Cerebral Cortex January 2007;18:1720-1726
doi:10.1093/cercor/bhm201
Advance Access publication November 21, 2007

Neural Correlates of Availability and Accessibility in Memory

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Failure to remember can be due to not having information available in memory or to an inability to access information that is available. We used functional magnetic resonance imaging to examine brain responses during encoding and successive cued recall and associative recognition tests of paired associates. Items were classified into 3 categories based on performance on the 2 retrieval tests: 1) successfully remembered (both recalled and recognized), 2) inaccessible (not recalled but later recognized), and 3) forgotten (neither recalled nor recognized). During cued recall, availability in memory was signaled in a network of regions including bilateral medial temporal lobe, left middle temporal cortex, and the parietal cortex. Memory access resulted in heightened activity in these regions as well as in left inferior frontal cortex. Encoding-related activity in hippocampus and inferior temporal cortex predicted subsequent availability and left inferior frontal activity predicted subsequent access. These results suggest that failure to access information that is available in memory may reflect weaker memory representations.

Keywords: encoding, fMRI, memory, recall, recognition, trace strength

Introduction

Forgetting a name or a fact only to have it come to mind moments later is a common everyday occurrence. Little is known about what causes memories to be temporarily inaccessible. The goal of the present functional magnetic resonance imaging (fMRI) study was to examine how neural activity during encoding and retrieval differ between successfully remembered, temporarily inaccessible, and forgotten memories.

The distinction between temporarily inaccessible and forgotten memories was first introduced by Tulving and Pearlstone (1966). In their study, subjects learned a series of categorized words followed by 2 consecutive tests—a free recall test followed by a cued recall test. Critically, some items that were not retrieved on the first test were successfully retrieved on the second test. Tulving and Pearlstone (1966) argued that such items, although not ***accessible*** on the first test, were still ***available*** in memory.

Although no functional neuroimaging study that we are aware of has examined the neural substrates of inaccessible memories (but see Brassen et al. 2006), much research has examined how the neural states of remembered memories differ from forgotten memories. During encoding, the main paradigm used to examine these differences is the subsequent memory paradigm. In this paradigm, neural activity is measured while subjects learn a series of stimuli. At a later time, subjects receive a memory test for the studied material intermixed with new items. Neural activity measured during the learning phase is then sorted on the basis of whether each item is subsequently remembered or forgotten. Differences due to memory (Dm) have been observed in the left and right prefrontal cortices as well as bilateral medial temporal lobes (MTL). Typically, activity is greater in these structures for subsequently remembered than forgotten memories (Brewer et al. 1998; Wagner et al. 1998; Kirchhoff et al. 2000; Otten and Rugg 2001; Otten et al. 2001, 2002; Paller and Wagner 2002; Jackson and Schacter 2004; Weis et al. 2004; Henson 2005; Henson et al. 2005; Staresina and Davachi 2006).

At retrieval, the difference between remembered and forgotten items has been examined by contrasting activity associated with remembered old items (hits) with activity associated with forgotten old items (misses). For example, Henson et al. (2005) compared hits and misses following shallow encoding of words and found greater activity for hits in bilateral intraparietal sulcus, bilateral precuneus, left middle frontal gyrus, and left frontopolar cortex. Other notable sites of differences between hits and misses include inferior frontal gyrus (Heun et al. 2004; de Zubicaray et al. 2007), the parietal cortex (Heun et al. 2004; Henson et al. 2005; de Zubicaray et al. 2007), and the MTL (de Zubicaray et al. 2007).

These studies show that brain activity during encoding and retrieval distinguish remembered from forgotten memories. The present study advances this traditional dichotomy by considering how neural activity differs from these endpoints for items that are neither forgotten nor immediately accessible. Briefly, subjects studied pairs of words followed by 2 consecutive memory tests: 1) cued recall, and 2) associative recognition. fMRI scans were acquired during each phase. During the critical cued recall task, items were classified as successfully remembered if they were both recalled and later recognized, as inaccessible if they were not recalled but were later recognized, or as forgotten if they were neither recalled nor later recognized. We hypothesize that inaccessible memories will activate the same set of brain regions, including the left prefrontal cortex and the MTL, as remembered memories, albeit more weakly (Brassen et al. 2006). Such a results pattern could indicate that the memory traces of inaccessible memories are “weaker” than the traces of successfully remembered memories and would reflect a quantitative (rather than qualitative) difference between remembered, inaccessible, and forgotten memories.

Materials and Methods

Subjects

Twenty right-handed normal volunteers (18-35; 8 males) each received a $30 gift card for participation. The study was approved by the Human Subjects Committee of Southern Illinois University Carbondale.

Procedure

The experiment consisted of 3 phases: 1) encoding, 2) cued recall, and 3) associative recognition. fMRI was carried out during each phase in a separate run lasting 4 min and 10 s. Four repetitions of these 3 runs, in the above sequence, were carried out.

During the encoding scans, subjects were presented with 60 pairs of unrelated words (e.g., Sister–Essay) on the center of an MRI compatible LCD screen (IFIS-SA; Intermagnetics, New York, NY). The LCD screen was attached to the back of a standard MRI head-coil. Subjects viewed the LCD screen via a mirror placed directly above their head. Word pairs were shown sequentially for 2.5 s and were separated by a fixation cross that was shown on the center of the screen for an average duration of 1 s (jittered between 500 and 1500 ms). Subjects were instructed to study the word pairs such that if later presented with the left-hand member of a pair, they could recall the right-hand member. They were informed that forming a mental image or sentence containing the 2 words would be beneficial for later remembering. While studying the pairs, subjects were instructed to indicate, by pressing MRI compatible response buttons, whether the words in each pair were related.

After a brief rest period following the encoding scan, subjects were shown 60 stimuli consisting of a question mark ("?") presented adjacent to a word (e.g., Sister–?) on the center of the LCD screen. Each stimulus was shown for 2.5 s. Stimuli were separated by a fixation cross that was shown on the center of the screen for an average duration of 1 s (jittered between 500 and 1500 ms). Forty of the 60 words were taken from the prior study phase, whereas the remaining 20 words were new. Subjects were instructed to indicate, by pressing the response buttons, whether they could recall what right-hand member was associated with each word. Subjects were informed about the presence of new items on the test list and were instructed to respond to these items in the same manner as other test items (i.e., indicate whether the right-hand member could be recalled). Because verbal responses were not recorded, the new items served as catch trials in order to provide an estimate of the guessing rate.

After another brief rest period, subjects were shown 60 word pairs. Each stimulus was shown for 2.5 s on the center of the LCD screen. Word pairs were separated by a fixation cross that was shown on the center of the screen for an average duration of 1 s (jittered between 500 and 1500 ms). Forty of the 60 word pairs were identical to those shown during the study and cued recall phases, whereas the remaining 20 consisted of recombined left- and right-hand members (i.e., the left-hand member of 1 pair combined with the right-hand member of a different pair). Subjects were instructed to indicate, by pressing the response buttons, whether each word pair was intact or recombined. Following these 3 scans, the same sequence was repeated 3 more times, each time with a different set of stimuli.

Such a design allowed us to define 3 critical categories for the old/intact items across the 2 tests: 1) those that were correctly recalled and recognized (successfully remembered, Rc+Rn+), 2) those that were not recalled but were later recognized (inaccessible, Rc–Rn+), and 3) those that were neither recalled nor recognized (forgotten, Rc–Rn–). (Although it cannot be definitively determined that an item is forgotten as it may be retrieved if additional retrieval cues are provided, Rc–Rn– items were not available during the course of the study and are hence classified as forgotten.) The critical comparison is between Rc–Rn+ and Rc–Rn–. This comparison was examined during both encoding and cued recall, but not during associative recognition. At the time of the cued recall test, the mnemonic status of these 2 sets of items was the same (i.e., subjects indicated that they could not remember the target word), but their subsequent retrievability (on the associative recognition test) differed (hit vs. miss). If the availability of items in memory is related to neural activity during encoding and cued recall, this comparison may reveal regions of higher activity for Rc–Rn+ than for Rc–Rn–, with highest activity for the available and accessible items (i.e. Rc+Rn+).

Scanning and Analysis

fMRI imaging was performed with a Philips Intera 1.5-T magnet using a standard head coil. Each functional run (12 in total = 4 encoding, 4 cued recall, 4 associative recognition) consisted of 92 contiguous whole brain volumes (T_2^* single-shot echo-planar image [EPI], time repetition = 2.5 s, time echo = 50 ms, flip angle = 90°, field of view = 220 × 220 mm^2, 64 × 64 matrix, 3.44 × 3.44 × 5.5 mm voxels, 26 × 5.5-mm axial slices, 0-mm gap, first 8 images were discarded). Conventional high-resolution T_1 weighted 3D structural images were acquired at the end of the functional imaging stage.

Data were analyzed with SPM 2 implemented in Matlab 6.51 (Mathworks, Natick, MA). Images were 1) slice time corrected for acquisition order, 2) realigned and motion corrected to the first image of the session, 3) normalized to a common template (Montreal Neurological Institute EPI template), 4) resliced to 2 × 2 × 2-mm voxels, and 5) spatially smoothed with a 10-mm Gaussian filter. A 128-s high-pass filter was applied to each time course in order to eliminate low frequency noise. Single-subject statistical contrasts were created using the general linear model. Conditions of interest (Rc–Rn–, Rc–Rn+, Rc+Rn+) during both encoding and cued recall runs were modeled using a canonical hemodynamic response function. Group comparisons were created using a random effects model. All contrasts were thresholded at $P < 0.001$, uncorrected for multiple comparisons. All coordinates are presented in the Talairach and Tournoux (1988) coordinate system.

Results

Behavior

During the cued recall test, subjects indicated that they could recall 65.3% of the studied word pairs. The false alarm rate (responding "Yes" to a new cue) during the cued recall test was 12.8%. During the associative recognition test, subjects correctly identified 76.6% of the intact word pairs. The false alarm rate (responding "Intact" to a recombined pair) was 22.1%. On both tests the hit rate was significantly greater than the false alarm rate (cued recall: $t(19) = 12.8$, $P < 0.001$; associative recognition: $t(19) = 13.0$, $P < 0.001$), whereas corrected performance (hits–false alarms) did not differ between the 2 tests (cued recall = 52.5%; associative recognition = 54.5%; $t(19) = 0.2$, $P > 0.05$).

All studied (old) test items were categorized based on whether they were recalled and recognized (Rc+Rn+), not recalled but recognized (Rc–Rn+), or neither recalled nor recognized (Rc–Rn–). The percentage of items falling into each of these categories is Rc+Rn+ = 53.9%, Rc–Rn+ = 22.6%, and Rc–Rn– = 12.7%.

Functional MRI

Encoding

To test the prediction that activity during encoding differs in a quantitative manner between subsequently forgotten, inaccessible, and remembered memories, a linear contrast (–1 0 1) was setup across the 3 conditions of interest (Rc–Rn–, Rc–Rn+, Rc+Rn+). This contrast revealed greater activity in 4 foci (see Fig. 1): 1) left inferior frontal gyrus (LIFG; xyz = –42 25 –15; Z = 3.52; k = 57; Brodmann area [BA] 47), 2) left hippocampus (LHC; xyz = –20 –9 –18; Z = 3.21; k = 11), 3) right hippocampus (RHC; xyz = 18 –7 –20; Z = 3.29; k = 7), and 4) left inferior temporal gyrus (LITG; xyz = –50 –51 –8; Z = 3.91; k = 16; BA 37). Activity in all 4 regions was lowest for Rc–Rn– (forgotten), intermediate for Rc–Rn+ (inaccessible), and highest for Rc+Rn+ (remembered).

Although the 4 regions identified above all show a linear increase from Rc–Rn– to Rc+Rn+, it is unclear whether inaccessible memories significantly differ from either endpoint of this linear contrast. To address this issue, paired-samples *t*-tests were carried out on the adjusted regression coefficients

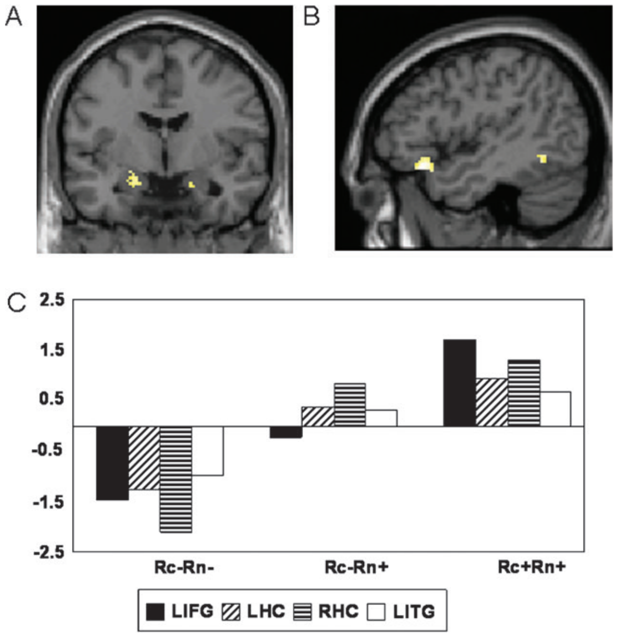

Figure 1. *A*) Coronal view of bilateral hippocampal (LHC/RHC) and *B*) sagittal view of left inferior frontal (LIFG) and left inferior temporal (LITG) activity during encoding of verbal paired-associates superimposed on a standard T_1-weighted MRI. *C*) Plot indicates activity (ordinate = standardized parameter estimates) as a function of the availability and accessibility of items (Rc−Rn− = unavailable, Rc−Rn+ = inaccessible, Rc+Rn+ = available and accessible).

of the 4 regions identified above between the Rc–Rn+ (inaccessible) condition and the other 2 conditions. Activity in the LHC ($t(19) = 2.4$, $P < 0.05$), RHC ($t(19) = 2.8$, $P < 0.05$), and LITG ($t(19) = 2.3$, $P < 0.05$) was significantly greater in the Rc–Rn+ condition than in the Rc–Rn– condition; the difference between the Rc–Rn+ and Rc+Rn+ conditions was not significant in these 3 foci. The opposite pattern was observed in the LIFG: activity was significantly greater in the Rc+Rn+ than in the Rc–Rn+ ($t(19) = 2.9$, $P < 0.01$), but the difference between the Rc–Rn+ and the Rc–Rn– did not reach significance. These results indicate that inaccessible memories are significantly different from at least 1 endpoint of the linear contrast.

Cued Recall

The same linear contrast between Rc–Rn–, Rc–Rn+, and Rc+Rn+ (–1 0 1) was performed on activity measured during the cued recall phase. This contrast revealed greater activity in a number of foci (see Fig. 2): left middle temporal gyrus (LMTG; xyz = –61 –39 0; $Z = 4.81$; $k = 1744$; BA 21), LIFG (xyz = –32 32 –13; $Z = 3.41$; $k = 25$; BA 47), and left superior frontal gyrus (LSFG; xyz = –14 48 34; $Z = 3.92$; $k = 133$; BA 9), left (LPHG; xyz = –20 –24 –12; $Z = 3.49$; $k = 43$; BA 35) and right (RPHG; xyz = 26 –19 –23; $Z = 3.85$; $k = 70$; BA 36) parahippocampal gyrus, precuneus (xyz = –2 –74 40; $Z = 3.61$; $k = 548$; BA 7), posterior cingulate (xyz = –6 –43 35; $Z = 3.43$; $k = 232$; BA 31), and left inferior parietal lobule (LIPL; xyz = –44 –54 47; $Z = 3.34$; $k = 93$; BA 40). Activity in all regions was lowest for Rc–Rn– (forgotten), intermediate for Rc–Rn+ (inaccessible), and highest for Rc+Rn+ (remembered).

As with the encoding data, paired-samples *t*-tests were carried out in order to assess whether activity associated with inaccessible memories significantly differed from activity associated with forgotten and successfully remembered memories. A significant difference between Rc–Rn– and Rc–Rn+ was noted in all regions with the exception of LIFG ($P > 0.20$) and LPHG, where the effect was marginally significant ($P = 0.085$). Three foci showed a significant difference between Rc–Rn+ and Rc+Rn+: 1) LMTG, 2) LPHG, and 3) LIFG.

Encoding—Cued Recall Overlap

A conjunction analysis (Nichols et al. 2005) was performed to examine common activations between encoding and cued recall related to the linear contrast between forgotten, inaccessible, and remembered memories (–1 0 1). The conjunction analysis revealed that only 2 foci showed a common a pattern of activity (see Fig. 3): 1) LIFG (xyz = –46 23 -9; $Z = 3.22$; $k = 102$; BA 47), and 2) LMTG (xyz = –50 –51 –8; $Z = 3.19$; $k = 79$; BA 21/37).

Discussion

The main purpose of this study was to examine the neural correlates of information that is available in memory but temporarily inaccessible. The paradigm adopted here to study temporarily inaccessible memories was a modification of the standard subsequent memory paradigm (Paller and Wagner 2002) in that a second test session (associative recognition) immediately followed the first test session (cued recall). This allowed us to sort items into 3 categories of interest: 1) items that were successfully remembered on both tests, 2) items that were not remembered on the first test but were successfully remembered on the second test, and 3) items that were not remembered on either test. In the standard subsequent memory paradigm, the latter 2 types of items would have been categorized as forgotten because on the first test subjects indicated that they could not remember either type of item. However, the modification of the standard subsequent memory paradigm adopted here allowed "forgotten" items to be divided into those that were only temporarily inaccessible and those that were unavailable (i.e., appeared to be forgotten within the context of the present study). This distinction is important because significant differences in activity were noted between unavailable and temporarily inaccessible items.

Not unlike the original design used by Tulving and Pearlstone (1966), availability and accessibility in the present study were defined by performance on 2 separate retrieval tests. The availability of an item in memory was determined by whether it could be recognized on the associative recognition test (Rn+). The accessibility of an available item was assessed by whether, in addition to being recognized, it could also be recalled (Rc+). Thus, availability in memory reflected systematic differences in brain activity between items that were successfully remembered (Rc+Rn+) and items that were inaccessible (Rc–Rn+) relative to items that were forgotten (Rc–Rn–), whereas accessibility reflected systematic differences in brain activity between available items that were successfully recalled (Rc+Rn+) relative to items that were not recalled (Rc–Rn+). Because availability and accessibility were always determined *within* a retrieval task (i.e., between remembered and forgotten items within the cued recall and associative recognition tests), qualitative differences between these 2 retrieval tasks should have little bearing on the findings of the present study. Nevertheless, an associative recognition task was adopted in the present study in order to minimize differences with the initial cued recall test. Prior imaging research has indicated that the same left prefrontal region that supports

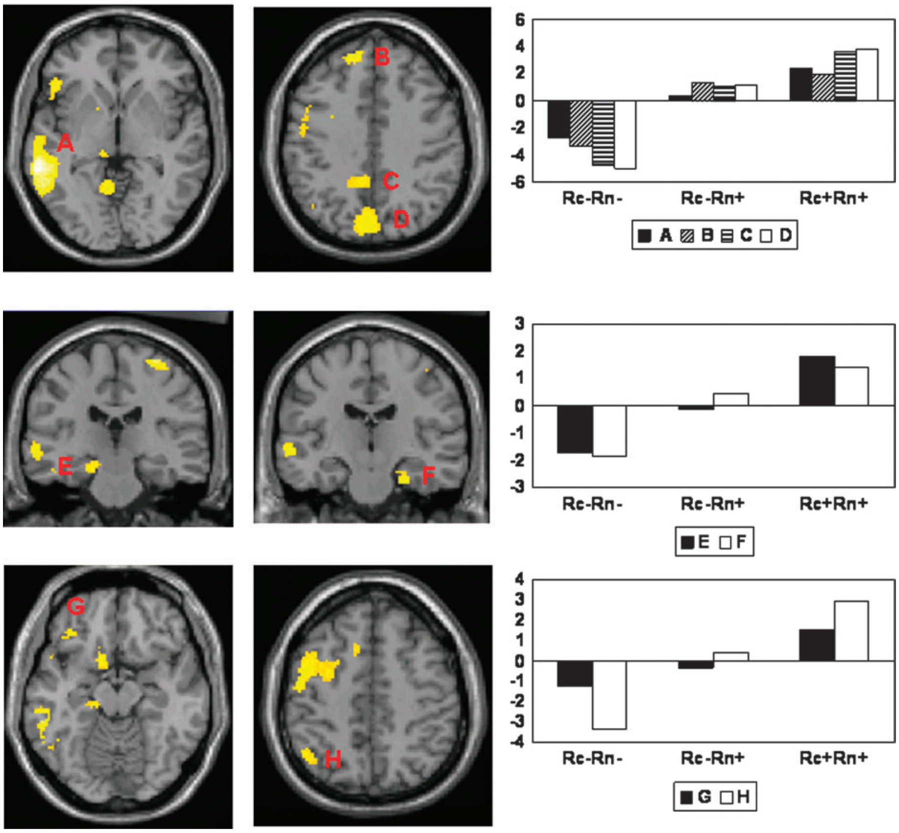

Figure 2. Brain regions demonstrating a graded increase in activity during cued recall of verbal paired associates superimposed on a standard T_1-weighted MRI. Top: Axial view of LMTG (A), LSFG (B), posterior cingulate (C), and precuneus (D). Middle: Coronal view of LPHG (E) and RPHG (F). Bottom: Axial view of LIFG (G) and LIPL (H). Plot indicates activity (ordinate = standardized parameter estimates) as a function of the availability and accessibility of items (Rc-Rn- = unavailable, Rc-Rn+ = inaccessible, Rc+Rn+ = available and accessible).

subsequent memory performance on cued recall also supports subsequent memory performance on associative recognition (but not item recognition; Staresina and Davachi 2006). Additionally, by eliminating familiarity as a source of the recognition decision (because all individual items were encountered during the study phase), subjects would likely rely on recollection for their recognition decision, similar to what would be required on a standard cued recall test (Yonelinas 2002).

Although familiarity cannot support recognition performance, the same cannot be said for recency. Because the cue item (left-hand word) of intact word pairs on the associative recognition test was presented twice (encoding and cued recall), whereas the cue item of recombined word pairs was presented only once (encoding), subjects could rely on the recency of the cue to determine whether an item was intact or recombined on the associative recognition test. This confound prevents us from determining which process, recollection of associative information or recency, contributed to the availability of items in memory. It does not, however, affect the comparison between successfully remembered, inaccessible, and forgotten items, on the cued recall test. That is, regardless of what processes determined the availability of an item in memory, activity for available items was greater than activity for forgotten items, and activity for successfully remembered available items was greater than activity for available but inaccessible items.

Availability in Memory

On the critical cued-recall test, availability of previously stored information in memory was signaled by activity in a distributed pattern of brain regions, including parahippocampal gyrus and medial and lateral parietal cortex [(Rc+Rn+) = (Rc–Rn+) > (Rc–Rn–)]. In previous research, these areas have been associated with retrieval from episodic memory (Fletcher et al. 1997; Henson 2005; Wagner et al. 2005). Here we extend these previous observations to hold for information that is available but not necessarily accessible in episodic memory.

The mnemonic response of parietal cortex is divergent and complex. Prior neuroimaging research has linked activity in the parietal cortex to retrieval success, perceived oldness, recollection and familiarity, and retrieval orientation (Wheeler and Buckner 2003; Wagner et al. 2005). The finding that parietal activity also distinguishes true recognition from false recognition is consistent with the present observation that information needs to be available in memory for parietal cortex to be active (Cabeza et al. 2001; Slotnick and Schacter 2004). A recent convergence analysis across a number of studies revealed that activity in the medial parietal region (precuneus extending into the posterior cingulate) and the LIPL was sensitive to successful retrieval (Wagner et al. 2005). It was hypothesized that activity in these parietal regions could reflect the accumulation of mnemonic evidence (Wagner et al. 2005). Our observation of greater activity for inaccessible than forgotten items in these same parietal regions supports this hypothesis by showing that

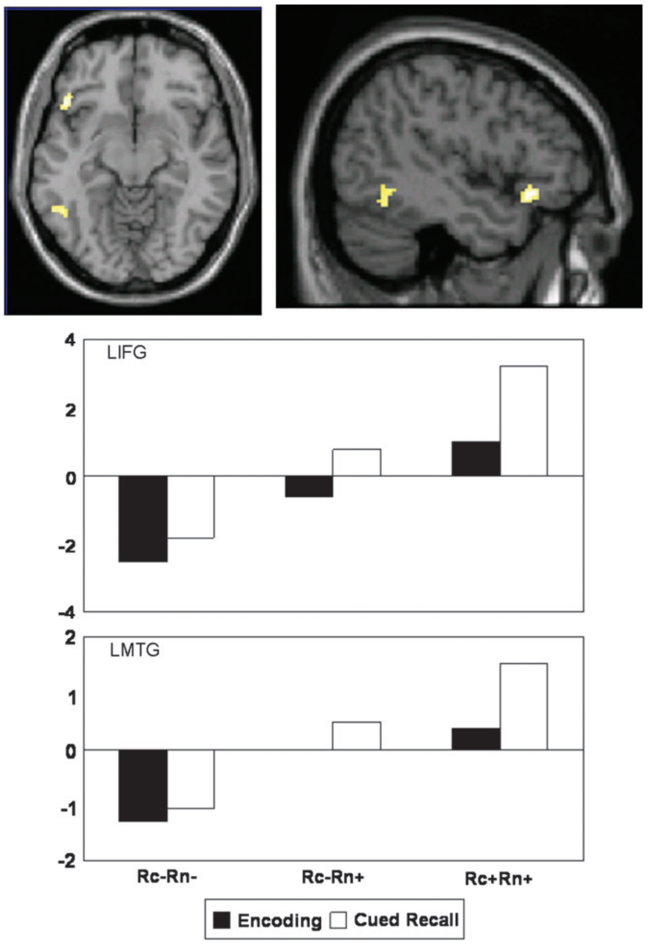

Figure 3. Conjunction of encoding and cued-recall activations superimposed on a standard axial and sagittal T_1-weighted MRI. Plots indicate activity (ordinate = standardized parameter estimates) as a function of the availability and accessibility of items (Rc−Rn− = unavailable, Rc−Rn+ = inaccessible, Rc+Rn+ = available and accessible).

parietal activity increased not only for successfully accessed information, but also during search for items not accessible but apparently available.

The availability of old information in memory was also signaled by activity in the parahippocampal gyrus. That is, in addition to activity in the medial and lateral parietal cortex, activity in the RPHG, and to a lesser extent LPHG, distinguished available memories (Rc–Rn+ and Rc+Rn+) from forgotten memories (Rc–Rn–). Consistent with these findings, electrophysiological research in monkeys has demonstrated that activity in the parahippocampal region is elevated during the retrieval of the target from a paired-associate retrieval cue (Naya et al. 1996), and human functional neuroimaging studies have found that the activity of a more dorsal portion of the parahippocampal gyrus (BA 27) distinguishes true from false recognition (Cabeza et al. 2001).

It should be noted that our design does not permit strong conclusions about whether the availability signal was driven by activity changes related to the missing to-be-remembered item, to the cue item itself, or perhaps most likely to some combination of these 2 items. It also remains to further characterize the nature of the availability signal in terms of a selective response during episodic retrieval, or a more general response that could be seen as an expression of some form of implicit memory. Tentatively, however, our observation of neural overlap between the availability signal at retrieval and encoding activations along with findings of pronounced differences between the encoding activations that predict episodic memory and perceptual priming (Schott et al. 2005, 2006) suggest that it reflected episodic representations.

Accessibility in Memory

Although all brain regions during both the encoding and cued recall phases showed a quantitative increase in activity from forgotten (Rc–Rn–) to inaccessible (Rc–Rn+) to successfully remembered (Rc+Rn+) memories (as a function of the –1 0 1 statistical contrast), pairwise comparisons revealed that the activity of only 3 structures, the LIFG, the LPHG, and the left middle temporal cortex, was diagnostic of the accessibility of mnemonic information that is available in memory. Critically, brain activity in the LIFG was not diagnostic of availability but specifically signaled successful access to the stored memory [(Rc+Rn+) > (Rc–Rn+) = (Rc–Rn–)]. At encoding, the pattern of activity in the left inferior frontal region mirrored the pattern during cued recall. Recently, Staresina and Davachi (2006) utilized a subsequent memory paradigm to identify a nearby left inferior frontal region (BA 45) that demonstrated greater encoding activity for words that were subsequently recalled or recognized on an associative recognition test in comparison with words that were subsequently recognized on an item recognition test. These authors hypothesized that activity in the LIFG during encoding may reflect the mental effort that is exerted in retrieving semantic information that is relevant to forming associations between stimuli. Similarly, Blumenfeld and Ranganath (2006) found increased activity in the LIFG (BA 47) during encoding trials that involved semantic processing (reorder trials) and Jackson and Schacter (2004) observed LIFG activity (BA 47) during encoding of items successfully recognized on an associative recognition test. Collectively, these results link left inferior frontal cortex to the formation of semantic associations, and the subsequent reactivation of such associations in conjunction with LIFG activity was necessary for successful retrieval to occur on the cued-recall test.

Left middle temporal cortex was the other region, in addition to LIFG, that was jointly activated at encoding and retrieval. At retrieval, a *graded* activation response was observed in the left middle temporal cortex [(Rc+Rn+) > (Rc–Rn+) > (Rc–Rn–)]. Thus, the left middle temporal cortex signaled *both* the availability and the accessibility of information in long-term memory. Previous neuronal recordings in monkeys have implicated inferotemporal cortex in encoding and storage of paired associate information (Miyashita 2004). In humans, the middle temporal cortex may serve a similar role in the encoding and storage of verbal associations. Supporting this hypothesis, Staresina and Davachi (2006) found a graded response in a nearby LMTG site (BA 21) during encoding as a function of the type of retrieval test (recall > associative recognition > item recognition) and Jackson and Schacter (2004) observed LMTG during subsequent memory performance on an associative recognition test. The increased activity in temporal cortex during actual memory access in cued recall may reflect reactivation of stored memory traces (Nyberg et al. 2000; Wheeler et al. 2000).

Neural Model of Availability and Accessibility in Memory

The present results suggest that the availability and accessibility of information in long-term memory is determined by the activity of specific brain regions during encoding and retrieval. Here we propose a tentative neural model to account for how activity in these regions contributes to the formation of memories that are remembered, inaccessible, or forgotten.

During the study phase, successful word-pair encoding was associated with bilateral hippocampal and left inferior frontal activity. Although these results are in agreement with past studies showing that encoding activity in the MTL and LIFG is correlated with successful subsequent remembering (Brewer et al. 1998; Wagner et al. 1998; Fernandez et al. 1998; Paller and Wagner 2002; Jackson and Schacter 2004), they further clarify the specific role each region serves during encoding. Specifically, activity in the MTL distinguished inaccessible from forgotten memories, whereas activity in the LIFG distinguished remembered from inaccessible memories. This dissociation between the LIFG and MTL suggests that although MTL activity is necessary for the formation of a memory trace, it does not necessarily ensure that the memory can later be retrieved, at least on a cued recall test. MTL activity must be supplemented with LIFG activity for a stored trace to be recoverable during cued recall. Additionally, left lateral temporal regions were engaged during encoding, which is consistent with the proposed role for this area in the storage of paired associate information (Miyashita 2004). Together, this network is hypothesized to underlie the retrieval of semantic information (LIFG) that is necessary for the successfully encoding (hippocampus) and storage (lateral temporal cortex) of paired-associate information in long-term memory.

During cued recall, the presentation of a visual cue that mapped onto information that was available in long-term memory (as confirmed by successful recovery on the subsequent associative recognition test) resulted in increased activity in a set of regions regardless of whether this information could be accessed. Activity in this network signals the availability of information in long-term memory. The network included the parahippocampal gyrus and the medial and lateral parietal cortices. In part, the salient role of the medial parietal cortex during retrieval may relate to the instructions presented to subjects at encoding to form mental images of the words in each pair (Fletcher et al. 1995). Alternatively, medial and lateral parietal regions may signal that information is available in memory, consistent with a proposed role in the accumulation of evidence in support of a memory decision (Wagner et al. 2005). Critically, this availability network also involved the left lateral temporal cortex, a region that has been hypothesized to store high-level representations of associative information (Miyashita 2004) and was active during the encoding of this associative information.

Access to available information during the cued recall test was defined by increased activity in the availability network in addition to unique activity in the LIFG. The LIFG likely contributes to the formation of semantic associations at encoding that was necessary for successful cued recall to occur at test (Jackson and Schacter 2004; Blumenfeld and Ranganath 2006; Staresina and Davachi 2006). Access to available memories also involved increased activity in LPHG and left lateral temporal cortex. This is in agreement with previous demonstrations of interactions between these 2 regions during retrieval of associative information (Miyashita 2004).

Finally, a graded pattern of neural activity was observed in both the availability and accessibility networks during both encoding and retrieval. At encoding, this graded pattern of activity may be correlated with the strength of the underlying memory trace. A similar conclusion was reached by Brassen et al. (2006) in their study examining encoding activity as a function of whether individual words were subsequently recalled, recognized, or forgotten. These authors found a graded pattern of activity (recalled > recognized > forgotten) in bilateral ventrolateral prefrontal cortex, bilateral dorsolateral prefrontal cortex, and bilateral hippocampus that they attributed to a quantitative difference in the strength of the underlying memory representation (Brassen et al. 2006). Human imaging (Law et al. 2005) and monkey electrophysiology (Wirth et al. 2003) research has indicated that activity in the MTL region gradually increases as associative memories are strengthened through repetition. During cued recall, this graded pattern of activity may reflect the strength of the reactivation of the memory trace and the ensuing confidence, vividness, or recollective experience associated with the recovered memory (Nyberg et al. 2000; Yonelinas et al. 2005).

Conclusion

In conclusion, these findings provide, for the first time, evidence that what is available in memory but cannot be accessed has a specific neural signature. Specifically, memories that are temporarily inaccessible are associated with lower levels of neural activity in several of the same regions of the brain that are activated for memories that are successfully retrieved. Accessibility of a trace relates in a systematic way to how the brain was activated during initial encoding and is reflected in regionally specific activity at retrieval.

Notes

The authors wish to thank Jessica Gerson and Ryan Cheperka for assistance with data collection and Julie Alstat and Gary Etherton for assistance with MRI scanning. *Conflict of Interest*: None declared.

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References

Blumenfeld RS, Ranganath C. 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci. 26:916–925.

Brassen S, Weber-Fahr W, Sommer T, Lehmbeck JT, Braus DF. 2006. Hippocampal-prefrontal encoding activation predicts whether words can be successfully recalled or only recognized. Behav Brain Res. 171:271–278.

Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD. 1998. Making memories: brain activity that predicts how well visual experience will be remembered. Science. 281:1185–1187.

Cabeza R, Rao SM, Wagner AD, Mayer AR, Schacter DL. 2001. Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci USA. 98:4805–4810.

de Zubicaray G, McMahon K, Eastburn M, Pringle AJ, Lorenz L, Humphreys MS. 2007. Support for an auto-associative model of spoken cued recall: evidence from fMRI. Neuropsychologia. 45:824–835.

Fernandez G, Weyerts H, Schrader-Bolsche M, et al. (11 co-authors). 1998. Successful verbal encoding into episodic memory engages the posterior hippocampus: a parametrically analyzed functional magnetic resonance imaging study. J Neurosci. 18:1841–1847.

Fletcher PC, Frith CD, Baker SC, Shallice T, Frackowiak RS, Dolan RJ. 1995. The mind's eye—precuneus activation in memory-related imagery. Neuroimage. 2:195–200.

Fletcher PC, Frith CD, Rugg MD. 1997. The functional neuroanatomy of episodic memory. Trends Neurosci. 20:213–218.

Henson R. 2005. A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. Q J Exp Psychol B. 58:340–360.

Henson RN, Hornberger M, Rugg MD. 2005. Further dissociating the processes involved in recognition memory: an FMRI study. J Cogn Neurosci. 17:1058–1073.

Heun R, Jessen F, Klose U, Erb M, Granath DO, Grodd W. 2004. Response-related fMRI of veridical and false recognition of words. Eur Psychiatry. 19:42–52.

Jackson O, 3rd, Schacter DL. 2004. Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. Neuroimage. 21:456–462.

Kirchhoff BA, Wagner AD, Maril A, Stern CE. 2000. Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci. 20:6173–6180.

Law JR, Flanery MA, Wirth S, Yanike M, Smith AC, Frank LM, Suzuki WA, Brown EN, Stark CE. 2005. Functional magnetic resonance imaging activity during the gradual acquisition and expression of paired-associate memory. J Neurosci. 25:5720–5729.

Miyashita Y. 2004. Cognitive memory: cellular and network machineries and their top-down control. Science. 306:435–440.

Naya Y, Sakai K, Miyashita Y. 1996. Activity of primate inferotemporal neurons related to a sought target in pair-association task. Proc Natl Acad Sci USA. 93:2664–2669.

Nichols T, Brett M, Andersson J, Wager T, Poline JB. 2005. Valid conjunction inference with the minimum statistic. Neuroimage. 25:653–660.

Nyberg L, Habib R, McIntosh AR, Tulving E. 2000. Reactivation of encoding-related brain activity during memory retrieval. Proc Natl Acad Sci USA. 97:11120–11124.

Otten LJ, Henson RN, Rugg MD. 2001. Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain. 124:399–412.

Otten LJ, Henson RN, Rugg MD. 2002. State-related and item-related neural correlates of successful memory encoding. Nat Neurosci. 5:1339–1344.

Otten LJ, Rugg MD. 2001. Task-dependency of the neural correlates of episodic encoding as measured by fMRI. Cereb Cortex. 11:1150–1160.

Paller KA, Wagner AD. 2002. Observing the transformation of experience into memory. Trends Cogn Sci. 6:93–102.

Schott BH, Henson RN, Richardson-Klavehn A, Becker C, Thoma V, Heinze HJ, Duzel E. 2005. Redefining implicit and explicit memory: the functional neuroanatomy of priming, remembering, and control of retrieval. Proc Natl Acad Sci USA. 102:1257–1262.

Schott BH, Richardson-Klavehn A, Henson RN, Becker C, Heinze HJ, Duzel E. 2006. Neuroanatomical dissociation of encoding processes related to priming and explicit memory. J Neurosci. 26:792–800.

Slotnick SD, Schacter DL. 2004. A sensory signature that distinguishes true from false memories. Nat Neurosci. 7:664–672.

Staresina BP, Davachi L. 2006. Differential encoding mechanisms for subsequent associative recognition and free recall. J Neurosci. 26:9162–9172.

Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. New York: Thieme.

Tulving E, Pearlstone Z. 1966. Availability versus accessibility of information in memory for words. J Verbal Learn Verbal Behav. 5:381–391.

Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL. 1998. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science. 281:1188–1191.

Wagner AD, Shannon BJ, Kahn I, Buckner RL. 2005. Parietal lobe contributions to episodic memory retrieval. Trends Cogn Sci. 9:445–453.

Weis S, Klaver P, Reul J, Elger CE, Fernandez G. 2004. Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. Cereb Cortex. 14:256–267.

Wheeler ME, Buckner RL. 2003. Functional dissociation among components of remembering: control, perceived oldness, and content. J Neurosci. 23:3869–3880.

Wheeler ME, Petersen SE, Buckner RL. 2000. Memory's echo: vivid remembering reactivates sensory-specific cortex. Proc Natl Acad Sci USA. 97:11125–11129.

Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, Suzuki WA. 2003. Single neurons in the monkey hippocampus and learning of new associations. Science. 300:1578–1581.

Yonelinas AP. 2002. The nature of recollection and familiarity: a review of 30 years of research. J Mem Lang. 46:441–517.

Yonelinas AP, Otten LJ, Shaw KN, Rugg MD. 2005. Separating the brain regions involved in recollection and familiarity in recognition memory. J Neurosci. 25:3002–3008.