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Differences in Mnemonic Processing by Neurons in the Human Hippocampus and Parahippocampal Regions

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Abstract

■ Different structures within the medial-temporal lobe likely make distinct contributions to declarative memory. In particular, several current psychological and computational models of memory predict that the hippocampus and parahippocampal regions play different roles in the formation and retrieval of declarative memories [e.g., Norman, K. A., & O'Reilly, R. C. Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning systems approach. *Psychological Review, 110,* 611–646, 2003]. Here, we examined the neuronal firing patterns in these two regions during recognition memory. Recording directly from neurons in humans, we find that cells in both regions respond to novel stimuli with an increase in firing (excitation). However, already on the second presentation of a stimulus, neurons in these regions show very different firing patterns. In the parahippocampal region there is dramatic decrease in the number of cells responding to the stimuli, whereas in the hippocampus there is recruitment of a large subset of neurons showing inhibitory (decrease from baseline firing) responses. These results suggest that inhibition is a mechanism used by cells in the human hippocampus to support sparse coding in mnemonic processing. The findings also provide further evidence for the division of labor in the medial-temporal lobe with respect to declarative memory processes. ■

INTRODUCTION

Overwhelming evidence indicates that acquisition and retrieval of declarative memories depend critically on the medial-temporal lobe (MTL) memory system (Squire & Zola, 1996; Schacter & Tulving, 1994; Squire, 1992). Distinguishing the contributions of subregions of the MTL to the processes underlying human memory remains a central issue in contemporary cognitive neuroscience (Squire, 2004; Schacter & Wagner, 1999). Neurophysiological studies in animals have shown that many neurons in the perirhinal cortex, a subregion of the parahippocampal gyrus, respond more to the first presentation of a visual stimulus than to subsequent presentations (Miller, Li, & Desimone, 1993; Brown, Wilson, & Riches, 1987). These novelty-detecting neurons are much less frequently found in the hippocampus (Brown et al., 1987). Furthermore, neuroimaging studies have also shown different patterns of blood oxygen level-dependent activation during encoding and retrieval of declarative memories in the parahippocampal region[1] and the hippocampus (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998). There is little evidence, however, addressing this question from direct neuronal recordings in humans.

The hippocampus is well-positioned to combine information from many domains and establish novel associations between items because it receives projections from all sensory modalities via adjacent cortical structures. Accordingly, neuroimaging studies have indicated that synaptic activity in the hippocampus and parahippocampal region during learning is associated with subsequent memory (Sperling et al., 2003; Davachi & Wagner, 2002; Strange, Otten, Josephs, Rugg, & Dolan, 2002), and that hippocampal activity accompanies successful retrieval of memories (Stark & Squire, 2000). Single-unit recordings in nonhuman primates have shown that cells in the hippocampus alter their response properties as new information is being learned (Wirth et al., 2003). Furthermore, direct recordings of hippocampal cells in humans have shown that these cells respond to conjunctions of features and that a relatively small subset of neurons in this region shows excitatory responses to particular stimuli during encoding and recognition phases (Fried, Cameron, Yashar, Fong, & Morrow, 2002; Fried, MacDonald, & Wilson, 1997).

Several models based on the anatomical connections of the MTL propose that memories are sparsely represented in the hippocampus, with encoding occurring in

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the inputs to the dentate gyrus from the entorhinal cortex (Norman & O'Reilly, 2003; McClelland, McNaughton, & O'Reilly, 1995; Treves & Rolls, 1994; Marr, 1971). Specifically, few cells in the hippocampus represent any given stimulus so that when the hippocampus is creating associations between items, the likelihood of representations overlapping in the region is minimized. These models further posit that the parahippocampal region serves a different role than the hippocampus, supporting familiarity-based recognition through the ''tuning'' of neuronal responses to repeated stimuli (Norman & O'Reilly, 2003). To assess the validity of these models, information about the behavior of individual neurons during acquisition and retrieval of memories is needed.

Here we used a rare opportunity to record from single neurons in patients with pharmacologically resistant epilepsy implanted with depth electrodes to identify seizure foci for potential surgical removal (Figure 1). By observing the pattern of neuronal firing in different MTL regions while the patients performed a continuous recognition task (see Figure 2), we investigated the dynamics of neural circuits within MTL subregions during recognition memory.

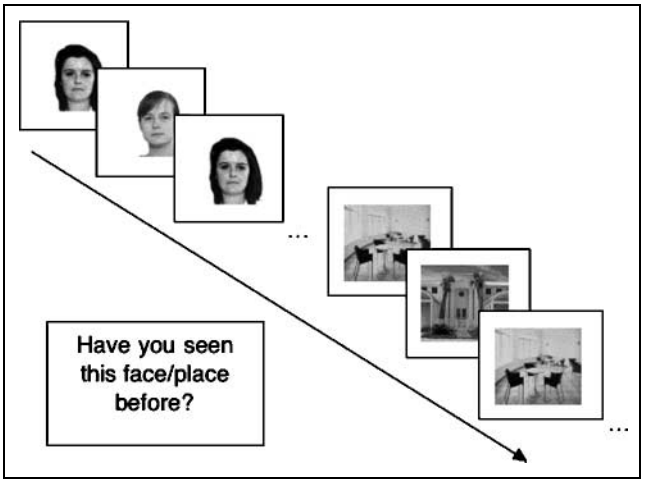

Figure 2. Experimental protocol. This figure shows the experimental setup. Patients saw images in blocks of faces and scenes, with each face/scene repeating once in the same block. Each image was displayed for 2 sec, followed by a blank screen during which the keypress, indicating whether the patient thought the image was new or repeated, was recorded.

METHODS

Patients

Participants were 11 patients with pharmacologically resistant epilepsy for whom extensive noninvasive evaluation failed to yield a single epileptogenic focus. For further monitoring, patients were stereotactically implanted with 6 to 14 electrodes from a lateral orthogonal approach based on clinical criteria (surgeries were performed by I. F.) for 1 to 2 weeks. Ten patients were right-handed and 5 were women. Patients had a mean

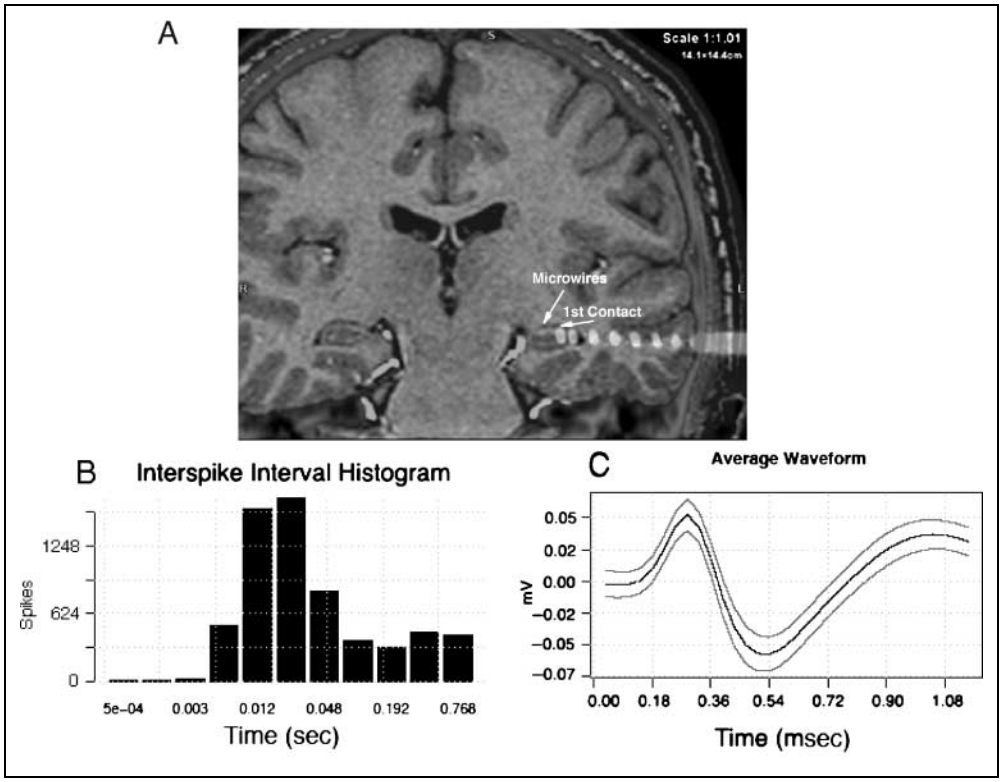

Figure 1. Anatomical placement of electrodes and cell properties. (A) A fused CT/MRI image indicating the first contact of the macro-electrode as well as the microelectrodes. (B) Distribution of interspike intervals. (C) Average waveform (black) with standard deviations (gray) of a typical cell in the hippocampus.

age of 32.8 years (±11.6) and a mean education of 14.4 years (±1.7). All patients provided informed consent and every session conformed with the guidelines of the Medical Institutional Review Board at UCLA.

Experimental Protocol

Patients were shown 20 black-and-white images in each block of nonfamous faces and indoor or outdoor scenes, and were asked to indicate via a button press whether each stimulus had been seen previously. Each stimulus was presented for 2 sec, and stimuli were shown in blocks of faces and scenes. Patients were instructed to make an old/new judgment only after the stimulus disappeared. Each patient completed at least two blocks and no more than four blocks in a session. Each stimulus was presented twice, once as a novel stimulus and the second time as a repeated stimulus. The distances between repeated stimuli varied randomly with the constraint that no more than 5 min elapsed between repetitions. The patients were able to discriminate new from previously seen stimuli reliably (hit rate = 80 ± 3.3%; false alarm rate = 17 ± 85.6%; $t = 6.42$, $p < .001$; $d' = 1.80$).

Recordings

At the tips of each electrode was a set of nine 40-μm platinum–iridium microwires. Anatomical locations of electrodes were verified via postplacement magnetic resonance imaging (MRI) scans and images, created by fusing computed tomography (CT) scans taken while electrodes were implanted with high-resolution MRI scans taken immediately before implantation.

Signals from each microwire were amplified (gain = 10,000), digitally sampled at 27.8 kHz, and recorded for off-line analysis using a 64-channel acquisition system (Neuralynx). Putative spike event times were identified by bandpass filtering (600–6000 Hz) and separating all events (1.18 msec wide), which exceeded 2.8 times the standard deviation. Waveforms of individual events were clustered using KlustaKwik (http://klustakwik.sourceforge.net; automated by S. N. Lu and P. N. S.) and classified by the same observer (I. V. V.) on the basis of waveform shape, interspike interval histograms, and the power spectral density of the spike times. Figure 1B shows a distribution of interspike intervals for a hippocampal cell and Figure 1C shows an example of a spike waveform for the same cell. During cell classification, we excluded clusters that showed ''spikes'' during an interspike interval of 1 msec or less to ensure that all cells displayed a biologically plausible refractory period.

Data Analysis

For all cells, we first identified those cells that were responsive to the stimuli as shown by a significant change in baseline firing for one or both stimulus categories. We then identified those neurons that were sensitive to the mnemonic properties of the stimuli, in that firing patterns differentiated between old and new items for at least one stimulus category. We were then able to compare the firing properties of old/new differentiating neurons in the hippocampus and the parahippocampal cortex.

To establish responsiveness in a cell, firing during the first and second seconds (separate epochs) following stimulus onset was compared with baseline firing using paired t tests ($p < .05$). To identify old/new differentiating cells, two-way analyses of variance (ANOVAs) were performed on baseline-corrected firing rates using image category (faces vs. scenes) and novelty (old vs. new) as factors. Separate ANOVAs were performed for each responsive cell for both the first and last seconds of the stimulus presentation. Alpha level was set at $p < .1$ for these ANOVAs in order to minimize Type II error in detecting old/new differentiating cells. Cells were considered to be old/new differentiating if the main effect of novelty or the interaction between novelty and the stimulus type was significant, and the cell showed a significant change from baseline firing for one stimulus type (novel/repeated or face/scene) but not the other ($p < .05$).

In order to ensure that firing patterns did not result from seizure activity, the responses of cells and their firing rates were compared with and without including cells in the seizure foci. Excluding cells from the seizure foci did not alter the responsiveness of each region, nor did the firing rates change significantly.

RESULTS

Across the 11 patients, we were able to record from 320 individual cells: 153 in the hippocampus and 167 in the parahippocampal region (102 in the entorhinal cortex and 65 in other regions of the parahippocampal gyrus). To evaluate the overall responsiveness of cells, we used t tests to compare the mean firing rates before the onset of the stimulus with those during stimulus presentation. Cells in which there was a difference in firing rate from baseline (t test exceeded test threshold corresponding to a false-positive rate of 0.05) during the stimulus period for at least one condition (old or new stimuli, either faces or scenes, or all stimuli) were considered responsive. We found that there were more responsive cells in the hippocampus than in the parahippocampal region: 82% of cells in the hippocampus and 58% of cells in the parahippocampal region changed firing rates from baseline in response to the visual stimuli under at least one condition [$\chi^2(1) = 20.96$, $p < .001$] (Figure 3A).

In order to identify cells most likely to be involved in distinguishing novelty (new vs. previously seen images) and stimulus type (faces vs. scenes), we computed the

F ratio corresponding to a two-way ANOVA for novelty and stimulus type. We then chose cells whose *F* ratio exceeded the test threshold corresponding to a false-positive rate of 0.05. These cells are most likely to be involved in distinguishing novelty and stimulus type, although the preselection based on responsiveness to these criteria precludes a direct calculation of significance level. In line with previous research showing robust category selectivity in single neurons (Kreiman, Koch, & Fried, 2000; Fried et al., 1997), we found a substantial number of neurons in each region that were differentially responsive to only one stimulus type (faces or scenes). Among responsive cells in the hippocampal and parahippocampal regions combined, 36% showed significantly different firing patterns for faces and scenes (significant main effect of stimulus type, and a significant change from baseline firing for only one stimulus type), with more of these showing responses to scenes (70%) than to faces. There were no differences between the regions in terms of either proportion of selective cells or preferred stimulus type (Figure 3).

We were primarily interested in assessing whether cells were sensitive to the mnemonic properties of the stimuli. We therefore identified those cells that differentiated between novel and repeated stimuli during performance of the continuous recognition task. To select cells that were likely to be involved in mnemonic processes, we used the following criteria: (1) a significant change in firing rate after stimulus onset compared with the second preceding stimulus onset for one stimulus type (i.e., novel stimuli), but *not* the other (i.e., previously seen stimuli) ($p < .05$) *and* (2) a significant main effect of novelty in a two-factor (stimulus novelty vs. stimulus category) ANOVA ($p < .1$). We found that by these criteria, 18% of hippocampal and 14% of parahippocampal region responsive cells differentiated

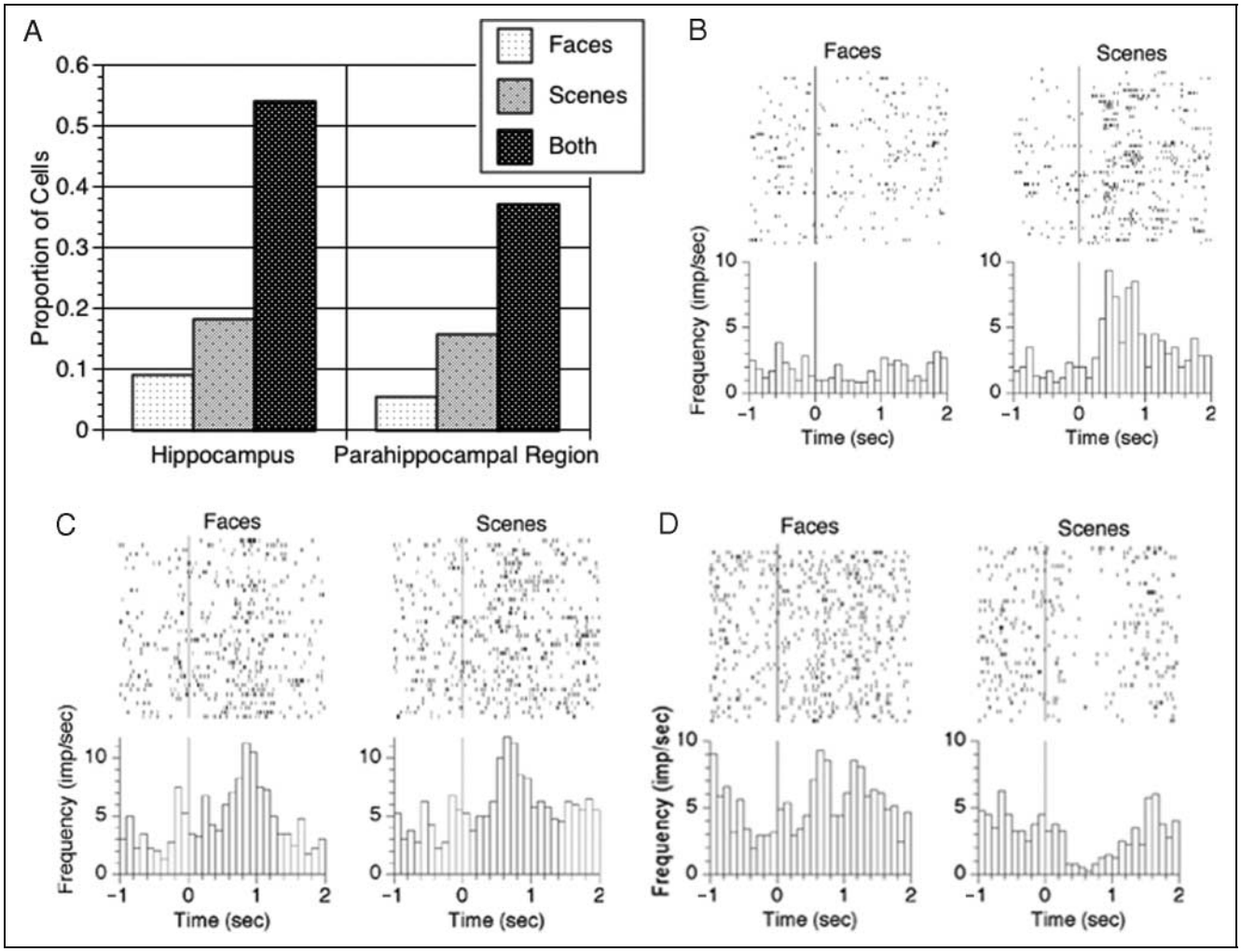

Figure 3. Materials-specific cells. (A) The proportion of cells that showed different firing patterns for different materials (faces or scenes) or responded similarly to images of both faces and scenes in the hippocampus and the parahippocampal region. (B–D) Raster plots and histograms of firing frequency for three individual neurons sorted by stimulus content: B shows the firing pattern of a hippocampal cell that selectively increases in firing to images of scenes, whereas C shows a hippocampal cell that responds to stimuli of both types; D shows a cell in the parahippocampal gyrus that responds with excitation to faces and with inhibition to scenes.

between novel and previously seen images. Across both regions, cells that preferred novel stimuli overwhelmingly showed excitatory responses (80%). In contrast, those cells that responded selectively to previously seen images were numerically more likely (59%) to decrease firing from baseline. As shown in Figure 4, the bars on the left (representing novelty-preferring cells) comprised more filled regions (representing proportion of increasing cells) than open areas (representing proportion of decreasing cells). This pattern is not seen in the bars on the right, which represent neurons selectively responsive to repeated stimuli. This difference in the direction of firing rate change (increase or decrease) for novel and previously seen images was statistically significant [$\chi^2(1) = 5.89, p < .025$].

Strikingly, the vast majority (90%) of those cells showing a selective reduction in firing rate to previously seen images were located in the hippocampus (see Figure 5A and B). By contrast, cells showing other firing patterns were distributed roughly equally between the hippocampus and the parahippocampal region. In the hippocampus, 69% of the neurons that selectively responded to previously seen stimuli decreased firing from baseline. This is shown in the second bar from the right in Figure 4. In fact, among the old/new differentiating cells in the hippocampus, there were three times as many decreasing cells that preferred repeated stimuli as there were decreasing cells that preferred novel stimuli.

In the parahippocampal region, the old/new differentiating cells showed very different patterns of firing compared to those in the hippocampus. Here, very few (7%) of the old/new differentiating cells specifically decreased firing from baseline for repeated items, as shown by the bar on the far right in Figure 4. The majority (64%) of old/new differentiating parahippocampal neurons selectively increased firing for novel stimuli and returned to baseline levels for repeated stimuli. In contrast to the hippocampus, where half of the old/new differentiating cells were selective for repeated items, only 29% of the old/new differentiating neurons in the parahippocampal region responded selectively to repeated items. In addition, most (75%) of these cells actually showed increases in firing; all of these repetition-selective increasing cells were localized to the entorhinal cortex (see Figure 5C and D).

Figure 6 shows a scatterplot with each differentiating cell plotted in terms of its baseline-corrected firing rate to novel and repeated stimuli. Those cells that selectively decrease firing below baseline to repeated stimuli are almost exclusively found in the hippocampus (crosses). In contrast, cells in the parahippocampal region were predominantly selective for novel stimuli (closed squares). Most of the cells that selectively increased for repeated stimuli were found in the entorhinal cortex (open squares).

In a set of further analyses, we examined the stimulus-selectivity for representative neurons in the hippocampal and parahippocampal regions. We selected three of the hippocampal neurons that selectively decreased firing for old stimuli (Figure 7) and three of the parahippocampal region neurons that selectively increased firing to new stimuli (Figure 8). For each of these neurons, we plotted each of the stimuli in terms of the baseline-corrected firing rate for the first and second presentations of the stimulus. For the three hippocampal neurons, there was a decrease in firing rate for almost all stimuli. However, for each of the cells, there were a few stimuli for which the firing rate increased during the second presentation. This pattern is consistent with the idea that hippocampal neurons encode features of stimuli in a competitive manner, with increasing firing to those stimuli that ''win'' the competition and a decrease in firing to others (Norman & O'Reilly, 2003). For the parahippocampal neurons, there is a selective increase in firing for the first presentation of most of the stimuli, but for a few stimuli the

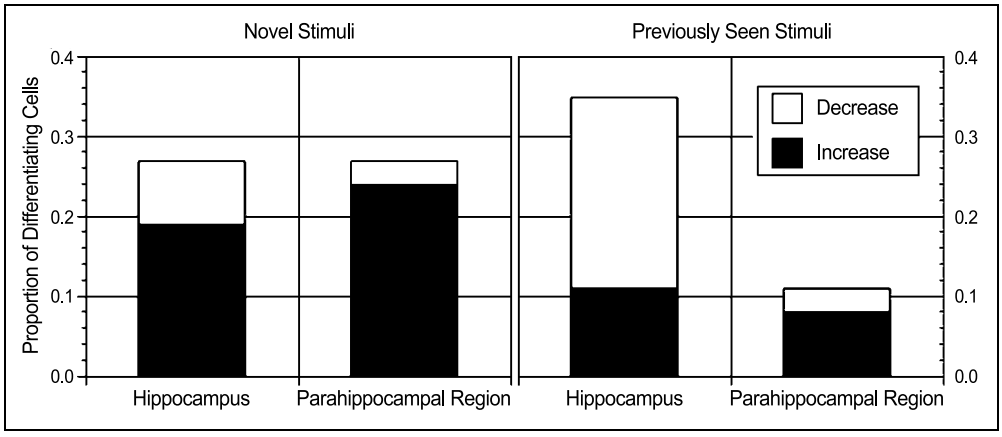

Figure 4. Regional distribution of mnemonic differentiating cells. This figure shows the proportion of differentiating cells that increases or decreases firing from baseline for either novel or previously seen images, in the hippocampal and parahippocampal regions. Note that these populations of cells were mutually exclusive—for those few cells that showed both an increase in firing in one condition and a decrease in the other, we classified the cell as selective for the stimulus type for which the change from baseline was greater.

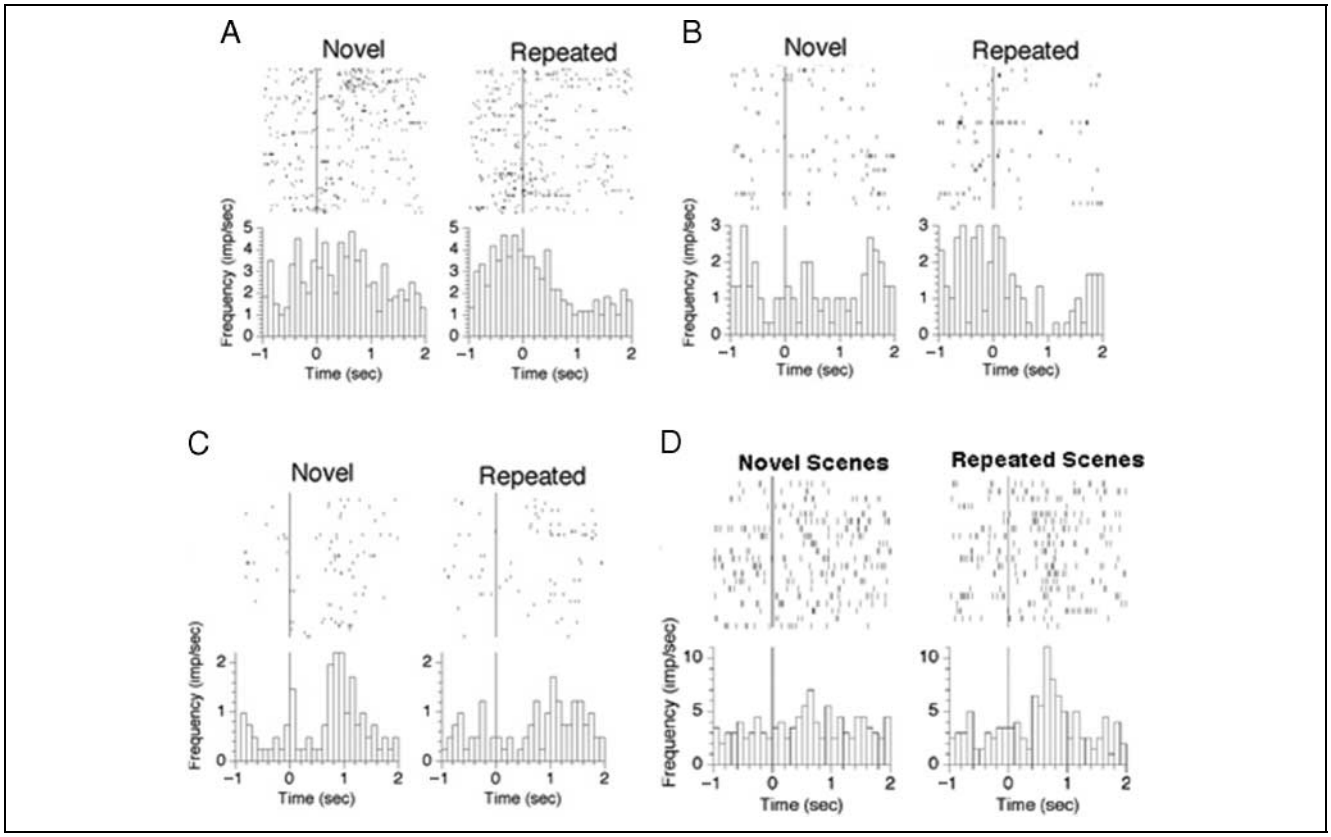

Figure 5. Cells coding mnemonic properties of stimuli. This figure shows raster plots and firing frequency histograms for four individual neurons sorted by the mnemonic property of the stimuli. (A and B) Responses of two hippocampal cells that decrease firing from baseline to repeated stimuli. (C) The response of a novelty-preferring cell in the entorhinal cortex. (D) Cell in the entorhinal cortex that is sharply tuned to the second presentation of scenes.

increase in firing was maintained in the second presentation. This observation is also consistent with the view that the neurons are continuing to respond to stimuli that ''win'' a competitive feature extraction process, whereas firing returns to baseline levels for other stimuli (Norman & O'Reilly, 2003).

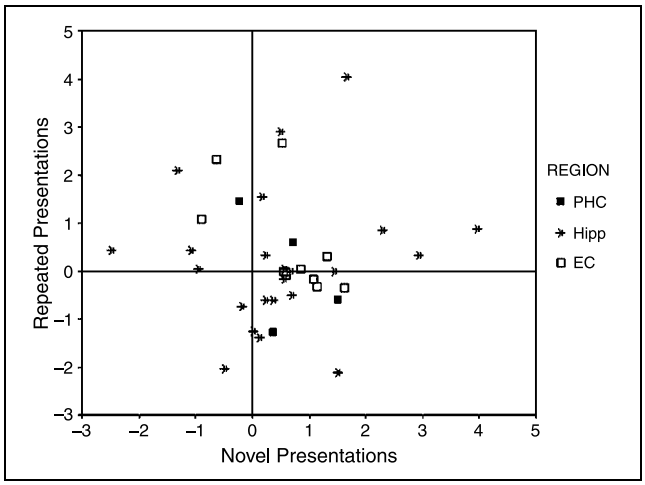

Figure 6. Old/new differentiating cells. This figure shows a scatterplot with each differentiating cell plotted in terms of its baseline-corrected firing rate to novel and repeated stimuli.

In addition to cells that differentiated stimuli on the basis of mnemonic properties, there was also a subset of responsive cells that distinguished new and previously seen stimuli, but for only one stimulus type (faces or scenes). These category-specific cells failed to show a significant main effect of novelty, but did show an interaction between novelty (new or repeated) and stimulus type (faces or scenes). Across both regions, 15% of responsive cells showed this interaction. Strikingly, 68% of these cells were found in the hippocampus. In contrast to the cells that showed an overall effect of novelty, category-specific mnemonic cells did not show a consistent tendency to decrease or increase firing from baseline for either novel or repeated stimuli. These hippocampal cells may play a different role in memory processing than the hippocampal cells that did not differentiate between new and previously seen items on the basis of stimulus type. In fact, these cells may be involved in the representation of specific stimulus properties during either encoding or retrieval. Finally, when both nonselective and materials-selective old/new differentiating cells are considered together, the hippocampus showed a greater proportion of old/

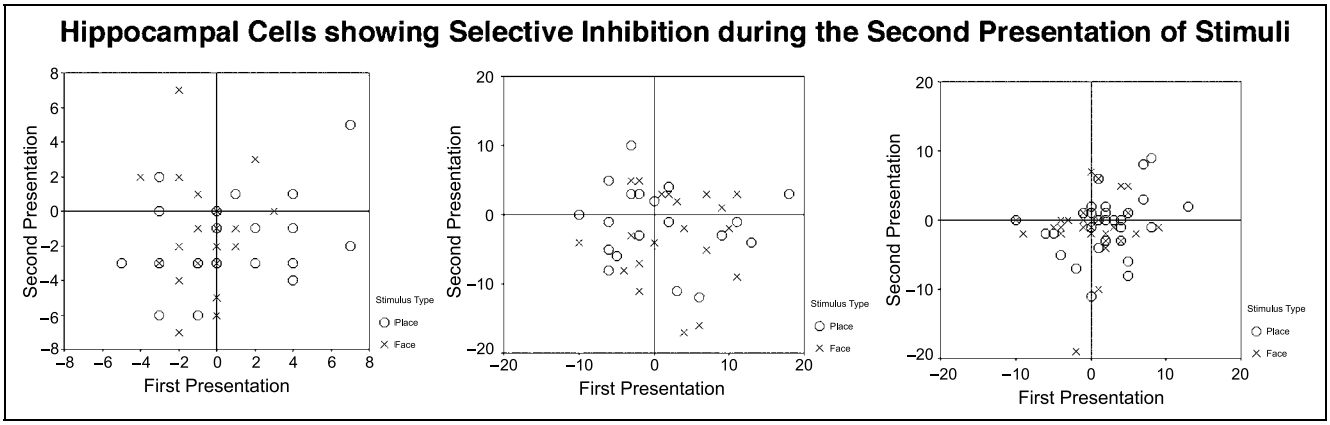

Figure 7. Three hippocampal neurons that selectively decreased firing for old stimuli. The scatterplots show the baseline-corrected firing rates for the first and second presentations of each stimulus.

new differentiating responsive cells than the parahippocampal gyrus [$\chi^2(1) = 5.20, p < .05$].

DISCUSSION

In contrast to the large number of hippocampal cells that signaled the presence of a repeated stimulus by inhibition of firing rate, relatively few repetition-selective cells responded with excitation (Figure 4). These findings indicate that the representation of a given stimulus within the hippocampus involves an increase in activity of relatively few neurons. Our data are consistent with the concept of ''sparse coding'' in the hippocampus, which has been theorized as a means to avoid the catastrophic interference and limited memory capacity resulting from excessive overlap between memory representations (Marr, 1971). Sparse coding confers enough pattern separation between memory representations to allow for a large number of items to be represented. In addition, our data indicate that a greater number of hippocampal cells decrease their activity to previously seen stimuli, presumably to increase the signal-to-noise ratio and permit effective memory retrieval by those few cells. In this way, the hippocampus is capable of binding together details of co-occurring stimuli.

The large proportion of hippocampal cells showing decreases in firing raises the question of the identity of these cells: Are they principal neurons or inhibitory interneurons? Although we are unable to definitively classify these cells, one of the parameters by which principal cells and interneurons are classified in the rodent literature is firing rate (Ranck, 1973), with pyramidal cells showing rates of <10 Hz and interneurons firing at rates of 10 Hz and higher. Those cells that selectively decreased firing for previously seen items had a mean firing rate of 3.66 Hz, which is consistent with our view that these cells are principal neurons. Likewise, those cells that responded with excitation to novel items showed a mean firing rate of 4.03 Hz, suggesting that they were also principal cells.

Our finding that many old/new differentiating hippocampal neurons showed inhibitory responses contrasts with results of a continuous recognition study in the macaque that showed that only about 2% of hippocampal

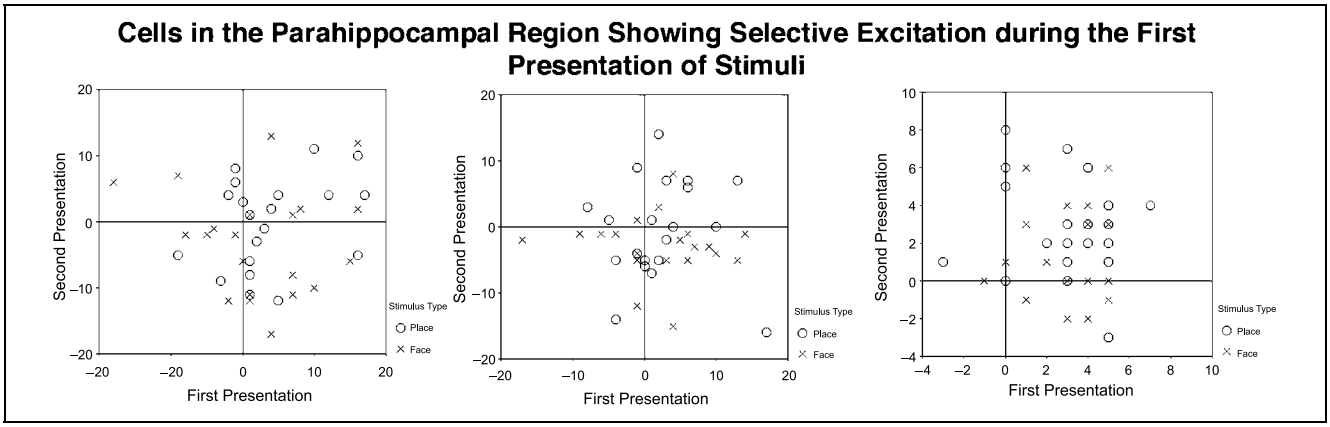

Figure 8. Three parahippocampal region neurons that selectively increased firing for new stimuli. The scatterplots show the baseline-corrected firing rates for the first and second presentations of each stimulus.

neurons differentiated between old and new items, and that almost all of these cells showed an increase from baseline for repeated stimuli (Rolls, Cahusac, Feigenbaum, & Miyashita, 1993). This disparity may be due to the fact that our stimuli were meaningful to the subjects (faces or scenes), and each stimulus was only presented twice. It is possible that in our procedure, subject responses were based on a mixture of recollections of previously seem items and relative familiarity. Because recollection is thought to activate the hippocampus more strongly than familiarity-based recognition (Ranganath et al., 2004; Yonelinas et al., 2002; Eldridge et al., 2000), the current task may have been more likely to engage hippocampal memory processes, resulting in the recruitment of a higher proportion of cells involved in retrieval.

The pattern of firing in the parahippocampal region, with suppression of firing (i.e., return to baseline) in a majority of differentiating neurons during the second presentation of an image, accompanied by the increase in firing for only a small subset of neurons, suggests that this region may support a signal indicating the familiarity of repeated items. The present findings are consistent with previous research in nonhuman primates that has shown that cells in the parahippocampal gyrus exhibit repetition suppression: With repeated stimulus exposures, firing rates return to baseline (Suzuki, Miller, & Desimone, 1997; Young, Otto, Fox, & Eichenbaum, 1997; Fahy, Riches, & Brown, 1993). Such repetition suppression is distinct from the inhibitory responses seen in the hippocampus in which cells that are unresponsive to novel stimuli show a decrease in firing below baseline for repeated stimuli (see Figure 5A, B, and C). Repetition suppression has also been shown in populations of neurons in humans using functional MRI (Henson, Cansino, Herron, Robb, & Rugg, 2003), although never at the single-unit level. Importantly, according to one prominent view, familiarity-based recognition is accompanied by an increase in firing in a small subset of neurons as well as a decrease in firing for repeated stimuli in a majority of parahippocampal neurons (Norman & O'Reilly, 2003; Brown & Xiang, 1998). Supporting this view, the current study demonstrates in humans the existence of those few cells that increase firing rate selectively for repeated stimuli in the parahippocampal region. Our results demonstrate the existence of repetition suppression in the human MTL and suggest that neurons in the entorhinal cortex, in particular, may become more sharply tuned to familiar stimuli.

Collectively, results from our recordings demonstrate the differences among the dynamics of neurons in the hippocampus and parahippocampal region during recognition memory. Presumably, those cells that respond selectively during the first presentation of each stimulus are involved in encoding processes. Likewise, cells that are selectively responsive during the second presentation are likely to be recruited by MTL regions to support retrieval processes. One of the striking results obtained here is the unique pattern of firing in the hippocampus. We suggest that the recruitment of hippocampal cells that decrease firing rate during recognition memory may serve to increase the signal-to-noise ratio and thereby allow sparse coding to be effective. Our data suggest that findings of increased hemodynamic response in the hippocampus found in functional neuroimaging studies of recognition (Kirwan & Stark, 2004; Duzel et al., 2003; Eldridge et al., 2000) may reflect synaptic activity that serves to inhibit firing in hippocampal neurons. That is, the net synaptic activity that results in increased blood flow may include activity that results in *both* the excitation and inhibition of hippocampus pyramidal cells. Certainly, the inhibitory responses of pyramidal cells that we have observed may result from an *increase* in synaptic activity between inhibitory interneurons and pyramidal cells. Our results provide a useful characterization of the changes that occur at the level of single neurons across MTL regions during recognition in humans. When previously viewed stimuli are presented, the hippocampus contrasts with the parahippocampal region by exhibiting a dramatic recruitment of cells showing inhibitory responses, even during only the second presentation of stimuli. Furthermore, these data are consistent with models of hippocampal functioning that utilize sparse coding as a mechanism to avoid interference across memories and provide new evidence for the role of inhibition as a mechanism supporting sparse coding. In contrast, the results from the parahippocampal region support a different role for these structures. In this region, the majority of responsive cells increased firing for novel stimuli, with a decrease back to baseline for repeated stimuli, A smaller number of responsive cells in the entorhinal cortex selectively increased firing for repeated stimuli, consistent with the view that tuning of neural responses in the parahippocampal region is a substrate of familiarity signal. Single-unit studies in humans such as this one allow investigators to describe the activity of populations of neurons which can be used to evaluate models of cognitive processes that make predictions at the neural circuit level.

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Note

1. We use the term ''parahippocampal region'' (Witter, 2002) to describe the following subregions of the MTL: entorhinal cortex, pre- and para-subiculum, perirhinal cortex, and other parts of the parahippocampal gyrus.

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