

- ciated variance-weighted SD (6) of the cycling of *G1* transcript levels in wild-type ( $23.9 \pm 1.9$  hours), *gi-1* ( $22.9 \pm 1.5$  hours), and *gi-2* ( $25.5 \pm 4.6$  hours) backgrounds were obtained from two independent trials with FFT-NLLS curve-fitting software (27). In extended DD, *LHY* transcript levels were too low or the time series were too short to obtain reliable period estimates. *CCA1* expression is reported to damp rapidly in DD (8) and was not considered here.
27. J. D. Plautz et al., *J. Biol. Rhythms* **12**, 204 (1997).
28. An *F<sub>2</sub>* population ( $n = 71$ ) of seedlings segregating for *gi-1* [*gi-1* (Col)  $\times$  2CAC] (6) and an *F<sub>2</sub>* population ( $n = 36$ ) of seedlings segregating for *gi-2* {[*gi-2* (Col)  $\times$  2CAC *F<sub>1</sub>*]  $\times$  Col} were scored for the correlation between the luminescence-based circadian phenotype and the presence of either a 5-bp deletion in *gi-1* or for a 7-bp deletion in *gi-2*. Each genotype was identified by PCR with primer pairs that uncovered a 5-bp deletion in *gi-1* (primer pairs, 5'-GGAGT-TGCAGCCTGGATCG-3' and 5'-AGATCTGATCACT-TGGAG-3') and a 7-bp deletion in *gi-2* (primer pairs, 5'-CAGAATGACTATTGGAGCA-3' and 5'-GGAGAAC-CACTAGTTGTAGC-3').
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30. This work was supported by grants from the Korean Ministry of Agriculture to H.G.N., from NSF to S.A.K. (grant MCB-9724120), and from NIH to S.A.K. (grant GM56006). D.E.S. was supported, in part, as an NSF Postdoctoral Fellow in Plant Biology (grant BIR-9403981).

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## Real-Time Tracking of Memory Formation in the Human Rhinal Cortex and Hippocampus

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A fundamental question about human memory is which brain structures are involved, and when, in transforming experiences into memories. This experiment sought to identify neural correlates of memory formation with the use of intracerebral electrodes implanted in the brains of patients with temporal lobe epilepsy. Event-related potentials (ERPs) were recorded directly from the medial temporal lobe (MTL) as the patients studied single words. ERPs elicited by words subsequently recalled in a memory test were contrasted with ERPs elicited by unrecalled words. Memory formation was associated with distinct but interrelated ERP differences within the rhinal cortex and the hippocampus, which arose after about 300 and 500 milliseconds, respectively. These findings suggest that declarative memory formation is dissociable into subprocesses and sequentially organized within the MTL.

How do brain processes during an experience that will be remembered differ from those during an experience that will be forgotten? Answering this question might elucidate memory formation or memory encoding, a process transforming sensory representations of an experience into the code of the declarative memory system. This system mediates conscious recollection of past events and facts (1, 2). It depends on the structural integrity of the MTL (3), and neuroimaging studies suggest that the MTL plays a crucial role during memory formation (4, 5). Efferences from association areas enter the MTL primarily via the perirhinal and parahippocampal cortices, providing the major input to the entorhinal cortex, which in turn provides the main input to the hippocampus (6). However, imaging (7), patient (8), and animal studies (1, 9) have produced inconsistent results regarding specific functions of and interactions between MTL substructures. This inconsistency has given rise to different ideas about the organizational structure of the MTL memory system, contrasting a rather unitary model with

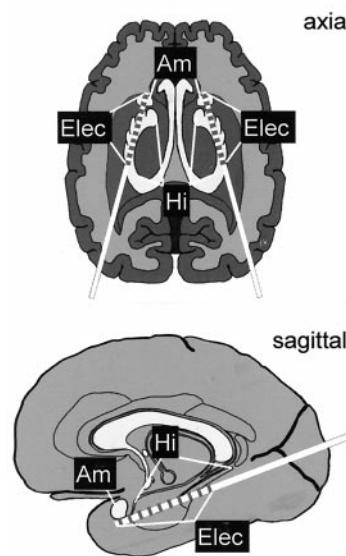
modular models featuring either serial or parallel processing modes (1, 9).

The question of when the process of declarative memory formation is initiated also remains unresolved. Neural processing at the time of stimulus encoding is critical for later retrievability (10), and functional magnetic resonance imaging (MRI) has offered evidence for time-locked posterior parahippocampal activity related to subsequent memory performance (4). Yet the exact time course of this activity cannot be assessed by this technique because functional MRI is based on indirect, hemodynamic measures. By contrast, ERPs enable direct, real-time monitoring of brain activity. Scalp ERPs recorded at the time of stimulus encoding and associated with subsequently recalled words begin to separate from those associated with subsequently forgotten words about 200 ms after stimulus onset (11, 12). This subsequent memory effect or difference due to memory (dm-effect) (11) has been differentiated from processes of implicit memory, semantic processing, and detection of distinctiveness (12). Hence, this effect may be related specifically to declarative memory formation. However, it remains unclear where this effect is generated because the generators of scalp ERPs are notoriously difficult to localize (13). ERPs

recorded invasively from depth electrodes placed directly into the MTL eliminate or mitigate the limitations of scalp-recorded ERPs and functional MRI by combining their advantages: direct measure of neural activity, real-time temporal resolution, and fine-grained spatial resolution within the MTL (14, 15).

In certain patients with medically refractory temporal lobe epilepsy, it is necessary to insert bilateral depth electrodes to define the zone of seizure origin for resective surgery (Fig. 1). If seizures are proved to originate unilaterally, contralateral electrodes enable recordings of MTL activity unrelated to epilepsy (16). We set out to use ERP recordings from such nonepileptic MTLs to define the time course of the initial steps of human declarative memory formation. Because electrodes enabled separate recordings within the hippocampus and the anterior parahippocampal gyrus (Figs. 1 and 2), we also examined whether memory formation is dissociable into subprocesses performed by these structures.

We recorded ERPs invasively (17) from 12 patients (18) with unilateral temporal lobe epilepsy (19). Each patient participated in 20 study-test blocks of a direct single-trial word



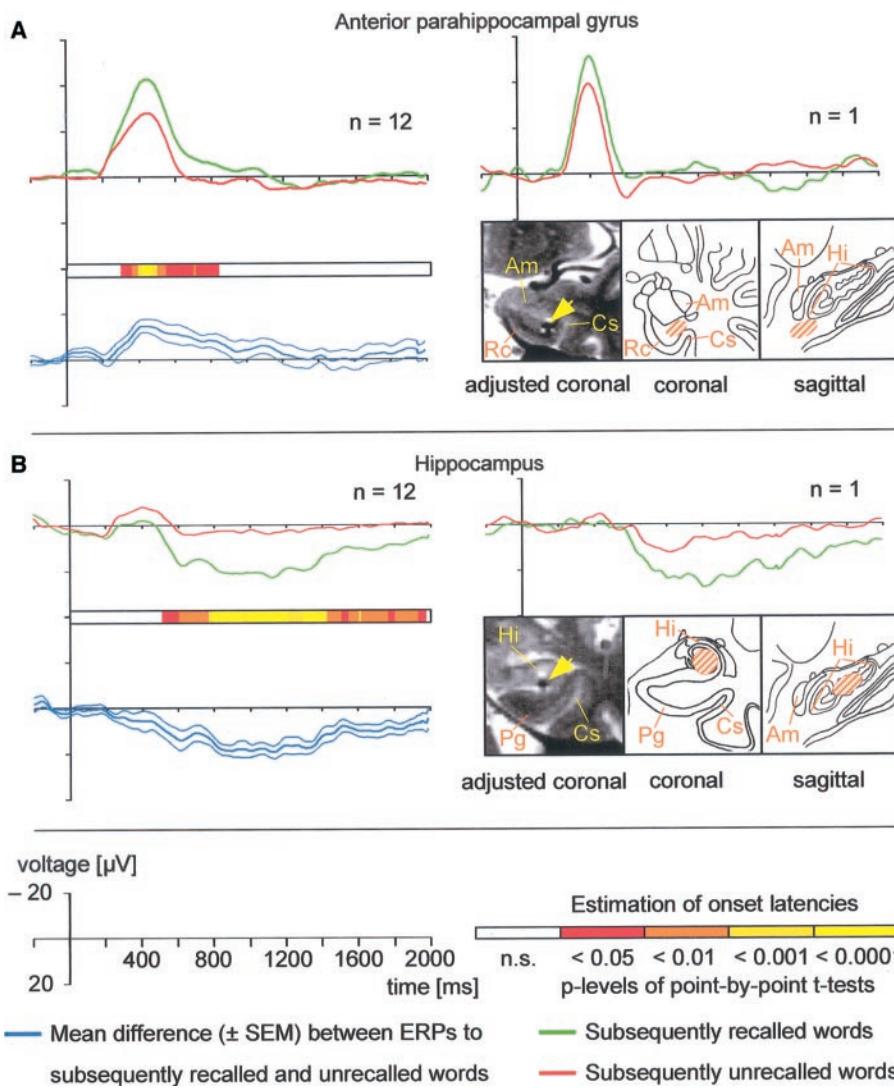
**Fig. 1.** Schematic drawings of multicontact depth electrodes reaching the anterior parahippocampal gyrus and the hippocampus on both sides (Am, amygdala; Elec, electrode; Hi, hippocampus).

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list learning paradigm (20), a procedure that makes great demands on declarative memory (21). During each block, patients were initially asked to memorize 12 words presented sequentially on a computer monitor. Thereafter, a distraction task was conducted to prevent ongoing rehearsal maintaining working memory. Finally, participants were instructed

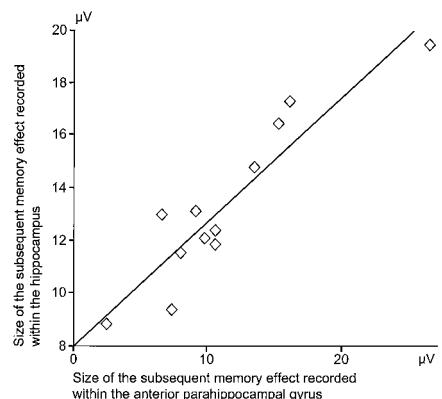
to freely recall previously presented words in any order (mean recall rate, 29.2%; range, 15 to 55%) (22). ERPs were recorded at study and separated off-line for subsequently recalled and unrecalled words. This procedure allowed a direct comparison between the neural correlates of successful and unsuccessful memory formation.



**Fig. 2.** Data from a contact in the anterior parahippocampal gyrus with the maximal AMTL-N400 (A) and from a contact in the hippocampus with the maximal late positive component (B), separately averaged. ERPs are depicted as grand averages (left column) of raw data and difference waveforms ( $\pm$ SEM) and as characteristic single-subject data (right column). MRI scans show examples with implanted electrodes (arrow). Hatched areas in standardized drawings indicate the localization of electrodes across patients where the most negative potential between 200 and 800 ms (A) and the most positive potential between 400 and 2000 ms (B) were recorded (17) (Am, amygdala; Cs, collateral sulcus; Hi, hippocampus; Pg, parahippocampal gyrus; Rc, rhinal cortex). Initially, ERPs were quantified by measuring mean amplitudes of consecutive 200-ms ranges with respect to the 200-ms baseline. Data were subjected separately to two-way ANOVAs using the within-subject factor of memory (recalled versus unrecalled) and the across-subject factor of hemisphere (left versus right). No main effect of, or interaction with, the factor of hemisphere occurred. In the anterior parahippocampal gyrus, data from latency ranges between 400 and 800 ms were more negative to subsequently recalled than unrecalled words [minimum  $F(1, 10) = 15.76, P < 0.01$ ; maximum  $F(1, 10) = 17.76, P < 0.01$ ]. Within the hippocampus, data from all latency ranges between 600 and 2000 ms were more positive to subsequently recalled than unrecalled words [minimum  $F(1, 10) = 12.61, P < 0.005$ ; maximum  $F(1, 10) = 96.47, P < 0.0001$ ]. Onset latency was defined as the latency from which at least 15 consecutive points of the recalled minus unrecalled difference waveforms differed significantly from zero ( $P < 0.05$ ) (30).

In the anterior parahippocampal gyrus, words elicited a large negative potential peaking about 440 ms after stimulus onset (Fig. 2A). This potential has been identified in previous studies using verbal stimuli, and it is referred to as anterior MTL-N400 or AMTL-N400 (14, 15). In our study, ERPs began to differ at about 310 ms after stimulus onset, with subsequently recalled words generating a larger AMTL-N400 than later forgotten words (Fig. 2A). This subsequent memory effect exhibited a steep voltage gradient over the neighboring electrode contacts. Six patients had additional subdural strip electrodes over the basal surface of the parahippocampal gyrus, anterior to the hippocampus. At these basal recording sides, the AMTL-N400 and its subsequent memory effect showed a phase reversal. Steep voltage gradients and phase reversals indicate that this effect was generated within the anterior parahippocampal gyrus, which is covered by the rhinal cortex (ento- and perirhinal cortex). As suggested previously (14), it might be generated within the depth of the anterior collateral sulcus.

Within the hippocampus, ERPs elicited by subsequently recalled and unrecalled words separated reliably from about 500 ms to the end of the averaging epoch (Fig. 2B). This subsequent memory effect had a positive polarity and was detectable within, but not immediately outside, the hippocampus. Hippocampal neurons are arranged cylindrically. Hence, they produce a radially symmetric field that is closed in the sense of being isopotentially zero outside the



**Fig. 3.** Scatterplot of the size of the anterior parahippocampal subsequent memory effect with the size of the hippocampal effect. Effect sizes correlated positively with each other when data from all subjects were included ( $r = 0.92, P < 0.0001$ ) and even when extreme values (minimum and maximum) were left out ( $r = 0.87, P < 0.001$ ). Effect sizes were defined as absolute mean amplitude differences between ERP waveforms elicited by subsequently recalled and unrecalled words. Measurements were taken from latency ranges that differ reliably (Fig. 2): 400 to 800 ms (anterior parahippocampal gyrus), 600 to 2000 ms (hippocampus).

hippocampus (23). Thus, this subsequent memory effect was generated within the hippocampus proper.

To test directly whether the rhinal and hippocampal subsequent memory effects arose sequentially, as indicated by the analyses already described (Fig. 2), we conducted a three-way analysis of variance (ANOVA) with the factors of region (rhinal cortex versus hippocampus), memory (subsequently recalled versus unrecalled), and time (300 to 500 ms versus 500 to 700 ms) (24). This analysis for mean amplitude data yielded an interaction between all three factors [ $F(1, 11) = 6.03, P < 0.05$ ]. Unfolding this triple interaction by computing separately subsidiary two-way ANOVAs for data from the early and the late epoch revealed a region  $\times$  memory interaction for each epoch [early:  $F(1, 11) = 28.68, P < 0.0001$ ; late:  $F(1, 11) = 15.50, P < 0.01$ ]. Post hoc *t* tests confirmed a reliable subsequent memory effect within the rhinal cortex for both epochs (early:  $t = 9.24, P < 0.0001$ ; late:  $t = 3.39, P < 0.01$ ) and within the hippocampus for the late but not the early epoch (early:  $t < 1.0$ , not significant; late:  $t = 3.34, P < 0.01$ ).

A functional connection between the rhinal and hippocampal subsequent memory effects is suggested by the positive correlation between their sizes (Fig. 3). However, such a correlation could be based either on a correlation occurring specifically between the effect sizes tested here or on generally similar ERP sizes within subjects. However, the peak amplitudes of the AMTL-N400 and the rhinal subsequent memory effect did not correlate with each other ( $r = 0.42$ , not significant). Thus, our findings indicate a specific correlation between both subsequent memory effects.

The sequential onset of the subsequent memory effects and the correlation between their sizes provide compelling evidence for interrelated and sequentially occurring processes related to declarative memory formation within the human MTL. Moreover, the results suggest that rhinal processing begins at around 300 ms, thus placing an upper bound on the time required by the brain to process visually presented words before the rhinal cortex is engaged in mnemonic operations influencing later memorability. The upper time bound for initiating a second stage of memory formation, performed by the hippocampus, is placed at around 500 ms.

To exclude the possibility that the subsequent memory effects are related to general,

ubiquitous effects found throughout the brain, we averaged ERPs recorded by additional subdural strip electrodes in the vicinity of Wernicke's area. Here a negative potential occurred, peaking initially at about 350 ms after stimulus onset (Fig. 4). This ERP component has been attributed to processes of semantic association and contextual integration (25). As depicted in Fig. 4, it did not show any subsequent memory effect, thereby dispelling doubts that the findings described above are merely effects of general fluctuations in neural activity. On the contrary, these data suggest parallel processes in temporal-parietal and medial temporal areas computing semantic and mnemonic operations, respectively.

No general inferences about hemispheric asymmetries of declarative memory formation can be drawn from our data, because recordings were taken from patients with an epileptic zone in the MTL contralateral to the one investigated here. However, considering results from patient (26) and imaging studies (4, 27), it seems plausible that there is actually an asymmetry in mnemonic MTL operations, depending on the material processed. Aside from this limitation, our findings can be generalized beyond the population of epileptic patients. Even if processing speed or ERP amplitudes might be slightly affected by medication or pathological state, ERPs are qualitatively unchanged (28). Furthermore, a direct comparison between ERPs from the MTLs of healthy nonhuman primates and ERPs from the MTL contralateral to the zone of seizure onset in epileptic patients showed that the latter represent normal activity unrelated to epilepsy (16).

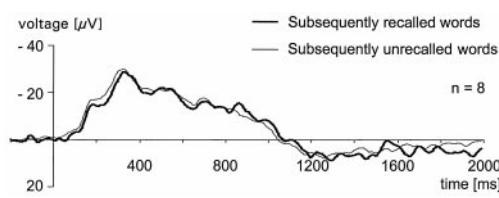
Our findings verify the participation of the rhinal cortex and the hippocampus in human declarative memory formation (5). They provide evidence that this mnemonic operation is dissociated into subprocesses, executed sequentially, and initiated within about 300 ms. Our findings are well in line with anatomical data indicating a close interaction between the rhinal cortex and the hippocampus (6). Together with the results of two event-related imaging studies (4), our results argue for a modularly structured and serially organized memory system comprising the posterior parahippocampal cortex, the rhinal cortex, and the hippocampus (29). Future research may clarify whether each module of this MTL

system contributes a behaviorally distinct operation to human declarative memory formation.

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**Fig. 4.** ERPs recorded by subdural strip electrodes covering the posterior part of the medial and superior temporal gyrus of the left hemisphere. Data were collected from eight patients with electrodes in that region. The remaining four patients had no electrodes outside the MTL.



## REPORTS

- = 3719 ms, echo time = 120 ms, flip angle = 90°, field of view = 22 cm; thickness, 2.0 mm; gap, 0.3 mm; 1.5 T) (ACS-II, Philips, Eindhoven, Netherlands).
18. All 12 patients (8 women; mean age 33.8 years, range 24 to 47) were native speakers of German and right-handed (left MTL seizure origin:  $n = 6$ ; right MTL seizure origin:  $n = 6$ ). At the time of the experiment, all patients received carbamazepine (plasma concentration, 8 to 12  $\mu\text{g}/\text{ml}$ ) as the only centrally acting drug. No seizure occurred within 24 hours before the experiment. Each patient gave written informed consent. The study was approved by the local medical ethics committee.
  19. To prove the unilaterality of the epileptic zone, we controlled the site of seizure onset in invasive recordings and the effect of resective surgery on seizure frequency. During the presurgical evaluation, at least three spontaneous seizures were recorded invasively from each patient. Each recorded seizure originated from the temporal lobe contralateral to the hemisphere investigated here. In the year before surgery, the range of the mean seizure frequencies per patient was 3.2 to 6.1 per month, and no month without any seizure occurred. After resection of the epileptic MTL, all patients remained seizure-free (follow-up, 5 to 13 months).
  20. After the entire procedure was explained to each patient, two training blocks were conducted immediately before the experiment to ensure that the patients had understood the task. Words were presented in uppercase letters (white against black background), in central vision (horizontal visual angle 3.0°), and for a duration of 400 ms (randomized interstimulus interval: mean 2.5 s, range 2.3 to 2.7 s). Patients were required to use a rote strategy to memorize each word; they could not use memory aids such as making rows, sentences, stories, or pictures. During the distraction task, which lasted 30 s, patients were instructed to count backward by threes, starting at a number between 81 and 99 displayed on screen. The following free-recall test lasted 90 s. Stimuli consisted of 240 semantically unrelated German nouns (word frequency, mean 75.24 per million, range 15 to 175; word length, mean 5.95 letters, range 4 to 11) [R. H. Baayen, R. Piepenbrock, H. van Rijn, *CELEX Lexical Database* (Linguistic Data Consortium, University of Pennsylvania, Philadelphia, 1993)]. The order of words was pseudorandomized under the constraints that (i) across subjects, each word occurred equally often within each quarter of the session and once at each list position; (ii) word length was balanced between lists; and (iii) neither semantic nor phonological similarities occurred within lists.
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