

Human Hippocampal Neurons Predict How Well Word Pairs Will Be Remembered

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Summary

What is the neuronal basis for whether an experience is recalled or forgotten? In contrast to recognition, recall is difficult to study in nonhuman primates and rarely is accessible at the single neuron level in humans. We recorded 128 medial temporal lobe (MTL) neurons in patients implanted with intracranial microelectrodes while they encoded and recalled word paired associates. Neurons in the amygdala, entorhinal cortex, and hippocampus showed altered activity during encoding (9%), recall (22%), and both task phases (23%). The responses of hippocampal neurons during *encoding* predicted whether or not subjects later remembered the pairs successfully. Entorhinal cortex neuronal activity during *retrieval* was correlated with recall success. These data provide support at the single neuron level for MTL contributions to encoding and retrieval, while also suggesting there may be differences in the level of contribution of MTL regions to these memory processes.

Introduction

The neuronal basis of human declarative memory has been a major focus of cognitive neuroscience research. It is well established that bilateral damage to the medial temporal lobe (MTL) in humans produces global amnesia—a profound memory deficit for new facts and events (Scoville and Milner, 1957; Cohen and Squire, 1980). MTL amnesics are impaired in their ability to learn and remember the associations between word pairs in paired associate learning paradigms (Scoville and Milner, 1957; Drachman and Arbit, 1966; Jones, 1974). Animals with MTL lesions also display memory deficits on delayed-response (Mishkin, 1978; Zola-Morgan and Squire, 1985; Squire and Zola-Morgan, 1991; Otto and Eichenbaum, 1992a) and nonverbal paired associate (Bunsey and Eichenbaum, 1993, 1996; Murray et al., 1993) tasks. Single-unit recording studies in animals describe MTL neurons with selective responses for the behaviorally relevant events of these tasks. MTL neurons code for particular stimulus attributes (Riches et al., 1991; Watanabe and Niki, 1995; Deadwyler et al.,

1996), task intervals (stimulus, delay periods; Riches et al., 1991; Watanabe and Niki, 1995), and response decisions (match, non-match; Otto and Eichenbaum, 1992b; Watanabe and Niki, 1995; Deadwyler et al., 1996; Desimone, 1996; Suzuki, 1999; Wiebe and Stäubli, 1999). There are also a few single neuron studies of recognition in humans showing that MTL neurons respond selectively to individual word and face stimuli (Heit et al., 1988), different stimulus categories (Fried et al., 1997; Kreiman et al., 2000), and to specific stimulus attributes (Fried et al., 1997). Such selective responses in both animal and human studies suggest neuronal mechanisms for memory processes.

In contrast to recognition memory, recall is difficult to study in animals. In particular, verbal memory can only be studied in humans. In the present study, we sought to provide evidence of MTL contributions to declarative verbal memory processes at the level of single neurons by directly recording from the human MTL while patients engaged in paired associate learning.

In studying the neuronal basis of declarative memory, a major question concerns the contribution of the MTL to specific memory processes. Memory deficits may be due to disruption of MTL participation in encoding, consolidation, retrieval, or a combination of these memory processes (Haxby, 1996). Neuroimaging methods provide the opportunity to measure brain activity separately for the encoding and retrieval stages of memory tasks in humans. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies implicate MTL regions in both encoding and retrieval memory processes (for reviews, see Lepage et al., 1998; Schacter and Wagner, 1999).

The question of whether MTL structures are especially important for the successful encoding of conscious experience into memory has recently been addressed. Fernández et al. (1998) conducted an fMRI study of word list encoding with free recall after distraction. Using a parametric analysis, they found that the degree of activation in posterior MTL and hippocampus was positively correlated with the number of successfully encoded words across short lists of five words (Fernández et al., 1998). The same group has also reported that the level of slowly modulated, sustained activity in entorhinal cortex during study correlated positively with subsequent cued-recall for words (Fernández et al., 1999a). Two event-related fMRI studies of the incidental encoding of words and pictures reported activation in the parahippocampal cortex that was greater during the encoding of individual stimuli that subjects later remembered compared to those that were later forgotten (words, Wagner et al., 1998; pictures, Brewer et al., 1998). Kirchoff et al. (2000) recently found posterior hippocampal and parahippocampal activations during the incidental encoding of words and pictures that were predictive of subjects' subsequent memory for pictures (but not words). While these results support the importance of MTL structures in successful memory encoding, there is little direct evidence of hippocampal activity that is predictive of subsequent memory performance from neuroimaging stud-

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ies, and none at the single-unit level. Neuroimaging studies may fail to find subsequent memory effects in the hippocampus itself because of the inherent difficulties in imaging this region due to susceptibility artifacts or the relatively small size of the hippocampus.

There is also some evidence of MTL activation during memory retrieval (Schacter and Wagner, 1999). Several studies implicate subicular (Gabrieli et al., 1997), hippocampal (Schacter et al., 1996; Eldridge et al., 2000; Stark and Squire, 2000), parahippocampal (Aguirre et al., 1996; Nyberg et al., 1996; Aguirre and D'Esposito, 1997; Schacter et al., 1997), and entorhinal (Klingberg et al., 1994) areas in retrieval-related memory processes. For example, in a recognition memory study, Stark and Squire (2000) found increased hippocampal activations during the retrieval of previously presented words or objects. Also, Eldridge et al. (2000) have recently suggested that hippocampal activation during recognition memory for words is selective for episodic, rather than nonepisodic, retrieval of words.

The choice of paired associate learning as a probe of declarative memory at the single neuron level has several advantages. It enables direct comparison of encoding and retrieval processes since the subject is engaged in alternating blocks of encoding and retrieval of word associations. In addition, this paradigm affords the study of recall as distinct from recognition of represented stimuli—a memory process that is difficult to approach in animal studies. Several neuroimaging studies have reported MTL activation during the encoding (Dolan and Fletcher, 1997; Rombouts et al., 1997; Henke et al., 1997, 1999) and retrieval (Klingberg et al., 1994) of visual (picture-face, line-drawings) (Klingberg et al., 1994; Henke et al., 1997; Rombouts et al., 1997) or verbal (Dolan and Fletcher, 1997; Henke et al., 1999) pairs. However, most of these studies measured MTL activity during only encoding or retrieval but not during both task phases.

In this study, recording directly from MTL neurons during paired associate learning, we addressed the following questions: Are there differences between the responses of MTL neurons during encoding compared to retrieval of word-word associations? Are there differences among the various subregions of the MTL in the neuronal responses during encoding and retrieval? And finally, is the activity of single neurons in the MTL correlated with successful performance on the paired associate memory task?

Results

MTL neuronal activity was recorded in 12 epilepsy patients implanted with intracranial depth electrodes as part of a clinical evaluation for elective surgery (Fried et al., 1999). Electrode locations were verified from post-implant MRI (Figure 1A). Single-unit activity was recorded continuously during seven blocks of alternating encoding and retrieval phases of paired associate learning (Figure 2). Patients were first shown 20 word pairs to be remembered: 10 related associates (e.g., dinner-food) and 10 unrelated associates (e.g., light-camp). Each pair was presented for 1 s with an interstimulus interval of 4 s (encoding). After a 1–2 min delay period,

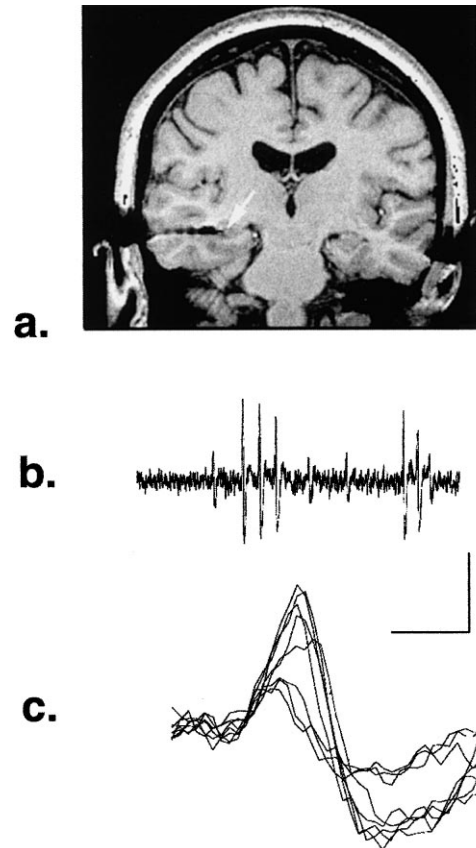


Figure 1. Depth Electrode Placement and Single-Unit Analysis

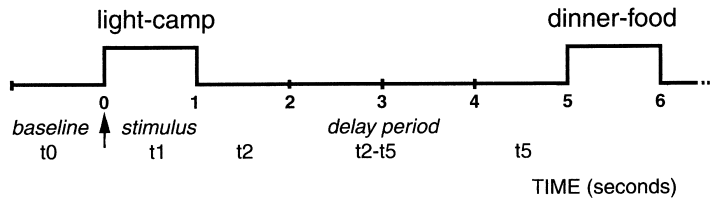
(A) Magnetic resonance image of the trajectory of a depth electrode targeted to the right hippocampus. Depth electrodes containing microwires were implanted bilaterally in the amygdala, entorhinal cortex, and hippocampus in 12 epilepsy patients in order to identify a potentially resectable seizure focus. The white arrow points to the dark, horizontal area of the protruding microwires. The probe with circular electrode contacts appears enlarged due to MRI artifact. (B) Amplified trace of extracellular neuronal activity recorded from a single microwire that depicts action potentials of varying amplitude from two different neurons. Negativity is up, with high-pass filtering at 300 Hz. Calibration: time = 20 ms, amplitude = 45 μ V. (C) Digitized action potentials from the trace in (B), separated based on waveform characteristics to yield single-unit activity. Calibration: time = 0.5 ms, amplitude = 83 μ V.

subjects were shown the first word of each pair as a cue and required to respond verbally with the word's associate (retrieval). The same set of 20 word pairs was presented and later tested seven times during alternating encoding and retrieval blocks. Thus, there were a total of 280 trials, 140 each for the "encoding" and "retrieval" phases of the task. Single-unit activity was recorded for each patient throughout the task, yielding recordings from a total of 128 neurons across all 12 subjects: 19 were recorded in the amygdala (A) in 5 subjects, 66 in the hippocampus (HC) in 11 subjects, and 43 in the entorhinal cortex (EC) in 7 subjects.

MTL Neuronal Responses during the Encoding and Retrieval of Paired Associates

More than half of the MTL neurons recorded (69/128, 54%) had significantly altered activity during paired as-

Encoding



Retrieval

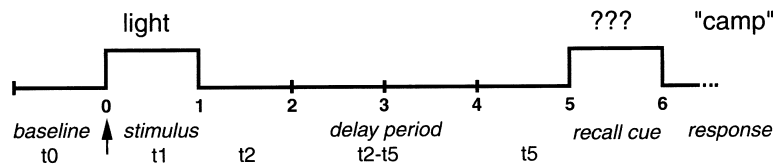


Figure 2. The Paired Associates Learning Task

During encoding, patients were shown 20 word pairs, one every 4 s. During retrieval, patients were presented with the first word of each pair, and required to verbally respond with the word's associate upon presentation of a recall cue after 4 s.

sociate learning (see Table 1, *t* tests, $p < 0.05$). They were located in both the language dominant (48%) and nondominant (52%) hemispheres. Twelve MTL neurons (9.4%) had significantly altered activity only during encoding, 28 (22%) only during retrieval, and 29 (23%) during both task phases (Table 1). These neurons were recorded in both the language dominant and nondominant hemispheres during encoding (8 and 4, respectively), during retrieval (11 and 17), and during both task phases (14 and 15). Most (83%) of the 29 neurons that responded during both phases displayed similar patterns of activity (i.e., either increases or decreases in firing rate) during encoding and retrieval, although retrieval responses were often more pronounced (66%, Figure 3).

Significant responses were found in all three MTL regions (see Table 1). In the amygdala the same number of neurons responded during the encoding (7, 37%) and retrieval (7, 37%) phases of the task (4 units responded during both). However, in the hippocampus, a greater number of neurons responded during retrieval (29, 44%) than encoding (19, 29%). A similar pattern was seen in

the entorhinal cortex, (21, 49%) during retrieval, and (15, 35%) during encoding. For hippocampal and entorhinal neurons combined, there were more neurons responding during retrieval (50, 46%) than during encoding (34, 31%; $\chi^2 = 4.96$, $p < 0.05$).

MTL neuronal responses occurred during stimulus presentation or in the delay period after stimulus offset (Figure 3). In the hippocampus, 6 out of the 19 neurons with significant encoding responses had altered activity during the second of stimulus presentation, 7 showed responses that began during stimulus presentation and continued during the first second of the delay interval, and 6 neurons responded only in the delay period. Of the 29 hippocampal neurons with significant responses during word pair recall, 10 responded during the stimulus, 12 in the stimulus and delay periods, and 7 only in the delay. In the entorhinal cortex, the 15 significant encoding responses were during the stimulus (6), stimulus and delay (3), or delay (6) intervals. During retrieval, the 21 significant responses were in the stimulus (5), stimulus and delay (6), or delay (10) periods. A majority of the neurons in the hippocampus and entorhinal cortex

Table 1. Summary of Significant Neuronal Response Increases (↑) or Decreases (↓) during the Encoding and Retrieval of Word Pairs

	Encoding Only	Both Encoding and Retrieval	Retrieval Only	Total Responding
Hippocampus (66 neurons)	5 2↑ 3↓	14 4↑ 8↓ 2↑↓	15 7↑ 8↓	34
Entorhinal cortex (43 neurons)	4 3↑ 1↓	11 7↑ 2↓ 2↑↓	10 8↑ 2↓	25
Amygdala (19 neurons)	3 1↑ 2↓	4 2↑ 1↓ 1↑↓	3 2↑ 1↓	10
Total responding (percentage of recorded neurons)	12 (9.4)	29 (23)	28 (22)	69 (54)

Cell counts based on changes in firing rate in stimulus or delay periods compared to baseline (*t* tests, $p < 0.05$).

(↑) Neuronal response increases, (↓) decreases, (↑↓) both increases and decreases in activity compared to baseline.

Table 2. Summary of Medial Temporal Lobe Neuronal Response Selectivity during Paired Associate Learning

128 Neurons	Hippocampus (66)	Entorhinal Cortex (43)	Amygdala (19)
Number (percentage) selective for:			
Task Phase (Encoding, Retrieval)	14 (21.2%) ^a	11 (25.6%) ^a	2 (10.5%)
Recall Success (Remembered, Forgotten pairs)	9 (13.6%) ^a	10 (23.3%) ^a	2 (10.5%)
Pair Type (Related, Unrelated pairs)	8 (12.1%)	7 (16.3%)	1 (5.3%)

Cell counts based on ANOVA ($p < 0.05$).

^aSignificance by goodness of fit chi-square test (see Experimental Procedures).

that had significantly altered firing rates during the presentation of word pairs at encoding also showed significant changes in activity during the presentation of the cue in recall trials (68%). In addition, about half of the hippocampal and entorhinal neurons that responded in the delay interval during encoding trials also responded during the delay for retrieval trials (55%). The breakdown of significant responses during stimulus, stimulus and delay, or delay intervals in the amygdala was (4, 2, 1) for encoding and (2, 3, 2) for retrieval.

The direction of neuronal responses with respect to prestimulus baseline was different in the hippocampus compared to entorhinal cortex (see Table 1). During encoding, the firing rates of most of the 19 responding neurons in the hippocampus decreased to below prestimulus baseline upon stimulus presentation. Eleven neurons had decreased activity (mean activity of 2.83 spikes/s, SD 4.39, representing an average decrease of 36% from baseline), six had increased activity (mean 4.27 spikes/s, SD 5.25, representing an average increase of 67% from baseline), and two had both increases and decreases in activity (see Figure 3 for examples). In the entorhinal cortex, the majority of the 15 neurons responding during encoding had increased firing rates compared to prestimulus baseline. Ten neurons had increased activity (mean 7.51 spikes/s, SD 9.04, representing a mean change of 23% from baseline) and three had decreased activity (mean 7.75 spikes/s, SD 9.71, representing a mean change of 17% from baseline). This difference in the number of response increases and decreases between the hippocampus and entorhinal cortex was significant ($\chi_1^2 = 5.16$, $p < 0.05$). There were also differences between the two regions during retrieval, namely 11 neurons with increased activity (mean 3.89 spikes/s, SD 4.05, 73% average increase) and 16 with decreased activity (mean 2.12 spikes/s, SD 2.53, 47% average decrease) in the hippocampus, and 15 neurons with increased activity (mean 6.5 spikes/s, SD 7.84, 35% average increase) and 4 with decreased activity (mean 6.31 spikes/s, SD 8.96, 22% average decrease) in the entorhinal cortex ($\chi_1^2 = 6.63$, $p < 0.01$).

Selective Responses of MTL Neurons to the Encoding and Retrieval Phases of Paired Associate Learning

To further explore the functional correlates of MTL neuronal activity during paired associate learning, we conducted an overall analysis of variance (ANOVA) of neuronal firing rates using Task Phase (encoding, retrieval), Recall Success (remembered, forgotten pairs), and Pair Type (related, unrelated pairs) as factors (see Experi-

mental Procedures). Selective MTL neuronal responses are shown in Table 2.

Neurons in each of the three MTL regions displayed selective responses for either the encoding or retrieval phase of paired associate learning, shown by a main effect of Task Phase ($p < 0.05$, Table 2). We applied a goodness of fit chi-square test to evaluate whether the total number of neurons with a selective response for Task Phase was greater than that expected by chance (see Experimental Procedures). There were a significant number of hippocampal (21%) and entorhinal (26%), but not amygdala (11%) neurons with Task Phase-selective responses (Table 2; HC: $\chi_4^2 = 88.18$, $p < 10^{-6}$; EC: $\chi_4^2 = 95.87$, $p < 10^{-6}$; A: $\chi_4^2 = 2.27$, $p < 0.685$). For example, the right hippocampal neuron in Figure 3A had a greater increase in activity during stimulus presentation in the retrieval than encoding phase. A left hippocampal neuron (Figure 3B) showed larger and more sustained decreases in firing rate for retrieval than encoding trials. Also, a right entorhinal cortex neuron (Figure 3C) showed increased activity after stimulus offset only during retrieval trials.

MTL Neuronal Activity Correlates with Successful Memory for Word Pairs

Such Task Phase-selective responses suggest MTL neuronal participation in word pair encoding and retrieval. However, neurons that selectively respond during encoding are not necessarily engaged in encoding-related memory processes. Other differences between encoding and retrieval trials, such as the presentation of two words in encoding versus one in retrieval, or preparation for a verbal response in retrieval, might underlie their responses. To examine further the involvement of MTL neurons in memory processes, we looked at the relationship of neuronal activity to the patient's success in performing the paired associate memory task.

Overall, patients remembered 71% of the pairs and forgot 29%. We coded each trial of the paired associate task for successful recall performance. Retrieval trials in which word pairs were remembered were separated from those in which pairs were forgotten. Encoding trials were coded based upon whether the associate of a given pair was successfully recalled on the immediately following retrieval trial. Across all trials, the responses of a significant number of hippocampal (14%) and entorhinal cortex (23%), but not amygdala (11%), neurons correlated with patients' memory performance, shown by a main effect of Recall Success (Table 2; HC: $\chi_4^2 = 20.20$, $p < 0.0005$; EC: $\chi_4^2 = 13.73$, $p < 0.008$; A: $\chi_4^2 =$

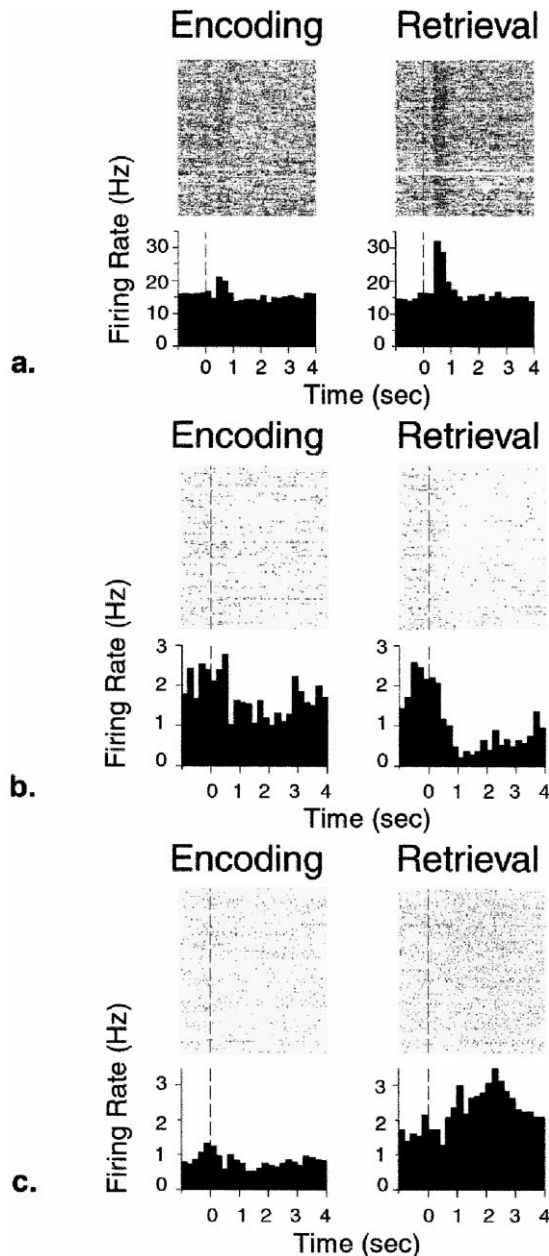


Figure 3. MTL Neuronal Responses during Encoding and Retrieval of Word Pairs

Perievent rasters and histograms of firing rates during encoding and retrieval. Dashed line marks stimulus onset at time 0, offset is at 1 s (x axis). Raster rows represent single trials, and each dot an action potential.

(A) Right hippocampal neuron (recorded from electrode in Figure 1A) selective for Task Phase (Table 2, $p < 0.002$, $F = 8.8$). Note that increases in activity during stimulus presentation are greater for retrieval ($p < 0.001$) than encoding ($p < 0.017$) trials (t tests).

(B) Left hippocampal neuron selective for Task Phase (Table 2, $p < 0.001$, $F = 10.48$). Note that decreases in activity during the stimulus (t1) and delay (t2) intervals are greater for retrieval (t1, $p < 0.013$; t2, $p < 0.000$) than encoding (t2, $p < 0.013$) trials (t tests).

(C) Right entorhinal cortex neuron selective for Task Phase (Table 2, $p < 0.000$, $F = 13.0$) showing increases in activity after stimulus offset only during retrieval (t2, $p < 0.000$).

2.27, $p < 0.685$). Thus, neuronal activity in the hippocampus and entorhinal cortex discriminated whether or not patients remembered paired associates.

Responses of Hippocampal Neurons Predict Subsequent Memory for Word Pairs

Although the above analysis shows that neuronal activity in the hippocampus and entorhinal cortex was correlated with recall success, it does not reveal at what stage of the memory process this activity occurs. We therefore performed separate analyses for the encoding and retrieval phases of the paired associate task. We first evaluated whether neuronal activity at the time of word pair encoding was predictive of the patients' subsequent recall performance. Encoding trials were analyzed separately for pairs that were later remembered and those later forgotten. An ANOVA of encoding trials alone revealed that hippocampal neuronal activity at encoding predicted whether word pairs were later remembered. The responses of a significant number of hippocampal neurons (13, 20%) discriminated subsequently remembered from forgotten pairs (main effect of Recall Success, $\chi^2 = 15.36$, $p < 0.004$). However, the number of entorhinal cortex neurons (6, 14%) whose activity at encoding predicted patients' later memory for word pairs was not greater than what might be expected by chance ($\chi^2 = 6.88$, $p < 0.142$). Thus, the firing rates of hippocampal neurons during encoding predicted whether or not word pairs would later be remembered. These subsequent memory effects were found in 7 out of the 11 subjects in which neurons were recorded in the hippocampus.

During the encoding of subsequently remembered pairs, 8 of the 13 hippocampal neurons whose activity predicted later memory for pairs had increased firing rates, and 5 decreased firing rates with respect to prestimulus baseline. Interestingly, hippocampal response increases were larger during the encoding of subsequently forgotten than remembered pairs for 7 out of the 8 response increases. For example, the hippocampal neuron in Figure 4 showed smaller increases in activity during the encoding of word pairs which were later remembered than during the encoding of pairs which were later forgotten ($F = 8.3$; $p < 0.005$). Also of note is that 3 out of the 5 hippocampal neurons that had decreased activity during the encoding of subsequently remembered pairs displayed response increases while encoding the pairs later forgotten.

Responses of Entorhinal Cortex Neurons during Retrieval Reflect Successful Recall of Word Pairs

When a separate ANOVA was carried out for neuronal activity during retrieval, the responses of a significant number of entorhinal cortex neurons (5, 12%), but not hippocampal neurons, reflected whether word pairs were successfully recalled (EC: $\chi^2 = 19.82$, $p < 0.00054$). Entorhinal neurons whose responses correlated with accurate retrieval were found in 4 out of the 7 subjects in which neurons were recorded in that area. For example, the entorhinal cortex neuron in Figure 5A displayed larger increases in firing rate in the delay interval during the retrieval of paired associates that were successfully

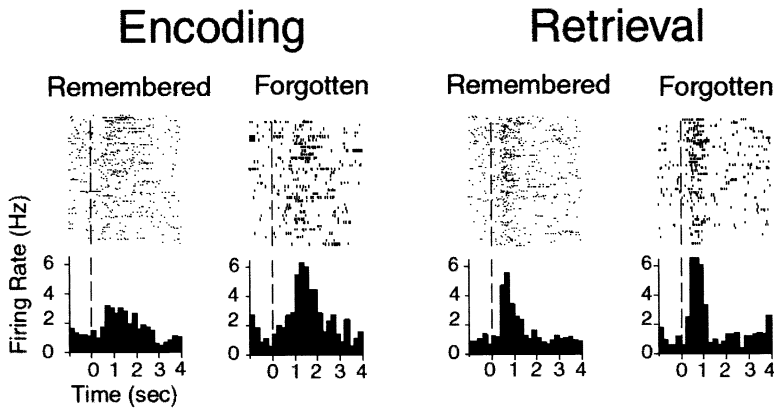


Figure 4. Hippocampal Neuronal Responses to Remembered and Forgotten Word Pairs

Perievent rasters and histograms of firing rates during the encoding and retrieval of remembered or forgotten word pairs. Dashed line marks stimulus onset at time 0, offset is at 1 s (x axis). Raster rows represent single trials, and each dot an action potential.

Right hippocampal neuron selective for Recall Success in the Encoding ANOVA ($p < 0.005$, $F = 8.3$), with smaller increases in activity during the encoding of remembered (t_1 , $p < 0.007$; t_2 , $p < 0.002$, t tests) than forgotten (t_2 , $p < 0.000$) pairs. During retrieval, this neuron had increased activity during the stimulus and delay intervals for remembered pairs (t_1 , $p < 0.000$; t_2 , $p < 0.003$), but only during stimulus presentation for forgotten pairs (t_1 ,

$p < 0.000$). This neuron was also selective for Recall Success in the Retrieval ANOVA ($p < 0.024$, $F = 5.2$) and had a significant interaction between Recall Success and Task Phase (Table 2, $p < 0.000$, $F = 13.7$).

compared to unsuccessfully recalled ($F = 10.1$; $p < 0.002$). However, neuronal activity associated with recall success was not always excitatory (i.e., increased firing rate). During retrieval, the hippocampal neuron in Figure 5B displayed decreases in firing rate below prestimulus baseline in response to word stimuli. These decreases were more pronounced during the recall of remembered pairs compared to forgotten pairs ($F = 4.8$; $p < 0.03$). Although the activity of this neuron during retrieval was correlated with recall success, the number of hippocampal neurons showing this phenomenon (12, 18%) was not greater than what might have been expected by chance ($\chi_4^2 = 4.3$, $p < 0.368$). Of note is that 4 of the 13 hippocampal neurons whose activity at encoding predicted later memory for word pairs also responded during retrieval with activity that was correlated with recall success.

Discussion

Responses of Single Neurons in the Hippocampus Predict Subsequent Memory for Word Pairs

What is the neuronal signature of human declarative memory formation? In this study we were able to address this question using a rare opportunity to record the activity of single neurons in the human MTL. During the initial encoding of word pairs, we found that the activity of hippocampal neurons predicted whether or not the pairs were later remembered or forgotten. This observation provides support at the single neuron level for the critical role of the human hippocampus in declarative memory formation and retrieval (Squire and Zola-Morgan, 1991; Eichenbaum et al., 1994).

Recent functional MRI studies report that focal activation in the parahippocampal (Brewer et al., 1998; Wagner et al., 1998) or posterior hippocampal (Fernández et al., 1998; Kirchoff et al., 2000) regions during encoding predicts success on subsequent retrieval of verbal or pictorial material. Since we did not record from posterior parahippocampal cortex, our results do not rule out the involvement of neurons in that region. In contrast to the fMRI data, we did find anterior hippocampal neuronal activity at encoding predictive of subsequent retrieval success. This discrepancy can be explained on several

grounds. First, fMRI provides an indirect, hemodynamic measure of neuronal activity and thus may not reflect all of the changes in firing that are clearly observed during direct electrophysiological recording. For instance, we found neurons with both increased and decreased discharge rates with respect to the prestimulus baseline during encoding and retrieval. There were also neurons that showed a lower discharge rate during successful encoding compared to unsuccessful encoding (Figure 4). Also, fMRI in the anterior MTL may be affected by susceptibility artifacts, which results in signal loss. In addition, there were important task differences between this study and previous neuroimaging studies reporting subsequent memory effects. In the paired associates task, we asked patients to repeatedly encode and recall the same word pairs in seven encoding sessions alternated with seven retrieval sessions. In neuroimaging studies, subjects were presented with items in a single encoding session and later tested on their recognition memory for those items in a single retrieval session. Finally, it is conceivable that the paired associate task used in the present study engages the hippocampus more than recognition tasks, reflecting a particular role of the hippocampus in encoding the relations between items or between an item and its context (Eichenbaum et al., 1994; Vargha-Khadem, et al., 1997; Squire and Zola-Morgan, 1998; Aggleton and Brown, 1999).

It is important to point out that the microelectrodes in this study were fixed and could not be moved in search of optimal responses. Perhaps for this reason the neuronal responses reported here in humans are smaller in magnitude (usually 2–10 Hz) than task- and stimulus-selective responses recorded in animals. However, the low mean firing rates of MTL neurons we recorded are consistent with animal studies. Perhaps because of the fixed electrode locations that were not biased toward sites with selective increases in firing rate, we were also able to observe many task-selective decreases in neuronal activity. Both increases and decreases appear to participate in the neuronal networks contributing to paired associate performance in these patients.

Our results at the single neuron level also support event-related potential (ERP) findings in which ERPs

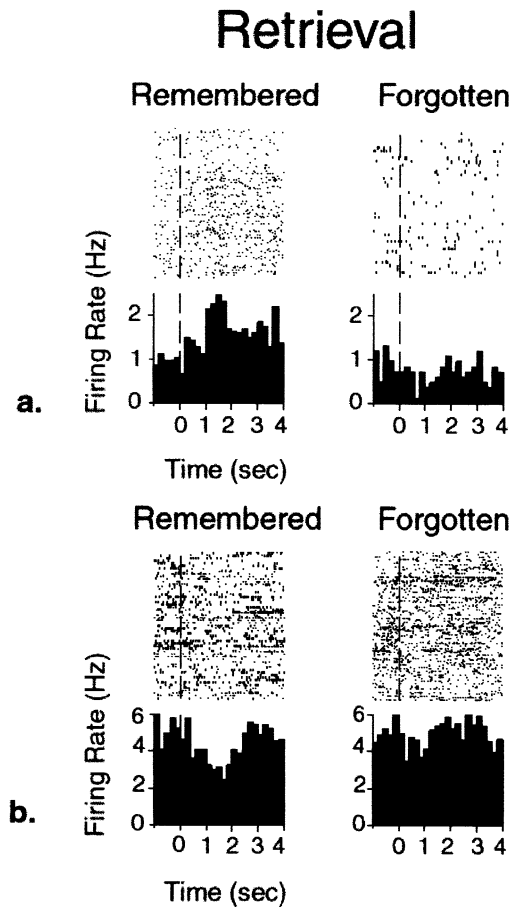


Figure 5. Hippocampal and Entorhinal Neuronal Responses during Paired Associate Retrieval

Perievent rasters and histograms of firing rates during the retrieval of remembered or forgotten word pairs. Dashed line marks stimulus onset at time 0, offset is at 1 s (x axis). Raster rows represent single trials and each dot an action potential.

(A) Left entorhinal cortex neuron with increased activity in the delay interval (t_2) during the retrieval (t_2 , $p < 0.000$) of remembered but not forgotten pairs (t tests), showing a selective response for Recall Success in the Retrieval ANOVA ($p < 0.002$, $F = 10.1$).

(B) Left hippocampal neuron with decreased activity during retrieval more for remembered than forgotten pairs (t_2 , $p < 0.001$) (t tests), showing a selective response for Recall Success in the Retrieval ANOVA ($p < 0.030$, $F = 4.8$).

recorded in the human hippocampus during word list encoding distinguished subsequently recalled from forgotten words (Fernández et al., 1999b). Single neurons in the hippocampus, such as those reported in our study, may participate in the generation of these ERPs.

Neuronal Activity in Entorhinal Cortex Reflects Successful Recall of Word Pairs

During retrieval, the activity of entorhinal cortex neurons reflected whether or not the patients were able to successfully recall paired associates. This observation supports the results of a previous PET study that found increases in regional cerebral blood flow in the left entorhinal cortex while subjects recalled fractal pattern paired associates (Klingberg et al., 1994). An important

role for the entorhinal cortex in retrieval memory processes is not surprising given its unique anatomical connections. Entorhinal cortex receives convergent input through adjacent perirhinal and parahippocampal cortices from widely distributed neocortical regions (Van Hoesen and Pandya, 1975a; Van Hoesen et al., 1975; Insausti et al., 1987) believed to be the substrate for long-term memory (Mishkin, 1982; Squire, 1987). It then provides the major source of input to the hippocampus (Van Hoesen and Pandya, 1975b). Hippocampal output returns to entorhinal cortex, whose divergent, reciprocal connections with perirhinal and parahippocampal cortices (Suzuki and Amaral, 1994) then project back to those same widely distributed, putative long-term memory networks in the neocortex.

Within the MTL, hippocampal, parahippocampal, and entorhinal regions are considered more critical for declarative memory processes than the amygdala (Zola-Morgan et al., 1989a, 1989b; Zola-Morgan and Squire, 1989). Whereas amygdala neurons responded to the word stimuli during encoding and during retrieval, the ANOVA across all trials did not show that these responses were related to the patients' verbal memory performance. A specialized role has been proposed for the amygdala in modulating declarative memory for emotionally arousing events (Cahill and McGaugh, 1990, 1998; McGaugh et al., 1996), but our paradigm was not directed at testing this hypothesis. Furthermore, it may be premature to draw conclusions about amygdala contributions to paired associate learning based on our study, since the sample of amygdala neurons was small.

MTL Neurons in both Hemispheres Contribute to Verbal Paired Associate Learning

Although previous lesion (Milner, 1958) and neuroimaging (Martin et al., 1997; Kelley et al., 1998) evidence suggests a specialized role for left MTL areas in verbal memory tasks, we did not find strong lateralization differences at the level of single neurons. MTL neurons that had significantly altered activity during paired associate learning were recorded from both the language-dominant (48%) and nondominant (52%) hemispheres. Since patients were able to use imagery as well as verbal codes (Paivio and Csapo, 1973) to learn and remember paired associates, our data do not conflict with the concept of hemispheric specialization for verbal and non-verbal memory processing. Entorhinal cortex neurons whose activity was correlated with accurate retrieval were found in both the language-dominant (3) and nondominant (2) hemispheres. Although there were a greater number of hippocampal neurons whose activity predicted subsequent memory for word pairs recorded from the language-dominant (69%) than nondominant (31%) hemispheres, the total number of neurons was small (13), and the differences were not significant.

MTL Neurons Participate in both Encoding- and Retrieval-Related Memory Processes

Suggestions that anterior or posterior MTL regions (Stern et al., 1996; Lepage et al., 1998; Schacter and Wagner, 1999) or different MTL structures (Gabrieli et al., 1997; Aggleton and Brown, 1999) are functionally specialized for the memory processes of encoding and

retrieval have recently been put forward. Although in this study we only recorded neurons from anterior MTL regions, there was an interesting difference between the hippocampus and entorhinal cortex. Whereas in the hippocampus neuronal activity during *encoding* predicted patients' later memory for word pairs, in the entorhinal cortex neuronal activity during *retrieval* reflected whether or not the pairs were successfully recalled. Therefore, our data suggest that the hippocampus plays a more critical role in encoding-related memory processes, and the entorhinal cortex in retrieval-related memory processes.

During retrieval, more MTL neurons were engaged compared to encoding, suggesting a subset of neurons that were not active during the encoding of word pairs but were selectively activated during the recall of word pairs. Although it is possible that these neurons responded selectively to single words and not to the same words when they were paired with another stimulus, a more plausible explanation is that the activity of these neurons was related to the recall phenomenon. At the same time, 23% of MTL neurons showed altered activity during both the initial encoding as well as the subsequent retrieval of word pairs. Most of these neurons (83%) responded similarly during the two task phases, i.e., with either increased or decreased firing rates in both phases of the task, although responses at retrieval were often more pronounced than during encoding. In addition, some hippocampal neurons whose activity at encoding predicted later memory for word pairs also responded during retrieval with activity that was correlated with recall success. These data suggest that some of the neurons that contributed to establishing the associations between word pairs at encoding were later "re-activated" as patients retrieved the correct paired associates from memory. Our data therefore support the notion that the neural processes of memory formation and retrieval within the medial temporal lobe are closely related, although the hippocampus may contribute more to encoding and entorhinal cortex more to retrieval.

Experimental Procedures

Subjects

The subjects were 12 epilepsy patients (5 female), mean age 36 (range 15–49), implanted with intracranial depth electrodes in bilateral MTL regions to identify the seizure focus. The electrodes' locations were based exclusively on clinical criteria. Behavioral protocols received Institutional Review Board approval and were conducted with each patient's informed consent.

Electrode Placement

The technique of electrode placement and single-unit recordings in these patients has been described in detail in previous publications (Fried et al., 1997, 1999). Depth electrodes were targeted to MTL structures using MRI and angiographic guidance (Fried et al., 1999). Typically, six electrodes were placed bilaterally in amygdala, hippocampal, and entorhinal regions in each patient. Depending upon the suspected seizure focus areas in each patient, three to four more electrodes were placed in various other locations, including parahippocampal and anterior cingulate gyri, orbitofrontal cortex, and pre-supplementary and supplementary motor cortices. Electrodes contained nine platinum-iridium microwires (40 μm) that protruded about 4 mm into the target tissue. Microwire tips usually spread out into the target tissue in a cone shape with a diameter of less than 4 mm. Probe locations were verified by postimplant MRI (Figure 1A). It should be noted that generalization about normal neuronal

function from recordings in epileptic patients constitutes a potential limitation. However, 80% of the recorded neurons were either contralateral or distant to the area of seizure onset, and we did not observe differences in waveforms or response properties of neurons near the seizure focus.

Paired Associate Task

Paired associate learning involved seven alternating blocks of "encoding" and "retrieval" trials. During encoding, patients were shown 20 word pairs to be remembered; 10 related (e.g., dinner–food) and 10 unrelated (e.g., light–camp) associates. Pairs were presented in random order every 4 s for 1 s each. After a 1–2 min delay period, patients were tested for their memory for the same 20 word pairs. During this retrieval phase, patients were shown the first word of each pair and required to respond verbally with the paired associate after a 4 s delay upon presentation of a recall cue (Figure 2).

Unit Recording

Details of single-unit recording methods were previously published (Fried et al., 1997, 1999). Briefly, extracellular neuronal activity from each microwire was amplified at a gain of 5000 over a bandpass of 0.3 Hz–6 kHz, recorded onto FM tape, then high-pass filtered (300 Hz–5 kHz) for stable triggering of action potentials above background noise (Figure 1B). Digitization (at 20 kHz) of 2 ms of electrophysiological activity surrounding each triggered action potential allowed separation of single units based on action potential amplitude, duration, slope, and other parameters of waveform morphology, using a manual cluster cutting method implemented in Datawave software (Datawave, Denver, CO) (Figure 1C). Neurons whose firing rates were less than 0.1 Hz were not included in the study. Mean firing rates in the amygdala, hippocampus, and entorhinal cortex were 1.77 Hz, 2.9 Hz, and 4.27 Hz, respectively.

Data Analyses

Mean neuronal firing rates were obtained for three 1 s intervals; the second prior to stimulus presentation (baseline, t_0), the second of stimulus presentation (stimulus, t_1), and the second after stimulus offset (delay, t_2) (Figure 2). We evaluated the activity of each neuron using pairwise *t* test comparisons of mean firing rates during the stimulus or delay intervals compared to baseline. Significant changes in neuronal activity during the stimulus or delay intervals were increases or decreases in mean firing rates compared to baseline, evaluated separately for encoding and retrieval trials at $p < 0.05$.

A separate repeated measures ANOVA was carried out for each neuron (across all subjects) of its firing rates during the stimulus and delay intervals corrected for baseline activity. Factors in the ANOVA were Task Phase (encoding, retrieval), Recall Success (remembered, forgotten pairs), Pair Type (related, unrelated), Time (t_1 , t_2), and their interactions (Table 2). We also conducted two separate repeated measures ANOVA for only encoding and only retrieval trials. The factors were Recall Success (remembered, forgotten pairs), Pair Type (related, unrelated), Time (t_1 , t_2), and their interactions. For all ANOVA, neurons were considered to have a selective response to a factor if either the main effect of that factor or its interaction with time was significant at $p < 0.05$.

Although neurons were considered to show selective responses if ANOVA results were significant at the $p < 0.05$ level, many of the neurons recorded were significantly below the $p < 0.01$ level. However, due to the number of neurons and multiple tests, a few such significant results might occur by chance. To evaluate whether more neurons showed selective responses than would be expected by chance, the number of neurons with significant results at each of five levels ($p = 0.05$ – 1.0 , $p = 0.01$ – 0.05 , $p = 0.005$ – 0.01 , $p = 0.001$ – 0.005 , $p < 0.001$) in the ANOVA was compared using a goodness of fit chi-square test with the number that would be predicted by chance (Rolls et al., 1989, 1993). For the test, we took into account that a factor was considered significant if either its main effect or interaction with time was significant. Significance by goodness of fit chi-square indicates that the number of neurons with a selective response to a factor was not merely due to chance.

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