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Responses of neurons in the medial temporal lobe during encoding and recognition of face-scene pairs

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Abstract

Associations between co-occurring stimuli are formed in the medial temporal lobe (MTL). Here, we recorded from 508 single and multi-units in the MTL while participants learned and retrieved associations between unfamiliar faces and unfamiliar scenes. Participant's memories for the face-scene pairs were later tested using cued recall and recognition tests. The results show that neurons in the parahippocampal cortex are most likely to respond with changes from baseline firing to these stimuli during both encoding and recognition, and this region showed the greatest proportion of cells showing differential responses depending on the phase of the task. Furthermore, we found that cells in the parahippocampal cortex that responded during both encoding and recognition were more likely to show decreases from baseline firing than cells that were only recruited during recognition, which were more likely to show increases in firing. Since all stimuli shown during recognition were familiar to the patients, these findings suggest that with familiarity, cell responses become more sharply tuned. No neurons in this region, however, were found to be affected by recombining face/scene pairs. Neurons in other MTL regions, particularly the hippocampus, were sensitive to stimulus configurations. Thus, the results support the idea that neurons in the parahippocampal cortex code for features of stimuli and neurons in the hippocampus are more likely to represent their specific configurations.

Keywords

Episodic memory; Hippocampus; Entorhinal cortex; Epilepsy; Electrophysiology

1. Introduction

To gain a complete understanding of memory representations in the brain, we need to understand the cellular basis of memory, in addition to the relationship between neural activity and memory function at the population level. Neuropsychological (e.g., Scoville and Milner, 1957; Reed and Squire, 1998) and neuroimaging (e.g. Wagner et al., 1998; Nyberg et al., 1996) studies can inform us as to the roles of different brain regions with respect to memory, but the level of resolution using these techniques does not go beyond relatively large ensembles of neurons. Many models of memory, however, make predictions at the

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level of single neurons (e.g. Norman and O'Reilly, 2003). Therefore, data concerning firing patterns of individual neurons are necessary to evaluate the appropriateness of current memory models.

Here, we survey the activity of individual neurons in the medial temporal lobe (MTL) over the course of memory encoding and retrieval. By observing the changes in particular neurons as memories are formed and retrieved, we may be able to infer the mechanisms that support memory processes at the neural circuit level. Previous work has shown that the hippocampus and surrounding cortical areas show changes in neural firing to items that are repeated in a continuous recognition procedure (Viskontas et al., 2006). In the parahippocampal region, many neurons responded to the novel stimuli, with firing returning to baseline for repeated presentations. These findings are consistent with findings of repetition suppression in the medial temporal lobe, and a novelty preference in these neurons. In the hippocampus, many units that did not respond to the initial presentation of a stimulus decreased firing below baseline during repeated presentations. This pattern may indicate that with repetition, activity is inhibited in neurons that do not respond to the stimulus, which may be a mechanism for enhancing the signal-to-noise ratio for recognizing sparsely coded items.

Rutishauser et al. (2006) also found neurons in the hippocampus and the amygdala that decreased firing with repetition, along with another population that increased firing with repetition, consistent with the idea that repetition involves tuning of activity in MTL. Pedreira et al. (2010) examined neurons that were selective for specific stimuli and found that these neurons generally reduce their responses when a preferred stimulus is repeated. Unlike neurons in other MTL regions examined, however, neurons in the parahippocampal cortex that were selective for specific stimuli actually increased activity with repetition. In the Pedreira et al. (2010) study, subjects were not performing an overt memory task, which may have contributed to the results. It is also likely that selective neurons and those neurons that were responsive to a large number of stimuli respond differently to repetition.

Previous recordings of MTL single neuron activity in humans have also shown that firing patterns of hippocampal cells during encoding predict subsequent memory, while firing patterns in the entorhinal cortex during retrieval reflected whether or not items were successfully recalled (Cameron et al., 2001). Furthermore, recordings from the human MTL have demonstrated that individual neurons can be highly selective in terms of the stimuli to which they respond (Quan-Quiroga et al., 2005). Out of a set of 100 visual images across several categories such as faces, animals and landmarks, some cells may show robust responses to only a handful of pictures, sometimes even pertaining to a single conceptual category, such a particular famous person. In addition, the more personally-relevant the stimulus, the more likely it is that selective neurons will be observed (Viskontas et al., 2009).

Selectivity of neuronal responses in humans has been found for stimulus categories such as faces or places (Kreiman et al., 2000), as well as for specific visual features (Fried et al., 1997) and even to individual words and faces (Heit et al., 1988). This selectivity may provide an important clue as to the mechanism by which the brain represents information currently in awareness. In fact, the idea that the MTL represents information using a sparse

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code is one of the basic tenets of most contemporary memory models (Norman and O'Reilly, 2003; Bogacz and Brown, 2003; Meterage et al., 2005).

In animals, sparse coding has also been observed in recordings from the MTL (Jung and McNaughton, 2003; Treves and Rolls, 1992). As mentioned above, neural responses showing increases from baseline firing that are selective to specific concepts (such as a particular famous individual or place) have also been well-documented in the human MTL (Quian-Quiroga et al., 2005) and these selective responses are most likely to be observed when the stimuli are personally-relevant and familiar (Viskontas et al., 2009). Recently, selective neurons that track the formation of associations between unfamiliar faces and places in the human MTL have also been reported (Ison et al., 2015). In this current study, we were interested in characterizing responses that were less selective in terms of individual stimuli but may also be involved in mnemonic processes.

Given that the hippocampus assigns only a very small number of neurons to a given stimulus, how does the MTL use this code to perform the memory processes that it supports? Previously, we have shown that many cells in the hippocampus proper have a tendency to reduce firing when a previously-seen stimulus comes into view, providing one mechanism by which the signal-to-noise ratio may be increased, allowing those few cells that represent that particular stimulus to be heard by downstream cortices (Viskontas et al., 2006). In the present study, we will examine differences in firing of neurons during encoding and recognition of the same stimuli. We hypothesize that different MTL regions may show different patterns of changes across encoding and recognition, with a majority of responsive hippocampal neurons showing a reduction in firing during the recognition phase based on the sparse coding of specific memories. In contrast, recognition may be accompanied by increases in firing in parahippocampal cortex that are associated with a familiarity signal.

While several studies have examined changes in firing patterns during repetition, subjects in these studies were performing tasks that were not highly dependent on the hippocampus. According to several current views, the hippocampus plays a role in associating items in context (Eichenbaum et al., 1994). Patients with selective damage to the hippocampus have particular difficulty with the rapid formation of arbitrary associations between stimuli and the context in which they occur (Yonelinas et al., 2002). It may be that when subjects are forming item in context associations, neural activity even at the single-cell level may reflect these associations. Our task is designed to mimic a real-life situation in which individuals must associate an item with its context. The premise is a situation in which the patient is meeting a new person. Patients are asked to 'remember where they met a particular person' and are shown non-famous faces superimposed on pictures of places. Their ability to remember the face/place conjunction is then assessed using recognition and cued recall tests. Using a similar task, Hannula and Ranganath (2008) demonstrated that hippocampal activity during the presentation of a scene cue was associated with correct memory responses when target and foil faces were presented. Based on the hippocampal dependence of this task, we hypothesize that cells in the hippocampus will be more sensitive to face/place conjunctions than neurons in the parahippocampal cortex given the purported role of the hippocampus in the formation of binding items to context.

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2. Methods

2.1. Patients

Participants were five patients with pharmacologically-resistant epilepsy for whom extensive non-invasive evaluation failed to yield a single epileptogenic focus. All five patients were right-handed and three were male. Each patient participated in the experiment at least two and up to four times, for a total of twelve sessions. For further monitoring, patients were stereotactically-implanted with 6–14 electrodes from a lateral orthogonal approach based on clinical criteria (surgeries were performed by I.F.) for one to two weeks. Patients had a mean age of 26.0 (±8.4, range:17–39) years and a mean education of 13.4 (±1.9, range: 11–16) years. All patients provided informed consent and every session conformed with the guidelines of the Medical Institutional Review Board at UCLA.

2.2. Experimental protocol

2.2.1. Encoding phase—Patients were shown 10 black and white images of a non-famous face from the Stirling Psychological Image Collection (PICS) database (http://pics.psych.stir.ac.uk/) superimposed onto an unfamiliar indoor or outdoor scene (with the exception of one session, in which we used 15 images for a patient with a particularly good memory). Patients were tested 2–4 times, with each session including unique images. Each stimulus was presented for 2 s and 6 times per encoding session (with the exception of one session in which the pairs were presented 8 times each to generate more trials for that particular patient). Patients were told that they were 'meeting these people for the first time', and need to remember where they met each person. They were also asked to judge whether the face was 'indoors' or 'outdoors' by button press. Patients were instructed to make a response only after the stimulus disappeared. The next trial began after the response. The distances between repeated stimuli varied randomly with the constraint that no more than two minutes elapsed between repetitions. The procedure is shown in Fig. 1a–c.

2.2.2. Recall phase—Immediately following the encoding phase, patients were cued with one member of the face-place pair and asked to indicate whether they remembered the paired item by pressing a button. Then, three stimuli were shown and patients were asked to choose the stimulus that matched their memory for the paired item by pressing the appropriate key. Every face and scene served as a cue. This procedure allowed us to estimate recall accuracy. The procedure is shown in Fig. 1b. Responding was self-paced. Each face and scene was repeated three times, in random order, with the constraint that the same stimulus did not occur twice in a row.

2.2.3. Recognition phase—After the recall phase, patients were shown either correctly matched or mismatched pairs (3 repetitions of correctly matched and 30 mismatched pairs, each of which was unique) and asked to indicate which pairs had been seen during the encoding phase via a button press. Responding was self-paced. Presentation order was randomized, with the constraint that the same stimulus did not occur twice in a row. This procedure is shown in Fig. 1c. This recognition phase enabled us to compare unit firing to intact and recombined face-scene pairs.

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2.2.4. Neural recordings—At the tips of each electrode was a set of nine 40-μm platinum-iridium microwires. Anatomical locations of electrodes were verified via post-placement MRI scans and images created by fusing CT scans taken while electrodes were implanted with high resolution MRI scans taken immediately before implantation. Recordings from microwires that were difficult to resolve in terms of location were not included in the analysis. Each patient had microwires in all MTL regions of interest (amygdala, entorhinal cortex, hippocampus, parahippocampal cortex) except for one patient who did not have electrodes in the amygdala.

Signals from each microwire were amplified (gain = 10,000), digitally sampled at 27.8 kHz and bandpass filtered between 1 and 6 kHz (Neuralynx, Tucson, AZ). Using the spike separation algorithm *wave_clus* (Quiroga et al., 2004), we isolated single unit activity during microwire recordings. Single units were defined as waveforms with clear refractory periods, were of high amplitude (>100 microvolts), and had fewer than 1% of spikes occurring at less than 3 msec; waveforms that appeared to be contaminated by more than one cell were labeled 'multi-units'. As an additional check for noise, we plotted the power spectral density (psd) using the times when spikes occurred for that unit; putative cell activity showing significant amounts of 60 Hz power-line activity were excluded from the analysis.

To classify single units as putative interneurons or pyramidal cells, we used the methods outlined in Viskontas et al. (2007). All single units from the four MTL regions were used in a K-means cluster analysis using three parameters: firing rate, burst inter-spike interval ratio (calculated as the proportion of spike intervals <10 ms) and a measure of action potential amplitude, the peak-to-valley ratio. We chose the K-means cluster analysis because we could specify the number of clusters and the algorithm minimizes variance within a cluster, by minimizing the Euclidean distance between each point and the centroid, thereby maximizing the variability between clusters. Before running the analysis, we standardized all of the variables into z-scores. To eliminate skew and to ensure homogeneity of variance (using Levene's test of homogeneity) between the clusters, we transformed the raw data using an inverse transformation for firing rate and a log transformation for the burst interspike interval ratio.

3. Results

3.1. Behavioral results

Patients were able to correctly recall on average 63% (±9%) of the face/place pairs during the cued recall phase. Because of low numbers of each type of recall trial and the fact that recall was often unsuccessful, we do not report electrophysiological data from this phase. During the recognition test, patients performed well above chance (mean hit rate:81%±5%; mean false alarm rate:19%±6%; hits>false alarms, $p<0.01$) with a mean d' of 2.68 (±0.59).

3.2. Distribution of neurons

Twelve sessions from five patients yielded a total of 508 single and multi-units in four regions:136 in the amygdala, 173 in the entorhinal cortex, 111 in the hippocampus and 88 in

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the posterior parahippocampal cortex. The distribution of single and multi-units by region is shown in Table 1.

Approximately half (47%) of these units were recorded from within the epileptogenic zones. The parahippocampal cortex had the largest proportion (70%) while the amygdala had the smallest proportion of units in these zones (36%). Table 2 summarizes these results. Previous analyses that included this data set found no effect of epileptogenic zone on firing rate, burst propensity or action potential duration for single units (Viskontas et al., 2007).

Single units were also previously classified as putative pyramidal cells and interneurons, and the distributions of these cell types by region are shown in Tables 3a and 3b.

3.3. Cell responses

We used a combination of *t*-tests, Kruskal-Wallis tests and ANOVAs to describe the firing patterns of our cells in response to the stimuli. Then, to look for regional differences in the numbers and types of responsive cells, we conducted Chi-square analyses.

3.4. Responsivity during encoding

Our first analysis was designed to describe firing rate changes that occurred in response to the presentation of the encoding stimuli. To this end, we compared the firing of each cell during the 700 msec window starting 300 msec post-stimulus onset (T1) with the 700 msec window occurring 300–1000 msec before stimulus onset (baseline) using paired *t*-tests (2-tailed, $p<0.05$). Table 4 shows the numbers and proportions of responsive units in each region. Among single units, neurons in the parahippocampal cortex were more likely to show significant changes from baseline firing than neurons in any other region ($\chi^2(3)=12.03$, $p<0.01$). Given our stimuli were scenes, the higher degree of responsiveness in the parahippocampal cortex is consistent with findings of increased activity in parahippocampal cortex for place stimuli (Ekstrom et al., 2003).

We were also interested to test whether there were regional differences in terms of the direction of the change in firing from baseline. Overall, when we collapsed across multi and single units and regions, we found that cells had a greater tendency to increase (rather than decrease) firing from baseline than would be expected by chance (binomial test: $z=2.46$, $p<0.01$). However, in the parahippocampal cortex, a similar proportion of neurons increased and decreased firing to the encoding stimuli. Table 5 shows the direction of change in firing rate by indicating the proportion of responsive cells in each region that increased firing from baseline activity. The remaining proportion showed decreases from baseline.

3.5. Encoding: effects of stimulus repetition on firing rate

To investigate whether firing patterns change with repetition during the encoding phase, we subtracted baseline firing rates from each trial for each cell, and conducted a Kruskal-Wallis test that allowed us to distinguish differential firing to different repetitions of the stimuli. We found that only a relatively small proportion of cells showed firing rate differences for different repetitions, once we corrected for baseline changes. When all units were considered together, 7 (5%) in the amygdala, 14 (8%) in the entorhinal cortex, 5 (5%) in the

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hippocampus and 3 (3%) in the parahippocampal cortex showed significant effects of repetition on firing rate at $p<0.05$. This test, however, may be masking an effect of repetition, such that cells that change firing rates from baseline for the second presentation of a stimulus, but return to baseline for subsequent presentations may not show an overall effect of repetition. A second possibility is that cells may show effects of repetition for some stimuli but not others. To investigate both of these possibilities, we collapsed across first, second and third repetitions, and fourth, fifth and sixth, and conducted a 2 (repetition) × 10 (stimulus) ANOVA for each cell. For one patient, who showed good remembering, we increased the number of pairs to 15 for one session. For another patient, who showed relatively poor memory, we included 8 repetitions, instead of 6 for a second session. In this case, we collapsed across the first and last four repetitions. We considered a unit as differentially responsive if it showed a significant main effect of repetition or a significant interaction with stimulus at $p<0.05$. This analysis yielded 34 (13%) of single units, with the largest contributing region being the en-torhinal cortex (38% of these cells), and 26 (10%) of multi-units, with the parahippocampal cortex contributing the most cells (31%). Most (64%) of the cells that showed a main effect of repetition did in fact show the greatest change from baseline in response to the first three repetitions, and most of these (61%) showed a decrease from baseline firing. Results are shown in Tables 6–8.

3.6. Responsivity during recognition

In order to identify cells that change firing rates from baseline in response to stimulus presentations during recognition, we once more compared firing during T1 with firing during baseline using paired *t*-tests with the alpha level set at $p<0.05$. The results of this analysis in terms of regional distributions of responsive cells are shown in Table 9. The parahippocampal cortex was more likely to show responsive cells than the amygdala ($\chi^2(1)=4.5$, $p<0.03$), but none of the other regional comparisons showed statistically-significant differences in responsivity during recognition. Similar to the pattern found during encoding, the parahippocampal cortex was somewhat more responsive during recognition, though this finding was not as robust for encoding, as somewhat fewer parahippocampal cells were responsive during recognition compared with encoding.

We were also interested in the direction of the change from baseline. The proportions of these responsive cells that show increases in firing from baseline are displayed in Table 10. Once again, the firing rates were more likely to increase from baseline than chance would predict: (binomial test: $z=2.84$, $p<0.01$).

3.7. Encoding vs recognition

Given that the same faces and places were shown during encoding and recognition, we were interested in observing to what extent cells differentiated firing patterns during these two phases of the experiment. Over the course of the two phases, each element of the face-scene pair was equally familiar to the patient. The only difference in terms of stimuli between encoding and recognition was the rearrangement of pairs during recognition to create equally familiar lures. To investigate differences in firing between the two phases, we compared the firing patterns directly using paired *t*-tests ($p<0.05$). The regional distributions of these cells are presented in Table 11. Compared to the other regions, cells in the

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parahippocampal region were more likely to respond differentially during the encoding and recognition phases ($\chi^2(1)=4.7$, $p<0.03$). Figs. 2–4 show examples of the firing patterns of cells in the parahippocampal and entorhinal cortices, as well as the hippocampus during encoding and recognition. When we looked at the relative number of spikes during encoding and recognition, we found no significant regional differences in terms of which condition yielded more responses, though this is likely a result of small sample sizes. In the amygdala, 53% of differentially responsive cells showed more spikes during recognition, whereas in the entorhinal and parahippocampal cortices, 40% and 63% did so respectively. In the hippocampus, the majority of responsive cells (67%) showed more spiking during encoding than recognition (Table 12).

We next examined whether neurons that increased or decreased firing during encoding differed in terms of changes in firing during recognition. In the entorhinal cortex, 9 (39%) of the cells that showed increases from baseline firing during encoding continued to increase firing during recognition. The remaining cells were not significantly responsive. Of the cells that showed significant decreases in firing during encoding in the entorhinal cortex, 3 (26%) showed responsivity during recognition, all of which continued to show decreases from baseline (Table 13).

This sharpening of representations was even more pronounced in the parahippocampal cortex. Of the 32 cells in the parahippocampal cortex that showed changes from baseline firing during encoding, 19 (60%) did not respond significantly to stimuli during recognition. Furthermore, of the 16 cells that showed increases in firing during encoding, only 4 (25%) continued to show increased firing to stimuli during recognition. Of the 16 cells that showed decreases from baseline during encoding, however, 9 (56%) showed significant responses during recognition, 8 (89%) of which continued to show decreases, while the remaining cell showed an increase from baseline (see Figs. 2 and 3 for examples). An additional 10 (18%) cells that showed no change from baseline during encoding were recruited during recognition, 9 (90%) of which showed increases in firing. This difference in the direction of firing of cells that were responsive during both encoding and recognition, and those that were only recruited during recognition is significant: ($\chi^2(1)=8.01$, $p<0.01$). That is, cells in the parahippocampal that were responsive during both encoding and recognition were more likely to show decreases from baseline firing, while those that were recognition-selective were more likely to show increases in firing from baseline in response to the stimulus. We did not observe the same pattern in the hippocampus, by contrast.

In the hippocampus, of the 23 cells that showed responsivity during encoding, 11 (48%) showed responsivity during recognition, 7 (64%) of which increased firing from baseline. An additional 11 cells were recruited during recognition, 6 (55%) of which showed increases from baseline, with the remaining 5 (45%) showing decreases (Table 14).

In the amygdala, only 3 (13%) of the 23 responsive cells during encoding showed similar responses during recognition. This difference in the fate of encoding-responsive cells between those in the amygdala and those in other MTL regions is significant, with cells in the amygdala being less likely to show responsivity during both encoding and recognition:

($\chi^2(1)=6.21$, $p<0.01$). An additional 17 cells were recruited during recognition, the majority of which (11 cells or 65%) showed increases in firing (Table 15).

These results are shown in Table 13.

3.8. Recognition: old vs. recombined pairs

In order to investigate whether MTL cells differentiate between correctly identified old pairs (hits) and correctly-identified recombined pairs (correct rejections) we compared firing during these two trial types using paired *t*-tests for T1. Overall, we found few cells that differentiated between these trial types (18 cells total: 5 in the amygdala (4%), 6 in entorhinal cortex (4%), 7 in the hippocampus (6%) and none in the parahippocampal cortex). These differentiating cells were approximately equally likely to show greater firing rates for hits as for correct rejections. We did not have enough miss and or false alarm trials to investigate differences in firing for correct and incorrect recognition. Fig. 5 shows a sparsely-firing hippocampal cell that fired selectively for correct rejections.

4. Discussion

This study was designed to characterize the firing patterns of individual neurons in the human MTL during declarative memory processes. Although the total number of neurons of each response type were fairly low, some descriptive patterns emerged suggesting differences in engagement of MTL regions. Three main findings are reported: 1) during the encoding of face-scene associations, cells in the parahippocampal cortex were most likely to show non-selective increases from baseline firing, 2) Cells in the parahippocampal cortex were more likely to respond differentially depending on whether stimuli were being encoded or recognized, and 3) neurons were present in MTL that were sensitive to the specific configuration of faces and scenes, but none of these cells was present in the parahippocampal cortex. The implications of each of these findings with respect to current memory models are discussed in turn.

One of the limitations in our study is the fact that we report data from multiple recording sessions in the same patients. To accommodate multiple sessions, we created new stimuli for each run with the same patient. Because more than 48 h elapsed between sessions, we cannot claim that we are recording from the same cells across sessions. Nor, however, can we be fully confident that the cells were entirely independent from one session to the next in a given patient. Furthermore, as in an earlier paper (Viskontas et al., 2007), we found that our putative pyramidal cells were non-bursting.

The stimuli used in our task are visually complex and demand a substantial amount of perceptual processing to be differentiated from one another. Therefore, it is not surprising that cells in the parahippocampal cortex, a region that receives projections from unimodal and polymodal sensory association areas, respond by changing their firing rates to the presentation of these stimuli. In fact, given that none of the cells that we recorded from in this region differentiated between matched and mismatched face-scene pairings, it is likely that the cells respond to specific stimulus features, rather than to the conjunction of elements. Instead, this conjunction of elements is more likely represented in the

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hippocampus, as predicted by most current memory models (Marr, 1971; Hasselmo and McClelland, 1999; Norman and O'Reilly, 2003; Ranganath, 2010), and as seen by the larger proportion (6%) of cells differentiating correct and incorrect pairings of familiar elements during recognition.

In contrast, we did not find any neurons in the parahippocampal cortex that were sensitive to mis-pairing even though there were a large number of cells that were responsive to the stimuli. These findings suggest that hippocampal neurons may be specifically recruited to encode item-in-context associations. The authors note that although this pattern was observed most in the hippocampus relative to other regions, it was a relatively small proportion of hippocampal neurons that selectively responded in this manner.

A smaller proportion of cells showed changes from baseline firing during encoding in the hippocampus than in the parahippocampal cortex, as predicted by the widely accepted notion of sparse coding (Marr, 1971; Rolls, 1996; Norman and O'Reilly, 2003). Most (74%) of these hippocampal cells showed increases in firing to stimuli. Of these cells, 41% continued to respond in the same way during recognition while 67% of the cells that showed a decrease in firing during encoding continued to do so during recognition. In total, 35% of cells across all regions showed the same type of response during encoding and recognition. Across all MTL regions, an additional 58 cells were recruited during recognition, 31% of which showed decreases in firing. But in the hippocampus, where 11 of these cells were located, the proportion of decreasing cells was 45% (5 cells), whereas all but one (90%) of the cells in the parahippocampal cortex that were recruited during recognition showed increases in firing.

This relatively large prevalence of firing reductions during recognition is consistent with findings from a previous study of responses human MTL neurons during encoding and recognition (Fried et al., 2002). The tendency for hippocampal cells to show reduced firing to previously-seen stimuli has been found even on the second presentation of a stimulus (Viskontas et al., 2006). This tendency for reductions in firing may be the result of an inhibitory mechanism by which the hippocampus is able to increase the signal-to-noise ratio, effectively enabling sparse coding. Electro-physiological studies of associative learning in the macaque also show that a substantial number of hippocampal neurons show reductions in firing during successful memory retrieval (Suzuki, 2007).

According to a recent instantiation of the Complementary Learning Systems (CLS) model of MTL memory processes, competitive self-organization (via Hebbian synaptic plasticity and competitive inhibition) sharpens representations of information in the entorhinal and parahippocampal cortices over repeated exposures (Norman and O'Reilly, 2003). In the parahippocampal cortex, we found that cells that show an increase in firing during encoding were likely to show no responsivity, or a decrease in firing to the same stimuli during recognition. Interestingly parahippocampal neurons that showed decreases in firing to stimuli during encoding were more likely to be responsive during recognition than neurons that increased firing during encoding suggesting that neural inhibition may play a role in memory encoding.

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The plasticity in firing rate changes reported here can be interpreted using the CLS framework if one considers that in general, the elements of stimuli seen during recognition are more familiar than stimuli seen during encoding. Cells that show increased firing during encoding are likely responding to inputs from sensory regions. After sufficient repetitions, sparser representations are created as only about 25% of these cells show excitatory responses during recognition. In this way, only a small number of cells 'win' the competition and continue to show increased firing. The 'losing' cells, those that failed to show increased firing during recognition, are then available for other representations (Norman and O'Reilly, 2003). Strikingly, more of the cells that reduced their firing during encoding also showed changes in firing during recognition. This decreased firing may represent an inhibitory process used by the parahippocampal cortex to create overlapping representations, thereby integrating frequently-encountered items into the permanent memory store. The specific mechanisms by which the cortex supports familiarity-based memory processes have yet to be fully understood and these findings suggest that inhibitory processes during encoding should be incorporated into memory models.

Our results also complement findings from a recent study by Ison et al. (2015) in which the authors used a similar memory paradigm, pairing unfamiliar faces and locations during encoding and then testing patients' recognition of the associations. Their analysis focused on cells that showed highly-selective increases from baseline firing to individual items, whereas we provide a more comprehensive description of cells that are responsive in general, with either increases or decreases from baseline across a number of trials with different stimuli. In the context of sparse coding, their results highlight cells that are specific to particular associations, whereas our results provide a picture of how other cells in the MTL might also participate in mnemonic processes, even if they are not highly-selective.

In summary, we have provided a detailed description of firing patterns in human MTL cells during encoding and recognition of face-scene pairs. These findings support several predictions of current memory models, including the concept of sparse coding in the hippocampus and sharper tuning of representations in the surrounding cortices. Furthermore, our data have shown that the frequently ignored mechanism of inhibition may support memory formation and retrieval in both the hippocampus and parahippocampal cortex.

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References

Bogacz R, Brown MW. Comparison of computational models of familiarity discrimination in the perirhinal cortex. Hippocampus. 2003; 13:494–524. [PubMed: 12836918]

Cameron KA, Yashar S, Wilson CL, Fried I. Human hippocampal neurons predict how well word pairs will be remembered. Neuron. 2001; 30:289–298. [PubMed: 11343662]

Eichenbaum H, Otto T, Cohen NJ. Two functional components of the hippocampal memory system. Behav Brain Sci. 1994; 17:449–472. 472–518.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I. Cellular networks underlying human spatial navigation. Nature. 2003; 425(6954):184–188. [PubMed: 12968182]

Fried I, Cameron KA, Yashar S, Fong R, Morrow JW. Inhibitory and excitatory responses of single neurons in the human medial temporal lobe during recognition of faces and objects. Cereb Cortex. 2002; 12:575–584. [PubMed: 12003857]

Fried I, MacDonald KA, Wilson CL. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron. 1997; 18:753–765. [PubMed: 9182800]

Hannula DE, Ranganath C. Medial temporal lobe activity predicts successful relational memory binding. J Neurosci. 2008; 28(1):116–124. [PubMed: 18171929]

Hasselmo ME, McClelland JL. Neural models of memory. Curr Opin Neurobiol. 1999; 2:184–188.

Heit G, Smith ME, Halgren E. Neural encoding of individual words and faces by the human hippocampus and amygdala. Nature. 1988; 333:773–775. [PubMed: 3386719]

Ison MJ, Quiroga RQ, Fried I. Rapid encoding of new memories by individual neurons in the human brain. Neuron. 2015; 87(1):220–230. [PubMed: 26139375]

Jung MW, McNaughton BL. Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus. 2003; 3:165–182.

Kreiman G, Koch C, Fried I. Imagery neurons in the human brain. Nature. 2000; 16:357–361.

Marr D. Simple memory: a theory for archicortex. Philos Trans R Soc Lond. 1971; 262:23–81. [PubMed: 4399412]

Meeter M, Myers CE, Gluck M. Integrating incremental learning and episodic memory models of the hippocampal region. Psychol Rev. 2005; 112:560–585. [PubMed: 16060751]

Nyberg L, McIntosh AR, Cabeza R, Habib R, Houle S, Tulving E. General and specific brain regions involved in encoding and retrieval of events: what, where, and when. Proc Natl Acad Sci. 1996; 93:11280–11285. [PubMed: 8855347]

Norman KA, O'Reilly RC. Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. Psychol Rev. 2003; 110:611–646. [PubMed: 14599236]

Pedreira C, Mormann F, Kraskov A, Cerf M, Fried I, Koch C, Quiroga RQ. Responses of human medial temporal lobe neurons are modulated by stimulus repetition. J Neurophysiol. 2010; 103(1): 97–107. [PubMed: 19864436]

Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I. Invariant visual representation by single neurons in the human brain. Nature. 2005; 435:1102–1107. [PubMed: 15973409]

Quiroga RQ, Nadasdy Z, Ben-Shaul Y. Unsupervised spike detection and sorting with wavelets and superparamagnetic clustering. Neural Comput. 2004; 16:1661–1687. [PubMed: 15228749]

Ranganath C. A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. Hippocampus. 2010; 20(11):1263–1290. [PubMed: 20928833]

Reed JM, Squire LR. Retrograde amnesia for facts and events: findings from four new cases. J Neurosci. 1998; 15:3943–3954.

Rolls ET. A theory of hippocampal function in memory. Hippocampus. 1996; 6:601–620. [PubMed: 9034849]

Rutishauser U, Mamelak AN, Schuman EM. Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. Neuron. 2006; 49:805–813. [PubMed: 16543129]

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry. 1957; 20:11–21. [PubMed: 13406589]

Suzuki WA. Integrating associative learning signals across the brain. Hippocampus. 2007; 17(9):842–850. [PubMed: 17598153]

Treves A, Rolls ET. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus. 1992; 2:189–199. [PubMed: 1308182]

Viskontas IV, Ekstrom AD, Wilson CL, Fried I. Characterizing inter-neuron and pyramidal cells in the human medial temporal lobe in vivo using extracellular recordings. Hippocampus. 2007; 17(1):49–57. [PubMed: 17143903]

Viskontas IV, Knowlton BJ, Steinmetz PN, Fried I. Differences in mnemonic processing by neurons in the human hippocampus and parahippocampal region. J Cognit Neurosci. 2006; 18(10):1654–1662. [PubMed: 17014370]

Viskontas IV, Quiroga RQ, Fried I. Human medial temporal lobe neurons respond preferentially to personally relevant images. Proc Natl Acad Sci. 2009; 106(50):21329–21334. [PubMed: 19955441]

Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science. 1998; 28l:1188–1191.

Yonelinas AP, et al. Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. Nat Neurosci. 2002; 5:1236–1241. [PubMed: 12379865]

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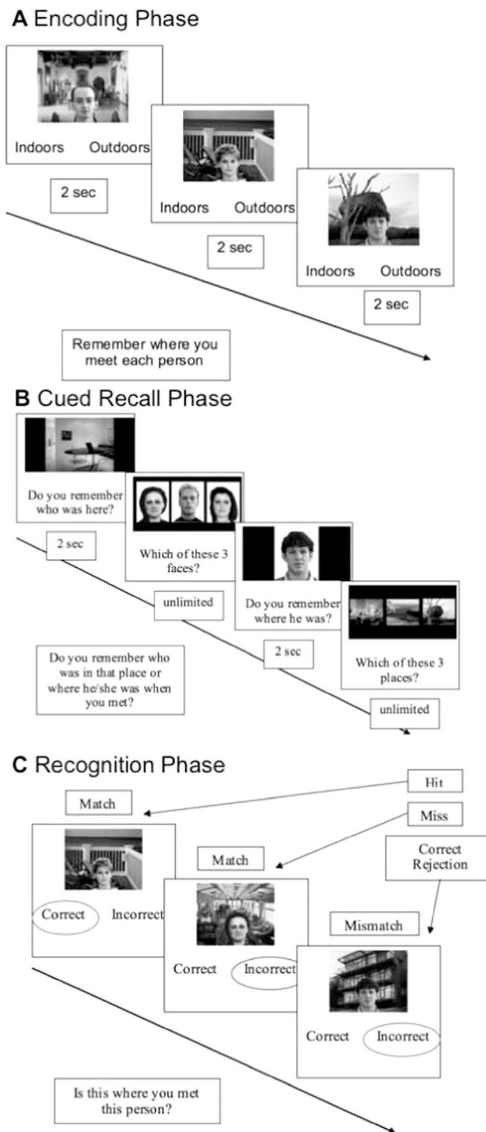

Fig. 1.
Schemata of experimental protocol. A) Encoding phase. Participants are shown faces superimposed on scenes and asked to remember the conjunction of stimuli for later recall. They are also asked to make an indoor/outdoor judgment. B) Recall phase. Participants were shown one element of the pair and asked to recall the second element. After an initial decision, they were forced to choose between three equally-familiar alternatives. C) Recognition phase. Participants are shown elements either grouped properly or mis-matched. Note that mis-matches are composed of equally-familiar elements.

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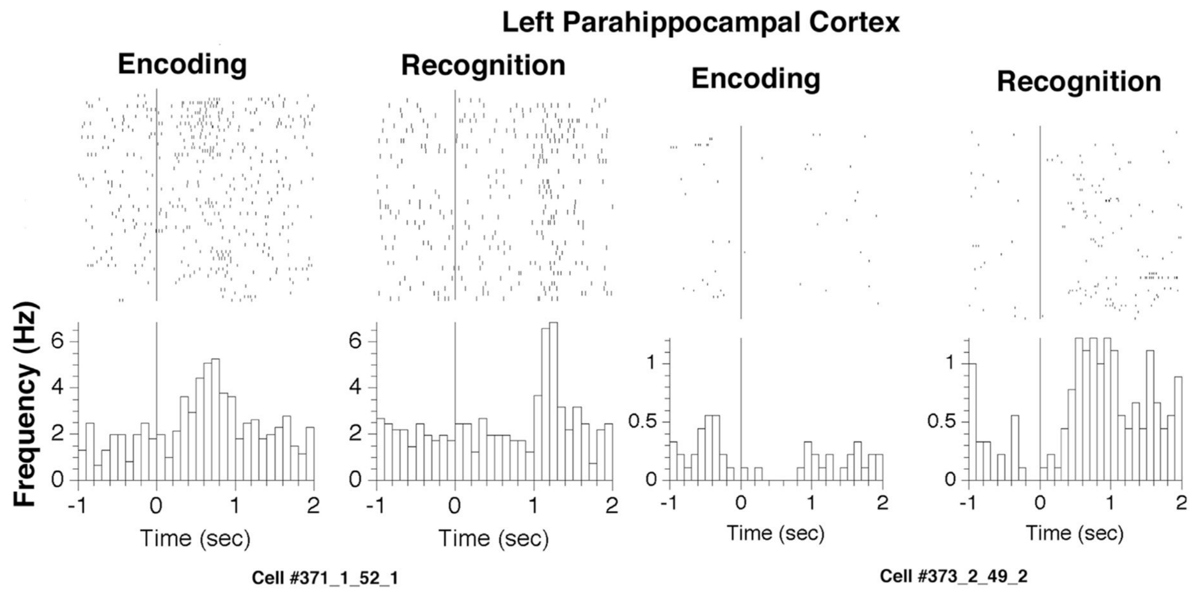

Fig. 2.

Firing patterns in two parahippocampal cortex cells. Cell #371_1_52_1 (mean firing rate=4.47 Hz, burst ISI ratio=0.00) shows increases in firing rates from baseline during both encoding and recognition phases, with recognition phase changes occurring slightly later in time. Cell #373_2_49_2 (mean firing rate=0.39 Hz, burst ISI ratio=0.04) shows decreases from baseline firing during encoding and increases during recognition.

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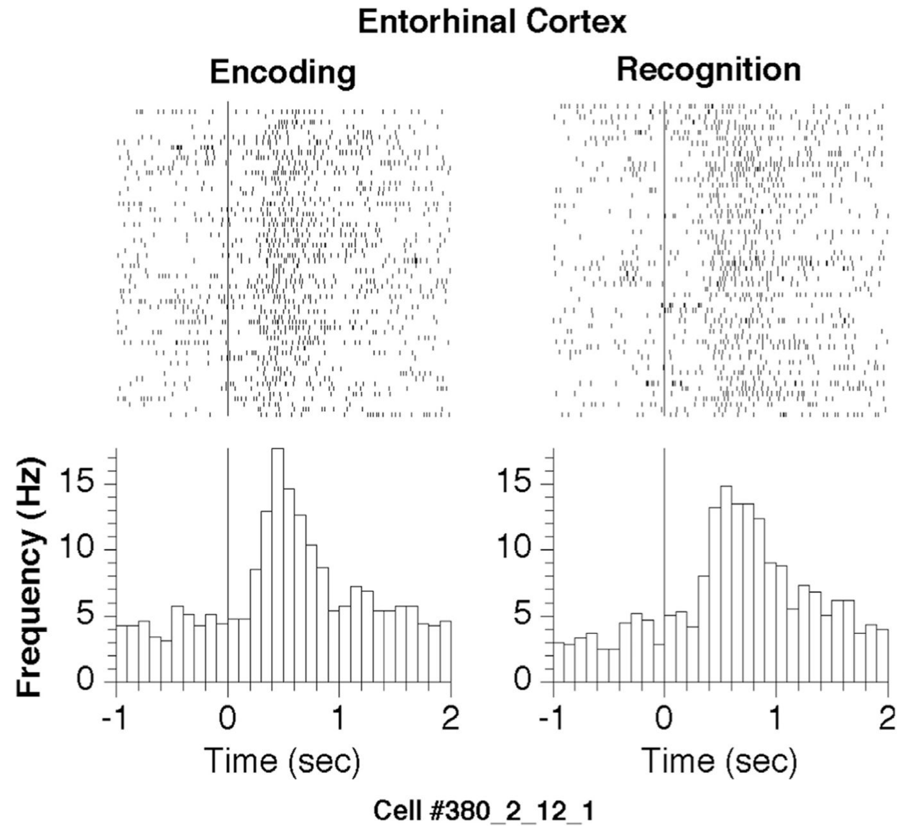

Fig. 3.

Firing patterns of an entorhinal cortex cell. Cell #380_2_12_2 (mean firing rate=6.08 Hz, burst ISI ratio=0.01) shows excitation during both encoding and recognition.

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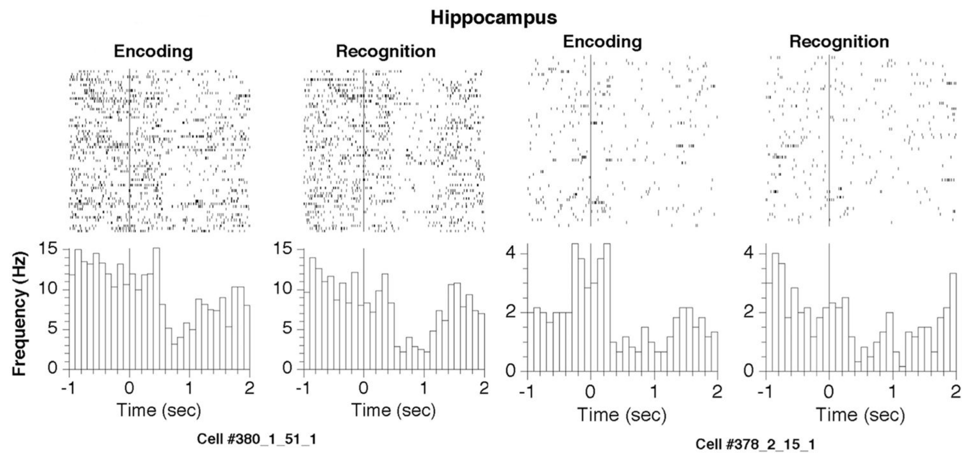

Fig. 4.

Decreases from baseline firing in hippocampal cells. Cell #380_1_51_1, a putative interneuron (mean firing rate=10.3 Hz, burst ISI ratio=0.28), shows more slightly longer decreases in firing during recognition. Cell #378_2_15_1, a putative pyramidal neuron (mean firing rate=1.82 Hz, burst ISI ratio=0.02) shows similar decreases in firing during both encoding and recognition.

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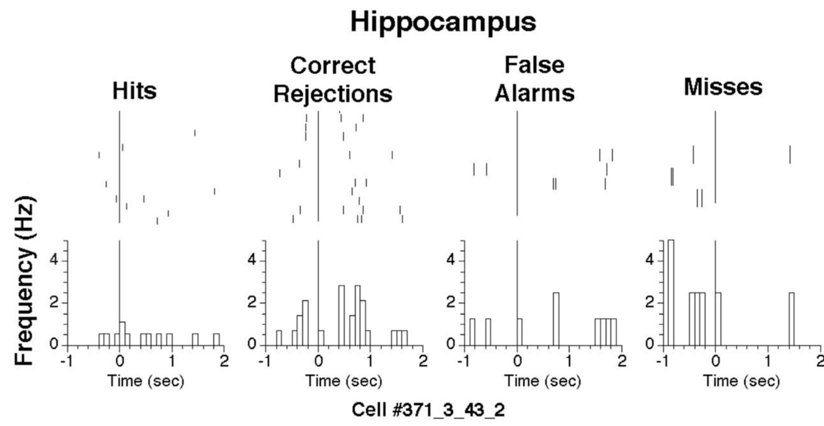

Fig. 5.

Sparsely-firing hippocampal putative pyramidal cell (mean firing rate=0.51 Hz, burst ISI ratio=0.02) showing selective increases in firing on correct rejection trials.

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Table 1

Regional distribution of units.

MTL region	Single units	Multi-units	Total
Amygdala	66	70	136
Entorhinal cortex	91	82	173
Hippocampus	57	54	111
Parahippocampal cortex	44	44	88
All regions	**258**	**250**	**508**

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Table 2

Proportion of units in the epileptogenic zone.

MTL region	Single units	Multi-units	Total
Amygdala	0.38	0.34	0.36
Entorhinal cortex	0.40	0.48	0.43
Hippocampus	0.49	0.48	0.49
Parahippocampal cortex	0.70	0.70	0.70

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Table 3a

Regional distribution of cell types.

MTL region	Interneurons	Pyramidal cells
Amygdala	8	58
Entorhinal cortex	7	84
Hippocampus	5	52
Parahippocampal cortex	4	40

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Table 3b

Mean firing rate, burst inter-spike interval (ISI) ratio and peak-to-valley ratio (spike amplitude measure) for each putative cell type. Standard error in parentheses.

Cell type	Firing rate (Hz)	Burst ISI ratio	Spike amplitude (Peak to valley ratio)
Interneuron	10.8±2.23	0.40±0.07	−4.74±0.22
Pyramidal cell	2.05±0.12	0.05±0.00	−4.25±0.06

Table 4

Regional distributions of responsive units during encoding. Proportions of cells in each region noted in parentheses.

MTL region	Single units	Multi-units	Total
Amygdala	7 (0.11)	16 (0.23)	23 (0.17)
Entorhinal cortex	17 (0.19)	17 (0.20)	34 (0.20)
Hippocampus	9 (0.16)	14 (0.26)	23 (0.21)
Parahippocampal cortex	16 (0.34)	16 (0.36)	32 (0.36)

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Table 5

Proportion of responsive cells showing increased firing from baseline during encoding.

MTL region	
Amygdala	0.61
Entorhinal cortex	0.67
Hippocampus	0.74
Parahippocampal cortex	0.50

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Table 6

Proportion of cells showing a significant effect of repetition or an interaction with stimulus.

MTL region	Single units	Multi-units
Amygdala	0.20	0.10
Entorhinal cortex	0.14	0.06
Hippocampus	0.05	0.11
Parahippocampal cortex	0.11	0.18

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Table 7

Proportion of cells showing changes from baseline for a type of repetition.

MTL region	Single units		Multi-units	
	Rep 1–3	**Rep 4–6**	**Rep 1–3**	**Rep 4–6**
Amygdala	0.08	0.03	0.03	0.03
Entorhinal cortex	0.08	0.02	0.02	0.02
Hippocampus	0.02	0.00	0.04	0.02
Parahippocampal cortex	0.00	0.05	0.09	0.05

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Table 8

Regional distribution of responsive cells in terms of direction of firing change.

MTL region	Repetitions 1–3		Repetitions 4–6	
	Increase	**Decrease**	**Increase**	**Decrease**
Amygdala	0.00	0.64	0.18	0.18
Entorhinal cortex	0.46	0.23	0.15	0.15
Hippocampus	0.25	0.50	0.25	0.00
Parahippocampal cortex	0.13	0.38	0.13	0.38

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Table 9

Regional distribution of cells responsive during recognition. Proportions of cells in each region denoted in parentheses.

MTL region	Single units	Multi units	Total
Amygdala	11 (0.17)	9 (0.13)	20 (0.15)
Entorhinal cortex	15 (0.16)	17 (0.21)	32 (0.18)
Hippocampus	9 (0.16)	13 (0.24)	22 (0.20)
Parahippocampal cortex	7 (0.16)	16 (0.36)	23 (0.26)

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Table 10

Proportion of responsive cells that increase firing from baseline during recognition.

MTL region	Single units	Multi units	Total
Amygdala	0.64	0.67	0.65
Entorhinal cortex	0.73	0.71	0.72
Hippocampus	0.44	0.69	0.59
Parahippocampal cortex	0.57	0.63	0.61

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Table 11

Regional distributions of cells that showed significantly different responses during encoding and recognition. Proportions of cells in each region denoted in parentheses.

MTL region	Single units	Multi units	Total
Amygdala	10 (0.15)	7 (0.10)	17 (0.13)
Entorhinal cortex	7 (0.08)	8 (0.10)	15 (0.09)
Hippocampus	6 (0.11)	6 (0.11)	12 (0.11)
Parahippocampal cortex	10 (0.23)	9 (0.20)	19 (0.22)

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Table 12

Regional distributions of cells showing more or fewer action potentials during encoding and recognition. Proportions of cells differentiating firing between encoding and recognition denoted in parentheses.

MTL region	More spikes encoding	More spikes recognition
Amygdala	9 (0.53)	8 (0.47)
Entorhinal cortex	6 (0.40)	9 (0.60)
Hippocampus	4 (0.33)	8 (0.67)
Parahippocampal cortex	12 (0.63)	7 (0.37)

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Table 13

Regional distributions of cells that were responsive during both encoding and recognition. Proportions of encoding-responsive cells in parentheses.

MTL region	Increased firing	Decreased firing	Total
Amygdala	2 (0.09)	1 (0.04)	3 (0.13)
Entorhinal cortex	9 (0.26)	3 (0.09)	12 (0.35)
Hippocampus	7 (0.30)	4 (0.17)	11 (0.48)
Parahippocampal cortex	4 (0.13)	9 (0.28)	13 (0.41)

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Table 14

Regional distributions of cells that were responsive only during encoding. Proportions of encoding responsive cells in parentheses.

MTL region	Increased firing	Decreased firing	Total
Amygdala	12 (0.52)	8 (0.35)	20 (0.87)
Entorhinal cortex	14 (0.41)	8 (0.24)	22 (0.65)
Hippocampus	10 (0.43)	2 (0.09)	12 (0.52)
Parahippocampal cortex	12 (0.38)	7 (0.22)	19 (0.59)

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Table 15

Regional distributions of cells that were responsive only during recognition. Proportions of recognition-responsive cells in parentheses.

MTL region	Increased firing	Decreased firing	Total
Amygdala	11 (0.65)	6 (0.35)	17 (0.85)
Entorhinal cortex	14 (0.70)	6 (0.30)	20 (0.63)
Hippocampus	6 (0.55)	5 (0.45)	11 (0.50)
Parahippocampal cortex	9 (0.90)	1 (0.10)	10 (0.43)