Supporting Information

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SI Text

Categorization of Differentially Responsive Cells. Differentially responsive cells fell into four categories, depending on whether their firing rates were enhanced or depressed upon stimulus onset, and whether firing rates were higher for Novel stimuli (Novelty responses) or for Repeat stimuli (Familiarity responses) (Table S1). Baseline firing rates were not significantly different between Novelty response cells (6.3 ± 1.4 spk/s) and Familiarity response cells (7.9 ± 2.5 ms; $P > 0.1$). However, there was a trend for Novelty response cells (112 ± 27 ms) to have a shorter response latency than Familiarity response cells (200 ± 45 ms; $P = 0.09$).

Correlation Between Firing-Rate Modulation and Memory Performance. To quantify recognition memory performance and firing-rate modulations on a trial-by-trial basis for each session, all stimuli for which the looking times were at least 600 ms for the Novel presentation were sorted in terms of increasing percent-change in looking time between the Novel and Repeat presentations (recognition memory performance). Bins of 30 stimuli each were defined, starting with the first 30 stimuli in the progression. Each subsequent bin overlapped with the previous bin by 20 stimuli, and included the next 10 stimuli. For each neuron, within each bin of 30 stimuli, average firing rates were calculated for the Novel and Repeat presentations (using the time period 100–600 ms after stimulus onset), and were normalized by dividing by the baseline firing rate of the neuron (the 800 ms preceding stimulus onset). The average firing rate for Repeat trials was subtracted from the average firing rate for Novel trials to obtain a difference; the absolute value of this difference was then taken, giving a "firing-rate difference" value for each neuron and each bin. This was done to include cells whose firing rates increased and those whose firing rates decreased between subsequent stimulus presentations. For each bin of stimuli, the average memory performance (percent-change in looking time) was also calculated across the stimuli in that bin. Finally, the correlation between memory performance and firing-rate difference was calculated across all neurons and all bins. To visually represent this correlation, the firing rate difference data were further distributed into 10 bins, based on the memory performance value of each data point. For each bin of data points, the average firing rate difference and memory performance value were calculated; these data are displayed on a scatter plot in Fig. 4C. In addition, we constructed a histogram of correlation coefficients for all neurons and determined whether this population deviated significantly from a zero median population using a sign test.

Correlation Between Firing-Rate Modulation and Memory Performance for Neuronal Subgroups. To determine the relative contribution of enhanced cells and depressed cells to this correlation, we performed the same analysis for each subset of the differentially responsive cells; the results of this analysis are depicted in Fig. S1A and B. The correlation was significant for the enhanced cells ($P < 0.01$) (see Fig. S1A), and there was a trend toward significance for the depressed cells ($P = 0.06$) (see Fig. S1B). We also performed the analysis separately for cells with Novelty responses and cells with Familiarity responses. Both subgroups showed significant correlations between difference in firing rate and memory performance ($P < 0.05$) Fig. S1 C and D).

Firing-Rate Modulations with Respect to Lag Interval Between Presentations. Stimuli were repeated with varying numbers of intervening trials; thus, it was also possible to measure the degree to which firing-rate modulations varied with increasing lag intervals between presentations. To determine whether firing-rate modulations were influenced by the delay between successive stimulus presentations, stimuli were divided into three categories: those with no intervening stimuli between presentations (Lag 0), those with one-to-three intervening stimuli (Lag 1–3), and those with four-to-eight intervening stimuli (Lag 4–8). Firing rates for Novel and Repeat trials were then calculated for each differentially responsive neuron, for the 15% of stimuli in each category for which the monkey showed the best subsequent recognition memory (High Recognition) and the 15% of stimuli for which the monkey showed the worst subsequent recognition memory (Low Recognition). The firing-rate difference for each condition, in each category, was then calculated as described in *Methods*, using the 100- to 600-ms period after stimulus onset and normalized to the baseline firing rate. The average firing-rate modulation across differentially responsive neurons for High and Low Recognition trials for all three Lag categories is depicted in Fig. S2. Paired t-tests revealed that the firing rate modulation was significantly different for the Lag 1 to 3 and Lag 4 to 8 categories ($P < 0.05$), but not for the Lag 0 category ($P > 0.1$). Behavioral performance did not vary across lag categories for High Recognition and Low Recognition trials (repeated-measures two-way ANOVA, no main effect of lag, $F[2,220] = 0.85$, $P > 0.1$).

**Classification of Neurons Based on Baseline Firing Rates.** To determine whether a particular cell type had greater representation among the differentially responsive neurons, we categorized neurons as putative principal cells or putative interneurons, taking into consideration both the average firing rate during the fixation period preceding stimulus onset and the width of spike waveforms. Spike waveforms were examined to determine the duration, defined as the time, in microseconds, from waveform trough to peak (1). One or both of these criteria have been used previously to classify hippocampal neurons as either putative principal cells or putative interneurons in the monkey (2) and rat (3–5). All neurons with baseline firing rates above 15 spk/s were classified as putative interneurons, and all other neurons were classified as putative principal neurons. This threshold was chosen after visual inspection of data, and based on previous reports that hippocampal interneurons often fire at rates above 15 spk/s (6). With this classification, the average waveform duration for putative interneurons was significantly shorter than that for putative principal cells (independent t-test, $P < 0.05$). Based on this analysis, 12 recorded neurons were classified as putative interneurons, 10 (83%) were visually responsive (compared to 74, or 62% of putative principal cells), and 3 (25%) were further classified as differentially responsive neurons (compared to 27, or 23% of visually responsive putative principal cells). One of these three neurons exhibited enhanced firing rates with stimulus presentation and gave a Novelty response; the other two had depressed firing rates, and gave Familiarity responses. Accordingly, the data do not suggest that recognition memory signals are restricted to one class of hippocampal neurons.

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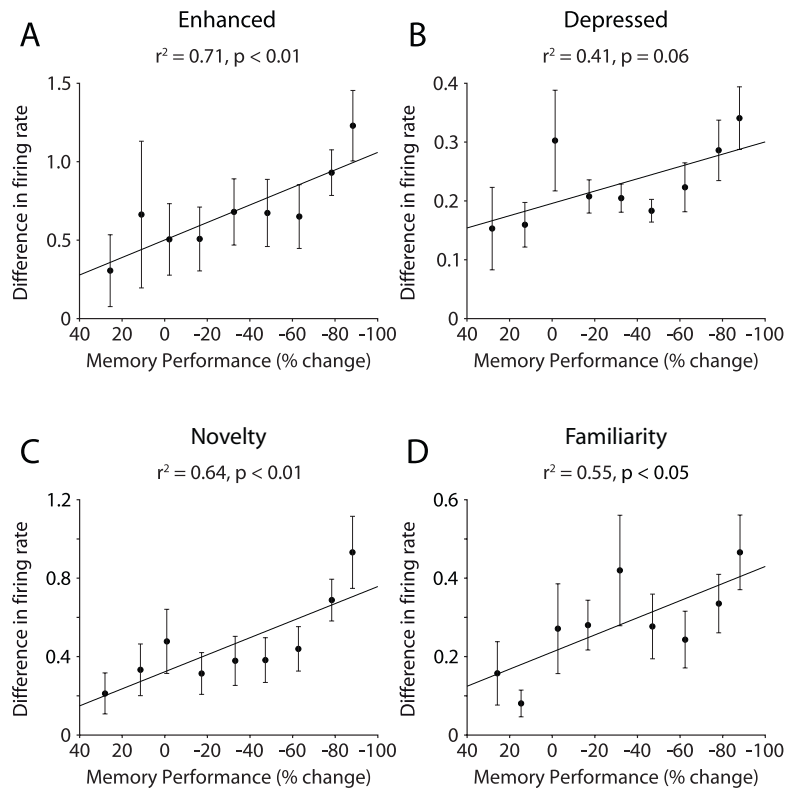
Fig. S1. Correlation between firing-rate modulation and memory performance for neuronal subgroups. (*A*) Difference in firing rates across all differentially-responsive neurons whose firing rates increased with visual stimulation (*n* = 11), organized from lowest to highest percent-change in looking time. Error bars represent SEM. Black line represents linear regression of data points. (*B*) Same as in (*A*), but for depressed differentially-responsive neurons (*n* = 19). (*C*) Same as in (*A*), but for differentially-responsive neurons with Novelty responses (*n* = 17). (*D*) Same as in (*A*), but for differentially-responsive neurons with Familiarity responses (*n* = 13).
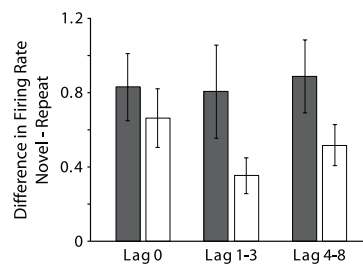
Fig. S2. Average difference in firing rates across differentially responsive neurons, normalized by baseline firing rate, for stimuli with no intervening trials (Lag 0), stimuli with one-to-three intervening trials (Lag 1–3), and stimuli with four-to-eight intervening trials (Lag 4–8). Each bar represents the average firing rate difference for the 15% of trials with the highest recognition memory (*gray bars*) and the 15% of trials with the lowest recognition memory (*white bars*) in each lag category.

Table S1. Numbers of enhanced and depressed neurons

	Novelty responses	Familiarity responses
Enhanced	7 (**23%**)	4 (**13%**)
Baseline firing rate (spk/s)	6.0 ± 3.0	6.0 ± 3.6
Response latency (ms)	134.6 ± 58.8	283.5 ± 135.2
Depressed	10 (**33%**)	9 (**30%**)
Baseline firing rate (spk/s)	6.6 ± 1.2	8.7 ± 3.4
Response latency (ms)	96.0 ± 21.1	162.1 ± 28.8

Total differentially responsive single units: 30. Numbers of enhanced and depressed neurons, further divided into those that gave Novelty responses (higher firing rate for Novel stimuli) and those that gave Familiarity responses (higher firing rate for Repeat stimuli). Percentages in bold are based on the total number of differentially responsive single units. Measures for average baseline firing rate and response latency for each category are presented $\pm$ SEM.