8 Visual Cognitive Adventures of Single Neurons in the Human Medial Temporal Lobe

Florian Mormann, Matias J. Ison, Rodrigo Quian Quiroga, Christof Koch, Itzhak Fried, and Gabriel Kreiman

Overview

Here we summarize some of the work examining visual cognition through recordings of single neurons in the human medial temporal lobe (MTL). These recordings were performed in patients with pharmacologically intractable epilepsy as part of the procedure to determine the seizure focus for surgical resection (as described in chapter 3). These surgical procedures provide a rare opportunity to listen to the activity of neural circuits in the human brain while subjects are awake and perform different types of cognitive tasks (Ojemann, 1997; Crick et al., 2004; Engel et al., 2005; Kreiman, 2007; Mukamel & Fried, 2012; Suthana et al., 2012). Throughout this chapter, we emphasize some of the opportunities, challenges and solutions, and progress and open questions, as well as some of the scientific and clinical implications of the work.

Medial Temporal Lobe Connectivity

We start by providing a brief overview of the neuroanatomical connections of the MTL. Most of our understanding about detailed connectivity is based on tracing studies in rodents or nonhuman primates. There has been increased interest recently in the use of noninvasive methods based on diffusion tensor imaging and related techniques to study connectivity patterns in the human brain (e.g., Marcus et al., 2011), but the most detailed studies of connectivity patterns have been conducted in monkeys and rodents.

The human MTL comprises three anatomical structures: amygdala, hippocampus, and parahippocampal gyrus. The parahippocampal gyrus features three functionally and histologically different types of cortex; these are—from posterior to anterior—parahippocampal, perirhinal, and entorhinal cortex. Studies on cytoarchitectonic organization and connectivity in nonhuman primates and rodents have established the entorhinal cortex as the main input region for the hippocampus. Neuronal signals predominantly propagate from superficial layers of the entorhinal cortex through specific hippocampal subregions (dentate gyrus → CA3 → CA1 → subiculum) back to deep entorhinal layers (Squire et al., 2004; Amaral & Lavenex, 2007). The entorhinal cortex receives its major inputs from the perirhinal and parahippocampal cortices (Suzuki & Amaral, 1994), which in turn have reciprocal connections to various multimodal
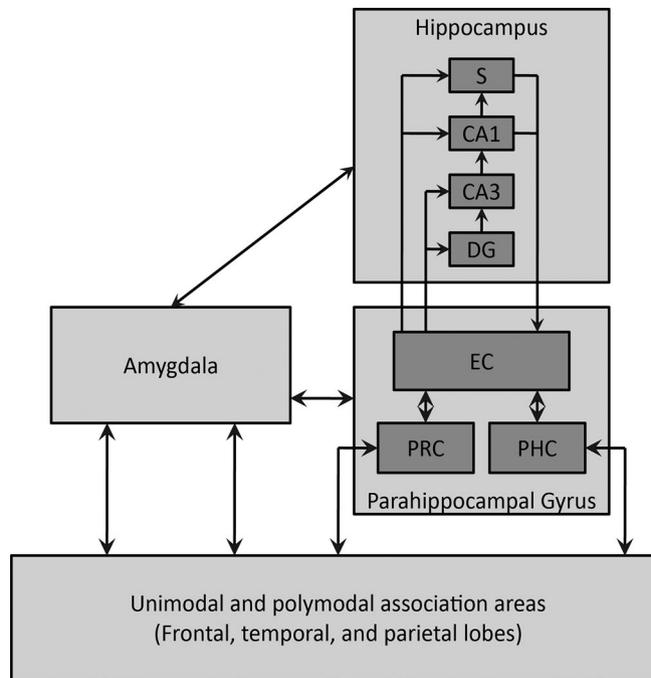
Figure 8.1
Schematic diagram of medial temporal lobe structures and their connectivity. S, subicular complex; DG, dentate gyrus; CA1, CA3, the CA fields of the hippocampus; EC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex. Adapted from Squire et al. (2004) and Suzuki (1996).

association areas in the frontal, temporal, and parietal lobe (see figure 8.1). The amygdala takes a special role within the MTL in that it has connections to virtually every other brain region and represents one of the major hubs in brain connectivity (Young et al., 1994).

The hippocampus, amygdala, entorhinal cortex, and parahippocampal cortex are frequent targets for implanted electrodes in epilepsy patients (see chapter 3). The perirhinal cortex is less often targeted by clinical procedures due to higher interindividual variability of its exact localization (Insausti et al., 1998).

The Medial Temporal Lobe and Memory
The functional role of neurons in the human MTL is still largely unknown. Insight about human MTL function has been derived mostly from lesion studies. The best known case is H.M., an epilepsy patient who underwent neurosurgical bilateral MTL resection in 1953 and subsequently suffered from a predominantly anterograde amnesia in the sense that he could never again encode explicit memories while still being able to recall memories from before his surgery (Scoville & Milner, 1957; Squire, 2009). From this and related cases, neuroscientists have learned that the

MTL plays a crucial role in memory formation. Rutishauser and colleagues review the role of single neurons in the human brain during several tasks that involve memory formation in chapter 7. Given the prominent role of the hippocampus and surrounding structures in declarative memory, the memory for facts and events that can later be consciously and explicitly recalled, it is important to ponder upon the relationship between the bewildering complexity of responses that we describe below and the consolidation of memories. It is tempting to speculate that some of the responses to complex stimuli described in this chapter constitute a backbone to form novel associations, to detect novelty, and ultimately to form long-term memories. We discuss this point further at the end of the chapter.

One Hat Does Not Fit All

An important cautionary note is pertinent here. While we seek to find unifying principles for MTL function, we should not ignore the fact that the MTL constitutes a large span of the brain, with multiple distinct structures, each with its own inputs and outputs. The history of biology teaches us once and again about the marvelous specificity encountered at all levels, from the molecular to the cellular to the neural circuit level. Thus, we need to sharpen our tools and our description to separately describe the activity of neurons in different structures. Documenting such specificity is not always easy given the difficulties inherent to precisely localizing electrodes and in achieving large sample numbers in our studies. We discuss below some important examples of specificity and their implications for elucidating the function and interactions among MTL structures.

Methodological Considerations

Patients with epilepsy who do not respond to medication go through a battery of tests to evaluate their suitability for resective surgery (Engel, 1996; Ojemann, 1997). As discussed in more detail in chapters 3 and 4, it is very important to describe the procedures and tests at full length to the patient (and to the families when appropriate) so that they can provide their informed consent about the surgical protocol, electrode implantation, and cognitive testing. The patients independently consent to the clinical procedures and any research-related procedures including cognitive testing. A description of the surgical procedure is provided in chapter 3. In addition to other institutional requirements, any person interested in working with patients must have a thorough understanding of the ethical considerations raised in chapter 4.

The quality of signals recorded from microwire electrodes depends on multiple factors. Neurophysiology in a hospital setting is not an easy endeavor, and there are abundant sources of electrical noise (many of which can appear to be deceptively similar to real spikes). Some of the critical factors include the electrode design and impedance and the cables and hardware used to amplify, filter, and condition the signals, or the presence of other electrical equipment in the room. These topics are discussed in more detail in chapter 5. Several aspects of the algorithms and software developed to process neurophysiological signals are discussed in chapter 6.

After electrodes have been implanted and all the hardware has been set up, several important considerations can help smooth the procedures for cognitive evaluation and testing. Of utmost importance is to understand that the goal of the whole procedure is to address the patients' seizure events. Thus, all clinical considerations must take priority over the research efforts. In addition to guaranteeing the patients' safety and conducting any necessary clinical procedures and evaluations, it is critical to understand the patients' needs, unique situations, and comforts. The patient is staying in a hospital, for several days, away from home, surrounded by a plethora of strange people that come in and out, with electrodes and cables implanted in his or her brain, with severely limited mobility, sometimes sleep deprived, sometimes in pain, sometimes mentally or emotionally affected by the withdrawal of antiepileptic medication, and with all sorts of equipment in his/her milieu. While we do not want to undermine the talent of the whole team of neurosurgeons, neurologists, nurses, technicians, engineers, and investigators, we doff our hats to the patients. They are the heroes of our scientific and clinical efforts. In spite of all the difficulties, they put forward their best faces and efforts to help advance medicine and push the frontiers of science.

It is essential for investigators to be aware of the environment and respect the patients' need for privacy, rest, and comfort. Investigators must also clearly convey the procedures to the patients. Whenever appropriate, these procedures also need to be communicated to the family. Investigators must constantly check for patient fatigue and ease during the entire testing procedure. Most patients are willing to perform several paradigms per day with ample breaks in between. For this purpose it has proven important to restrict the duration of each individual paradigm to a maximum of 30 to 45 minutes in order to prevent fatigue, which could compromise continued participation. Due to a number of factors, not all patients will be able to complete all types of tests. It should be clearly understood that participation in experiments occurs on a strictly voluntary basis and that patients are free to pause, halt, or quit experiments at any time. On some occasions, this may entail adaptability and the design of adequate tests to meet the requirements of the ongoing conditions. When patients see that effort is taken to meet their individual needs, it is our experience that they are usually more than willing to participate in cognitive experiments, as they rightly feel that they participate in advancing science and potentially helping future patients.

Almost all experiments discussed here have involved presenting visual stimuli for a certain amount of time (e.g., among many others, Heit et al., 1988; Fried et al., 1997; Kreiman et al., 2000a; Quian Quiroga et al., 2005; Rutishauser et al., 2006; Mormann et al., 2008; Ison et al., 2011; Mormann et al., 2011; Rutishauser et al., 2011). Stimuli are typically presented on a laptop computer situated in front of the patient at a distance of approximately 50 to 80 cm. The receptive field sizes of neurons in the human MTL are not exactly known. However, extrapolating from intracranial field potential studies in humans (Yoshor et al., 2007; Agam et al., 2010) and from single cell studies in monkey inferior temporal cortex (ITC; Logothetis & Sheinberg, 1996; Tanaka, 1996), it is likely that many receptive fields span many degrees of visual angle and include the fovea. Largely, stimuli subtending ~2–10 degrees of visual angle have been presented

at the fovea. Little do we know about the preferences of neurons in the human MTL (with some notable exceptions highlighted below). Because the type of stimuli often used in "low-level" vision experiments (e.g., Gabor patches, curvatures, etc.) are not directly meaningful to the subjects, typically, investigators have used a large battery of "natural" stimuli including animals, human faces (famous or not, depicting specific emotions or not), scenes, household objects, and abstract patterns. Stimuli have been presented in color or gray scale. Stimuli are presented for as short as 33 ms and as long as several seconds. Unless strongly required by the characteristics of the task, it is advisable to use event-related designs with a randomized order of presentation to avoid confounding factors. We discuss the response properties elicited by visual stimuli in further detail below.

In some cases, investigators have followed a two-step procedure whereby they first present a battery of pictures and then select the ones that elicit stronger responses for further investigation. In these cases, neural responses are evaluated immediately after the session or even in real time. A smaller subset of stimuli that elicit selective responses in one or more of the neurons can then be used for subsequent experimental paradigms. In some cases, the pictures presented in these sessions can be chosen based on the likings and interests of the patients. Asking patients, for example, about their favorite TV shows, their hobbies, sports, political interests, places they have visited, and so on is helpful in selecting stimuli that are meaningful for the patients. Experience has shown that the more familiar and relevant a stimulus is for a patient, the higher the likelihood of finding a MTL neuron responding to this stimulus. This anecdotal notion was confirmed in a quantitative study in which pictures of people that were personally known to the patient such as family members, friends, or medical personnel were more likely to elicit neuronal responses than famous people not known personally, which in turn were more likely to elicit responses than people unknown to the patient (Viskontas et al., 2007). In several recordings, selective responses were even observed to pictures of the experimenters themselves who had been unknown to the patients until a day or two before the recordings (e.g., Viskontas et al., 2007; Quian Quiroga et al., 2009; Cerf et al., 2010). These reports are evidence for the strong degree of plasticity in the MTL and will be an important subject for future research. When neurons recorded from particular microwires change their response behavior between recording sessions, it is difficult to decide whether this is due to micromovements of the wires (i.e., recording from different neurons) or is due to altered response tuning within the same neuron (i.e., plasticity). On the other hand, anecdotal evidence shows that at least in some cases selective response behavior in a recording channel (i.e., a "similar-looking" unit responding to the same single person in a set of over 100 stimuli) remains constant over five days or more.

Fewer experiments have investigated the responses to auditory stimuli. Chords, speech, and complex pieces of music have been presented to exceptionally rare cases of patients with microwires implanted in auditory cortex (Mukamel et al., 2005; Nir et al., 2007; Bitterman et al., 2008). Most of these studies examining responses to nonverbal acoustic stimuli focused on neurons outside the MTL and are therefore beyond the scope of this chapter. In patients with MTL microwires, use of auditory stimuli has included tones and words spoken by a computer

R

voice, for example, names of persons, objects, and so on (see "A Plethora of Visually Evoked Responses" below).

A large variety of tasks have been implemented to study how the MTL orchestrates different aspects of cognition. As a general rule, even when the main interest centers around the physiological responses to the stimuli, it is advisable to have subjects perform a simple (unrelated) task as opposed to passive viewing conditions under which subjects might doze off or not pay attention to the stimuli. For example, after image offset, subjects may have to answer a simple question such as whether the picture contained certain features or belonged to a particular stimulus category. Such a simple task requires them to attend to the pictures. Every stimulus presentation is preceded by a fixation cross for a few hundred milliseconds to assess baseline firing activity.

Most epilepsy patients are capable of participating in cognitive paradigms. Depending on the location of the epileptic focus, patients may exhibit localization-related neuropsychological deficits such as mnemonic deficits in MTL epilepsy or executive function deficits in frontal lobe epilepsy. In dubious cases it may be advisable to perform a cognitive screening prior to implanting electrodes in order to assess patients' capability to participate in the planned research. Moreover, a battery of neuropsychological test results is usually available to the attending physician to help decide whether or not a patient may be suited for a particular research paradigm.

When taking advantage of the unique access to studying the brain activity of patients undergoing epilepsy monitoring, one should always realize that these patients usually have a functionally and structurally altered brain, which is what causes them to suffer from epileptic seizures in the first place. These alterations, however, are focally confined, which is why neurosurgical removal of the seizure-generating focal region ideally leads to freedom from seizures. It is therefore reasonable to assume that the majority of the brain behaves like any normal human brain. Nevertheless, researchers are well-advised to always ensure that their reported findings remain valid after excluding data obtained from these focal regions, particularly if a hemispheric asymmetry of findings is observed (Mormann et al., 2011).

A Plethora of Visually Evoked Responses

Background: Inferior Temporal Cortex

With the exception of primary visual cortex (area V1), the stimulus features that lead to high firing rates in neurons along the ventral visual stream remain poorly understood (Logothetis & Sheinberg, 1996; Tanaka, 1996; Riesenhuber & Poggio, 2000; Connor et al., 2007; Serre et al., 2007). This has not precluded investigators from correlating neuronal responses with the presentation of simple and complex shapes including faces, fractals, paper clips, and many more. The ventral visual stream is organized in a coarsely hierarchical fashion. At the highest echelon of the visual hierarchy, ITC, neurons typically show strong responses to complex shapes (Rolls, 1991; Logothetis & Sheinberg, 1996; Tanaka, 1996). The neurophysiological responses in monkey ITC have latencies of approximately 100 ms (Eskandar et al., 1992; Keysers et al.,

2001; Hung et al., 2005). Interestingly, ITC neurons show a significant degree of robustness to transformations in properties of the image including scale, position, some degree of rotation, color, and other cues (Rolls, 1991; Logothetis et al., 1994; Ito et al., 1995; Logothetis et al., 1995; Logothetis & Sheinberg, 1996; Grill-Spector et al., 1998). As succinctly outlined above (see "Medial Temporal Lobe Connectivity"), it is likely that ITC signals constitute the main input to the MTL structures discussed in this chapter (including direct and indirect input depending on the particular substructure within the MTL).

While the ITC in nonhuman primates has been investigated rather extensively, electrophysiological studies in this brain region have been rather rare in humans. In fact, it is not even clear what the human homologue of monkey ITC actually is. Evidence from intracranial field potentials (but not single units) recorded from several areas along the ventral occipital and temporal lobe show strong selectivity to complex shapes, tolerance to object transformations, and short latencies, properties that are coarsely comparable to the results reported in the macaque monkey ITC (Allison et al., 1999; McCarthy et al., 1999; Liu et al., 2009; Agam et al., 2010). Likewise, the hierarchical clustering of different stimuli, based on similar neuronal response patterns, is preserved across species—that is, the same stimuli tend to group together both in humans and in monkeys (Kriegeskorte et al., 2008). These functional homologies can in turn be used to map anatomical regions subserving the same specific functions between human and nonhuman primates (e.g., Tsao et al., 2008a). Yet, these functional similarities should not be interpreted to imply direct homology at the anatomical, cellular, or connectivity levels between human and monkey structures, species whose last common ancestor lived about 30 million years ago. More work is needed to establish homologies between macaque studies and human studies to better understand the inputs to the MTL.

Responses to Complex Shapes

A variety of responses to visual shapes have been demonstrated in the human MTL (Heit et al., 1988; Kreiman et al., 2000a; Mormann et al., 2008). Given the strong inputs from ITC, some MTL neurons may also inherit some of the dependence on low-level image properties such as contrast (Steinmetz et al., 2011).

Action potentials recorded from extracellular microwires in the human MTL exhibit regional differences in amplitude (see figure 8.2A). Given the dependence on action potential amplitude on the distance between the microwire and neuronal soma (see chapter 6), the origin of this difference might be related to the local density of different areas in the MTL. If the distance between the tip of the electrode and a given cell was larger in amygdala than in hippocampus, then the average amplitude would be expected to be larger in the hippocampus (since the amplitude of an extracellularly recorded spike decreases as a function of distance; see chapter 6). Interestingly, in mice the neuronal density in the hippocampus (CA1, CA2/3) has been found to be twice as large as the neuronal density in amygdala, strongly supporting this finding (von Bohlen und Halbach and Unsicker, 2002). In the human brain, a study with patients with either hippocampal sclerosis or lesional temporal lobe epilepsy found evidence that the density in the

hippocampal region is lower than the density in the entorhinal cortex (Dawodu & Thom, 2005). This is also consistent with the larger amplitude exhibited by entorhinal cortex neurons. The difference with respect to hippocampal cells was marginally significant (Wilcoxon rank-sum test, p = 0.04).

The spontaneous firing rates in the human MTL are typically quite low (mean of 0.6 spikes/s, SD = 0.9 spikes/s for putative pyramidal cells; Ison et al., 2011; figure 8.2C, D). The baseline firing rates before stimulus presentation show differences across different parts of the MTL (e.g., Mormann et al., 2008, figure 8.2C) and are consistent with those reported in the rodent and macaque literature. Intriguingly, some of the MTL neurons exhibit a remarkably low firing rate (with less than one spike per minute) but show transient increased firing in response to a preferred stimulus (e.g., Quian Quiroga et al., 2005; figure 8.2D). This sparse response suggests that some of the single electrode studies where investigators try to move an electrode to isolate neurons with high sustained firing rate could be missing some of the extremely "shy" neurons (see the discussion in Shoham et al., 2006). In contrast, microelectrodes used for single unit recordings in humans cannot be moved and thus may provide a more "unbiased" sample of units including those with low firing rates.

The MTL contains various neuron classes (Lein et al., 2004), including a majority of (excitatory) principal cells and several types of (inhibitory) interneurons. Investigators have used electrophysiological features like the baseline firing activity and spike duration to separate putative pyramidal cells from putative interneurons (e.g., Ison et al., 2011, figure 8.2B). In general, putative interneurons defined in this fashion show more graded responses to multiple stimuli, which has been interpreted to reflect a plausible mechanism to generate sparse representations by combining cell populations with different selectivity (Ison et al., 2011).

Invariance Properties

Critical to visual recognition as well as to the formation of episodic memories is the need to build representations that discount many of the basic metric properties of the stimuli as they are usually irrelevant to the task at hand (Squire & Zola-Morgan, 1991; Wagner et al., 1999; Dudai,

Figure 8.2
Properties of medial temporal lobe (MTL) neurons. (A) Mean waveforms for visually selective putative pyramidal cells (N = 155) recorded from the hippocampus (H; N = 49), entorhinal cortex (EC; N = 32), parahippocampal cortex (PHC; N = 22), and amygdala (A; N = 52). Bands show the mean ±SEM. Entorhinal neurons show the highest amplitudes, followed by hippocampal neurons. Waveforms recorded from the amygdala and parahippocampal cortex exhibit smaller amplitudes. Cell identity was determined with k-means clustering based on firing rate and spike width (Ison et al., 2011). (B) Normalized waveforms of putative pyramidal cells and interneurons. (C) Mean baseline firing rate (FR) for MTL putative pyramidal cells (N = 155). Error bars denote SEM. (D) Mean peak FR over all stimuli. (E) Response latency for MTL putative pyramidal cells responding to one or more stimuli. Latencies were defined as the first time point where the instantaneous firing rate (IFR) crossed a threshold given by 3 SD above the mean baseline IFR. (F) Selectivity of putative pyramidal cells. Stimulus selectivity was assessed using the selectivity index introduced by Quian Quiroga et al. (2005). This measure of selectivity is close to 0 for uniformly distributed random firings and approaches 1 the more selective the neuron is. (G) Spike detection threshold estimated from the median absolute amplitudes of the high-pass filtered signal for MTL responsive units (single and multiunits, N = 579). (H) Mean spike amplitude for MTL responsive units.
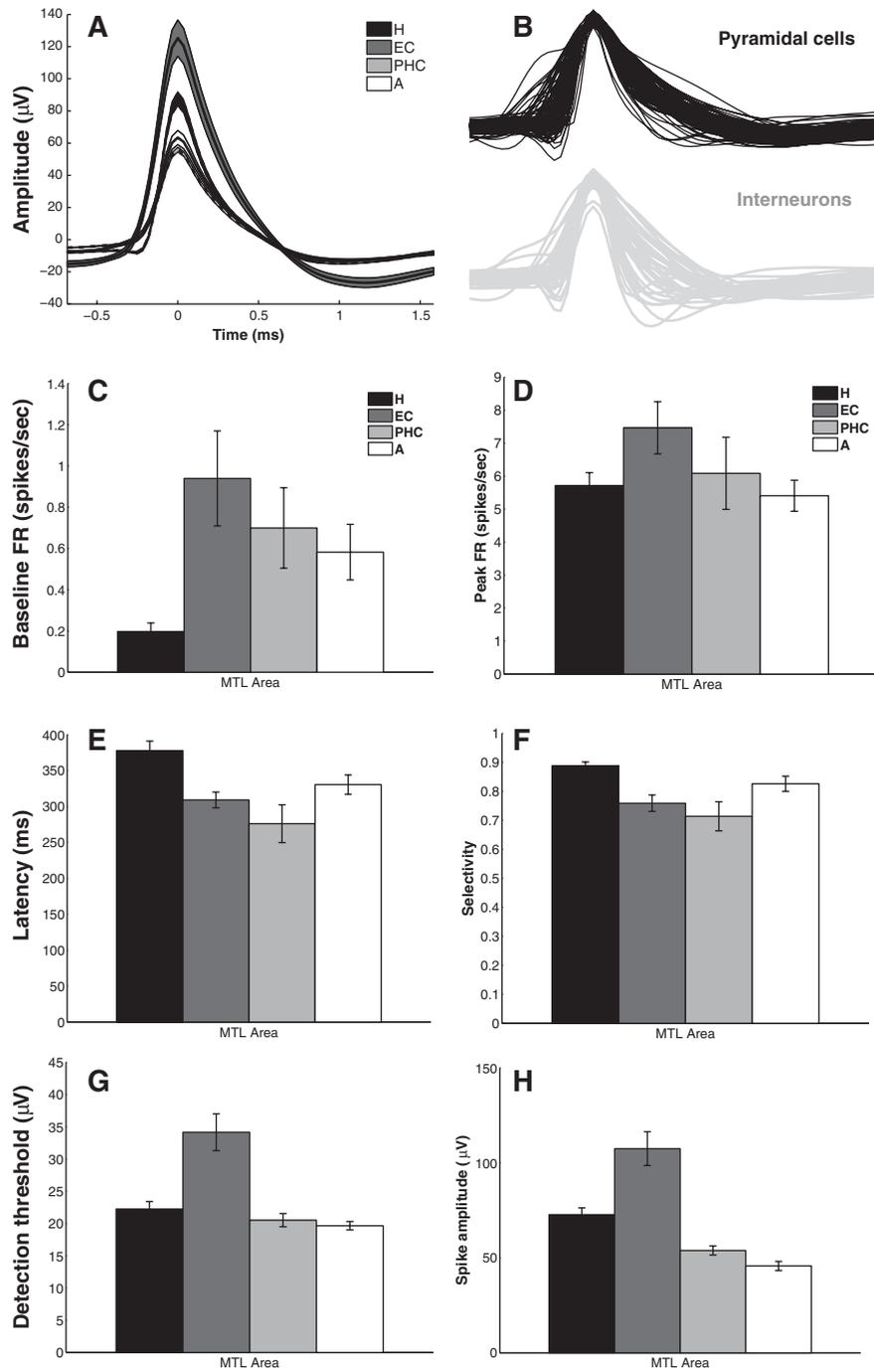
2012). Indeed, neurons in the human MTL show a remarkable degree of tolerance to many image transformations. We discuss a few striking examples here.

Some neurons respond to multiple different images that are quite distinct at the pixel level but which belong to the same category. The word "category" signifies many different things. In a remarkable study describing the activity of neurons in the macaque ITC and prefrontal cortex, Miller's group parametrically varied the shape of various synthetic images of cats and dogs and trained monkeys to separate these into two visual categories (Freedman et al., 2001; Meyers et al., 2008). What's particularly interesting about this study is that the distance (at least defined in pixel space) between two stimuli belonging to the same "category" was the same as the distance between two stimuli belonging to different categories (see also Sigala & Logothetis, 2002), thus showing the task-dependent categorical nature of the responses.

In human cognitive studies, the word "category" is often taken to imply "semantic" categories such as humans, animals, objects, and so on. In one of the first studies describing visual responses in the human MTL, the authors described single neuron responses to subsets of the presented stimuli that constituted semantic categories such as animals, household objects, cars, spatial scenes, and famous and unknown faces (Kreiman et al., 2000a). Extending these findings, a recent study described a specific response preference for the category of animals in neurons from the right, but not left, human amygdala (Mormann et al., 2011). An example of such a response to "animals" is shown in figure 8.3 (plate 6). This categorical selectivity was confirmed in a separate functional magnetic resonance imaging (fMRI) experiment in healthy subjects and appeared to be independent of emotional dimensions such as valence or arousal. A plausible evolutionary explanation is that the phylogenetic importance of animals, which could represent either predators or prey, has resulted in neural adaptations for the dedicated processing of these biologically salient stimuli in a phylogenetically old structure like the amygdala.

Two cautionary notes should be mentioned here. First, as emphasized above, only a limited number of stimuli were presented and we cannot be sure that the neuron would respond to all possible images of animals. Second, it is possible that stimuli belonging to the same category share basic metric properties that distinguish them from stimuli in other categories.

Another seminal study described neurons representing a specific semantic concept in the human MTL (Quian Quiroga et al., 2005). An example of this type of responses is shown in figure 8.4 (plate 7). These cells may respond to very different pictures of a given person that the patient is familiar with. The notion that simple metric or pixel properties can describe those responses is even harder to reconcile with the activity of some neurons that also responded to the written or spoken name (Quian Quiroga et al., 2005; Quian Quiroga et al., 2009). These responses to visual stimuli, text, and voices do not directly bring us any closer to understanding the origin of this type of sparse, selective, and invariant neuronal preference. Under several strong assumptions, investigators were able to estimate that a single person is likely to be represented by up to a few million neurons (but possibly a much smaller number) and that, conversely, a given neuron can represent tens to hundreds of different people (Waydo et al., 2006). Indeed, this type of encoding of semantic information in such an explicit and specific way is more in
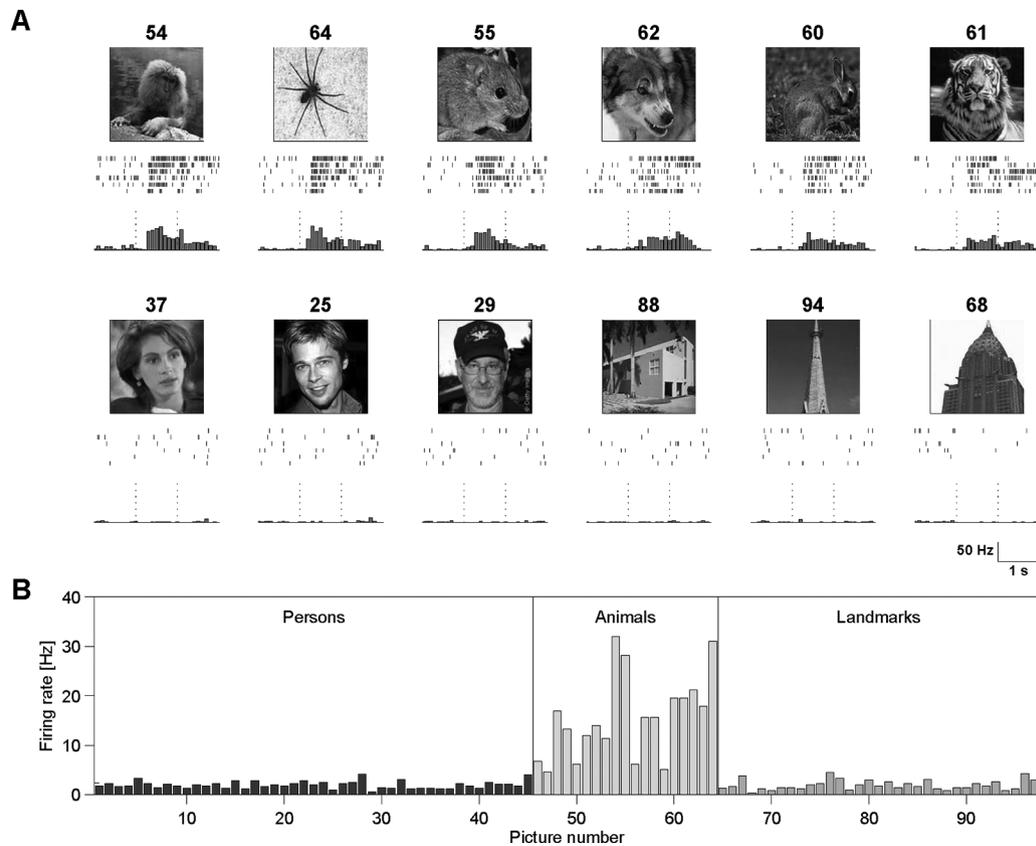
Figure 8.3 (plate 6)
A single unit in the amygdala activated by multiple different pictures containing animals. (A) Responses of a neuron in the right amygdala to pictures from different stimulus categories, presented in randomized order. Here we show the responses to 12 of the 97 pictures shown in this experiment. For each picture, the corresponding raster plots (trial order is from top to bottom) and peristimulus time histograms are given. Vertical dashed lines indicate image onset and offset (1 s apart). (B) The mean response firing rates of this neuron between image onset and offset across six presentations for all individual pictures. Pictures of persons, animals, and landmarks are denoted by brown, yellow, and cyan bars, respectively. Modified from Mormann et al. (2011).
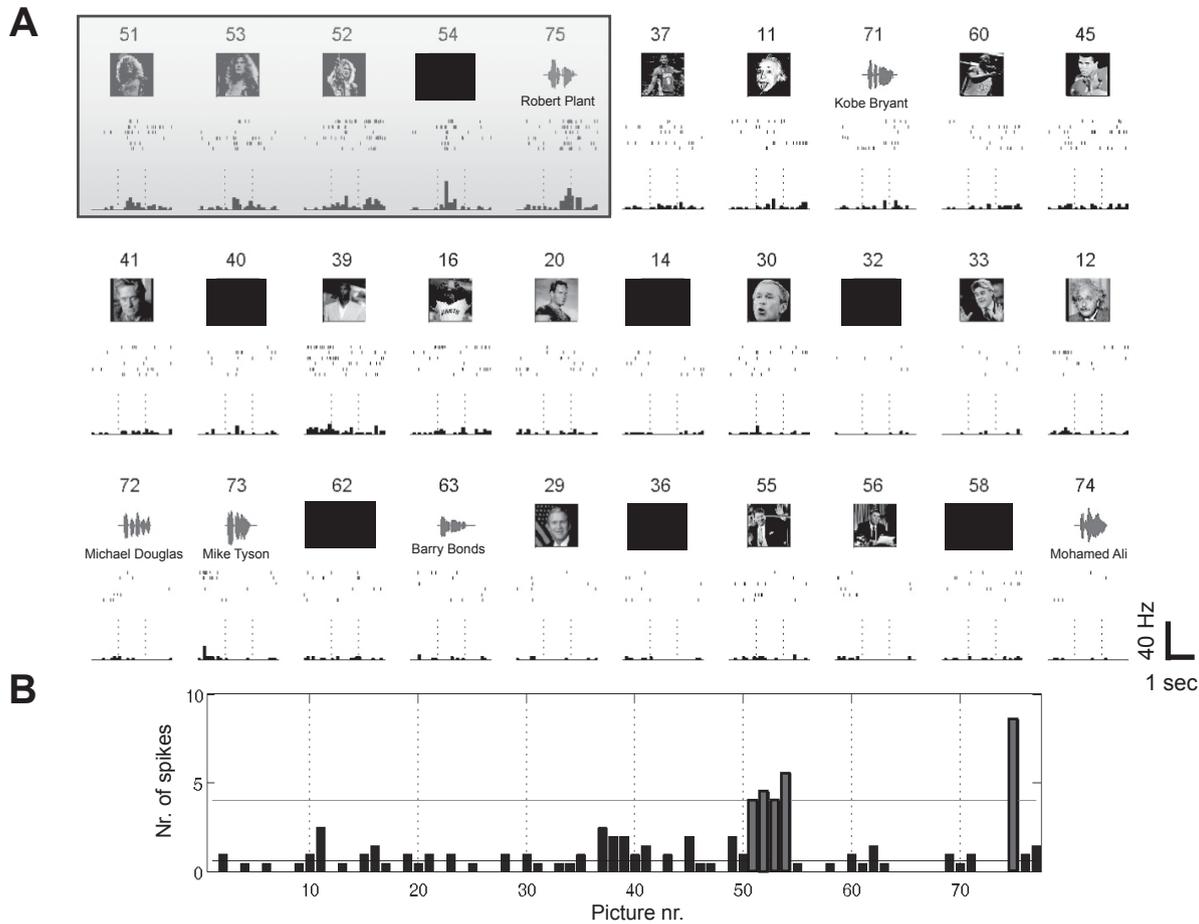
Figure 8.4 (plate 7)
A single unit in the entorhinal cortex responding to multiple different stimuli representing the same individual person. (A) A neuron in the entorhinal cortex that responded selectively to pictures of singer Robert Plant (stimulus 51, 53, and 52), as well as to his written (stimulus 54) and spoken (stimulus 75) name. There were no significant responses to any other picture, sound, or text presentations. For space reasons, only the largest 30 (out of 78) responses are displayed. In each case the raster plots for the six trials, peristimulus time histograms, and the corresponding pictures are shown. The vertical dotted lines mark picture onset and offset (1 s apart). (B) Median number (Nr) of spikes (across trials) for all stimuli. Presentations of Robert Plant are marked with red bars. Stimulus numbers correspond to the ones shown above each picture in (A). The gray horizontal line shows 5 SD above the baseline threshold used for defining significant responses. Modified from Quian Quiroga et al. (2009).

agreement with a sparse coding theory than a distributed code (Barlow, 1972; Quian Quiroga et al., 2008; Quian Quiroga & Kreiman, 2010). The bewildering nature of this type of responses is illustrated by the variety of names that have been used to describe these neurons including "grandmother cells," "concept cells," "Jennifer Aniston cells" (referring to the best known such example), "visually selective cells," "sparse but distributed cells," "semantic neurons," and many more (Quian Quiroga et al., 2005; Quian Quiroga et al., 2008; Quian Quiroga & Kreiman, 2010).

Ultimately, one of the major challenges in this type of recording is that we only have a limited amount of recording time (30 to 45 minutes for a typical experiment). Under such conditions, it is very difficult to assess with any degree of certainty what the neurons truly respond to given the lack of a systematic and theoretical understanding of the origins of such responses. In early visual areas including the retina and primary visual cortex, investigators often display tuning curves where the responses of a neuron show a smooth variation according to specific stimulus parameters such as its position or its orientation. A problem in determining the precise tuning curves of semantic neurons in the MTL is to find a suitable parameterization of the stimulus space—that is, among all the possible stimuli that could in theory be presented. In other words, it is difficult to determine the semantic distance between two stimuli, or categories of stimuli, particularly for complex shapes that are not designed to quantitatively evaluate differences and distances (Freedman et al., 2001; Serre et al., 2007; Pinto et al., 2008; Huth et al., 2012). The problems of determining the preferences of neurons outside of the sensory periphery are common to neurophysiological recordings across many other brain areas and species. Yet, they are compounded in human studies by the short duration of any one experiment in any one patient.

Response Latencies

An intriguing aspect of the MTL responses is the rather long response latency compared to response times in the monkey and cognitive processing times in humans. Neurons in entorhinal cortex, hippocampus, and amygdala typically show latencies in the range of ~300 to ~500 ms after stimulus onset (Kreiman et al., 2000a; Mormann et al., 2008; Ison et al., 2011). Responses in parahippocampal cortex have an onset latency between ~200 and ~400 ms and are, on average, ~120 ms earlier than in the other three regions. This is considerably longer than the latencies in the macaque ITC. One possibility is that latencies in the human brain are longer (perhaps due to a larger brain). However, intracranial field potential recordings in the human ITC yield response latencies of ~100 to 150 ms (McCarthy et al., 1999; Liu et al., 2009), which are only slightly longer than the single unit or local field potential (LFP) latencies in the macaque ITC. The nature of the intracranial field potential signals is poorly understood, but direct comparisons of spikes and LFPs reveal similar latencies in ITC (Kreiman et al., 2006; Nielsen et al., 2006) as well as other areas (Katzner et al., 2009; Rasch et al., 2009; Burns et al., 2010). Another possibility is that human ITC does not project directly to the human MTL, or at least that there are many more synapses in between. Little can we currently say about this possibility. Yet, it is intriguing to note that recordings in macaque MTL (entorhinal cortex, hippocampus, amygdala)

also show significantly longer latencies (150–250 ms) than in ITC (70–150 ms), although not as long as the ones in humans (Miyashita et al., 1989; Rolls et al., 1989; Suzuki et al., 1997; Wirth et al., 2003; Yanike et al., 2004) (see also table 1 in Mormann et al., 2008). The human parahippocampal cortex shows shorter latencies and may therefore be involved in object recognition or at least receive direct input from areas involved in object recognition, while the substantially longer latencies in entorhinal cortex, hippocampus, and amygdala may reflect the need for recurrent processing and further computations (see "Discussion" below).

Some recent studies have proposed a hierarchy of activation latencies within the MTL (Mormann et al., 2008; Ison et al., 2011). It should be noted that the relative latencies across these different steps are much more widely spaced apart than the relative latencies described in the macaque visual system hierarchy (e.g., Schmolesky et al., 1998). On the other hand, a direct correlation between response latency and stimulus selectivity as an indicator for hierarchical processing was found not only between but also within human MTL regions, at least for the parahippocampal cortex, entorhinal cortex, and hippocampus (Mormann et al., 2008). Hierarchical processing along the visual cortex has been widely debated, and there is no shortage of feedback loops, horizontal connections, bypass routes, and other complications. Yet, the coarse hierarchy has led to initial steps en route toward building systematic computational models of visual recognition (Fukushima, 1980; Rolls, 1991; Riesenhuber & Poggio, 1999; Serre et al., 2007). One can only hope that, to the extent that there is some hierarchy in the MTL, this may also help point to initial computational rules and models.

Regional Specificity

Lumping together all neurons within the MTL is a major oversimplification. As we collect more data and probe the system in more sophisticated ways, it is likely that we will encounter more and more differentiation. Plenty of evidence from the rodent and macaque neurophysiology literature suggests that the parahippocampal gyrus, hippocampus, entorhinal cortex, and amygdala have their own properties and caprices. Each of these areas can further be subdivided into specific computational domains including different layers in the entorhinal cortex, different areas in the hippocampus (e.g., CA3, CA1, dentate gyrus), and different nuclei in the amygdala (Lavenex & Amaral, 2000). Traditionally, there have been two challenges in further elucidating the different roles of neurons in these different structures. The first one simply concerns the low number of neurons in each area. The more we split, the fewer neurons we end up with in each area for rigorous statistical analysis. The second one concerns the difficulty in precise localization of the microelectrodes within each area (Ekstrom et al., 2008).

In spite of these difficulties, many studies have now documented important differences across these different areas. As mentioned in the previous section, parahippocampal neurons respond significantly earlier than those in other studied MTL regions (Mormann et al., 2008). Parahippocampal neurons also differ from entorhinal, hippocampal, and amygdala cells in that they tend to respond to a larger percentage of the presented stimuli, thus exhibiting lower response selectivity, whereas selectivity is highest for principal cells in hippocampus (Mormann et al., 2008;

Ison et al., 2011). Finally, the parahippocampal cortex is the only one among the four MTL regions studied whose neurons are not modulated by repeated stimulus presentation in the sense of repetition suppression (Pedreira et al., 2010). With respect to sensory modalities, the parahippocampal cortex again takes a special role by exhibiting no auditory responses and accordingly no semantic invariance to auditory stimuli (Quian Quiroga et al., 2009).

Regional preferences for certain classes of stimuli, possibly indicative of domain-specific processing, are found in several MTL regions. For instance, neurons in the right, but not left, amygdala show an increased response to the category of animals (Mormann et al., 2011). Unpublished anecdotal evidence furthermore suggests that neurons in the parahippocampal cortex preferentially respond to spatial scenes (perhaps reflecting the neuronal basis of the notion proposed by blood flow studies in the so-called parahippocampal place area; Epstein et al., 1999) whereas entorhinal neurons tend to show a slight category preference for objects, in agreement with functional imaging studies in humans (Litman et al., 2009).

Given that the MTL does not seem to be directly involved in visual recognition (see below for details), it seems intriguing that neurons would show this type of preference, lateralization, or other type of specificity to anthropomorphically defined "categories" and that the stimuli in those studies shared specific features that correlated with the interests of the neurons recorded from. For example, responses in the amygdala to animals could perhaps relate to the evolutionary relevance of these stimuli rather than any representation of the shape of animals. We hope that future studies will reveal further insights about the interpretation of this type of complex response.

Lesion Studies

As noted above (see "The Medial Temporal Lobe and Memory"; see also chapters 3 and 7 and Scoville and Milner, 1957; Squire et al., 2004), bilateral removal of the hippocampus and surrounding structures leads to deficits in memory consolidation. In spite of significant efforts in the field, no impairments have been observed in visual recognition or visual perception (Squire et al., 2004; Shrager et al., 2006). In the few cases where visual deficits are described, they typically can be ascribed to a learning component in the task or extension of the lesion to perirhinal and ITC. It seems likely that the type of responses described above may therefore not be concerned with the process of recognition per se (see further discussion of this point below).

In patients with congenital bilateral lesions of the amygdala (Siebert et al., 2003), recognition of emotional facial expressions is impaired due to altered processing of facial features and a relative neglect of the eye region (Adolphs et al., 2005). The possibility of studying acute impairment of amygdala function may arise in patients with acute limbic encephalitis who often present with bilateral MRI lesions in the amygdala and anterior hippocampus during early stages of the disease (Bien & Elger, 2007). While it is difficult to dissociate amygdala and hippocampal involvement in these lesions, they still offer a unique possibility to study amygdala lesions in the absence of long-term adaptation processes that can be expected for congenital lesions.

Visual Imagery

Given the striking responses to a wide variety of stimulus transformations described above, several investigators wondered whether it would be possible to completely remove the stimulus and evaluate whether neuronal responses in the MTL could be modulated by asking subjects to volitionally create mental imagery (Kreiman et al., 2000b; Gelbard-Sagiv et al., 2008; Cerf et al., 2010).

These mental imagery exercises constitute good examples of tasks that are difficult to implement in animal models. Still, several investigators have conjectured that animals create mental images when they need to remember information for several seconds. For example, in delayed-match-to-sample tasks, correct performance relies on subjects' ability to retain information during the delay period. It is tempting to speculate that subjects (humans and nonhumans) are mentally rehearsing/holding pertinent information during the delay. Indeed, several studies have demonstrated that neurons can show selective modulation during such conditions in the macaque ITC, MTL, and prefrontal cortex (Miyashita & Chang, 1988; Miyashita, 1993; Higuchi & Miyashita, 1996; Naya et al., 1996; Rao et al., 1997; Suzuki et al., 1997; Rainer et al., 1999; Naya & Suzuki, 2011).

While recording the activity from a neuron that showed enhanced responses to a particular image A compared to another image B, investigators asked subjects to mentally imagine A or B in the absence of any visual stimulus upon listening to a tone that was associated with A or another tone that indicated B. They observed that MTL neurons modulated their spiking activity in the absence of a visual stimulus and that this modulation showed the same preferences as the responses elicited by a visual input (Kreiman et al., 2000b). In another study, subjects were shown brief video clips and were later asked to freely recall aspects of those video clips. Again, MTL neurons showed activation patterns in the absence of a visual stimulus and in the absence of any instructing tone. Those activation events were correlated with the contents of their recall imagery as described by the subjects and were also consistent with the neuronal responses elicited by visual presentation (Gelbard-Sagiv et al., 2008). In a more recent instantiation and extension of these findings, investigators showed that they can decode these volitionally initiated changes in firing rate in real time (Cerf et al., 2010). Furthermore, the patients were able to willfully increase or decrease the firing rate of these neurons in a highly selective manner. That is, the firing neurons of at least some of the MTL neurons are at least under partial voluntary control.

Perhaps not surprisingly, the responses elicited in the absence of a visual stimulus were typically smaller in magnitude and showed larger trial-to-trial variability than those evoked by visual stimulation. However, these differences may be partly attributable to the precision by which we can control the onset of visual stimuli and the relative imprecision by which we can characterize the onset of recall. Even in the presence of equally strong responses, variability in the onset times could lead to the appearance of weaker and delayed responses.

Consciousness

Several investigators have tried to elucidate the neuronal correlates of consciousness (e.g., among many others, Crick, 1994; Crick & Koch, 1995; Rees et al., 2002; Koch, 2005). Arguably one of the greatest challenges for scientific reductionism, the quest involves trying to explain the subjective world of feelings, perceptions, and other sensations purely based on the activity of neurons and their interactions. In other words, while many centers, departments, and textbooks still discuss the mind and the brain as two separate entities (a remnant of Descartes' dualism), the hope is to unify these two descriptions into a single one where the mind can be explained by biological circuitry. Given the difficulties inherent in examining subjective perception in animal models, the welcome opportunity to investigate the human brain from the inside holds the potential to offer important insights in this field.

An important experimental paradigm in the field has been the study of binocular rivalry (Leopold & Logothetis, 1999; Blake & Logothetis, 2002). When two different stimuli, A and B, are shown to the two eyes, perception typically alternates in a seemingly random fashion between the two percepts. Several investigators have been intrigued by the notion of finding where these subjective percepts take place in the brain given that the stimulus is essentially constant in the sensory periphery. A series of elegant experiments by Logothetis's group has shown that there is a progression in the proportion of neurons that correlate with subjective perception from almost none in early areas such as lateral geniculate nucleus and V1 (Lehky & Maunsell, 1996; Leopold & Logothetis, 1996) all the way to almost all in ITC (Sheinberg & Logothetis, 1997). Consistent with these findings, most of the visually selective neurons in the human MTL also modulated their responses with the alternating percept (Kreiman et al., 2002; see figure 8.5). Similar conclusions were reached in a study where stimuli were flashed for brief periods of time and then instantly masked to avoid retinal afterimages; MTL neurons fired if and only if subjects were aware of the stimulus (Quiroga et al., 2008).

A particularly intriguing aspect of consciousness is the notion of free will. At any given time, we have a strong feeling that we are the owners of our actions, that we can choose to go right or left as we please. The feeling of "authorship" or "will" can be considered to be another example of a conscious sensation, and it is therefore legitimate to ask where/when/how this content of consciousness is encoded. Libet introduced a simple experimental paradigm to examine volition that has led to endless discussions in the literature (Libet, 1985). In brief, subjects were instructed to tap their index finger at will while monitoring the internal time when they felt the "urge" to execute the movement. By relating this internal decision time with averaged scalp signals from electroencephalographic recordings, Libet argued that major changes in brain oscillations take place hundreds of milliseconds, and in some cases seconds, before subjects became aware of their own intentions to move.

Following Libet's observation, Fried et al. (1991) reported that stimulation in the supplementary motor area elicited in subjects a sensation of urge to perform particular motor acts. More
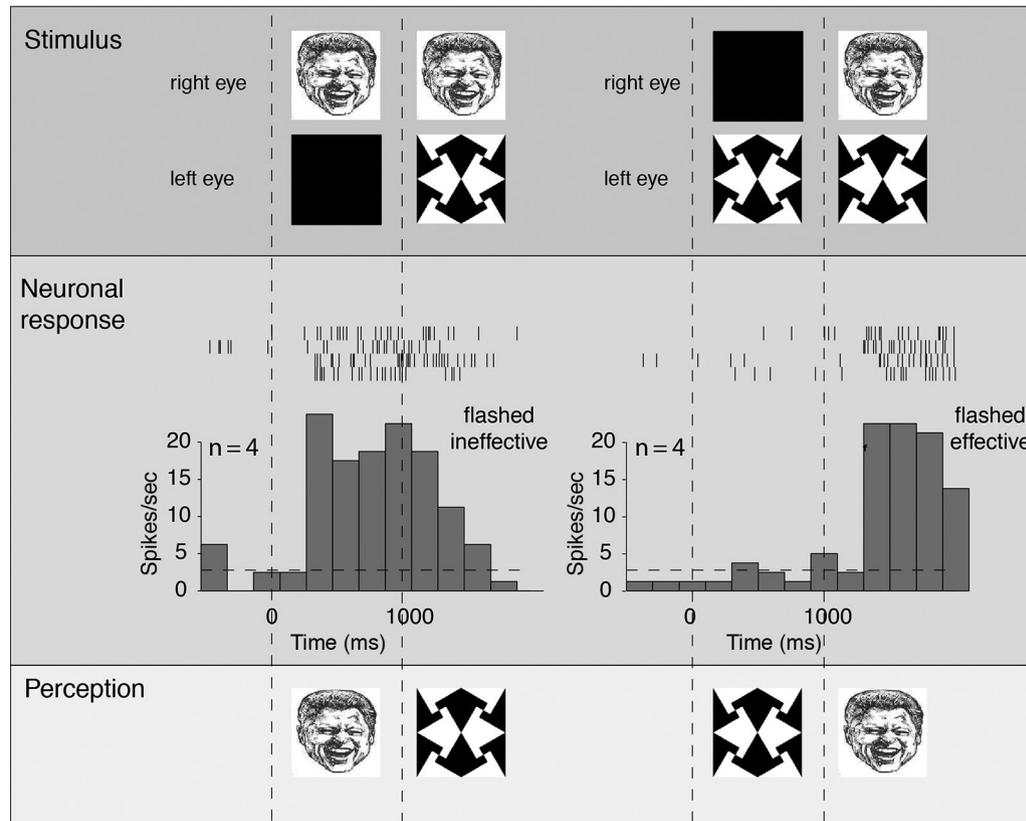
Figure 8.5

Right amygdala neuron that follows the subjective percept. (A) Stimulus presentation: An image is presented monocularly for 1000 ms. The same image then is flashed onto the same ipsilateral eye while a different image is flashed to the contralateral eye for 500 ms. (A1) A picture of Clinton is presented monocularly, and a black-and-white pattern is later flashed onto the other eye. (A2) The pattern is presented monocularly, and Clinton is flashed to the contralateral eye (right). Images were chosen randomly with the constraint that the two pictures could not belong to the same category. (C) Subjective percept. (C1) The picture of Clinton is suppressed during the binocular period by the pattern. (C2) The picture of Clinton perceptually suppresses the pattern. (B) Neural response. This neuron responded selectively to Clinton among 49 different stimuli. (B1) Responses when Clinton was shown monocularly and a different ineffective stimulus was flashed. Although there seems to be elevated firing activity during the binocular period, it is not statistically significant after taking into account the response latency. (B2) Responses when an ineffective stimulus was shown monocularly and the picture of Clinton was flashed and perceptually suppressed the ineffective stimulus. Bin size, 200 ms. The dashed lines denote the onset of the monocular image and the flash. The horizontal dashed line shows the baseline activity of the neuron (2.8 Hz). The number of repetitions of each stimulus is shown above the histogram. Modified from (Kreiman et al., 2002).

recently, Fried and colleagues showed that neurons in the medial frontal cortex (particularly those in the supplementary motor area, presupplementary motor areas, and dorsal/rostral aspects of the anterior cingulate) showed strong changes that predicted when subjects would decide to execute a movement in this paradigm (in single trials; Fried et al., 2011). In contrast, MTL neurons showed only marginal above-chance performance in this task (tentatively interpreted by the authors as a consequence of the memory component of the task).

The relationship between consciousness and MTL activity is called into question by neurological and lesion studies. While bilateral removal of the hippocampus can lead to severe impairment in memory consolidation, no changes have been documented in the moment-to-moment awareness or consciousness of these subjects (Scoville & Milner, 1957; Milner et al., 1968; Squire et al., 2004). Bilateral removal of the amygdala can lead to significant impairment in interpreting emotions, but it also does not seem to directly affect conscious processing (Adolphs et al., 2005). In other words, neurological evidence (as well as lesion studies in animal models) seems to argue that MTL is not necessary for consciousness.

In fact, some investigators have argued that causality works in the opposite direction here. Perhaps activity in the hippocampus and entorhinal cortex is not necessary for conscious perception but consciousness is necessary for activation of these areas. That is, we propose that information reaching the hippocampus and its input structures has already been processed in such a way that unconscious activity is filtered out. At the very least, it seems likely that conscious awareness may enhance the probability of recalling information and provide flexibility to what, when, and how information is consolidated into memories (Lisman & Sternberg, 2013).

Certain aspects of content do seem to require an intact amygdala (also see chapter 13). In particular, as noted above, recognition of fearful facial expressions is impaired by lesions to the amygdala (Adolphs et al., 1994). Other evidence also seems to imply that unconscious activity may reach the amygdala. For example, in a functional neuroimaging study, investigators found amygdala activation (i.e., blood flow changes) even when the faces denoting emotional expressions were perceptually suppressed (Morris et al., 1998; Whalen et al., 1998). Amygdala blood-oxygen-level-dependent activation by emotional facial expressions was also reported in a subject with cortical blindness (Pegna et al., 2005). These findings have led researchers to hypothesize the existence of a subcortical pathway to the amygdala that bypasses visual cortex and provides rapid activation of the amygdala by fear-related stimuli prior to conscious perception to prime early visual processing of these stimuli (Phelps & LeDoux, 2005; Ohman et al., 2007). However, there is no clear evidence for such a pathway in humans and the notion of rapid subcortical signals to the amygdala seems controversial (Pessoa & Adolphs, 2010; Cauchoix & Crouzet, 2013). The neuronal responses to animals in the right human amygdala (Mormann et al., 2011) were independent of emotional stimulus content, and the visual response latencies in the human amygdala are similar to those found in other regions in the temporal lobe (Mormann et al., 2008; Liu et al., 2009). These responses therefore do not support the notion of a distinct fast subcortical route and are more likely to be generated along the cortical object recognition pathway.

R

Discussion: Trying to Put All the Pieces Together Again

Sparse Coding

For the single unit recordings currently possible in humans, it is important to realize that the brain's networks of neurons are vastly undersampled. For example, recording from 64 microwires, one can obtain a total yield of tens of single and multiunits from various regions, which represents just a tiny sample of the several billion neurons the human brain consists of (Herculano-Houzel, 2009). Hence, it is legitimate to ask, "What can we actually expect to learn despite this vast spatial undersampling?"

This, in turn, depends on how our environment is represented by the neuronal activity in our brains. The question of how the brain encodes semantic information such as the identity of objects or persons has been a key focus in neuroscience for decades. Two opposing theories have been formulated. One theory assumes representation by a complex network in which a large number of neurons encode a certain concept in their entirety (distributed coding). Another theory describes a sparse coding in which just a few neurons encode an explicit representation of a specific concept. Taken to the extreme, this type of coding could be implemented by a single cell representing a single semantic concept, for example, that of one's grandmother, which is why this idea has been termed "grandmother cell" (Gross, 2002). A grandmother cell would thus be activated whenever one sees their grandmother, hears about her, talks to her on the phone, thinks of her, and so on.

Under multiple assumptions, it has been argued that distributed coding is far more cost-efficient than sparse coding. For example, a network of 8 neurons, half of which are activated by any given stimulus, can encode and distinguish between 70 different stimuli, whereas a sparse network of 8 neurons can only encode 8 stimuli in an independent on/off manner. For an efficient distributed code, one would also expect each neuron in the distributed network to respond to a substantial fraction of all presented stimuli. In this way, the selectivity of observed responses can provide an indication about which of the two types of coding is present.

Semantic neurons—that is, neurons which encode the semantic contents of a stimulus in an invariant manner—have been described in the human MTL, but not in other regions such as orbitofrontal cortex or anterior cingulate from which human single units have also been recorded. Given that a distributed code appears to be more cost-efficient than a sparse representation of abstract semantic concepts, an obvious question is why the brain would allow itself the "luxury" of an explicit, sparse, and invariant code for semantic information. This apparent luxury might be better understood once we realize how episodic memory formation, one of the main functions of the human MTL, might be connected to semantic representations.

You Shall Remember This

The process of encoding episodic memories consists of associating pieces of semantic information (what happened where with whom involved and so on) in a defined temporal order. Lesion

R

studies in humans have shown that structures in the MTL are essential for the encoding of episodic memories (Squire et al., 2004; Squire et al., 2007; Squire, 2009; Milner et al., 1968, Scoville & Millner, 1957). Representations of semantic information at the single unit level are frequently found in these very structures and thus might provide a unique opportunity to investigate how our brain links pieces of semantic information together into episodic memories (Quiroga, 2012). To learn novel information in high-dimensional space, it pays to have sparse representations, since they are easy to manipulate. It is also easy to learn a new high-level concept (i.e., a new movie star) without having to change all the low-level representations (i.e., to move all of the boundaries between the categories). In rodent navigation one can distinguish path integration (dead reckoning navigation) along a linear track from landmark navigation (map navigation) in a two-dimensional environment. The majority of place cells found on a linear track are unidirectional, that is, they respond only during runs in one of the two directions and in this sense are context dependent. Place cells in a two-dimensional environment, on the other hand, are omnidirectional, that is, independent of the direction from which the animal approaches the place field and thus also independent of the temporal context. These two phenomena bear a certain analogy to episodic and semantic memory formation, respectively. Episodic memories are always context dependent whereas semantic memories are context invariant and can emerge via generalization of recurring context-dependent experiences (Buzsáki, 2005).

Based on this analogy, one may hypothesize that the basic neural mechanisms during the exploration of a new environment in rodents could also play a role for encoding memories. A phenomenon of particular interest in this context is the reactivation of sequences of single neuron activity observed in rodents. Here sequences of place cell activity (see chapter 9) that were activated during the exploration of an environment are "replayed" during a subsequent resting period and particularly during sleep (Skaggs & McNaughton, 1996; Louie & Wilson, 2001). These replayed sequences exhibit a high temporal compression and can occur in forward and reverse order (Nadasdy et al., 1999; Foster & Wilson, 2006; Diba & Buzsáki, 2007).

In rodents the replay of these sequences typically occurs during brief periods (ca. 100 ms) of high-frequency activity termed sharp wave/ripples in the LFP and is assumed to serve for consolidation of spatial memories by transferring the sequences into cortex for permanent storage (O'Neill et al., 2010). By analogy one may hypothesize that consolidation of episodic memories in humans is likewise achieved by reactivation of a previously experienced sequence of semantic neurons in the homologous brain structures. These sequences might serve to link information of an experienced episode such as who, what, where, and so forth and to bring them into a defined temporal order (Howard & Kahana, 1999).

Apparent Lack of Topography

Essentially all of sensory neocortex in macaque monkeys is characterized by elegant topography (less clearly so in the mouse neocortex). Nearby neurons share similar properties such as visual field proximity or correlated wavelength sensitivity in primary visual cortex blobs. Particularly

striking demonstrations of this topography abound in the visual system where nearby neurons display related receptive field structures and hence form a retinotopic map of visual space (Hubel & Wiesel, 1962; Wandell, 1995). Similar claims have been made in higher cortical areas (e.g., Mountcastle, 1957; Tanaka, 1996; Kreiman et al., 2006; Tsao et al., 2008b). Several suggestions have been advanced to describe the advantage of topographical arrangements of neurons including the minimization of wire lengths.

Many investigators have tried to find evidence for topographic mapping in the hippocampus and surrounding structures with no success. Two nearby neurons can show completely different place fields in rodents (O'Keefe & Nadel, 1978) and may respond to distinct stimuli in humans. For instance, a neuron in the right human amygdala may respond to various animals while another neuron recorded on the same microwire may respond to a single individual person (Mormann et al., 2011).

While the semantically invariant neurons found in the human MTL are in many ways reminiscent of rodent place cells, they do not appear to be confined to the hippocampus but instead are found also in the entorhinal cortex, amygdala, and—with a lesser degree of invariance—in the parahippocampal cortex. The function of certain cell types in the MTL of rodents shows a clear topography and has been well characterized, for example, grid cells in entorhinal cortex (Hafting et al., 2005; Killian et al., 2012), head direction cells in the subiculum (Taube et al., 1990), and hippocampal place cells (O'Keefe & Dostrovsky, 1971). However, it remains unclear to what extent functional analogies between these spatial responses and the semantic responses observed in human studies exist.

Amygdala and Emotions

The amygdala has been implicated in the processing of biologically relevant information, including both aversive (e.g., threat- or fear-related) and appetitive (e.g., reward-related) stimuli (Baxter & Murray, 2002; Phelps & LeDoux, 2005; Adolphs, 2008; Pessoa, 2008; see chapter 13). Earlier notions that the amygdala might be specialized to elicit or mediate fear responses (LeDoux, 1996) have been supplemented by more abstract accounts whereby the amygdala processes ambiguity or unpredictability in the environment (Herry et al., 2007) and mediates an organism's vigilance and arousal (Davis & Whalen, 2001). Electrophysiological recordings in monkeys have found amygdala neurons that respond selectively to complex stimuli. These include single neurons that respond to faces (Leonard et al., 1985), as well as cells responding selectively to the identity or expression of monkey faces or to human faces or objects (Gothard et al., 2007). Furthermore, amygdala neurons in the macaque were shown to encode the reward value of stimuli (Nishijo et al., 1988; Paton et al., 2006) during reinforcement learning in a highly adaptive manner that is modulated by attention and arousal (Belova et al., 2007). In humans, neuroimaging studies of the amygdala argue for a broad role in processing stimuli that are strongly rewarding or punishing (Sander et al., 2003; Ohman et al., 2007). This plethora of diverse findings has left it unclear what stimulus categories the amygdala might encode, limiting current theories of amygdala function.

In human fMRI memory studies, increased blood flow in the amygdala during encoding was found to correlate with improved memory formation (e.g., Canli et al., 2000). In addition, the phase locking of human amygdala neurons to ongoing theta oscillations was found to predict memory formation (Rutishauser et al., 2011, see also chapter 7). It is thus conceivable that the amygdala plays a key role in filtering out biologically relevant information for memory encoding and consolidation. One should be aware, though, that the amygdala consists of many nuclei that have different connections and subserve diverse functions. With our electrophysiological studies in humans, we are currently only tapping the surface of this complex functionality. More work will be needed in our single unit studies to understand the interactions between emotions, memory formation, and the responses to complex stimuli described here.

Open Questions

The proverbial parable of blind people examining an elephant and drawing different conclusions depending on their vantage point can hardly be more appropriate here. Take the recordings from the hippocampus from different investigators. Some will claim, "These neurons represent space!" (e.g., see chapter 9). Others will adamantly point to how well these neurons can help predict what people will remember (e.g., see chapter 7). Yet others will point to the strong degree of tolerance of some of these neurons in response to different images of the same familiar person (e.g., this chapter). This is, of course, only an oversimplification, and there could be even more descriptions if we included other manuscripts, other species, and other experimental paradigms. It is tempting to speculate that many of these observations could be described within a common theoretical framework. Perhaps this is only part of our will to push Occam's principle, but it seems worth trying.

While we hope that future studies will help unify and consolidate our understanding of different responses elicited by distinct tasks and paradigms, we should not lose track of the important anatomical and functional demarcations among different MTL structures. Several of these differences have been pointed out above (see "One hat does not fit all" and "Regional Specificity"). Sometimes when the differences are not black and white, the small numbers of neurons sampled may preclude our drawing sharp differences across areas. Pooling data across studies (whenever possible) may help ameliorate such practical difficulties. Meta-analyses have been quite frequent and useful in other domains, and we are just beginning to accumulate sufficient data in the field where such comparisons may yield interesting insights.

We suggested above that there might be a distinction between the hippocampus and the amygdala in terms of the extent to which unconscious information reaches those areas. If indeed unconscious information can reach the amygdala but not the hippocampus and surrounding structures (a highly tentative notion that will require further investigation), this may provide interesting opportunities to examine differential inputs to the two structures and how those inputs correlate with the contents of consciousness.

Neurons in the MTL take visual information from the highest echelons of visual cortex and can perform seemingly magic transformations. Hippocampal neurons show a remarkable degree

of abstraction in responding to pictures but also to text, with visual input or during visual imagery, detecting associations between stimuli, how novel they are and whether they should be remembered or not. In this sense, the rhinal–hippocampus axis seems to be a fabulous arena to examine the transformation of sensory information into semantic and cognitive information. A large volume of studies has focused on purely sensory aspects (e.g., what is the receptive field size of neurons in ITC and how do these neurons respond with more than one stimulus within their receptive field?). Another growing volume of studies, partly summarized in this chapter, has focused on purely cognitive aspects (e.g., can neurons respond to abstract properties of the stimuli or even in the absence of a stimulus?). The necessary and sufficient transformation that can link these two worlds, the strictly sensory one and the inner cognitive domain, seems to be a critical theme for further investigation.

Clinical Implications

For many years, clinicians performed drastic cuts along the corpus callosum in their efforts to treat seizures. Clinical practice was influenced by the elegant studies of Roger Sperry, inspired by the work describing the organization of the visual and language systems (Sperry, 1982). One can only hope that the growing body of neurophysiological recordings will help inspire and inform further improving ways to treat epilepsy. This may take the form of further quantifying and documenting the effects of removing the epileptogenic areas in order to improve surgical approaches. Most neurophysiologists are surprised by the notion that unilateral removal of relatively large spans of MTL cortex does not seem to lead to very obvious cognitive deficiencies although some loss of verbal (predominant in left MTL) or nonverbal (predominant in right MTL) memory function can be detected in almost all cases when sensitive neuropsychological tests are used (Gleissner et al., 2002). This striking observation may well speak to the enormous amount of redundancy in the network, or it may be ascribed to plasticity and adaptation postresection (although even acute studies do not seem to reveal major deficits; see however Bartsch et al., 2010). Alternatively, it may very well be that we have not yet examined the right type of behavior. In parallel to the work of Sperry mentioned above, many behavioral studies had failed to find any cognitive deficit after callosotomies. Neurophysiological recordings may help provide clues about the functions of neurons in different parts of the MTL and thus inspire direct behavioral evaluation. In addition, microelectrode recordings from seizure-generating brain regions will provide fuel for studies investigating the mechanisms involved in seizure generation, propagation, and termination, both at the level of LFPs (Stead et al., 2010; Jacobs et al., 2012) and unit activity (chapter 18).

Learning and memory challenges are common in many epileptic patients. Additionally, the hippocampus is one of the key areas that show significant deterioration in patients with Alzheimer's disease. Neurophysiological recordings in the MTL can lead to a better understanding of how neural circuits orchestrate learning and memory formation and may thus provide novel ideas to help alleviate cognitive deficits in patients suffering from epilepsy, dementia, and other cognitive challenges that depend on the MTL.

References

Adolphs, R. (2008). Fear, faces, and the human amydgala. *Current Opinion in Neurobiology*, *18*, 166–172.

Adolphs, R., Gosselin, F., Buchanan, T., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*, *433*, 68–72.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the amygdala. *Nature*, *372*, 669–672.

Agam, Y., Liu, H., Pappanastassiou, A., Buia, C., Golby, A. J., Madsen, J. R., et al. (2010). Robust selectivity to two-object images in human visual cortex. *Current Biology*, *20*, 872–879.

Allison, T., Puce, A., Spencer, D., & McCarthy, G. (1999). Electrophysiological studies of human face perception: I. Potentials generated in occipitotemporal cortex by face and non-face stimuli. *Cerebral Cortex*, *9*, 415–430.

Amaral, D. G., & Lavenex, P. (2007). Hippocampal neuroanatomy. In P. Andersen, R. G. M. Morris, D. G. Amaral, T. Bliss, & J. O'Keefe (Eds.), *The hippocampus book*. New York: Oxford University Press.

Barlow, H. (1972). Single units and sensation: A neuron doctrine for perception. *Perception*, *1*, 371–394.

Bartsch, T., Schonfeld, R., Muller, F. J., Alfke, K., Leplow, B., Aldenhoff, J., et al. (2010). Focal lesions of human hippocampal CA1 neurons in transient global amnesia impair place memory. *Science*, *328*, 1412–1415.

Baxter, M. G., & Murray, E. A. (2002). The amygdala and reward. *Nature Reviews. Neuroscience*, *3*, 563–573.

Belova, M. A., Paton, J. J., Morrison, S. E., & Salzman, C. D. (2007). Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. *Neuron*, *55*, 970–984.

Bien, C. G., & Elger, C. E. (2007). Limbic encephalitis: A cause of temporal lobe epilepsy with onset in adult life. *Epilepsy & Behavior*, *10*, 529–538.

Bitterman, Y., Mukamel, R., Malach, R., Fried, I., & Nelken, I. (2008). Ultra-fine frequency tuning revealed in single neurons of human auditory cortex. *Nature*, *451*, 197–201.

Blake, R., & Logothetis, N. (2002). Visual competition. *Nature Reviews. Neuroscience*, *3*, 13–21.

Burns, S. P., Xing, D., & Shapley, R. M. (2010). Comparisons of the dynamics of local field potential and multiunit activity signals in macaque visual cortex. *Journal of Neuroscience*, *30*, 13739–13749.

Buzsáki, G. (2005). Theta rhythm of navigation: Link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus*, *15*, 827–840.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience*, *20*, RC99.

Cauchoix, M., & Crouzet, S. M. (2013). How plausible is a subcortical account of rapid visual recognition? *Frontiers in Human Neuroscience*, *7*, 39.

Cerf, M., Thiruvengadam, N., Mormann, F., Kraskov, A., Quiroga, R. Q., Koch, C., et al. (2010). On-line, voluntary control of human temporal lobe neurons. *Nature*, *467*, 1104–1108.

Connor, C. E., Brincat, S. L., & Pasupathy, A. (2007). Transformation of shape information in the ventral pathway. *Current Opinion in Neurobiology*, *17*, 140–147.

Crick, F. (1994). *The astonishing hypothesis*. New York: Simon & Schuster.

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature*, *375*, 121–123.

Crick, F., Koch, C., Kreiman, G., & Fried, I. (2004). Consciousness and neurosurgery. *Neurosurgery*, *55*, 273–282.

Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, *6*, 13–34.

R

Dawodu, S., & Thom, M. (2005). Quantitative neuropathology of the entorhinal cortex region in patients with hippocampal sclerosis and temporal lobe epilepsy. *Epilepsia*, *46*, 23–30.

Diba, K., & Buzsáki, G. (2007). Forward and reverse hippocampal place-cell sequences during ripples. *Nature Neuroscience*, *10*, 1241–1242.

Dudai, Y. (2012). The restless engram: Consolidations never end. *Annual Review of Neuroscience*, *35*, 227–247.

Ekstrom, A., Suthana, N., Behnke, E., Salamon, N., Bookheimer, S., & Fried, I. (2008). High-resolution depth electrode localization and imaging in patients with pharmacologically intractable epilepsy. *Journal of Neurosurgery*, *108*, 812–815.

Engel, A. K., Moll, C. K., Fried, I., & Ojemann, G. A. (2005). Invasive recordings from the human brain: Clinical insights and beyond. *Nature Reviews. Neuroscience*, *6*, 35–47.

Engel, J. (1996). Surgery for seizures. *New England Journal of Medicine*, *334*, 647–652.

Epstein, R., Harris, A., Stanley, D., & Kanwisher, N. (1999). The parahippocampal place area: Recognition, navigation, or encoding? *Neuron*, *23*, 115–125.

Eskandar, E. N., Richmond, B. J., & Optican, L. M. (1992). Role of inferior temporal neurons in visual memory: I. Temporal encoding of information about visual images, recalled images, and behavioral context. *Journal of Neurophysiology*, *68*, 1277–1295.

Foster, D. J., & Wilson, M. A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature*, *440*, 680–683.

Freedman, D., Riesenhuber, M., Poggio, T., & Miller, E. (2001). Categorical representation of visual stimuli in the primate prefrontal cortex. *Science*, *291*, 312–316.

Fried, I., Katz, A., McCarthy, G., Sass, K. J., Williamson, P., Spencer, S. S., et al. (1991). Functional organization of human supplementary motor cortex studied by electrical stimulation. *Journal of Neuroscience*, *11*, 3656–3666.

Fried, I., MacDonald, K. A., & Wilson, C. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron*, *18*, 753–765.

Fried, I., Mukamel, R., & Kreiman, G. (2011). Internally generated preactivation of single neurons in the human brain predicts volition. *Neuron*, *69*, 548–562.

Fukushima, K. (1980). Neocognitron: A self organizing neural network model for a mechanism of pattern recognition unaffected by shift in position. *Biological Cybernetics*, *36*, 193–202.

Gelbard-Sagiv, H., Mukamel, R., Harel, M., Malach, R., & Fried, I. (2008). Internally generated reactivation of single neurons in human hippocampus during free recall. *Science*, *322*, 96–101.

Gleissner, U., Helmstaedter, C., Schramm, J., & Elger, C. E. (2002). Memory outcome after selective amygdalohippocampectomy: A study in 140 patients with temporal lobe epilepsy. *Epilepsia*, *43*, 87–95.

Gothard, K. M., Battaglia, F. P., Erickson, C. A., Spitler, K. M., & Amaral, D. G. (2007). Neural responses to facial expression and face identity in the monkey amygdala. *Journal of Neurophysiology*, *97*, 1671–1683.

Grill-Spector, K., Kushnir, T., Edelman, S., Itzchak, Y., & Malach, R. (1998). Cue-invariant activation in object-related areas of the human occipital lobe. *Neuron*, *21*, 191–202.

Gross, C. (2002). Genealogy of the "grandmother cell." *Neuroscientist*, *8*, 512–518.

Hafting, T., Fyhn, M., Molden, S., Moser, M. B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature*, *436*, 801–806.

Heit, G., Smith, M. E., & Halgren, E. (1988). Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature*, *333*, 773–775.

Herculano-Houzel, S. (2009). The human brain in numbers: A linearly scaled-up primate brain. *Frontiers in Human Neuroscience*, *3*, 31.

Herry, C., Bach, D. R., Esposito, F., Di Salle, F., Perrig, W. J., Scheffler, K., et al. (2007). Processing of temporal unpredictability in human and animal amygdala. *Journal of Neuroscience*, *27*, 5958–5966.

Higuchi, S., & Miyashita, Y. (1996). Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 739–743.

R

Howard, M. W., & Kahana, M. J. (1999). Contextual variability and serial position effects in free recall. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *25*, 923–941.

Hubel, D. H., & Wiesel, T. N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *Journal of Physiology*, *160*, 106–154.

Hung, C., Kreiman, G., Poggio, T., & DiCarlo, J. (2005). Fast read-out of object identity from macaque inferior temporal cortex. *Science*, *310*, 863–866.

Huth, A. G., Nishimoto, S., Vu, A. T., & Gallant, J. L. (2012). A continuous semantic space describes the representation of thousands of object and action categories across the human brain. *Neuron*, *76*, 1210–1224.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A., Partanen, K., Vainio, P., et al. (1998). MR volumetric analysis of the human entorhinal, perirhinal and temporopolar cortices. *AJNR. American Journal of Neuroradiology*, *19*, 659–671.

Ison, M. J., Mormann, F., Cerf, M., Koch, C., Fried, I., & Quiroga, R. Q. (2011). Selectivity of pyramidal cells and interneurons in the human medial temporal lobe. *Journal of Neurophysiology*, *106*, 1713–1721.

Ito, M., Tamura, H., Fujita, I., & Tanaka, K. (1995). Size and position invariance of neuronal responses in monkey inferotemporal cortex. *Journal of Neurophysiology*, *73*, 218–226.

Jacobs, J., Staba, R., Asano, E., Otsubo, H., Wu, J. Y., Zijlmans, M., et al. (2012). High-frequency oscillations (HFOs) in clinical epilepsy. *Progress in Neurobiology*, *98*, 302–315.

Katzner, S., Nauhaus, I., Benucci, A., Bonin, V., Ringach, D. L., & Carandini, M. (2009). Local origin of field potentials in visual cortex. *Neuron*, *61*, 35–41.

Keysers, C., Xiao, D. K., Foldiak, P., & Perret, D. I. (2001). The speed of sight. *Journal of Cognitive Neuroscience*, *13*, 90–101.

Killian, N. J., Jutras, M. J., & Buffalo, E. A. (2012). A map of visual space in the primate entorhinal cortex. *Nature*, *491*, 761–764.

Koch, C. (2005). *The quest for consciousness* (1st ed.). Los Angeles: Roberts & Company Publishers.

Kreiman, G. (2007). Single neuron approaches to human vision and memories. *Current Opinion in Neurobiology*, *17*, 471–475.

Kreiman, G., Fried, I., & Koch, C. (2002). Single neuron correlates of subjective vision in the human medial temporal lobe. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 8378–8383.

Kreiman, G., Hung, C., Quian Quiroga, R., Kraskov, A., Poggio, T., & DiCarlo, J. (2006). Object selectivity of local field potentials and spikes in the inferior temporal cortex of macaque monkeys. *Neuron*, *49*, 433–445.

Kreiman, G., Koch, C., & Fried, I. (2000a). Category-specific visual responses of single neurons in the human medial temporal lobe. *Nature Neuroscience*, *3*, 946–953.

Kreiman, G., Koch, C., & Fried, I. (2000b). Imagery neurons in the human brain. *Nature*, *408*, 357–361.

Kriegeskorte, N., Mur, M., Ruff, D. A., Kiani, R., Bodurka, J., Esteky, H., et al. (2008). Matching categorical object representations in inferior temporal cortex of man and monkey. *Neuron*, *60*, 1126–1141.

Lavenex, P., & Amaral, D. G. (2000). Hippocampal–neocortical interaction: A hierarchy of associativity. *Hippocampus*, *10*, 420–430.

LeDoux, J. (1996). *The emotional brain*. New York: Simon & Schuster.

Lehky, S. R., & Maunsell, J. H. R. (1996). No binocular rivalry in the LGN of alert monkeys. *Vision Research*, *36*, 1225–1234.

Lein, E. S., Zhao, X., & Gage, F. H. (2004). Defining a molecular atlas of the hippocampus using DNA microarrays and high-throughput in situ hybridization. *Journal of Neuroscience*, *24*, 3879–3889.

Leonard, C. M., Rolls, E. T., Wilson, F. A. W., & Baylis, G. C. (1985). Neurons in the amygdala of the monkey with responses selective for faces. *Behavioural Brain Research*, *15*, 159–176.

Leopold, D. A., & Logothetis, N. K. (1996). Activity changes in early visual cortex reflect monkeys' percepts during binocular rivalry. *Nature*, *379*, 549–553.

Leopold, D. A., & Logothetis, N. K. (1999). Multistable phenomena: Changing views in perception. *Trends in Cognitive Sciences*, *3*, 254–264.

R

Libet, B. (1985). Unconscious cerebral initiative and the role of conscious will in voluntary action. *Behavioral and Brain Sciences*, *8*, 529–566.

Lisman, J., & Sternberg, E. J. (2013). Habit and nonhabit systems for unconscious and conscious behavior: Implications for multitasking. *Journal of Cognitive Neuroscience*, *25*, 273–283.

Litman, L., Awipi, T., & Davachi, L. (2009). Category-specificity in the human medial temporal lobe cortex. *Hippocampus*, *19*, 308–319.

Liu, H., Agam, Y., Madsen, J. R., & Kreiman, G. (2009). Timing, timing, timing: Fast decoding of object information from intracranial field potentials in human visual cortex. *Neuron*, *62*, 281–290.

Logothetis, N. K., Pauls, J., Bulthoff, H. H., & Poggio, T. (1994). View-dependent object recognition by monkeys. *Current Biology*, *4*, 401–414.

Logothetis, N. K., Pauls, J., & Poggio, T. (1995). Shape representation in the inferior temporal cortex of monkeys. *Current Biology*, *5*, 552–563.

Logothetis, N. K., & Sheinberg, D. L. (1996). Visual object recognition. *Annual Review of Neuroscience*, *19*, 577–621.

Louie, K., & Wilson, M. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron*, *29*, 145–156.

Marcus, D. S., Harwell, J., Olsen, T., & Van Essen, D. C. (2011). The human connectome project informatics platform. *Frontiers in Neuroscience*, *5*.

McCarthy, G., Puce, A., Belger, A., & Allison, T. (1999). Electrophysiological studies of human face perception: II. Response properties of face-specific potentials generated in occipitotemporal cortex. *Cerebral Cortex*, *9*, 431–444.

Meyers, E., Freedman, D., Kreiman, G., Miller, E., & Poggio, T. (2008). Dynamic population coding of category information in ITC and PFC. *Journal of Neurophysiology*, *100*, 1407–1419.

Milner, B., Corkin, S., & Teuber, H. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H. M. *Neurpsychologia*, *6*, 215–234.

Miyashita, Y. (1993). Inferior temporal cortex: Where visual perception meets memory. *Annual Review of Neuroscience*, *16*, 245–263.

Miyashita, Y., & Chang, H. S. (1988). Neuronal correlate of pictorial short-term memory in the primate temporal cortex. *Nature*, *331*, 68–71.

Miyashita, Y., Rolls, E. T., Cahusac, P. M. B., Niki, H., & Feigenbaum, J. D. (1989). Activity of hippocampal formation neurons in the monkey related to a conditional spatial response task. *Journal of Neurophysiology*, *61*, 669–678.

Mormann, F., Dubois, J., Kornblith, S., Milosavljevic, M., Cerf, M., Ison, M., et al. (2011). A category-specific response to animals in the right human amygdala. *Nature Neuroscience*, *14*, 1247–1249.

Mormann, F., Kornblith, S., Quiroga, R. Q., Kraskov, A., Cerf, M., Fried, I., et al. (2008). Latency and selectivity of single neurons indicate hierarchical processing in the human medial temporal lobe. *Journal of Neuroscience*, *28*, 8865–8872.

Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature*, *393*, 467–470.

Mountcastle, V. B. (1957). Modality and topographic properties of single neurons of cat's somatic sensory cortex. *Journal of Neurophysiology*, *20*, 408–434.

Mukamel, R., & Fried, I. (2012). Human intracranial recordings and cognitive neuroscience. *Annual Review of Psychology*, *63*, 511–537.

Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science*, *309*, 951–954.

Nadasdy, Z., Hirase, H., Czurko, A., Csicsvari, J., & Buzsaki, G. (1999). Replay and time compression of recurring spike sequences in the hippocampus. *Journal of Neuroscience*, *19*, 9497–9507.

Naya, Y., Sakai, K., & Miyashita, Y. (1996). Activity of primate inferotemporal neurons related to a sought target in a paired-association task. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 2664–2669.

Naya, Y., & Suzuki, W. (2011). Integrating what and when across the primate medial temporal lobe. *Science*, *333*, 4.

Naya, Y., Sakai, K., & Miyashita, Y. (1996). Activity of primate inferotemporal neurons related to a sought target in a paired-association task. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 2664–2669.

Nielsen, K., Logothetis, N., & Rainer, G. (2006). Dissociation between LFP and spiking activity in macaque inferior temporal cortex reveals diagnostic parts-based encoding of complex objects. *Journal of Neuroscience*, *26*, 9639–9645.

Nir, Y., Fisch, L., Mukamel, R., Gelbard-Sagiv, H., Arieli, A., Fried, I., et al. (2007). Coupling between neuronal firing rate, gamma LFP, and BOLD fMRI is related to inter-neuronal correlations. *Current Biology*, *17*, 1275–1285.

Nishijo, H., Ono, T., & Nishino, H. (1988). Single neuron responses in amygdala of alert monkeys during complex sensory stimulation with affective significance. *Journal of Neuroscience*, *8*, 3570–3583.

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map: Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, *34*, 171–175.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. London: Clarendon Press.

Ohman, A., Carlsson, E., Lundgvist, D., & Ingvar, M. (2007). On the unconscious subcortical origin of human fear. *Physiology & Behavior*, *92*, 180–185.

Ojemann, G. A. (1997). Treatment of temporal lobe epilepsy. *Annual Review of Medicine*, *48*, 317–328.

O'Neill, J., Pleydell-Bouverie, B., Dupret, D., & Csicsvari, J. (2010). Play it again: Reactivation of waking experience and memory. *Trends in Neurosciences*, *33*, 220–229.

Paton, J. J., Belova, M. A., Morrison, S. E., & Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature*, *439*, 865–870.

Pedreira, C., Mormann, F., Kraskov, A., Cerf, M., Fried, I., Koch, C., et al. (2010). Responses of human medial temporal lobe neurons are modulated by stimulus repetition. *Journal of Neurophysiology*, *103*, 97–107.

Pegna, A. J., Khateb, A., Lazeyras, F., & Seghier, M. L. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. *Nature Neuroscience*, *8*, 24–25.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews. Neuroscience*, *9*, 148–158.

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: From a "low road" to "many roads" of evaluating biological significance. *Nature Reviews. Neuroscience*, *11*, 773–783.

Phelps, E. A., & LeDoux, J. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, *48*, 175–187.

Pinto, N., Cox, D. D., & DiCarlo, J. J. (2008). Why is real-world visual object recognition hard? *PLoS Computational Biology*, *4*, e27.

Quian Quiroga, R., Kraskov, A., Koch, C., & Fried, I. (2009). Explicit encoding of multimodal percepts by single neurons in the human brain. *Current Biology*, *19*, 1308–1313.

Quian Quiroga, R., & Kreiman, G. (2010). Measuring sparseness in the brain. *Psychological Review*, *117*, 291–297.

Quian Quiroga, R., Kreiman, G., Koch, C., & Fried, I. (2008). Sparse but not "Grandmother-cell" coding in the medial temporal lobe. *Trends in Cognitive Sciences*, *12*, 87–91.

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

Quiroga, R. (2012). Concept cells: The building blocks of declarative memory functions. *Nature Reviews. Neuroscience*, *13*, 587–597.

Quiroga, R. Q., Mukamel, R., Isham, E. A., Malach, R., & Fried, I. (2008). Human single-neuron responses at the threshold of conscious recognition. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 3599–3604.

Rainer, G., Rao, S., & Miller, E. (1999). Prospective coding for objects in primate prefrontal cortex. *Journal of Neuroscience*, *19*, 5493–5505.

Rao, S., Rainer, G., & Miller, E. (1997). Integration of what and where in the primate prefrontal cortex. *Science*, *276*, 821–824.

Rasch, M., Logothetis, N. K., & Kreiman, G. (2009). From neurons to circuits: Linear estimation of local field potentials. *Journal of Neuroscience*, *29*, 13785–13796.

R

Rees, G., Kreiman, G., & Koch, C. (2002). Neural correlates of consciousness in humans. *Nature Reviews. Neuroscience*, *3*, 261–270.

Riesenhuber, M., & Poggio, T. (1999). Hierarchical models of object recognition in cortex. *Nature Neuroscience*, *2*, 1019–1025.

Riesenhuber, M., & Poggio, T. (2000). Models of object recognition. *Nature Neuroscience*, *3*(Suppl), 1199–1204.

Rolls, E. (1991). Neural organization of higher visual functions. *Current Opinion in Neurobiology*, *1*, 274–278.

Rolls, E. T., Miyashita, Y., Cahusac, P. M. B., Kesner, R. P., Niki, H., Feigenbaum, J. D., et al. (1989). Hippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. *Journal of Neuroscience*, *9*, 1835–1845.

Rutishauser, U., Mamelak, A. N., & Schuman, E. M. (2006). Single-trial learning of novel stimuli by individual neurons of the human hippocampus–amygdala complex. *Neuron*, *49*, 805–813.

Rutishauser, U., Ross, I. B., Mamelak, A. N., Schuman, E. M. (2011). Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature*, *464*, 903–907.

Rutishauser, U., Tudusciuc, O., Neumann, D., Mamelak, A., Heller, C., Ross, I., et al. (2011). Single-unit responses selective for whole faces in the human amygdala. *Current Biology*, *21*, 1654–1660.

Sander, D., Gradman, J., & Zalla, T. (2003). The human amygdala: An evolved system for relevance detection. *Reviews in the Neurosciences*, *14*, 303–316.

Schmolesky, M., Wang, Y., Hanes, D., Thompson, K., Leutgeb, S., Schall, J., et al. (1998). Signal timing across the macaque visual system. *Journal of Neurophysiology*, *79*, 3272–3278.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *20*, 11–21.

Serre, T., Kreiman, G., Kouh, M., Cadieu, C., Knoblich, U., & Poggio, T. (2007). A quantitative theory of immediate visual recognition. *Progress in Brain Research*, *165C*, 33–56.

Sheinberg, D. L., & Logothetis, N. K. (1997). The role of temporal areas in perceptual organization. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 3408–3413.

Shoham, S., O'Connor, D. H., & Segev, R. (2006). How silent is the brain: Is there a "dark matter" problem in neuroscience? *Journal of Comparative Physiology. A, Neuroethology, Sensory, Neural, and Behavioral Physiology*, *192*, 777–784.

Shrager, Y., Gold, J. J., Hopkins, R. O., & Squire, L. R. (2006). Intact visual perception in memory-impaired patients with medial temporal lobe lesions. *Journal of Neuroscience*, *26*, 2235–2240.

Siebert, M., Markowitsch, H. J., & Bartel, P. (2003). Amygdala, affect and cognition: Evidence from 10 patients with Urbach-Wiethe disease. *Brain*, *126*, 2627–2637.

Sigala, N., & Logothetis, N. (2002). Visual categorization shapes feature selectivity in the primate temporal cortex. *Nature*, *415*, 318–320.

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*, *271*, 1870–1873.

Sperry, R. (1982). Some effects of disconnecting the cerebral hemispheres. *Science*, *217*, 1223–1226.

Squire, L., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*, 1380–1386.

Squire, L. R. (2009). The legacy of patient H.M. for neuroscience. *Neuron*, *61*, 6–9.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*, 279–306.

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: A new perspective. *Nature Reviews. Neuroscience*, *8*, 872–883.

Stead, M., Bower, M., Brinkmann, B. H., Lee, K., Marsh, W. R., Meyer, F. B., et al. (2010). Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain*, *133*, 2789–2797.

Steinmetz, P. N., Cabrales, E., Wilson, M. S., Baker, C. P., Thorp, C. K., Smith, K. A., et al. (2011). Neurons in the human hippocampus and amygdala respond to both low- and high-level image properties. *Journal of Neurophysiology*, *105*, 2874–2884.

R

Suthana, N., Haneef, Z., Stern, J., Mukamel, R., Behnke, E., Knowlton, B., et al. (2012). Memory enhancement and deep-brain stimulation of the entorhinal area. *New England Journal of Medicine*, *366*, 502–510.

Suzuki, W., Miller, E., & Desimone, R. (1997). Object and place memory in the macaque entorhinal cortex. *Journal of Neurophysiology*, *78*, 1062–1081.

Suzuki, W. A. (1996). Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: Organization of cortical inputs and interconnections with amygdala and striatum. *Seminars in Neuroscience*, *8*, 3–12.

Suzuki, W. A., & Amaral, D. G. (1994). Perrirhinal and parahippocampal cortices of the macaque monkey: Cortical afferents. *Journal of Comparative Neurology*, *350*, 497–533.

Tanaka, K. (1996). Inferotemporal cortex and object vision. *Annual Review of Neuroscience*, *19*, 109–139.

Taube, J. S., Muller, R. U., & Ranck, J. B. J. (1990). Head-direction cells recorded from the postsubiculum in freely moving rats: I. Description and quantitative analysis. *Journal of Neuroscience*, *10*, 420–435.

Tsao, D. Y., Moeller, S., & Freiwald, W. A. (2008a). Comparing face patch systems in macaques and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 19514–19519.

Tsao, D. Y., Schweers, N., Moeller, S., & Freiwald, W. A. (2008b). Patches of face-selective cortex in the macaque frontal lobe. *Nature Neuroscience*, *11*, 877–879.

Viskontas, I. V., Ekstrom, A. D., Wilson, C. L., & Fried, I. (2007). Characterizing interneuron and pyramidal cells in the human medial temporal lobe in vivo using extracellular recordings. *Hippocampus*, *17*, 49–57.

von Bohlen und Halbach, O., & Unsicker, K. (2002). Morphological alterations in the amygdala and hippocampus of mice during ageing. *European Journal of Neuroscience*, *16*, 2434–2440.

Wagner, A. D., Koutstaal, W., & Schacter, D. L. (1999). When encoding yields remembering: Insights from event-related neuroimaging. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *354*, 1307–1324.

Wandell, B. A. (1995). *Foundations of vision*. Sunderland, MA: Sinauer Associates.

Waydo, S., Kraskov, A., Quian Quiroga, R., Fried, I., & Koch, C. (2006). Sparse representation in the human medial temporal lobe. *Journal of Neuroscience*, *26*, 10232–10234.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amydgala activity without explicit knowledge. *Journal of Neuroscience*, *18*, 411–418.

Wirth, S., Yanike, M., Frank, L. M., Smith, A. C., Brown, E. N., & Suzuki, W. A. (2003). Single neurons in the monkey hippocampus and learning of new associations. *Science*, *300*, 1578–1581.

Yanike, M., Wirth, S., & Suzuki, W. A. (2004). Representation of well-learned information in the monkey hippocampus. *Neuron*, *42*, 477–487.

Yoshor, D., Bosking, W. H., Ghose, G. M., & Maunsell, J. H. (2007). Receptive fields in human visual cortex mapped with surface electrodes. *Cerebral Cortex*, *17*, 2293–2302.

Young, M. P., Scannell, J. W., Burns, G. A., & Blackmore, C. (1994). Analysis of connectivity: Neural systems in the cerebral cortex. *Reviews in the Neurosciences*, *5*, 227–250.

R