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Ison MJ, Mormann F, Cerf M, Koch C, Fried I, Quian Quiroga R. Selectivity of pyramidal cells and interneurons in the human medial temporal lobe. *J Neurophysiol* 106: 1713–1721, 2011. First published June 29, 2011; doi:10.1152/jn.00576.2010.—Neurons in the medial temporal lobe (MTL) respond selectively to pictures of specific individuals, objects, and places. However, the underlying mechanisms leading to such degree of stimulus selectivity are largely unknown. A necessary step to move forward in this direction involves the identification and characterization of the different neuron types present in MTL circuitry. We show that putative principal cells recorded in vivo from the human MTL are more selective than putative interneurons. Furthermore, we report that putative hippocampal pyramidal cells exhibit the highest degree of selectivity within the MTL, reflecting the hierarchical processing of visual information. We interpret these differences in selectivity as a plausible mechanism for generating sparse responses.

sparse coding; hippocampus; memory formation; hierarchical processing; winner-take-all; epilepsy

UNDERSTANDING HOW HUMANS ARE capable of recognizing objects fast and accurately is one of the major challenges in neuroscience. This requires understanding what kind of information is encoded by neurons and, perhaps more importantly, how that information is represented. There is vast evidence showing that the processing of visual information follows a hierarchical organization (Ungerleider and Mishkin 1982; Van Essen and Maunsell 1983). Along the ventral visual pathway extending from the primary visual area (V1) to the inferotemporal cortex (IT), neurons respond to increasingly complex stimulus features. Beyond the ventral visual pathway, cells in the medial temporal lobe (MTL) have been shown to respond selectively to stimulus categories (Fried et al. 1997; Kreiman et al. 2000) and even to pictures of given individuals or objects (Quian Quiroga et al. 2009; Quiroga et al. 2005).

The MTL contains various neuron classes, including a majority of principal cells and several types of interneurons (Freund and Buzsáki 1996; Klausberger et al. 2003; Klausberger and Somogyi 2008). In the last 10 years, there have been numerous studies showing that it is possible to provide a classification of putative excitatory pyramidal cells and inhibitory interneurons from extracellular recordings in different brain areas and species (Constantinidis and Goldman-Rakic 2002; Csicsvari et al. 1999; Frank et al. 2001; Henze et al. 2000; Johnston et al. 2009; Le Van Quyen et al. 2008; Likhtik et al. 2006; Maurer et al. 2006; Mitchell et al. 2007; Viskontas et al. 2007). With very few notable exceptions where the identity of the cells could be verified physiologically by means of juxtacellular labeling in simultaneous extra- and intracellular recordings (Henze et al. 2000) or using antidromic activation to identify pyramidal cells (Johnston et al. 2009; Likhtik et al. 2006), the majority of these studies classify both neuronal groups exclusively based on electrophysiological features derived from extracellular recordings. In particular, they exploit the fact that pyramidal cells and interneurons typically exhibit different spike durations and discharge frequencies. Despite the problems of classifications based on extracellular features (see, for instance, Likhtik et al. 2006), advances in understanding the characteristics of both neuronal groups are of great importance since they contribute to different aspects of brain function. Previous classifications were based solely on spike duration (Bartho et al. 2004; Le Van Quyen et al. 2008), on a combination of spike duration and discharge rate (Constantinidis and Goldman-Rakic 2002; Fox and Ranck Jr. 1981; Frank et al. 2001; Likhtik et al. 2006; Rosenkranz and Grace 2001), or on these two features combined with a measure of the burst propensity of the cells (Csicsvari et al. 1999; Viskontas et al. 2007). These studies have provided valuable information regarding the specific roles of both neuron populations in information processing. However, very few studies have yet focused on the relative contributions of pyramidal cells and interneurons to higher cognitive processing in awake animals (Johnston et al. 2009; Marshall et al. 2002; Maurer et al. 2006; Wiebe and Staubli 2001). Most investigations involving the MTL focused on recordings from the hippocampus, and to a lesser degree from the entorhinal cortex (EC), while animals performed spatial tasks. However, to date, no study has investigated the encoding properties of pyramidal cells and interneurons in the different structures of the MTL, as reflected by their stimulus selectivity.

We report that putative pyramidal cells identified from extracellular recordings in the human MTL are more selective than putative interneurons. We propose the existence of two neuron populations with different selectivities arising naturally

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as a mechanism to generate a sparse representation (Olshausen and Field 2004; Vinje and Gallant 2000; Young and Yamane 1992). In addition, we found significant differences in the stimulus selectivity of cells recorded from several areas in the MTL and put forward that this reflects the hierarchical processing of visual information.

MATERIALS AND METHODS

Data were collected from 76 experimental sessions in 31 patients with pharmacologically intractable epilepsy (27 right handed, 17 male, 17–54 yr old). Extensive noninvasive monitoring did not yield concordant data corresponding to a single resectable epileptogenic focus. Therefore, they were implanted with chronic depth electrodes for 7–10 days to determine the seizure focus for possible surgical resection (Fried et al. 1997). Subjects sat in bed facing a laptop computer on which pictures were presented. They were instructed to respond whether the image showed a person or not by pressing the "Y" and "N" keys, respectively. The pictures covered ~1.5° of visual angle and were displayed 6 times in pseudorandom order for 1 s. Each recording session lasted ~30 min. An average of 111 images were shown in each session (SD: 29, range: 63–192). Presented images consisted on photos of famous and nonfamous persons, landmarks, animals, and objects (Quiroga et al. 2005).

Here, we report data from sites in hippocampus, EC, parahippocampal cortex (PHC), and amygdala. Electrode locations were determined exclusively by clinical criteria and were verified by MRI or computer tomography coregistered to preoperative MRI. All patients gave their written informed consent to participate in this study, which conformed to the guidelines of and was approved by the Medical Institutional Review Board at University of California, Los Angeles. Each electrode probe had nine microwires at its end, with eight acting as high-impedance recording channels and the ninth as a low-impedance reference. The microwires were not moved by the clinicians after surgery.

The differential signal from the microwires was amplified using a 64-channel Neuralynx system (Bozeman, MT), filtered between 1 and 9,000 Hz and sampled at 28 kHz. After band-pass filtering the signals between 300 and 3,000 Hz, spikes were detected and sorted using wave_clus (Quiroga et al. 2004).

We recorded from a total of 4,379 units (1,210 single and 3,169 multiunits, see below for criteria). Of these, 579 units (13.2%, 194 single units and 385 multiunits) were responsive. In the following sections, we consider further only the single units that responded to ≥1 picture. Responses were either positive (exhibiting an increase in the firing rate above baseline) or negative (decrease in the firing rate). Positive responses were identified following techniques developed in previous works (Quiroga et al. 2005; Quian Quiroga et al. 2009). In short, responses were defined as the median number of spikes across trials (between 100 and 1,000 ms) following picture onset. Similarly, the baseline for each picture was defined as the median spike count (from -1,000 to -100 ms) before stimulus onset. A unit was considered responsive if all of the following were fulfilled: *1*) the median number of spikes exceeded 5 SD of the baseline distribution across stimuli per session; *2*) the median number of spikes was ≥2; and *3*) a paired *t*-test between the baseline and response period showed significant differences using $\alpha = 0.05$ as significance level. An inhibitory response was considered significant if it fulfilled 4 criteria: *1*) the median number of spikes in the interval 100–1,000 ms after picture onset was ≥2 SD below the baseline activity; *2*) the median number of spikes during baseline was ≥2; *3*) a paired *t*-test comparing the baseline and response period for the particular stimulus showed a significant difference using $\alpha = 0.05$ as significance level; and *4*) the median difference between response and baseline for the particular stimulus exceeded the 95th percentile of the permutation distribution of 100 random shuffles, where each shuffle was taken from the baseline activity for all pictures within each of the 6 presentation cycles and the test statistic was the median difference between the median response and the median activity of a random shuffle. This final criterion was introduced to avoid cases with spontaneously large firing during the baseline period in some of the trials.

Single- and multiunit activity were classified by an expert viewer based on spike shape, variance, and the presence of a refractory period for the single units [i.e., <1% spikes within <3-ms interspike-interval (ISI) distributions]. To assess further the isolation of the cells, we calculated the percentage of ISI that fell within 3 ms. The median number across all single units was 0.10% (compared with 0.88% for multiunits), indicating a very clear unit isolation for single units and a relatively clear unit isolation for multiunits. However, since the spike waveform is a relevant feature for the identification of the cell type, we applied a conservative criterion and only attempted a classification of clear single units.

We used two different criteria to divide the single units into putative pyramidal cells and interneurons. Criterion 1 combined information from the baseline firing rate and the spike duration to separate the two groups. As in Constantinidis and Goldman-Rakic (2002) and Viskontas et al. (2007), we used *k*-means clustering, a standard clustering algorithm that assigns observations to the cluster with the nearest mean (Duda and Stork 2000). We used *z*-score standardized variables mean baseline firing rate over the set of stimuli and spike width (measured as the peak-to-through distance). Criterion 2 employed a fixed-width threshold (0.65; see Fig. 1) to separate both groups (Le Van Quyen et al. 2008). The rationale was that the use of a criterion independent of the firing rate would not lead to (possible) artificial correlations between firing rate and any spike train property under study. The classifications using both criteria are shown in Fig. 2. The two populations of cells showed significant differences in width

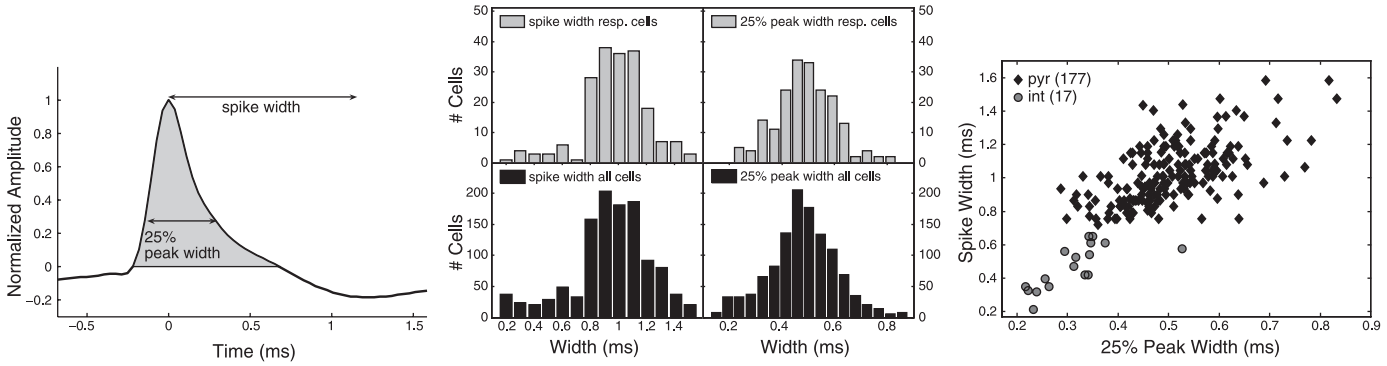

Fig. 1. *Left*: spike duration definitions. In addition to the peak-to-through distance (spike width), we also show the width at 25% amplitude. *Middle*: width distributions for responsive (resp.) single units (*top*) and all single units (*bottom*). *Right*: cluster separation based on spike width. pyr, Pyramidal cells; int, interneurons.

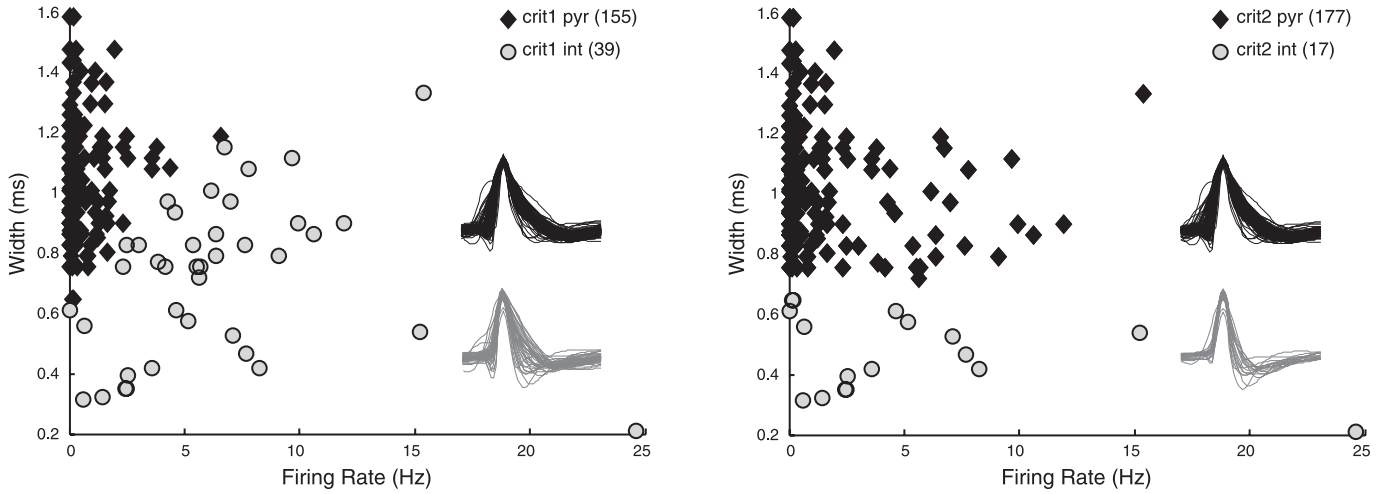

Fig. 2. Classification criteria (crit). Identification of putative pyramidal cells (black diamonds) and interneurons (gray circles) from extracellular recordings using *k*-means clustering on *z*-score standardized variables firing rate (FR) and width (criterion 1; *left*) and separation based on the spike width (criterion 2; *right*). *Insets*: normalized waveforms of identified pyramidal cells (black lines) and interneurons (gray lines).

($P < 10^{-11}$ and $P < 10^{-12}$ using criterion 1 and 2, respectively, Wilcoxon rank sum test) and firing rate ($P < 10^{-18}$ and $P < 10^{-4}$, respectively). It can be seen that both criteria agree on identifying cells with short spike duration as putative interneurons but differ in the classification of cells with high firing rate and long spike durations. Exclusion of these cells did not affect any of the conclusions of this study.

To evaluate possible differences in the firing patterns between pyramidal cells and interneurons, we calculated, in addition to the firing rate, the autocorrelograms of the spike trains, the coefficient of variation of the ISI (CV), which is a common measure of the variability of the spike train (Softky and Koch 1993), and the burst proportion (BP) associated with ISI of <10 ms (Buzsaki et al. 1996; Frank et al. 2001).

Stimulus selectivity was assessed by using the selectivity index introduced by Quiroga et al. (2007). For completeness, we present here the definition of the selectivity index S. The relative number of stimuli R(T) eliciting a response larger than a threshold T is

$$\mathrm{R(T)} = \frac{1}{N}\sum_{i=1}^{N} \theta(\mathrm{f}_i - \mathrm{T}) \qquad (1)$$

where f_i denotes the firing rate of a given neuron to the stimulus i ($i = 1, \ldots, N$), N denotes the size of the stimulus set, and $\theta(x) = 1$ for $x > 0$; $\theta(x) = 0$ for $x \leq 0$. The selectivity index is defined as

$$\mathrm{S} = 1 - \frac{2}{M}\sum_{j=1}^{M} \mathrm{R(T}_j) \qquad (2)$$

where $\mathrm{T}_j = \mathrm{f}_{min} + j(\mathrm{f}_{max} - \mathrm{f}_{min})/M$ are equidistant thresholds between the minimum and maximum firing (f_{min} and f_{max}, respectively), $j = 1, \ldots, M$, and M indicates the number of threshold values (we used $M = 1{,}000$). This measure is independent of the threshold used to define responses, is close to 0 for uniformly distributed random firings, and approaches 1 the more selective the neuron is. To test whether the results depended on any particular details of this selectivity measure, we also studied other selectivity measures described in the literature, namely Rolls sparseness (Rolls and Tovee 1995; Vinje and Gallant 2000), depth of selectivity (Moody and Wise 2000; Wirth et al. 2003), nonparametric entropy selectivity (Lehky et al. 2005), breadth of tuning entropy (Smith and Travers 1979), and the number of stimuli to which a neuron responded (Mormann et al. 2008; Quiroga RQ et al. 2005; see supplemental material for details on the different selectivity measures used in this study, available in the data supplement online at the *Journal of Neurophysiology* web site). These measures of selectivity assess "lifetime sparseness" (Willmore and Tolhurst 2001), i.e., the number of stimuli to which a neuron responds. Although lifetime sparseness has been shown to be related to "population sparseness," the number of neurons that responds to one stimulus, the correspondence between these two measures is not necessarily straightforward, since very few neurons can respond to many stimuli and vice versa (Franco et al. 2007; Ison and Quiroga 2008).

Statistical analyses were performed using nonparametric tests to avoid assumptions about the data being normally distributed. Pairwise comparisons were made using the Wilcoxon rank sum test. For comparisons between groups, we used the Kruskal-Wallis one-way ANOVA test followed by Bonferroni post hoc analysis for multiple comparisons. Differences with $P \leq 0.05$ were considered statistically significant.

RESULTS

Table 1 illustrates the firing rate, spike width, proportion of bursts, and number of cells for putative pyramidal cells and interneurons identified with the two criteria used in this study. The results using both classifications showed similar spike train characteristics. In the following sections, we will mainly present results based on criterion 1 (clustering analysis combining the information of firing rate and spike duration) as it has been shown to provide a consistent classification across species, brain regions, and laboratories (Constantinidis and Goldman-Rakic 2002; Frank et al. 2001; Likhtik et al. 2006). Two exemplary neurons and their 10 largest responses are

Table 1. *Spike train variables of putative pyramidal cells and interneurons*

	Firing Rate, Hz	Spike Width, ms	Burst Proportion	*N*
Crit 1 pyr	0.6 (0.9)	1.05 (0.18)	0.18 (0.27)	155
Crit 1 int	6.4 (4.7)	0.72 (0.26)	0.10 (0.13)	39
Crit 2 pyr	1.4 (2.6)	1.03 (0.18)	0.17 (0.26)	177
Crit 2 int	5.1 (6.4)	0.47 (0.13)	0.14 (0.17)	17

Values are means (SD). Identification using criterion (Crit) 1 (*k*-means clustering on spike width and baseline firing rate over the set of stimuli) and criterion 2 (separation based on the spike width). Burst proportion indicates the proportion of consecutive spikes with interspike intervals <10 ms. pyr, Pyramidal cells; int, interneurons.

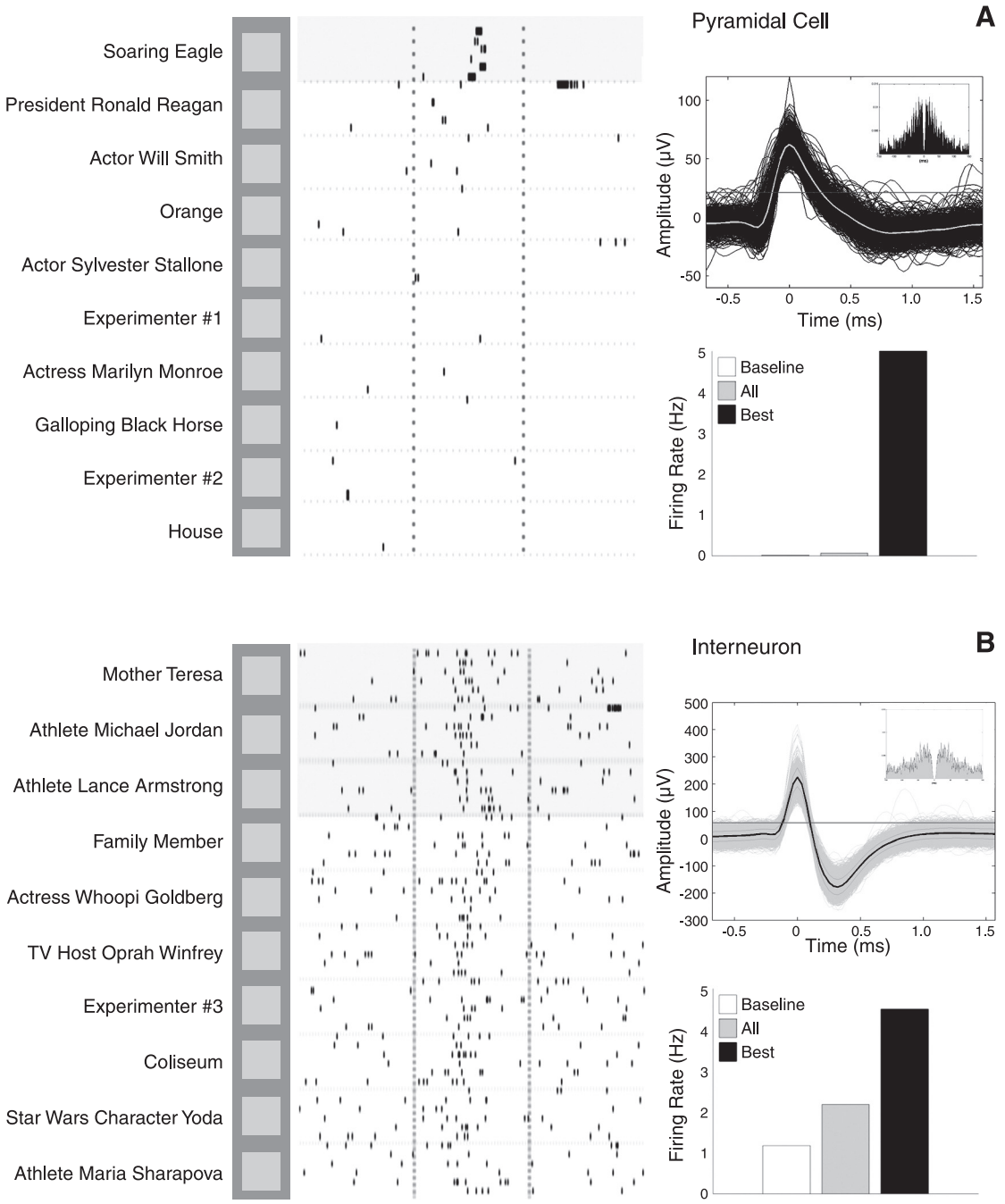

Fig. 3. Exemplary responses. Responses of a putative pyramidal cell recorded from the hippocampus (*A*) and a putative interneuron in the amygdala (*B*). *Left*: the 10 largest responses (out of 97) are displayed. For each case, the raster plots for the 6 trials and names representing the corresponding pictures actually used in the study are shown. The vertical dotted lines mark picture onset and offset, 1 s apart. *Top right*: associated waveforms and threshold used for spike detection (horizontal line). *Bottom right*: mean FR during baseline (white), during presentation of all stimuli (gray), and during the presentation of pictures eliciting significant responses (black). Note the much higher selectivity of the pyramidal cell (S = 0.97), which essentially fires to only 1 picture, compared with that of the interneuron (S = 0.09). To see the actual images that were viewed by the subjects in the study, go to the authors' web site at http://www.le.ac.uk/neuroengineering.

shown in Fig. 3 (see also http://www.le.ac.uk/neuroengineering for more examples). Putative pyramidal cells typically responded with a 10-fold increase in their firing rate (mean peak firing rate: 6 Hz, mean baseline firing rate: 0.6 Hz; see Fig. 4). Putative interneurons typically increased their firing rate from 6 to 15 Hz (and up to 40 Hz).

The CV of both groups indicated that the variability in the firing was higher than the one corresponding to a Poisson process (CV = 1). Consistent with earlier findings (Csicsvari et al. 1999), the median CV of pyramidal cells (1.72) was significantly higher than the median CV of interneurons (1.14; $P < 10^{-11}$). The proportion of bursting cells was larger for pyramidal cells than for interneurons (P = not significant). Figure 5 illustrates the average autocorrelograms of both neuronal populations. Both groups showed a clear refractory period. Putative pyramidal cells exhibited a characteristic early peak rep-

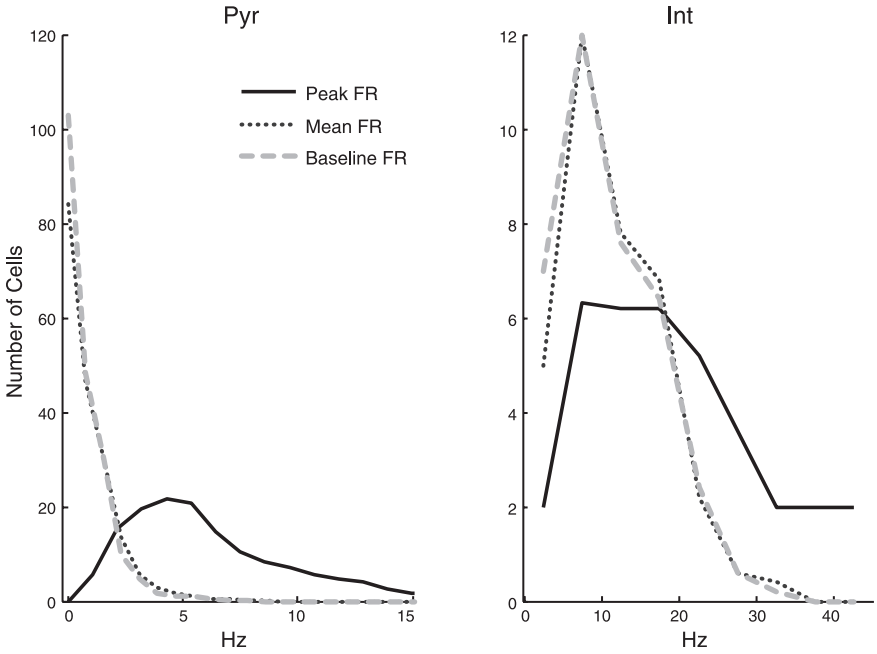

Fig. 4. FR distributions for putative pyramidal cells (*left*) and interneurons (*right*). Peak FR (continuous black line) denotes the maximum FR over all stimuli; Mean FR (dotted gray line) denotes the grand mean FR across all stimuli; Baseline FR (dashed gray line) indicates the mean baseline FR.

resenting bursting behavior that was not present for putative interneurons. Interestingly, not all pyramidal cells exhibited "bursty" autocorrelations. Indeed, we found that the proportion of neurons firing in bursts was much larger in hippocampus (<BP> = 0.25) and amygdala (<BP> = 0.25; Kruskal-Wallis test with Bonferroni correction) than in EC (<BP> = 0.07) and PHC (<BP> = 0.06; also see Supplemental Fig. S1). In an experiment performed in the rat brain, it was also found that the BP of pyramidal cells in hippocampus was significantly larger than the one observed in cells recorded from the EC (Frank et al. 2001). Within the hippocampus, a recent study reported that pyramidal cells in the ventral hippocampus bursted significantly less than cells in the dorsal hippocampus (Royer et al. 2010).

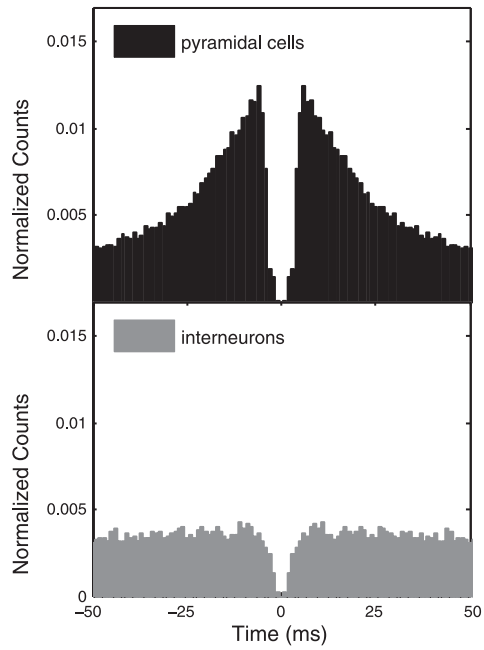

Fig. 5. Average normalized autocorrelograms for putative pyramidal cells (n = 155) and interneurons (n = 39). Note a clear refractory period for both neuronal populations.

To check the consistency of our classification across different areas of the MTL, we identified the location of each cell and performed comparisons between putative pyramidal cells and interneurons within each region. Pairwise comparisons between the width of pyramidal cells and interneurons and between the discharge rate of the two groups in all subregions were significant ($P < 0.05$; Fig. 6).

Selectivity in pyramidal cells and interneurons. We found that pyramidal cells are highly selective and, on average, more selective than interneurons. Using the definition for selectivity introduced in Quiroga et al. (2007), we found that pyramidal cells had a median selectivity index of 0.87, whereas the median selectivity of interneurons was 0.38 ($P < 10^{-13}$ and $P < 0.007$ for the 2 criteria used for classifying pyramidal cells and interneurons; Fig. 7).

To ensure that the difference in stimulus selectivity we found was not the result of the particular definition of selectivity, we repeated the analysis with alternative well-established selectivity measures. Using our main classification method, all six selectivity measures used consistently revealed that pyramidal cells were significantly more selective than interneurons ($P < 0.01$; see Supplemental Fig. S2). Using the more conservative criterion for classification (criterion 2) with less statistical power, we found consistent statistical differences in selectivity ($P < 0.05$) for five of the selectivity measures.

We then investigated seperately neurons showing an increase and a decrease of firing rate on picture presentation. Out of 155 putative pyramidal cells, 149 presented excitatory (positive) responses, and 6 units showed inhibitory (negative) responses. The distribution of positive/negative responses for putative interneurons was different (Fisher exact test, $P < 10^{-9}$). From the sample of 39 putative interneurons, 18 neurons showed positive responses, whereas 16 showed negative responses, and 5 units had mixed responses (positive or nega-

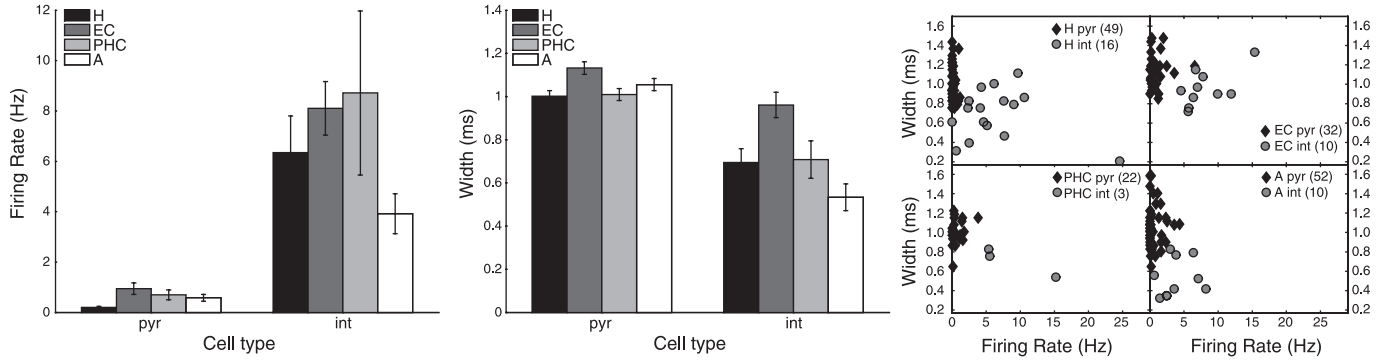

Fig. 6. Consistency of the classification. *Left* and *middle*: regional differences in distinctive features for pyramidal cells and interneurons (H, hippocampus; EC, entorhinal cortex; PHC, parahippocampal cortex; A, amygdala). Comparisons of each feature between pyramidal cells and interneurons in each area were statistically different. *Right*: *k*-means classification scatter plot for all medial temporal lobe (MTL) regions.

tive depending on the stimulus). Keeping only neurons with positive responses, the difference in selectivity between both groups was still highly significant ($P < 10^{-6}$; see Supplemental Fig. S3). To determine the relative contribution of identity and response type, we performed a 2-way ANOVA, where the 2 factors were Identity (pyramidal cells or interneurons) and Response type (positive or negative). The analysis showed a significant main effect for both factors ($P < 10^{-8}$).

We also investigated possible differences between the selectivity of single units and that of multiunits. The multiunit activity consists of the summed activity of neurons that are not close enough to the recording electrode to be identified as single units. Since many neurons can in principle contribute to this signal, we hypothesized that the measured selectivity of multiunits will be lower than the ones of single units. Indeed, the median selectivity of single units (S = 0.80) was significantly higher than that of the multiunits (S = 0.51; $P < 10^{-16}$, Wilcoxon rank sum test).

Next, we compared stimulus selectivity for all MTL areas we recorded from. In Fig. 8, we show the selectivity index for both cell types separately for the four MTL areas. It can be seen that the selectivity of pyramidal cells increases along the hierarchical structure of the MTL. Pyramidal hippocampal cells exhibit the highest degree of selectivity, followed by that in amygdala, EC, and PHC, respectively. Hippocampal neurons were significantly more selective than cells in the other three subregions ($P < 0.05$, Kruskal-Wallis test followed by Bonferroni corrected multiple comparisons among group ranks). The difference in selectivity between putative pyramidal cells and interneurons was consistent across different areas (Fig. 8 and Supplemental Fig. S4). To further quantify the difference in selectivity between pyramidal cells and interneurons, we calculated the average distance in selectivity between both neuronal populations $d = S_{pyr} - S_{int}$. We found that the distance was highest in the hippocampus (0.59), followed by the EC (0.44), the amygdala (0.29), and the PHC (0.25).

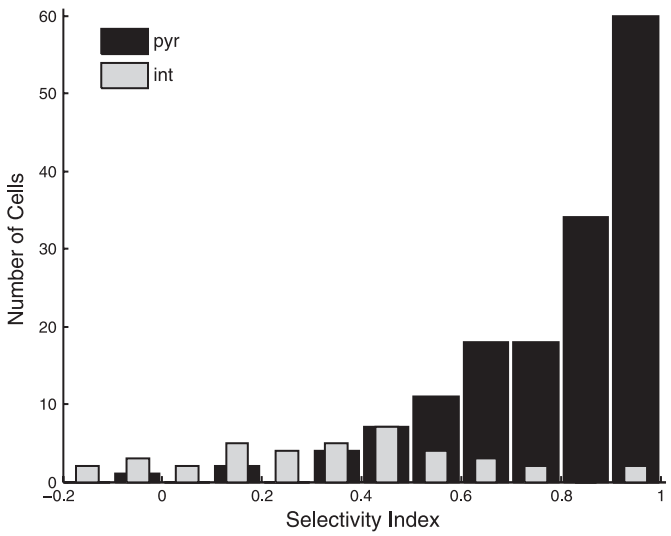

Fig. 7. Selectivity distributions. Distribution of selectivity for responsive pyramidal cells (black bars) and interneurons (gray bars) classified with *k*-means clustering based on FR and spike width (see MATERIALS AND METHODS).

DISCUSSION

We examined the response properties of a large set of cells recorded from the human MTL. After distinguishing between putative pyramidal cells and interneurons based on their electrophysiological signatures, we found that *1*) pyramidal cells are, particularly in the hippocampus, highly selective; *2*) py-

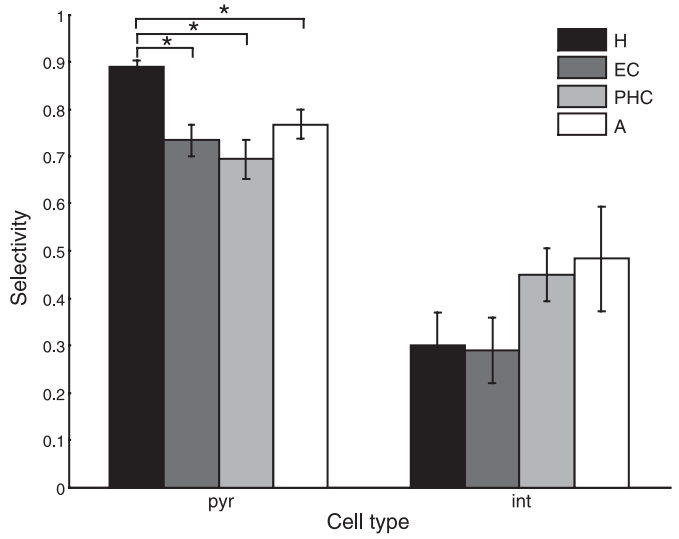

Fig. 8. Selectivity index for different cell types and areas. Pairwise statistical comparisons between cells from different groups in the same area showed all differences to be statistically significant ($P < 0.05$, Wilcoxon rank sum test). *Significant regional differences with hippocampal pyramidal cells ($P < 0.05$, Kruskal-Wallis test followed by Bonferroni-corrected pairwise comparisons between average group ranks). Error bars denote SE.

ramidal cells show higher stimulus selectivity than interneurons; *3*) some spike train properties (CV and proportion of spikes associated with bursts) depend on both the neuron type and area; *4*) multiunits, reflecting the parallel activity of several single units are less selective than single units; and *5*) stimulus selectivity increases along the anatomic pathway of the MTL.

We have previously reported that the representation in the MTL is explicit and sparse, with cells that respond to the identity of a given stimulus across different sensory modalities irrespective of any specific details (Quian Quiroga et al. 2009; Quiroga et al. 2005). For instance, a cell that responded to pictures of Oprah Winfrey also responded to her written and spoken name. Evidence of an ultrasparse representation of information has also been reported in other systems, most notably in the insect olfactory system (Assisi et al. 2007; Jortner et al. 2007; Perez-Orive et al. 2002) and in birdsong production (Hahnloser et al. 2002). How might such selective responses arise in the MTL? We suggest that a winner-take-all mechanism could be implemented in this area (Alvarez and Squire 1994; O'Reilly and McClelland 1994). A key element that could facilitate such a mechanism is the high reliability of synaptic transmission between pyramidal cells and interneurons compared with the weak synapses among principal cells (Csicsvari et al. 1998; Holmgren et al. 2003; Marshall et al. 2002). Even though the firing of a given neuron depends on a complex pattern of connections, we can gain some insight by considering a simple scenario: if one stimulus elicits the activity of a pyramidal cell, which then recruits an interneuron, the interneuron firing might in turn suppress the activity of its target pyramidal cells. In this sense, the interplay between excitation and inhibition helps to make the representation sparser. In principle, the stimulus selectivity of the postsynaptic interneuron could be similar to its presynaptic pyramidal cell. However, this appears unlikely because a single action potential of the presynaptic pyramidal cell can be sufficient to discharge its postsynaptic interneuron (Csicsvari et al. 1998), which suggests that the same interneuron should also fire when a different innervating pyramidal cell is firing (very likely to a different stimulus), thus making the interneuron less selective. A typical pyramidal cell in the MTL also innervates many other pyramidal cells. It could be argued that a presynaptic pyramidal cell also shapes the firing characteristics of its postsynaptic pyramidal cells. However, the contribution from a single pyramidal cell to its postsynaptic pyramidal cells is typically weak, which implies that the selectivity of the target pyramidal cell is not driven by the selectivity of only one of its afferents.

A very limited number of animal studies have previously examined the stimulus selectivity of excitatory and inhibitory neurons. Recording from adjacent neurons in anterior IT from anesthetized macaques, Tamura et al. (2004) found no difference in stimulus selectivity between inhibitory and excitatory neurons. However, they found that the stimulus preference of inhibitory neurons differed from the 1 of their target neurons, suggesting that inhibitory IT neurons are involved in shaping stimulus preferences by providing stimulus-specific inhibition. A more recent study of a rather small population (94 units) of awake monkeys' IT neurons found that putative interneurons had a tendency to be less selective (Zoccolan et al. 2007). In the MTL, recordings from hippocampal CA1 pyramidal cells and interneurons in rats (Marshall et al. 2002) and simultaneous recordings from excitatory and inhibitory neurons from CA1 and EC in rats (Frank et al. 2001) measured the spatial specificity for each type of unit. It was found that putative inhibitory unit fields covered significantly larger fractions of the environment than those of excitatory principal cells, i.e., their selectivity was smaller, but see Wilent and Nitz (2007) for contrasting results. Taken together, these studies indicate that our findings may not be specific to the human MTL, suggesting that the proposed mechanism for generating sparse responses might be a rather general strategy used to represent spatial and nonspatial information. However, in other areas, more distributed representations providing robustness against neuronal variability and efficient discriminative ability could be implemented (Rolls and Tovee 1995).

By comparing several definitions for selectivity, we showed that our findings are not a consequence of the particular definition we used since pyramidal cells exhibited higher selectivity values than interneurons in all cases. We also developed a set of simulations of Poisson neurons with the statistics of both neuronal groups and showed that the selectivity difference we observed could not be due to the limited number of trials (see Supplemental Fig. S5). Within each group, we observed a significant inverse correlation between selectivity and the baseline firing rate (Pearson rank correlation coefficient: -0.74, $P < 10^{-29}$ and -0.48, $P = 0.002$ for putative pyramidal/interneurons; see also Mormann et al. 2008). This difference reflects the fact that a few spikes of a silent neuron that selectively fires to a given stimulus are much more informative than the ones corresponding to a cell with high firing rate.

The separation between putative pyramidal cells and interneurons we found is consistent with the one described in previous studies. Some of the numerical values of the physiological properties in this work (Table 1) differ from the animal literature but are consistent with the ones found in previous studies recording from the human brain (Le Van Quyen et al. 2008; Viskontas et al. 2007). As noted by Likhtik and colleagues (2006), neuronal classification based on extracellular features in the amygdala is more difficult than in other regions, since interneurons and pyramidal cells are intermingled and their dendrites randomly oriented. We reclassified our amygdala cells according to the criterion proposed by these authors (based on firing rate and duration cutoffs) and verified that our results remain valid. Regardless of the general problem of potential technical issues with the classification of neurons recorded extracellularly, where the identity of the recorded neurons cannot be determined with certainty, we did find a significant difference in the selectivity of putative pyramidal cells and interneurons for each of the two alternative methods we used for classification. This further reassures that we are describing two different populations of neurons. The much larger proportion of pyramidal cells firing in bursts in the hippocampus and amygdala compared with cells in EC and PHC extends a previous study performed in the rat brain (Frank et al. 2001), where CA1 excitatory pyramidal cells were found to fire in bursts much more frequently than pyramidal cells in EC.

Most pyramidal cells exhibited positive responses, whereas interneurons were more likely to exhibit negative responses. This difference could arise from the fact that it is technically difficult to measure a negative response from a cell with a low

firing rate. However, in terms of neural coding, it would be inefficient for a silent neuron to encode information by decreasing its firing rate. A cell with a firing rate of 0.6 Hz (the mean firing rate of all pyramidal cells; Table 1) would need ≥1.7 s (1/0.6 Hz) to transmit any rate-related information. Interestingly, in a previous study with human MTL neurons in a memory paradigm, cells with negative responses were not as selective for stimulus features (such as sex and emotional processing of faces) as neurons with positive responses (Fried et al. 2002).

Hippocampal pyramidal cells showed the highest selectivity within the MTL for our set of visual images. The changes in stimulus selectivity in different subregions are in line with the hierarchical organization of the MTL (Mormann et al. 2008; Quian Quiroga et al. 2009) and further extend the processing of information in earlier areas along the ventral visual pathway, where the degree of invariance and selectivity increases from the V1 to IT. In particular, a much smaller degree of selectivity in EC and PHC can possibly be understood from the anatomic connectivity in the MTL, since the PHC projects to EC, which in turn is the major source of projections to the hippocampus (Squire and Zola-Morgan 1991). The hierarchical processing of information is also reflected by the average distance in selectivity between pyramidal cells and interneurons, which increases from PHC to EC, and to hippocampus, where it was found to be maximal.

In rats, hippocampal place cells form a representation of the spatial environment that is vital for the animal's survival. The study of the firing properties of medial EC cells that project directly to the hippocampus showed that, even when these cells exhibit some location specificity, their spatial selectivity is less than the one shown by hippocampal cells (Quirk et al. 1992). We have previously put forward the analogy between the highly selective cells in humans and place cells in rodents (Quiroga et al. 2005). Whereas rodents need to encode relevant features of the environment in a physical space, humans also encode features in a more conceptual space. Our results further extend the similarity showing that hippocampal pyramidal cells are also encoding nonspatial information more selectively than cells in the EC and PHC and refine our previous finding that parahippocampal single and multiunits responded earlier and less selectively than units in other MTL subregions (Mormann et al. 2008). Interestingly, the hierarchical organization of selectivity also fits nicely with our recent report of an increase in the degree of multimodal invariance along the hierarchical structure within the MTL (Quian Quiroga et al. 2009).

In this work, we studied the stimulus selectivity of relatively large populations of putative pyramidal cells and interneurons recorded in vivo from the human MTL of patients engaged in an active behavioral task. We found that putative pyramidal cells are more selective than putative interneurons and that stimulus selectivity increases along the processing pathway of the MTL. Our results suggest the existence of a general mechanism to generate sparse representations by combining cell populations with different selectivity. Whether different subtypes of interneurons contribute differently to stimulus selectivity and whether such a mechanism can be put into a general quantitative theory of neural computation remains a subject to be investigated.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

Alvarez P, Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. *Proc Natl Acad Sci USA* 91: 7041–7045, 1994.

Assisi C, Stopfer M, Laurent G, Bazhenov M. Adaptive regulation of sparseness by feedforward inhibition. *Nat Neurosci* 10: 1176–1184, 2007.

Bartho P, Hirase H, Monconduit L, Zugaro M, Harris KD, Buzsaki G. Characterization of neocortical principal cells and interneurons by network interactions and extracellular features. *J Neurophysiol* 92: 600–608, 2004.

Buzsaki G, Penttonen M, Nadasdy Z, Bragin A. Pattern and inhibition-dependent invasion of pyramidal cell dendrites by fast spikes in the hippocampus in vivo. *Proc Natl Acad Sci USA* 93: 9921–9925, 1996.

Constantinidis C, Goldman-Rakic PS. Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. *J Neurophysiol* 88: 3487–3497, 2002.

Csicsvari J, Hirase H, Czurko A, Buzsáki G. Reliability and state dependence of pyramidal cell-interneuron synapses in the hippocampus: an ensemble approach in the behaving rat. *Neuron* 21: 179–189, 1998.

Csicsvari J, Hirase H, Czurkó A, Mamiya A, Buzsáki G. Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat. *J Neurosci* 19: 274–287, 1999.

Duda RO, Stork DG. *Pattern Classification*. New York: Wiley, 2000.

Fox SE, Ranck JB Jr. Electrophysiological characteristics of hippocampal complex-spike cells and theta cells. *Exp Brain Res* 41: 399–410, 1981.

Franco L, Rolls ET, Aggelopoulos NC, Jerez JM. Neuronal selectivity, population sparseness, and ergodicity in the inferior temporal visual cortex. *Biol Cybern* 96: 547–560, 2007.

Frank LM, Brown EN, Wilson MA. A comparison of the firing properties of putative excitatory and inhibitory neurons from CA1 and the entorhinal cortex. *J Neurophysiol* 86: 2029–2040, 2001.

Freund TF, Buzsáki G. Interneurons of the hippocampus. *Hippocampus* 6: 347–470, 1996.

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* 12: 575–584, 2002.

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

Hahnloser RH, Kozhevnikov AA, Fee MS. An ultra-sparse code underlies the generation of neural sequences in a songbird. *Nature* 419: 65–70, 2002.

Henze DA, Borhegyi Z, Csicsvari J, Mamiya A, Harris KD, Buzsaki G. Intracellular features predicted by extracellular recordings in the hippocampus in vivo. *J Neurophysiol* 84: 390–400, 2000.

Holmgren C, Harkany T, Svennenfors B, Zilberter Y. Pyramidal cell communication within local networks in layer 2/3 of rat neocortex. *J Physiol* 551: 139–153, 2003.

Ison MJ, Quiroga RQ. Selectivity and invariance for visual object perception. *Front Biosci* 13: 4889–4903, 2008.

Johnston K, DeSouza JF, Everling S. Monkey prefrontal cortical pyramidal and putative interneurons exhibit differential patterns of activity between prosaccade and antisaccade tasks. *J Neurosci* 29: 5516–5524, 2009.

Jortner RA, Farivar SS, Laurent G. A simple connectivity scheme for sparse coding in an olfactory system. *J Neurosci* 27: 1659–1669, 2007.

Klausberger T, Magill PJ, Márton LF, Roberts JD, Cobden PM, Buzsáki G, Somogyi P. Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature* 421: 844–848, 2003.

Klausberger T, Somogyi P. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* 321: 53–57, 2008.

Kreiman G, Koch C, Fried I. Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat Neurosci* 3: 946–953, 2000.

Le Van Quyen M, Bragin A, Staba R, Crepon B, Wilson CL, Engel J. Cell type-specific firing during ripple oscillations in the hippocampal formation of humans. *J Neurosci* 28: 6104–6110, 2008.

Lehky SR, Sejnowski TJ, Desimone R. Selectivity and sparseness in the responses of striate complex cells. *Vision Res* 45: 57–73, 2005.

Likhtik E, Pelletier JG, Popescu AT, Pare D. Identification of basolateral amygdala projection cells and interneurons using extracellular recordings. *J Neurophysiol* 96: 3257–3265, 2006.

Marshall L, Henze DA, Hirase H, Leinekugel X, Dragoi G, Buzsáki G. Hippocampal pyramidal cell-interneuron spike transmission is frequency dependent and responsible for place modulation of interneuron discharge. *J Neurosci* 22: 2002.

Maurer AP, Cowen SL, Burke SN, Barnes CA, McNaughton BL. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci* 26: 13485–13492, 2006.

Mitchell JF, Sundberg KA, Reynolds JH. Differential attention-dependent response modulation across cell classes in macaque visual area V4. *Neuron* 55: 131–141, 2007.

Moody SL, Wise SP. A model that accounts for activity prior to sensory inputs and responses during matching-to-sample tasks. *J Cogn Neurosci* 12: 429–448, 2000.

Mormann F, Kornblith S, Quiroga RQ, Kraskov A, Cerf M, Fried I, Koch C. Latency and selectivity of single neurons indicate hierarchical processing in the human medial temporal lobe. *J Neurosci* 28: 8865–8872, 2008.

O'Reilly RC, McClelland JL. Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. *Hippocampus* 4: 661–682, 1994.

Olshausen BA, Field DJ. Sparse coding of sensory inputs. *Curr Opin Neurobiol* 14: 481–487, 2004.

Perez-Orive J, Mazor O, Turner GC, Cassenaer S, Wilson RI, Laurent G. Oscillations and sparsening of odor representations in the mushroom body. *Science* 297: 359–365, 2002.

Quian Quiroga R, Kraskov A, Koch C, Fried I. Explicit encoding of multimodal percepts by single neurons in the human brain. *Curr Biol* 19: 1308–1313, 2009.

Quirk GJ, Muller RU, Kubie JL, Ranck JB Jr. The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. *J Neurosci* 12: 1945–1963, 1992.

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

Quiroga RQ, Reddy L, Koch C, Fried I. Decoding visual inputs from multiple neurons in the human temporal lobe. *J Neurophysiol* 98: 1997–2007, 2007.

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

Rolls ET, Tovee MJ. Sparseness of the neuronal representation of stimuli in the primate temporal visual cortex. *J Neurophysiol* 73: 713–726, 1995.

Rosenkranz JA, Grace AA. Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *J Neurosci* 21: 4090–4103, 2001.

Royer S, Sirota A, Patel J, Buzsaki G. Distinct representations and theta dynamics in dorsal and ventral hippocampus. *J Neurosci* 30: 1777–1787, 2010.

Smith DV, Travers JB. A metric for the breadth of tuning of gustatory neurons. *Chemical Senses and Flavor* 4: 215–229, 1979.

Softky WR, Koch C. The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *J Neurosci* 13: 334–350, 1993.

Squire LR, Zola-Morgan S. The medial temporal lobe memory system. *Science* 253: 1380–1386, 1991.

Tamura H, Kaneko H, Kawasaki K, Fujita I. Presumed inhibitory neurons in the macaque inferior temporal cortex: visual response properties and functional interactions with adjacent neurons. *J Neurophysiol* 91: 2782–2796, 2004.

Ungerleider LG, Mishkin M. Two cortical visual systems. In: *Analysis of Visual Behavior*, edited by Ingle DJ, Goodale MA, and Mansfield RJ. Cambridge, MA: MIT Press, 1982, p. 549–585.

Van Essen DC, Maunsell JH. Hierarchical organization and functional streams in the visual cortex. *Trends Neurosci* 6: 370–375, 1983.

Vinje WE, Gallant JL. Sparse coding and decorrelation in primary visual cortex during natural vision. *Science* 287: 1273–1276, 2000.

Viskontas IV, Ekstrom AD, Wilson CL, Fried I. Characterizing interneuron and pyramidal cells in the human medial temporal lobe in vivo using extracellular recordings. *Hippocampus* 17: 49–57, 2007.

Wiebe SP, Staubli UV. Recognition memory correlates of hippocampal theta cells. *J Neurosci* 21: 3955–3967, 2001.

Wilent WB, Nitz DA. Discrete place fields of hippocampal formation interneurons. *J Neurophysiol* 97: 4152–4161, 2007.

Willmore B, Tolhurst DJ. Characterizing the sparseness of neural codes. *Network* 12: 255–270, 2001.

Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, Suzuki WA. Single neurons in the monkey hippocampus and learning of new associations. *Science* 300: 1578–1581, 2003.

Young M, Yamane S. Sparse population coding of faces in the inferotemporal cortex. *Science* 256: 1327–1331, 1992.

Zoccolan D, Kouh M, Poggio T, DiCarlo JJ. Trade-off between object selectivity and tolerance in monkey inferotemporal cortex. *J Neurosci* 27: 12292–12307, 2007.