

Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity

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Published online 15 October 2002; doi:10.1038/nn961

Memory for past events can be based on recollection or on assessments of familiarity. These two forms of human memory have been studied extensively by philosophers and psychologists, but their neuroanatomical substrates are largely unknown. Here we examined the brain regions that are involved in these two forms of memory by studying patients with damage to different temporal lobe regions. Our results come from (i) structural covariance modeling of recall and recognition, (ii) introspective reports during recognition and (iii) analysis of receiver operating characteristics. In sum, we found that the regions disrupted in mild hypoxia, such as the hippocampus, are centrally involved in conscious recollection, whereas the surrounding temporal lobe supports familiarity-based memory discrimination.

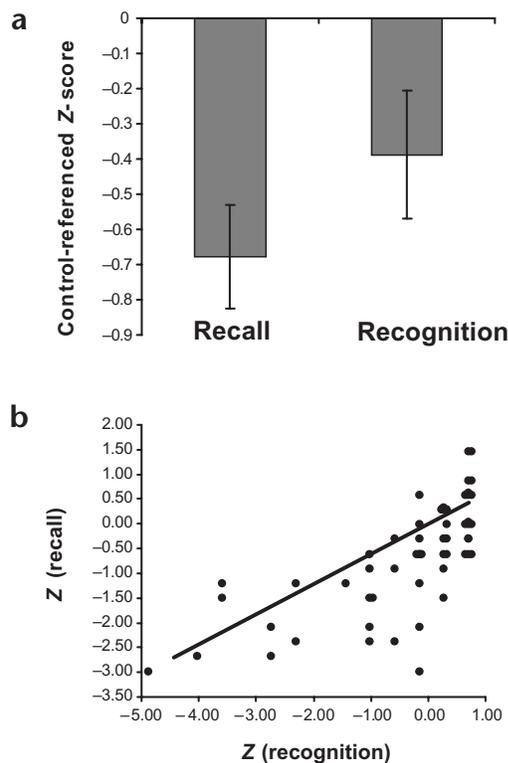
Patients with damage to the medial temporal lobe (MTL) show impaired performance on memory tests such as free recall and recognition^{1,2}, indicating that the MTL has an essential role in human memory. The MTL consists of several anatomically distinct subregions, including the hippocampus and the surrounding parahippocampal gyrus^{3,4}, that may support distinct mnemonic functions. For example, studies of rats and nonhuman primates indicate that the hippocampus is important for recollection of arbitrary associations between features of previous events, whereas regions within the parahippocampal gyrus are important for familiarity-based memory judgments such as identifying recently presented items^{5,6}. Whether there are similar functional specializations in the human MTL, however, is unknown. Neuroimaging studies have led to somewhat mixed conclusions regarding the mnemonic functions of these regions⁷⁻⁹. In human amnesic patients, both recollection and familiarity-based memory judgments are reported to be impaired¹⁰, but because these studies include patients with damage to the hippocampus and the surrounding parahippocampal gyrus, it is not clear whether these two regions are differentially involved in recollection and familiarity. To determine the functions of the different regions within the temporal lobe, it is necessary to examine patients with less extensive damage. Studies of hypoxic-ischemic patients should be particularly useful in addressing this issue because structural neuroimaging and histological studies have indicated that mild hypoxia (temporary loss of oxygen) leads to severe hippocampal atrophy but leaves the surrounding parahippocampal gyrus relatively preserved¹¹⁻¹³.

Although these patients show less severe memory impairments than patients with more extensive temporal lobe lesions^{14,15}, it is not known if they exhibit selective recollection deficits.

Here we examined the memory performance of mild hypoxic patients using tests of recall and recognition (experiment 1), reports of remember responses during recognition (experiment 2) and the analyses of recognition confidence responses (experiment 3). The patients had pronounced recollection deficits, but normal levels of familiarity-based responses. In contrast, patients with more extensive temporal lobe damage showed pronounced deficits in both recollection and familiarity.

RESULTS

To examine the effect of hypoxia on recollection and familiarity, we first examined delayed recall and recognition for a previously studied list of words in a hypoxic-ischemic group of 56 cardiac arrest patients, and a control group of 55 healthy subjects. Each patient was tested 6 months after successful resuscitation. The hypoxics performed more poorly than the control subjects on the recall and recognition tests, and their recall deficit was significantly ($P < 0.05$) greater than their recognition deficit (Fig. 1a and b). Recall requires recollection, whereas recognition judgments can be based on either recollection or on assessments of test-item familiarity¹⁶. Therefore, the results indicate that recollection was more disrupted by hypoxia than was familiarity. This dissociation cannot be attributed to differences in test materials or measurement scales, as both tests measured memory for the same materials and the analysis was based on standardized test



scores relative to control distributions¹⁷. The disproportionate deficit in recall compared to recognition is similar to the pattern of memory deficits seen in patients with frontal lobe damage¹⁸. However, it is unlikely that the current results are related to frontal damage because the hypoxic-ischemic severity of the patients described here is not associated with frontal pathology, and the current patients showed no evidence of frontal lobe dysfunction.

The results suggest that the brain regions damaged in hypoxia are more important for recollection than familiarity, but it is not clear whether familiarity is completely preserved because the small recognition deficit observed in the hypoxic patients could partly reflect a deficit in familiarity. To quantify the effects of hypoxia on recollection and familiarity, we generated a structural model of the covariances^{19,20} between hypoxic severity and memory performance (Fig. 2a). We used coma duration as a measure of hypoxic severity because it was the most reliable predictor of memory impairment²¹. Moreover, to account for potential differences in reliability between recall and recognition tests, we incorporated repeated measures of each memory test that were conducted at 3 and 6 months after injury. The model identified a large effect of hypoxic severity on recollection, but no effect on familiarity. To quantify these effects further, we plotted the expected change in recollection and familiarity as a function of hypoxic severity (Fig. 2b) and found that hypoxia did not influence familiarity but did impair recollection. This indicates that the regions damaged in the hypoxic patients are necessary for recollection but not for familiarity-based memory judgments.

An additional analysis was used to verify the results of the structural model by directly examining the correlations between memory performance and coma duration. If recognition relies on two processes, and is affected by hypoxia through a process shared by recall, the correlation between recognition and coma duration should be zero when the correlation between coma

Fig. 1. Recall and recognition in hypoxia. **(a)** Recall and recognition deficits of the hypoxic patient group. Recall deficits were significantly greater than recognition deficits ($P < 0.05$). **(b)** Each patient's recall score plotted against their recognition score. The dark line represents the results of a linear regression on recall and recognition scores in healthy control subjects. Most patients had a more pronounced recall than recognition deficit (points beneath regression line).

duration and recall is removed. Our findings were consistent with these predictions. For example, for the tests completed 3 months after injury, removing recall variance led to a reduction in the correlation between coma duration and recognition from -0.20 to -0.03 . Similarly, for memory tests conducted three months later, the correlation decreased from -0.30 to 0.03 . The reduced correlations could not be explained by the low reliability of the recognition measures because the correlation between the two recognition measures was 0.77 and remained high when recall variance was removed ($r = 0.58$ and $r = 0.60$ for the first and second test sessions, respectively).

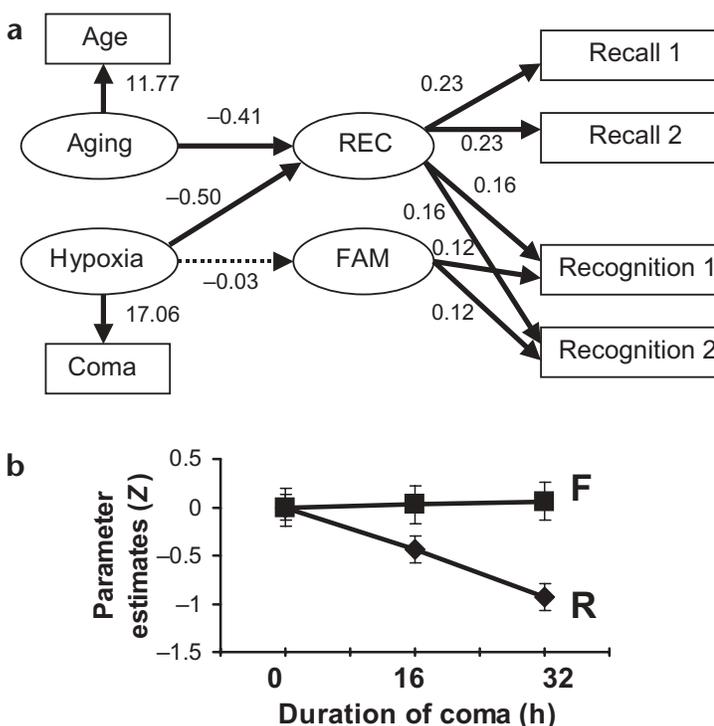
Next, we investigated whether familiarity depends on the temporal lobe regions surrounding the hippocampus, and whether the results from the recall/recognition analysis would replicate using more direct measures of recollection and familiarity. We thus compared recognition performance in a group of patients with damage that included the hippocampus and the surrounding parahippocampal gyrus (H+ group) to that of a group of hypoxic patients (H group) and to that of healthy, age-matched controls. The H+ group consisted of two patients with infarctions of the left posterior cerebral artery (Fig. 3a) and three patients that had undergone left temporal lobectomy for treatment of intractable epilepsy (Fig. 3b). The H group consisted of four hypoxic patients from the sample of cardiac arrest patients described above with memory deficits that were comparable to those of the H+ group. After studying a list of words, subjects were given a recognition test in which they were instructed to respond 'remember' if they could recollect any qualitative information about the item from the study episode, 'familiar' if they knew the item was from the study list because it seemed familiar but could not recollect any specific information about studying it, or 'new' if the word was not studied²². The proportion of remember responses was used to estimate recollection, whereas familiarity was estimated as the probability of a familiar response given that the item was not recollected. Estimates of recollection and familiarity (Fig. 4a) indicated that the H and H+ groups had significant deficits in recollection, whereas only the H+ group showed a deficit in familiarity.

In another recognition experiment, subjects made old versus new recognition confidence judgments on a six-point scale. Confidence-based receiver operating characteristics²³ (ROCs) were plotted (Fig. 4b) to model the contributions of recollection and familiarity¹⁰. Consistent with the results of the two previous experiments, the ROC analysis indicated that both patient groups had deficits in recollection, whereas only the H+ group had deficits in familiarity (Fig. 4c).

DISCUSSION

In these experiments, we used three separate methods to measure recollection and familiarity: structural covariance modeling of recall and recognition, analysis of remember-familiar responses and ROC analysis of recognition memory. We found that hypoxic-ischemic patients were impaired in recollection, but familiarity-based memory responses were intact. In contrast, patients with extensive temporal lobe damage showed deficits in

Fig. 2. Modeling the effects of hypoxia on recollection and familiarity. (a) Path model relating hypoxia to recall and recognition memory performance. The ellipses and rectangles represent latent and measured variables, respectively. Solid arrows reflect significant regression coefficients, and dotted arrows reflect non-significant coefficients. Coefficients between latent variables represent predicted changes in standard scores, whereas those between latent and measured variables represent predicted changes in raw scores (age in years, coma duration in hours, and probability of recall and recognition). The model assumes that recognition relies on recollection (REC) and familiarity (FAM), whereas recall relies solely on recollection. Coma duration (bottom left) was allowed to influence both recollection and familiarity in this model. Two measures of recognition and recall were included; parallel tests using different sets of words were conducted 3 and 6 months after cardiac arrest. The tests were treated as repeated measures, except that an additional factor was assumed to add variance to the initial tests ($\beta = 0.10, P < 0.01$). Patient age was assumed to influence only recollection⁴⁹, but this assumption was not critical because allowing age to influence both memory factors did not change the outcome of the model. The model provided a statistically acceptable account of the observed covariance ($\chi^2 = 9.06, d.f. = 9, n = 56, P = 0.43; R^2$ values were 0.89, 0.87, 0.88 and 0.85 for the recall 1 and 2, and recognition 1 and 2, respectively). Notably, the model indicated that hypoxia has a significant influence on the recollection component ($\beta = -0.50, P < 0.01$), but not the familiarity component ($\beta = -0.03, P > 0.05$). (b) Model-based measures of recollection and familiarity plotted as a function of coma duration. Estimates were derived for three levels of hypoxic severity—coma duration of 0, 16 and 32 h—using the regression coefficients from the model that linked coma duration to the recollection and familiarity variables. Hypoxic severity was related to a decrease in recollection and no change in familiarity.



both recollection and familiarity. The convergence of results from these methods strongly indicates that different groups of amnesic patients have distinct patterns of memory impairments. Notably, we did not find that the H+ patients were simply more severely memory impaired than the H patients. The two groups showed similar levels of overall recognition memory accuracy (ROCs in Fig. 4b) and comparable Wechsler Memory Scale Revised (WMSr) delayed memory scores. Moreover, familiarity was weaker in the H+ than in the H group, whereas recollection did not differ between the groups. In fact, numerically there was a trend for recollection to be worse in the H group in both the remember-know and ROC experiments. This slightly lower recollection score seen in the H group may reflect the fact that the damage was bilateral in that group and only unilateral in the H+ group.

The results are consistent with studies in rats and nonhuman primates that show the hippocampus to be critical for recollection, and the surrounding parahippocampal gyrus to be involved in familiarity discrimination^{5,6}. The results are also consistent with neuroimaging studies of humans indicating that the hippocampus is involved in recollection but not familiarity^{9,24}. Taken together, these findings are problematic for earlier memory theories that treated the different components of the MTL as a single functional memory system^{25–27}.

Our results, however, do not support the type of detailed neuroanatomical specificity that has been provided animal studies to date. For example, these studies have suggested that the perirhinal cortex (an anterior portion of the parahippocampal gyrus)

is critical for familiarity. The H+ group in the present study included patients with damage to either the anterior section of the parahippocampal gyrus or the posterior section along with the surrounding fusiform and lingual gyri. Direct examination of remember-familiar responses in these two types of patients,

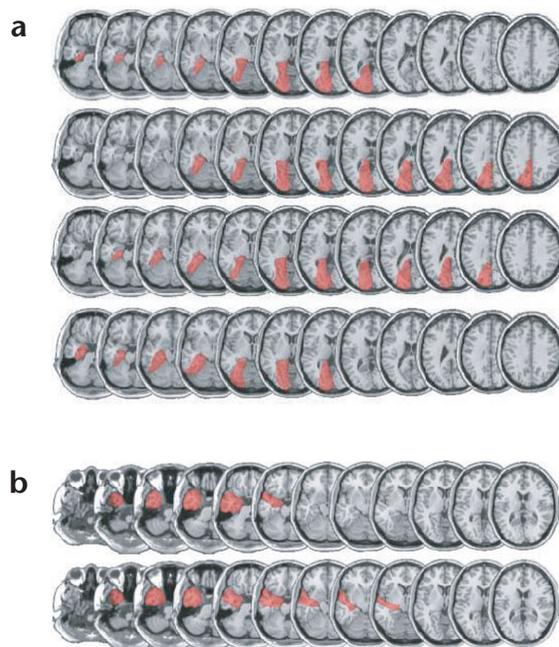


Fig. 3. Lesion reconstructions for the (a) left posterior cerebral artery infarct patients and (b) left temporal lobectomy patients.

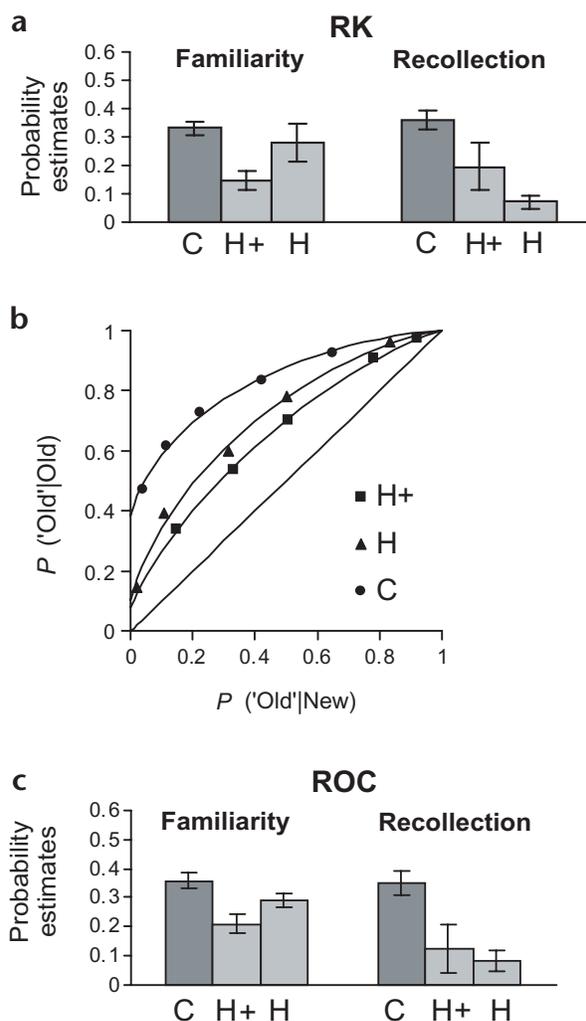


Fig. 4. Estimating recollection and familiarity in recognition memory. (a) Estimates of familiarity and recollection for the control (C), hypoxic (H) and hippocampal plus (H+) groups derived from the remember-know (RK) test. There was a significant group \times memory process interaction when comparing the H group to controls ($P < 0.001$), indicating that hypoxia had larger effects on recollection than on familiarity. In contrast, no interaction was found when comparing the H+ and control groups, but there was an overall effect of group ($P < 0.05$), indicating that H+ lesions led to similar reductions in recollection and familiarity. Direct comparisons indicated that the familiarity estimate for the H+ group was lower than that of the H group, and only the H+ group showed a significant familiarity deficit relative to controls ($P < 0.05$, all direct comparisons were one-tailed). The recollection estimate for the H+ group was numerically higher than that of the H group, but the difference was not significant, and both groups were impaired relative to controls ($P < 0.05$). (b) ROC points for each group along with the least-squares model fits. The left-most point on each function reflects the most confidently recognized items, and each consecutive point includes the next most confidently recognized items. (c) Estimates of familiarity and recollection based on the ROC analysis. Relative to controls, the hypoxics had numerically larger deficits on recollection than familiarity, but the group \times memory process interaction did not quite reach significance ($P = 0.062$). In contrast, no evidence of an interaction was observed when comparing the H+ and control groups, but there was an overall effect of group ($P < 0.01$), indicating that H+ lesions led to comparable reductions in recollection and familiarity. As in the RK experiment, the familiarity estimate for the H+ group was lower than that of the H group, but in this case the difference was not significant ($P = 0.068$), possibly because fewer patients were tested in this experiment. Notably, the H+ group had a significant familiarity deficit relative to the controls ($P < 0.05$), whereas the H group did not. Moreover, the recollection estimates of the two patient groups did not differ, but both were significantly lower than that of the controls ($P < 0.05$).

however, showed that both groups had deficits in familiarity, suggesting that both anterior and posterior regions of the temporal lobe are involved in familiarity.

Although hypoxia has pronounced effects on the hippocampus, other brain regions, including the thalamus and the watershed regions in the cerebral cortex and cerebellum, can also be affected^{28–31}. It is therefore impossible to determine with certainty exactly which brain regions are affected in these patients. However, in cases in which the cognitive deficits are restricted primarily to memory, as in the current hypoxic patients, volumetric neuroimaging^{13,32–35} and postmortem neuropathological analysis^{11,36,37} indicate that the hippocampus is the primary region influenced by hypoxia and is the most likely cause of the memory impairments. Although the severity of the hypoxic event has not been reported in many of these previous studies, for those that did, the patients suffered comparable or more severe hypoxic events than the patients studied here. The duration of cardiac arrest in our hypoxic group was, on average, 2.1 minutes, and the average coma duration was 16 hours. The duration of the hypoxic events suffered by patients in previous studies ranged from several minutes³⁶ to 20 minutes¹³. In the former case, a post-mortem microscopic tissue analysis indicated pronounced cell abnormalities within the hippocampus but no abnormali-

ties in the subiculum, parahippocampal gyrus or the underlying temporal lobe white matter. Other brain regions, such as the frontal and temporal lobes, basal ganglia and mammillary bodies, were also unremarkable, with the exception of a small infarct in the right frontoparietal cortex and in the inferior aspect of the left thalamus. The latter study examined high-resolution magnetic resonance scans of five hypoxic patients and revealed severe bilateral hippocampal atrophy in all cases. All other brain regions appeared normal, with the exception of gray matter reductions in the putamen and the ventral part of the thalamus. In another study, the coma duration of the patient was approximately two days³⁵, and the brain MR scans were normal with the exception of abnormalities in the CA1 and CA2 fields of the hippocampus and amygdala.

Whether recollection is selectively disrupted in more severe hypoxic patients is not yet clear. As hypoxic severity increases, brain regions outside the hippocampus are more likely to be compromised³⁸, and thus familiarity may also become disrupted. Moreover, it is not clear how these processes might be affected in patients with hypoxia that was induced by events other than cardiac arrest, such as carbon monoxide poisoning, anesthetic accidents or drowning.

The present results are consistent with studies of patients who suffered brief hypoxic events early in life^{13,32,39,40}. These patients show more severe deficits in recall than in recognition^{13,32}, and scalp-recorded event related potentials associated with recollection are disrupted, but not those associated with familiarity⁴⁰. This suggests that they also suffer from selective recollection deficits. These patients have relatively preserved semantic knowledge despite their amnesia³², suggesting that the regions supporting the acquisition of knowledge can operate

partially independently of the hippocampus. Although only speculative, it is possible that the same brain regions supporting familiarity are those involved in supporting the acquisition of semantic knowledge.

The finding that familiarity relies on regions in the temporal lobe indicates that this form of memory is partially distinct from repetition priming as measured on tasks such as stem completion and perceptual identification^{41,42}. For example, neuroimaging studies have indicated that these latter tasks rely on regions in sensory cortex, rather than the temporal lobes^{43,44}. Moreover, patients with extensive temporal lobe lesions have been shown to exhibit normal priming on these tests, yet are at chance on recognition memory tests⁴⁵, indicating that perceptual priming can be subserved by structures other than those supporting familiarity or recollection.

METHODS

Informed consent was obtained from all subjects, and the study was approved by the Committee on Human Research at the University of California.

Recall versus recognition

Subjects. The cardiac arrest patients ($n = 56$) suffered a brief period of hypoxia (time to the onset of cardiopulmonary resuscitation: mean (μ) = 2.1 min, range 30 s to 7 min) associated with coma (time before regaining consciousness: $\mu = 16$ h, range 5 min to 72 h), and none had prior history of brain pathology. The patients had defibrillators, which prevented the use of high-resolution brain scans to quantify the cortical atrophy. With the exception of memory impairments, the patients were cognitively intact. For example, verbal fluency scores ($\mu = 41.6$) and intelligence quotients ($\mu = 106$) were normal. Healthy controls ($n = 55$) were selected to be matched in age ($\mu = 60.6$) to the patient group ($\mu = 61.8$, $P = 0.57$).

Procedures. Retention of a 15-word list was assessed 20 min after learning using a free recall test and an old/new recognition test that included a mixture of 15 studied words and 15 lure words that were new to the experiment⁴⁶. Recall was scored as the proportion of studied words recalled, whereas recognition was scored as the proportion of correct 'old' responses minus the proportion of incorrect 'old' responses. The patients were tested 3 and 6 months after cardiac arrest on parallel tests with different stimuli. The results of the two test sessions were similar. To directly contrast the long term effects of hypoxia on recall and recognition, only the results from the second test were assessed. In the structural modeling analysis, however, the first test was also included, but was allowed to be influenced by an additional source of variance to allow for incomplete recovery at the 3 month timepoint. To control for differences in task difficulty and for differences in performance variability between the recall and recognition tests, the memory scores for the patients were converted to control-referenced Z-scores using the distribution means and standard deviations of the memory scores from the control subjects¹⁷.

Remember-know and ROC recognition

Subjects. In the remember-know experiment, the hippocampal-plus (H+) group included three epileptic left temporal lobectomy patients and two patients with infarcts of the left posterior cerebral artery, whereas the hypoxic (H) group consisted of 4 cardiac arrest patients. The ROC experiment included the same patients, except only three of the four cardiac arrest patients completed the test, and the two lobectomy patients in the H+ group were replaced with two additional posterior cerebral artery infarct patients. Each patient was age-matched to a healthy control subject (mean ages were 54, 56 and 55 for the H, H+ and control groups, respectively). Lesion reconstructions based on MR scans are presented in Fig. 2. The damage in the infarct patients included the hippocampus, fornix, posterior portion of the parahippocampal gyrus extending up to the posterior surface of the amygdala, and the surrounding fusiform and lingual gyri (Fig. 2a). The mean lesion volume was 52.6 ml. The lobectomy patients all underwent a standard left hemi-

sphere on block anterior temporal lobe resection to remove the anterior 4.5 cm of the temporal lobe, including the anterior half of the hippocampus, the amygdala and the anterior third of the parahippocampal gyrus. MRIs from two of the three patients verify the extent of the lesions (Fig. 2a). The mean lesion volume was 42.2 ml. The patients scored normally on tests in intelligence ($\mu = 99$ and 102 for the H and H+ groups, respectively). Moreover, on the WMSr⁴⁷, they were normal on the attentional subscales ($\mu = 97$ and 91), but impaired on the delayed memory subscales ($\mu = 74$ and 73).

Procedures. In the remember-know experiment, each subject heard 50 words and was required to indicate how many syllables were in each word. An additional 50 words were presented with pleasantness rating instructions, but were not analyzed because subsequent recognition performance in the control subjects was at ceiling. Subjects received a recognition test in which they heard all the studied items mixed with 50 new words and were required to make a remember, familiar or new response to each item. For the first 20 test items, and for several items spread throughout the test list, each subject was required to explain why they made each response. This ensured that the subjects understood the remember-know distinction, which is problematic for some amnesics³⁹. Recollection was estimated as the probability that an old item received a remember response minus the probability that a new item received a remember response. Because familiarity responses could only be made for items that were not recollected, familiarity was estimated as the probability of a familiar response to an old item given it was not remembered, minus the same estimate for new items⁴⁸. This allows for the parallel and independent contribution of the two memory processes, even though the remember and know responses were mutually exclusive.

In the ROC experiment, each subject was tested on two parallel sessions, each with a different set of words. In each session, subjects studied 80 words under syllable counting instructions and 80 words under pleasantness rating instructions; then they were given a recognition test including all the studied items plus 80 new words and asked to rate the confidence of their recognition response on a 6-point scale. Performance was collapsed across encoding conditions and test sessions because these factors did not change the pattern of results. ROCs were plotted as a function of response confidence²³, and estimates of recollection and familiarity were derived using a least-squares method¹⁰. The model equation, $P(\text{'old'}|\text{old}) = P(\text{'old'}|\text{new}) + R + (1 - R) \Phi(d'/2 - c_i) - \Phi(-d'/2 - c_i)$, assumes that recognition reflects the contribution of recollection (R) and an independent familiarity process. The variable d' reflects the distance between two equal-variance Gaussian strength distributions, c_i reflects the response criterion at point i , and Φ is the cumulative response function. To facilitate comparison to recollection, which was measured as a probability, each d' value was converted to the probability of a hit given a false alarm rate of 0.10.

Acknowledgments

This work was supported by the National Institutes of Health (grants MH59352, NS12135 and NS40813).

Competing interests statement

The authors declare that they have no competing financial interests.

RECEIVED 25 JULY; ACCEPTED 25 SEPTEMBER 2002

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