions, then it seems reasonable to suggest that increasing activity in perirhinal cortex also predicts recollection-based decisions. Conversely, if increasing activity in perirhinal cortex is thought to predict increasing numbers of familiarity-based decisions, then it seems reasonable to suggest that increasing activity in hippocampus also predicts familiarity-based decisions. We suggest that activity in both hippocampus and perirhinal cortex during learning is predictive of the subsequent memory strength of remembered items, regardless of whether memory is based on recollection or familiarity. We further suggest that quantitative differences in memory strength, not just differences in the quality of memory, are an important determinant of activity in fMRI studies of recognition memory.

EXPERIMENTAL PROCEDURES

Participants

Fourteen right-handed volunteers (6 female; mean age, 27.3; range, 18–34) recruited from the University community gave written informed consent prior to participation.

Materials

The stimuli were 720 nouns with a mean frequency of 27 (range, 1–198) and concreteness ratings greater than 500 (mean, 573; Wilson, 1988). Half the words were assigned to six 60 word study lists, and half the words served as foils for the retrieval test. The assignment of words to the study and test conditions was counterbalanced across participants.

Procedure

Participants were scanned in six separate runs (~2 min delay between runs), during which the 360 target words were presented (Figure 1). Participants made a pleasant/unpleasant rating for each word (2.5 s presentation time). Responses were collected via an MR-compatible button box. Participants were not informed that their memory for words would be tested. An odd/even digit task was intermixed with the word presentation and served as a baseline against which the hemodynamic response was estimated. For the digit task, participants saw a digit (1–8) for 1.25 s and indicated by button press whether the digit was odd or even. Digit task trials (144 trials per scan run) were pseudorandomly intermixed with the encoding trials with the following constraints: each scan run began and ended with at least 12 digit trials, and all digit trials occurred in groups of 2, 4, or 6 so as to fit within the 2.5 s repetition time (TR; see below). Participants were given a short practice block prior to scanning to ensure that they understood the task and the button assignments.

Following scanning (~15 min delay), participants took a surprise postscan recognition memory test. They saw all 360 words from the scan session (targets) and 360 novel foils one at a time (3.5 s per word) in random order. For each word, participants made a recognition confidence judgment on a scale from 1 to 6 (1, “definitely new”; 2, “probably new”; 3, “maybe new”; 4, “maybe old”; 5, “probably old”; and 6, “definitely old”). Before testing, participants completed a short practice block to ensure that they understood the instructions and the confidence rating scale.

fMRI Imaging

Imaging was carried out on a 3T GE scanner at the Center for Functional MRI (University of California, San Diego). Functional images were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (TR, 2500 ms; TE, 30 ms; flip angle, 90°; matrix size, 64 × 64; field of view, 22 cm). The first five TRs acquired were discarded to allow for T1 equilibration. Forty-two oblique coronal slices (slice thickness = 5 mm, 0 gap) were acquired perpendicular to the long axis of the hippocampus and covering the whole brain. Following the six functional runs, a high-resolution structural image was acquired using a T1-weighted, fast spoiled gradient-echo (FSPGR) pulse sequence (flip angle, 12°; TE, 3.1 ms; 172 slices; 1 mm slice thickness; matrix size, 256 × 256; field of view, 25 cm).

fMRI Data Analysis

fMRI data were analyzed using the AFNI suite of programs (Cox, 1996). Functional data were coregistered in three dimensions to the whole-brain anatomical data and coregistered through time to reduce effects of head motion. Motion events, defined as TRs in which there was more than 0.3° of rotation or 0.6 mm of translation in any direction were eliminated from the analysis (as well as the TR immediately preceding and following the motion-contaminated TR). Behavioral vectors were created that coded each study trial for subsequent recognition confidence rating (i.e., memory strengths 1–6). Trials in which there was no response for either the pleasantness rating task or for the subsequent recognition memory test (mean = 5 per participant) were excluded from further analysis. Due to low rates of high-confidence misses (see Behavioral Results), memory strengths 1 and 2 were combined into a single vector. The five behavioral vectors and six vectors that coded for motion (three for translation and three for rotation) were used in a deconvolution analysis of the fMRI time series data. The resultant fit coefficients (β coefficients) represent activity versus baseline in each voxel for a given time point and each of five trial types (memory strength 1&2, 3, 4, 5, and 6). This activity was summed over the expected hemodynamic response (0–15 s after trial onset) and taken as the estimate of the response to each trial type (relative to the digit task baseline). Functional data were smoothed with a 4 mm FWHM Gaussian filter and spatially normalized using the ROI-LDDMM (Miller et al., 2005) alignment technique (see Supplemental Data and Kirwan et al. [2007] for detailed methods).

SUPPLEMENTAL DATA

The Supplemental Data include Supplemental Experimental Procedures, a table, and figures and can be found with this article online at <http://www.neuron.org/cgi/content/full/59/4/547/DC1>.

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REFERENCES

- Baker, J.T., Sanders, A.L., Maccotta, L., and Buckner, R.L. (2001). Neural correlates of verbal memory encoding during semantic and structural processing tasks. *Neuroreport* 12, 1251–1256.
- Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S., Rao, S.M., and Cox, R.W. (1999). Conceptual processing during the conscious resting state. A functional MRI study. *J. Cogn. Neurosci.* 11, 80–95.
- Brown, M.W., and Aggleton, J.P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61.
- Buckner, R.L., Wheeler, M.E., and Sheridan, M.A. (2001). Encoding processes during retrieval tasks. *J. Cogn. Neurosci.* 13, 406–415.
- Buckner, R.L., Andrews-Hanna, J., and Schacter, D.L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N Y Acad. Sci.* 1124, 1–38.
- Cabeza, R., Daselaar, S.M., Dolcos, F., Prince, S.E., Budde, M., and Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb. Cortex* 14, 364–375.
- Cox, R.W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research* 29, 162–173.
- Daselaar, S.M., Prince, S.E., and Cabeza, R. (2004). When less means more: deactivations during encoding that predict subsequent memory. *Neuroimage* 23, 921–927.
- Davachi, L., and Wagner, A.D. (2002). Hippocampal contributions to episodic encoding: insights from relational and item-based learning. *J. Neurophysiol.* 88, 982–990.
- Davachi, L., Mitchell, J.P., and Wagner, A.D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. USA* 100, 2157–2162.
- Diana, R.A., Yonelinas, A.P., and Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: A three-component model. *Trends Cogn. Sci.* 11, 379–386.
- Eichenbaum, H., Yonelinas, A.P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152.
- Gold, J.J., Smith, C.N., Bayley, P.J., Shrago, Y., Brewer, J.B., Stark, C.E., Hopkins, R.O., and Squire, L.R. (2006). Item memory, source memory, and the medial temporal lobe: concordant findings from fMRI and memory-impaired patients. *Proc. Natl. Acad. Sci. USA* 103, 9351–9356.
- Gusnard, D.A., and Raichle, M.E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2, 685–694.
- Gusnard, D.A., Akbudak, E., Shulman, G.L., and Raichle, M.E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98, 4259–4264.
- Kensinger, E.A., and Schacter, D.L. (2006). Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *J. Neurosci.* 26, 2564–2570.
- Kirwan, C.B., Jones, C.K., Miller, M.I., and Stark, C.E. (2007). High-resolution fMRI investigation of the medial temporal lobe. *Hum. Brain Mapp.* 28, 959–966.

- Kopelman, M.D., Bright, P., Buckman, J., Fradera, A., Yoshimasu, H., Jacobson, C., and Colchester, A.C. (2007). Recall and recognition memory in amnesia: patients with hippocampal, medial temporal, temporal lobe or frontal pathology. *Neuropsychologia* 45, 1232–1246.
- Mandler, G. (1980). Recognizing: the judgment of previous occurrence. *Psychol. Rev.* 87, 252–271.
- Manns, J.R., Hopkins, R.O., Reed, J.M., Kitchener, E.G., and Squire, L.R. (2003). Recognition memory and the human hippocampus. *Neuron* 37, 171–180.
- Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., and Macrae, C.N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science* 315, 393–395.
- Miller, M.I., Beg, M.F., Ceritoglu, C., and Stark, C. (2005). Increasing the power of functional maps of the medial temporal lobe by using large deformation diffeomorphic metric mapping. *Proc. Natl. Acad. Sci. USA* 102, 9685–9690.
- Otten, L.J., and Rugg, M.D. (2001a). Task-dependency of the neural correlates of episodic encoding as measured by fMRI. *Cereb. Cortex* 11, 1150–1160.
- Otten, L.J., and Rugg, M.D. (2001b). When more means less: neural activity related to unsuccessful memory encoding. *Curr. Biol.* 11, 1528–1530.
- Paller, K.A., and Wagner, A.D. (2002). Observing the transformation of experience into memory. *Trends Cogn. Sci.* 6, 93–102.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., and Shulman, G.L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98, 676–682.
- Ranganath, C., Yonelinas, A.P., Cohen, M.X., Dy, C.J., Tom, S.M., and D'Esposito, M. (2004). Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia* 42, 2–13.
- Reynolds, J.R., Donaldson, D.I., Wagner, A.D., and Braver, T.S. (2004). Item- and task-level processes in the left inferior prefrontal cortex: positive and negative correlates of encoding. *Neuroimage* 21, 1472–1483.
- Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., and Petersen, S.E. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J. Cogn. Neurosci.* 9, 648–663.
- Slotnick, S.D., and Dodson, C.S. (2005). Support for a continuous (single-process) model of recognition memory and source memory. *Mem. Cognit.* 33, 151–170.
- Squire, L.R., Stark, C.E., and Clark, R.E. (2004). The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306.
- Squire, L.R., Wixted, J.T., and Clark, R.E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nat. Rev. Neurosci.* 8, 872–883.
- Uncapher, M.R., and Rugg, M.D. (2005). Encoding and the durability of episodic memory: a functional magnetic resonance imaging study. *J. Neurosci.* 25, 7260–7267.
- Uncapher, M.R., Otten, L.J., and Rugg, M.D. (2006). Episodic encoding is more than the sum of its parts: an fMRI investigation of multifunctional contextual encoding. *Neuron* 52, 547–556.
- Wagner, A.D., and Davachi, L. (2001). Cognitive neuroscience: forgetting of things past. *Curr. Biol.* 11, R964–R967.
- Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B.R., and Buckner, R.L. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 281, 1188–1191.
- Wais, P.E., Wixted, J.T., Hopkins, R.O., and Squire, L.R. (2006). The hippocampus supports both the recollection and the familiarity components of recognition memory. *Neuron* 49, 459–466.
- Weissman, D.H., Roberts, K.C., Visscher, K.M., and Woldorff, M.G. (2006). The neural bases of momentary lapses in attention. *Nat. Neurosci.* 9, 971–978.
- Wilson, M.D. (1988). The MRC psycholinguistic database: machine readable dictionary, version 2. *Behav. Res. Methods Instrum. Comput.* 20, 6–11.
- Wixted, J.T. (2007). Dual-process theory and signal-detection theory of recognition memory. *Psychol. Rev.* 114, 152–176.