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Plugging in to Human Memory: Advantages, Challenges, and Insights from Human Single-Neuron Recordings

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We describe single-neuron recordings in the human hippocampal formation, performed in epileptic patients for clinical reasons, and highlight their advantages, challenges, and limitations compared with non-invasive recordings in humans and invasive recordings in animals. We propose a unified framework to explain different findings—responses to novel stimuli, spatial locations, and specific concepts—linking the rodent and human literature regarding the function of the hippocampal formation. Moreover, we propose a model of how memories are encoded in this area, suggesting that the context-independent, invariant coding by concept cells may provide a uniquely human neural mechanism underlying memory representations.

In the 1980s, zoologist Hans Kummer reported a now very famous observation of a female Hamadrya baboon grooming with a young male hiding behind a big rock but keeping part of the body visible to her own male, who was feeding several meters away, unaware of the situation (Whiten and Byrne, 1988). This and similar types of behaviors have been offered as evidence that non-human primates have a "theory of mind"; that is, the ability to understand other subjects' thoughts. However, this interpretation has been disputed by behavioralists (see comments in Whiten and Byrne (1988), who argue that the animal may have learned to act this way without truly understanding why; that means, without necessarily wondering what her male was thinking. The problem is that we cannot get into the animal's head or simply ask her why she hid behind the rock. In fact, pinning down the real motives or thoughts of animals is difficult and requires well-controlled paradigms (one such study showed decades later that non-human primates do indeed have a theory of mind [Krupenye et al., 2016]). The same applies to memory, particularly to episodic memory (i.e., the memory of our experiences) because we cannot interrogate animals about their thoughts and recollections.

A key challenge in neuroscience is to understand how the firing of neurons underlies behavior. However, advances in this area face some very basic limitations. On one hand, non-invasive recording techniques—e.g., electroencephalography (EEG), magnetoencephalography (MEG), and fMRI—are used with human subjects for obvious ethical reasons, but, although these methods have provided insights into the activation of brain areas during different tasks, they can only offer an indirect and vague measure of the activity of individual neurons (Logothetis, 2008). On the other hand, invasive recordings provide direct access to study the firing of multiple neurons but can usually only be performed in animals, and, as the story of Kummer illustrates, the lack of direct verbal feedback limits our understanding of what is going on in the animal's brain. Moreover, the types of experiments and questions that can be addressed with animals are limited because they need extensive reward-driven training to perform different tasks, far from the natural conditions of how these behaviors occur in real-life situations.

In very particular cases, however, it is possible to perform invasive recordings in human subjects for clinical reasons. This is the case with patients suffering from epilepsy refractory to medication, who are implanted with intracranial electrodes to determine the seizure-originating area and evaluate the possibility of its surgical resection (Rey et al., 2015a), offering the extraordinary opportunity to record the activity of multiple single neurons in awake and behaving human subjects performing different tasks. (Single-cell recordings are also performed during deep brain stimulation [DBS], and we refer to Engel et al. [2005] for a review of these studies, which will not be covered here.)

Single-Neuron Recordings in Humans

The first recordings of individual neurons in the human brain were performed in the 1950s, using a glass pipette attached to a micromanipulator during epilepsy surgery (Ward and Thomas, 1955). Later on, in the 1970s, a procedure was developed to record from multiple microwires that were inserted through hollow-depth intracranial electrodes protruding a few millimeters from their end (Babb et al., 1973), a design that it is still used today (Figures 1A–1C). Contacts placed along the depth electrodes allow recording of intracranial electroencephalographic (iEEG) data used for clinical assessment of the patients, whereas the microwires provide recordings of multiple single neurons and local field potentials (LFPs) (Figures 1D and 1E). Recording sites often cover the medial

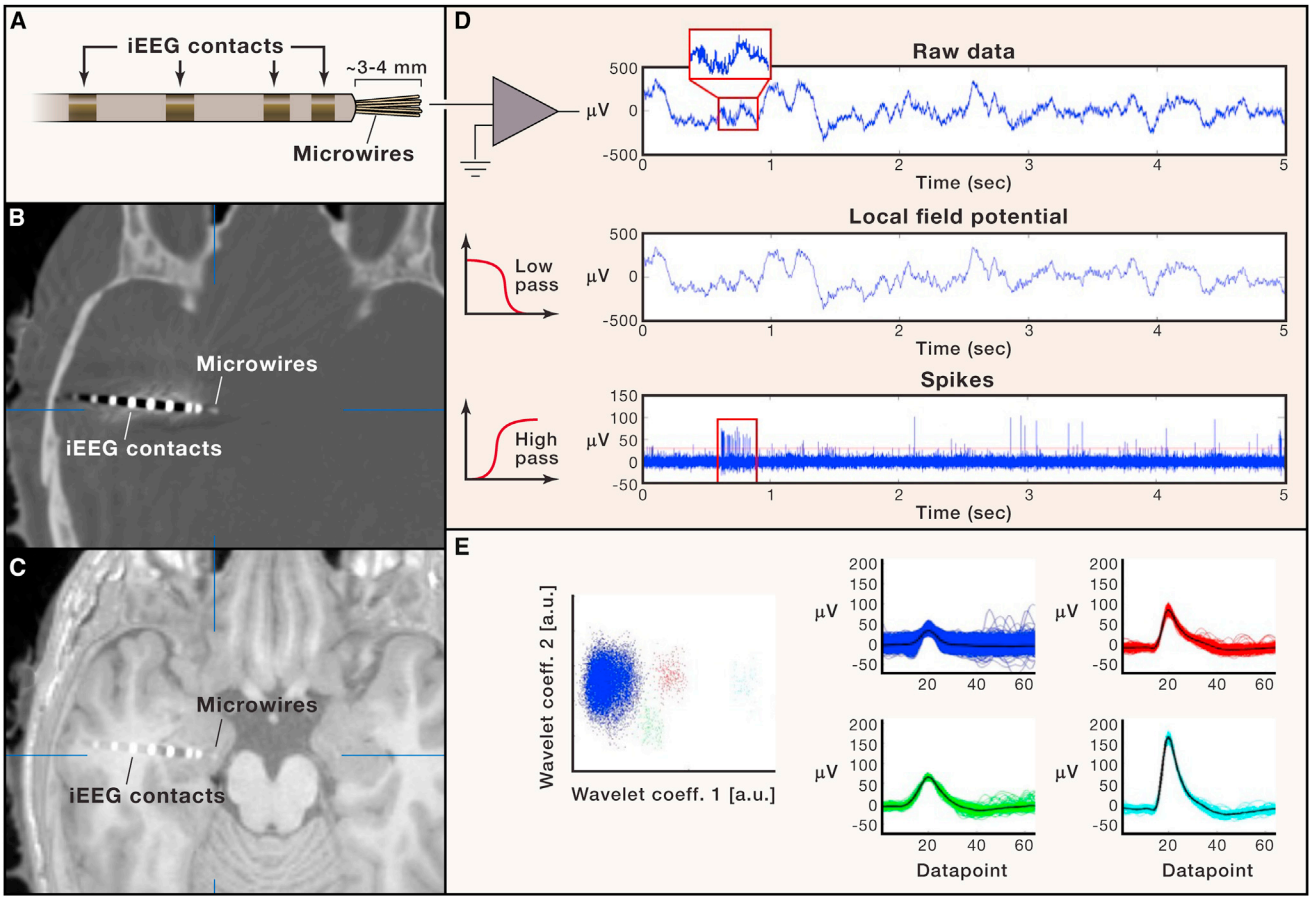

Figure 1. Human Single-Neuron Recordings

(A) Electrodes used for intracranial recordings. The intracranial EEG (iEEG) contacts are used to localize the epileptic activity, whereas local field potentials (LFPs) and spiking activity are recorded from the microwires protruding from the electrode tip.

(B and C) Computed tomography (CT) (B) and CT fused with MRI (C) of one electrode implanted in the hippocampal formation.

(D) Raw data recorded from the microwires, where spikes are hardly visible (inset) because of the presence of large-amplitude, low-frequency activity. From the raw data, LFPs are obtained by low-pass filtering, and spikes are visualized after high-pass filtering (the marked segment correspond to the inset in the raw data).

(E) Spikes are represented in a feature space (in this case, the first two wavelet coefficients) in which the classification of the spike shapes of the different neurons (i.e., spike sorting) is done. Clusters with relatively few spikes (the ones in red, green, and cyan) are typically difficult to identify because they tend to be merged with larger clusters (the one in blue).

temporal lobe (MTL; the hippocampal formation and its surrounding cortex) because of the involvement of this area in different forms of epilepsy (Niedermeyer, 1993). Subjects remain with the electrodes implanted for about a week and are monitored to record a sufficient number of spontaneous seizures to evaluate an eventual surgical resection of the epileptic focus.

Advantages

Advantages Compared with Non-invasive Recordings in Humans. Compared with non-invasive studies, the key advantage of single-neuron recordings is the possibility of having access to the activity of individual neurons, which can be measured only indirectly with non-invasive methods. Let us illustrate this with two concrete cases. First, it is common that MTL neurons respond sparsely to very few pictures (Quian Quiroga et al., 2007). Because of a general lack of topographic organization in the MTL (i.e., responses are not spatially clustered, and nearby neurons fire to completely different stimuli; De Falco et al., 2016), there is not a common and localized activation that can be observed at the more macroscopic level of fMRI or EEG/MEG recordings, and, therefore, these responses are only identified at the single-neuron level. Second, besides providing information about neuronal responses that cannot be seen with non-invasive methods, single-neuron recordings can also validate and provide further mechanistic evidence of fMRI and EEG/MEG findings. For example, fMRI studies have consistently shown the presence of preferential responses to scenes in the parahippocampal place area (PPA) (Epstein and Kanwisher, 1998). However, fMRI recordings cannot distinguish between different mechanisms that can produce these responses: (1) each PPA neuron may respond sparsely to one or relatively few scenes, giving category scene responses when averaging the activity of neighboring neurons constituting each voxel; (2) PPA neurons may be tuned to visual features that are more

prevalent in scene images, showing scene responses in the population average but some visual feature tuning, rather than scene selectivity, at the single-neuron level; (3) PPA neurons may be scene-selective, responding preferentially to pictures of scenes. Analysis of about 2,000 human MTL neurons clearly showed that the latter was the case; parahippocampal neurons had a tendency to respond to scenes (Mormann et al., 2017; Figure 2A) with much broader category tuning compared with the selective responses found for known people (Quian Quiroga et al., 2007).

Advantages Compared with Invasive Recordings in Animals. Compared with recordings with animals, a first obvious advantage is that, if the ultimate goal is to understand the human brain (although this need not necessarily be the case), then, by performing recordings directly in humans, we can avoid the potentially false assumption of similar brain functioning in animal models and humans. Another advantage of human single-neuron recordings is the possibility of communicating with and getting direct feedback from the subjects, which allows us to perform experiments that cannot be done in other animals. This is particularly the case when studying internally generated top-down activations, such as those arising during memory recall (Gelbard-Sagiv et al., 2008; Ison et al., 2015), imagery (Kreiman et al., 2000), or voluntary control of the neuron's firing based on the subject's thoughts (Cerf et al., 2010).

Another key advantage is the possibility of directly explaining the experiments to the subjects without the need of extensive reward-driven training and the ensuing potential caveats of overtraining effects that could influence the neurons' responses after months of performing the same task. Moreover, communication with the subjects permits tuning the experiments according to their background and interests. For example, Figure 2B shows the responses of a neuron in a subject interested in mathematics that fired to different equations and math-related stimuli, whereas Figure 2C shows a neuron's responses to "Mr. T," a character in the film *Rocky III*, in a subject who was a fan of this movie. The rationale for presenting equations (among other things) to the first subject and characters from the *Rocky* films to the second was that we expected to find more responses to personally relevant things, as was shown to be the case from analysis of a large number of responses (Viskontas et al., 2009).

Disadvantages and Limitations

Limitations Arising from Performing Recordings with Patients. Human single-neuron recordings offer clear advantages but have also several limitations, mainly because of recording constraints and the fact that these experiments are performed with patients in a clinical environment.

A major limitation is the availability of patients. Most hospitals performing these recordings have relatively few implantations a year, and it may take several years to get a sufficient number of neurons to have statistically sound results. Moreover, the time to perform experiments with each patient is also limited, and it is not always possible to consider all of the control experiments that one would like to do. In addition, recordings are performed in a clinical environment, which can be very noisy, and there is relatively little time to sort out technical issues compared with a standard laboratory environment.

The fact that recordings are done in patients with epilepsy also raises the concern that the obtained results may reflect different aspects of this pathology rather than normal brain functioning. This is, however, very unlikely given that similar types of responses have been obtained in recordings close to the seizure-originating area and in more distant areas, including the non-seizure-originating hemisphere (Mormann et al., 2008). Moreover, results are similar for patients with different types of epilepsy involving different pathophysiological mechanisms (Niedermeyer, 1993). In addition, epileptic activity is, in principle, expected to produce an increase in neural excitability and connectivity, which would give a global increase in the neurons' responsiveness, contrary to the very high selectivity observed in these recordings (Quian Quiroga et al., 2007).

Results could also be attributed to effects of the medication taken by the patients. This is particularly a concern when considering, for example, the relatively late onset of MTL neuron responses compared with response onsets in animals (Mormann et al., 2008). However, different patients have different medications and dosages, and, furthermore, medication is gradually tapered down during the time the patient is in the hospital to increase the chances of recording seizures. Because similar results are obtained in different patients and at different days of the intervention, the effects of medication in the MTL responses can be ruled out.

Limitations Arising from the Location of Intracranial Recordings. A caveat of human single neuron recordings is their limited coverage compared with non-invasive techniques. The location of the intracranial electrodes is always determined by clinical criteria. Consequently, scientist do not have—and should not have—a say in decisions about the implantation of the electrodes, which may not necessarily cover the key areas involved in the processes under study. Moreover, as with chronic recordings, electrodes cannot be externally moved to search for responsive neurons, and millimeter variations in the electrode implantation can mean the difference between obtaining and not obtaining single-neuron recordings. However, because the electrodes are fixed, there are no potential biases as there can be with acute recordings: moving the electrodes and targeting easily identifiable neurons with high firing rates can lead to sparsely firing neurons being overlooked (Shoham et al., 2006).

Recording sites typically include the MTL because of the involvement of this area in different forms of epilepsy (Niedermeyer, 1993). This is ideal to study memory processes, given the well-documented role of the MTL in declarative memory (Squire and Zola-Morgan, 1991). However, the study of MTL neurons provides only a limited picture of memory functions, which should ideally also consider interactions with the diencephalon (Aggleton and Brown, 1999) and neocortical areas (Eichenbaum, 2017; Fletcher and Henson, 2001; Sekeres et al., 2018). This is particularly important to study memory consolidation and the interplay of these areas in the coding of episodic and semantic memories (Moscovitch et al., 2005; Squire and Zola-Morgan, 1991). It is, however, possible to extract some information about neocortical activations from the iEEG contacts of the depth electrodes (Figure 1). In this respect, of particular interest is analysis of high-frequency oscillations, which correlate with local neuronal activity (Fisch et al., 2009; Lachaux et al., 2012;

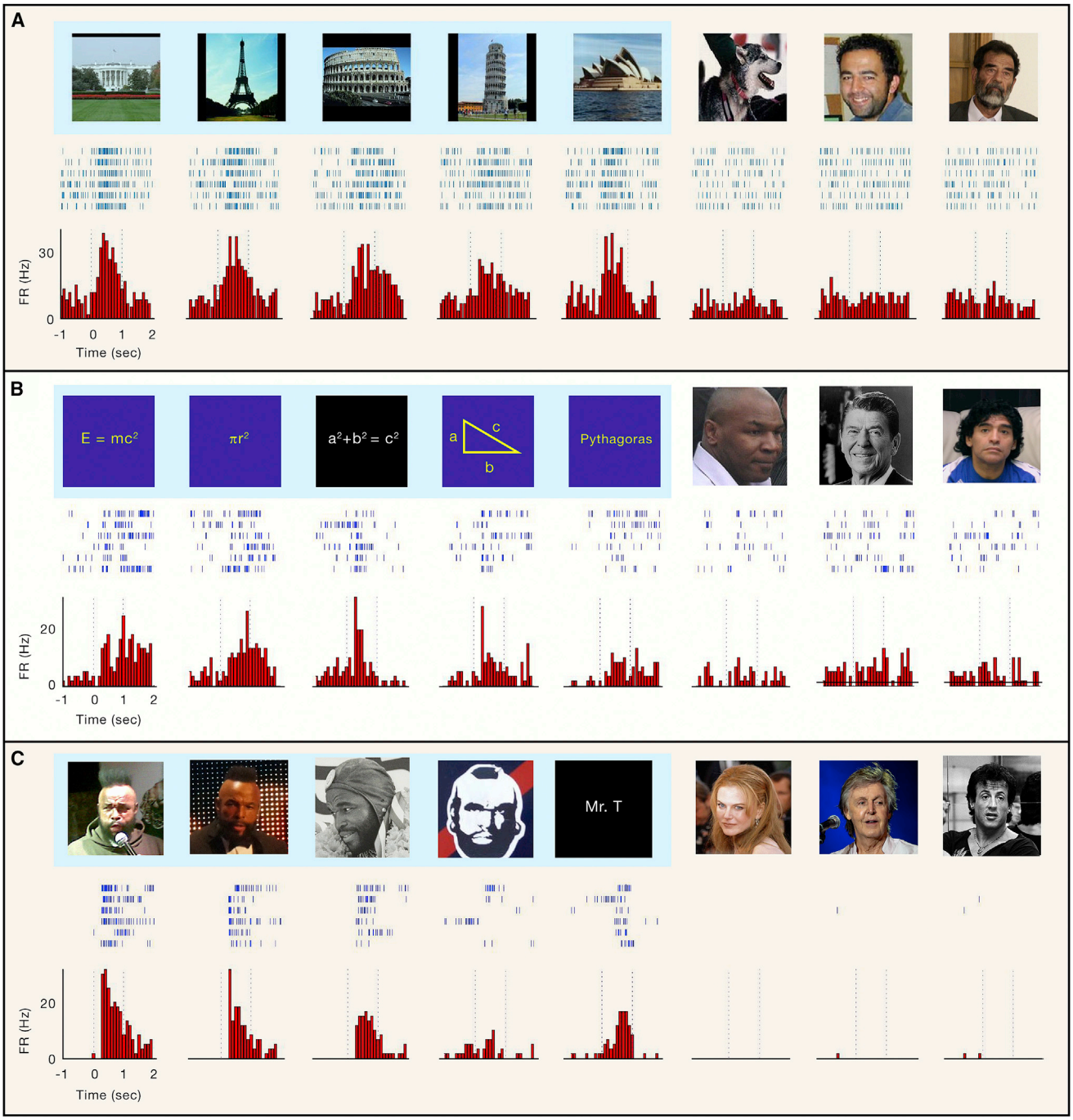

Figure 2. Examples of Single-Neuron Responses in the Human MTL

(A) Pictures of landmark scenes (highlighted box) that elicited responses of a neuron in the parahippocampal cortex. The second and third rows correspond to the raster plot and the peristimulus time histogram, respectively. Dashed vertical lines show the time of picture onset and offset, 1 s apart.

(B) Images of equations and math-related stimuli (highlighted) that elicited responses in a neuron in the entorhinal cortex in a subject interested in mathematics.

(C) Images of "Mr. T," including his written name (highlighted), that elicited responses in a neuron in the amygdala in a subject who was fan of the film *Rocky III*.

Due to copyright issues, in this and the following figures some of the pictures were replaced by copyright-free pictures of the same persons.

Rich and Wallis, 2017; Watson et al., 2018) although, of course, not giving single-neuron resolution, as with implanted microwires (e.g., to estimate stimulus selectivity; Rey et al., 2014).

Another caveat is that it is not possible to give a precise location of the microwires used for human recordings. Animal studies, particularly with rodents, have offered clear evidence

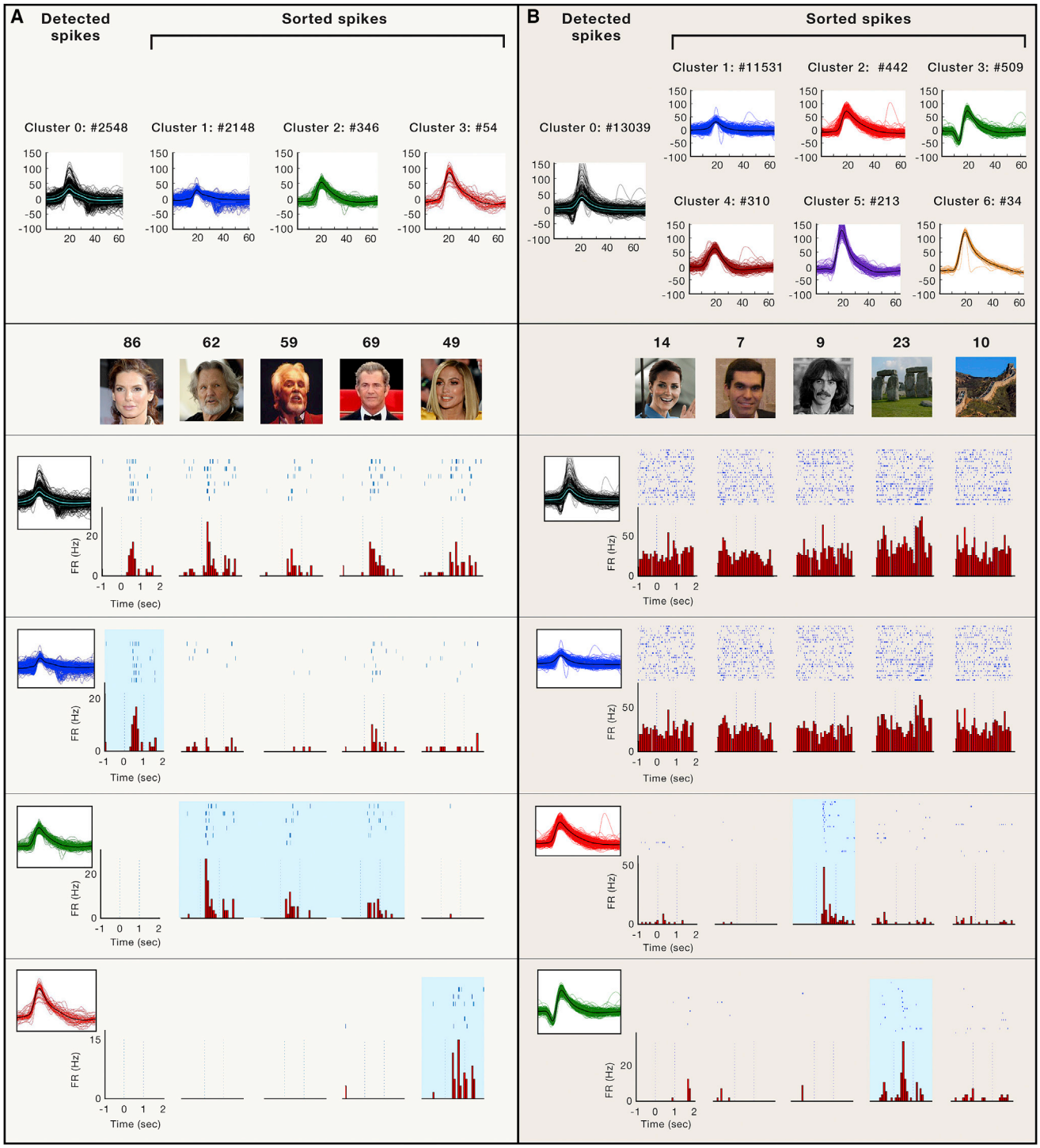

Figure 3. Single-Neuron Responses Identified after Spike Sorting

(A) Spike sorting from an electrode in the amygdala. From the detected spikes, we observe responses to all 5 pictures depicted. However, after spike sorting, we rather see that there is multiunit (blue) responding mainly to actress Sandra Bullock (stimulus 86) and a single unit (green) responding to Kris Kristofferson (stim. 62) and Kenny Rogers (stim. 59), both actors and country singers, and to actor Mel Gibson (stim 69), who was costar with Kristofferson in the movie *Payback*. The other single unit (red) responded only to actress Jennifer Lopez (stim. 49). For space reasons, the responses to only 5 of 105 pictures presented are shown (but there were no significant responses to the pictures not included in the figure).

(legend continued on next page)

of distinct roles of substructures within the hippocampus (see, e.g., Treves and Rolls [1994]). But with human single-cell recordings, it is difficult to delineate the hippocampal substructures in the co-registered MRI scans (Wisse et al., 2017), and it is also very difficult to visualize the microwires in the CT scans (Figures 1B and 1C) (and even if we could, we would not know which microwire is which).

Limitations Arising from the Number of Recorded Neurons. Another major limitation is given by the number of microwires implanted for single-neuron recordings. MTL neurons tend to show very sparse responses, firing to relatively few stimuli (Mormann et al., 2008; Quian Quiroga et al., 2007). Consequently, it is difficult to trigger the neurons' responses (that is why we use the "screening sessions" described below), and it is very unlikely to record simultaneously from two or more neurons responding to a particular stimulus, although it is still possible to infer properties at the population level by using statistical arguments (e.g., Waydo et al. [2006]). Moreover, the number of identified units can be increased using optimal spike sorting algorithms (see next section) (Rey et al., 2015b) and, particularly, new electrode designs. Spectacular advances have been made in the design of electrodes used for animal studies (e.g., Jun et al. [2017]), but we have essentially been using the same type of electrodes for human single-cell recordings since the 1970s (Babb et al., 1973), in spite of the fact that progress in this area is likely to have a large effect on the recording conditions.

Stability of the Recordings, Consolidation, and Long-Term Representations

Using chronic recordings in animals, it has been shown that it is possible to record from the same neurons during several days (Dhawale et al., 2017; Okun et al., 2016). Tracking neurons over days is indeed critical for human MTL recordings because it allows us to assess the stability/plasticity of the responses and study consolidation mechanisms. In particular, there has been a long ongoing dispute about the role of the MTL in memory coding. Supporters of the standard consolidation model (Squire et al., 2015; Squire and Zola-Morgan, 1991) argue that the MTL encodes memories only during learning and not after their consolidation in the neocortex, whereas supporters of the multiple trace theory (Nadel and Moscovitch, 1997; Sekeres et al., 2018) argue that the MTL continues to remain critical for (episodic) memory after learning, thus providing a long-term representation. Evidence backing one or the other theory comes mainly from two sources: behavioral studies in patients with lesions, which, because of the variability of the precise location and extent of the lesions, have provided mixed results (Moscovitch et al., 2005), and non-invasive (fMRI) recordings (Moscovitch et al., 2005), but this technique cannot directly assess, at the single-cell level, the stability and plasticity of neuronal representations.

Tracking neurons in time is a challenging task with recordings in epileptic patients (and patients typically have the electrodes implanted for no longer than a week). This is because, in the clinical environment where the experiments are performed, the signal and noise conditions can change abruptly, and electrodes may also move; for example, when the patients have seizures with abrupt contractions. In spite of this limitation, first results show that it is at least possible to track neurons producing similar responses on consecutive days (Niediek et al., 2016). However, it is still difficult to quantitatively assess the stability and plasticity of the neural representations—i.e., what the neurons fire to—across days because different responses could arise from different neurons being recorded. To address this issue, it is important to perform continuous 24/7 recordings and track the neurons' properties (e.g., spike shape, firing characteristics) to check their identity, ensuring that any changes in the neurons' properties are relatively smooth (Harris et al., 2016). In this respect, it should be noted that, although it is difficult to record from the same neurons over several days in humans, it is, however, possible to infer whether responses are created *de novo* during the task or whether they reflect a long-term representation. The latter seems to be the case, given that MTL responses are observed during passive viewing the first time the patient sees a picture of a particular person (or place, animal, etc.), meaning that the neuron was already encoding this person before the experiment took place (Pedreira et al., 2010; Rey et al., 2015a).

Silent Neurons—Screening Sessions

The spikes fired by the neurons are metabolically expensive (Attwell and Laughlin, 2001), and it has been argued that, similar to the dark matter problem in physics, a large proportion of neurons may remain silent most of the time and are therefore not observed with extracellular recordings (Shoham et al., 2006). Figure 3 shows two hippocampal recordings where the activity of different neurons was identified after spike sorting. In both cases, we observe units with very sparse responses that fired only to one or a few of the pictures shown and remained nearly silent during the rest of the recording. These neurons are difficult to detect for two reasons: first, their responses are masked by the firing of other nearby neurons recorded from the same electrode (Harris et al., 2016; Rey et al., 2015a), and second, the neurons cannot be detected unless the right stimulus is shown.

With respect to the first problem, it is challenging to separate clusters with relatively very few spikes from other, much larger clusters, but current spike-sorting algorithms can deal with sparsely firing neurons (Figure 1E; Rey et al., 2015b). Note that an optimal separation of the neurons recorded from a single electrode is important not only to identify sparse responses that would not be observed otherwise (Figure 3B; Rey et al., 2015a) (and that cannot be detected with non-invasive recordings) but also to avoid misinterpretations about coding principles underlying the firing of these neurons (Figure 3A); for example, without proper sorting, it would be difficult to assess the neurons' very high selectivity (Quian Quiroga et al., 2007) and their tendency to fire to related concepts (De Falco et al., 2016).

(B) Spike sorting from an electrode in the hippocampus. In this case, we do not observe any response for the detected spikes, but after spike sorting, we see that one multiunit (blue) and 5 single units were identified, with one of them (in red) firing to musician George Harrison (stim 9) and another one (in green) firing only to a picture of Stonehenge (stim 23). Note that the multiunit does not have clear responses and masks the responses of the single units before spike sorting is done. The responses to 5 of 24 pictures presented are shown, but there were no significant responses to the other pictures.

Concerning the second problem, we do not know *a priori* which pictures trigger the neurons' responses. As illustrated in Figures 2B and 2C, based on interactions with the patients, we know about their interests and we therefore tend to use pictures of things that are familiar to them. Besides tuning the stimulus set based on the patient's interests, screening sessions can be performed in which a large number of pictures is shown repeatedly and in pseudorandom order to determine which of the pictures trigger neuronal activations, and then use these specific pictures in follow-up experiments. This way, responses in the screening sessions were used to study how the firing of MTL neurons correlates with conscious perception (Quian Quiroga et al., 2014, 2008), internally generated processes (Cerf et al., 2010), working memory (Kornblith et al., 2017; Reddy et al., 2006), and rapid formation of associations (Ison et al., 2015), among other functions. The screening sessions also provide valuable data to estimate the coding properties of MTL neurons, such as their degree of selectivity (Waydo et al., 2006).

Memory Coding in the Human MTL

The seminal study of patient H.M. showed the critical role of the MTL in declarative memory (i.e., memories of facts and experiences; Scoville and Milner, 1957). Investigations in patients with similar lesions (Moscovitch et al., 2005; Nadel and Moscovitch, 1997), evidence from animal studies (Squire and Zola-Morgan, 1991), and imaging studies in normal subjects (Paller and Wagner, 2002) have provided further support of the role of the MTL in the coding and consolidation of episodic memories (Sekeres et al., 2018; Squire et al., 2015) but cannot address how neurons in the human MTL underlie memory functions. In this section, we describe three lines of research with human single-neuron recordings that have shown the involvement of MTL neurons in memory and propose a unified framework to explain these responses.

Recognition Memory and Novelty Responses

Episodic memories are based on single experiences, and, therefore, many studies have focused on how the MTL responds to novel stimuli. Imaging studies in humans (Paller and Wagner, 2002) and electrophysiology studies in monkeys (Brown and Xiang, 1998) have established that the MTL is involved in the encoding of novel items using recognition memory paradigms (Bird, 2017) and that such activations can predict later recall (Paller and Wagner, 2002). Implementing a similar approach with human intracranial recordings, it has been shown that MTL neurons respond to novel stimuli (Fried et al., 1997; Heit et al., 1988). Further studies showed that, in contrast to the very selective responses to familiar persons (Quian Quiroga et al., 2007), responses to novel stimuli are not selective because a relatively large proportion of MTL neurons (~20%) change their firing in response to most novel stimuli (Rutishauser et al., 2006; Rutishauser et al., 2008; Viskontas et al., 2006). Interestingly, a more recent study showed that the precise timing of MTL neurons' firing, occurring at specific phases of local theta oscillations, signaled whether novel items would later be recognized (Rutishauser et al., 2010), a finding in line with other studies showing correlations between the precise timing of the neurons' firing and the phase of LFPs in specific frequency bands (Quian Quiroga and Panzeri, 2009).

Concept Cells

Several advances, including the use of screening sessions with stimulus sets tuned for each subject to maximize the chance of getting responses (Figures 2B and 2C) and the use of an advanced spike-sorting algorithm to identify nearly silent neurons (Figure 3), led to the finding of MTL neurons with very sparse and invariant responses. Figure 4 shows two neurons from a recording in the amygdala that were separated after spike sorting. The first one fired to one of the experimenters performing recordings with the patient and to his name (Arne) presented on the screen and pronounced by a computer-synthetized voice (but not to the other 95 pictures and names shown). That means that the neuron responded to the concept "Arne" but not to the details of the visual or auditory stimuli used. The second neuron responded to actor Michael Douglas, but in this case, the response to the written name was not significant. In fact, about 20%–30% of amygdala neurons responding to the picture of a person also responded to his/her name, whereas about 50% did so in the hippocampus, which shows a higher degree of abstraction in this area, going beyond a specific sensory modality. More generally, there is an increase of abstraction and multimodal invariance along the anatomically hierarchical structure of the MTL; about half of the neurons in the parahippocampal cortex, at the bottom of this hierarchy, show visual invariance but no multisensory responses, whereas more than 70% of the neurons show visual invariance and about half multisensory responses in the entorhinal cortex and the hippocampus, at the top of this hierarchy (Quian Quiroga, 2012, 2009).

Concept cells can be characterized as neurons in the human MTL that (1) respond very selectively to specific and well-known concepts (like a famous person or place), (2) have a high degree of multimodal invariance (i.e., responding to different pictures of the same person, irrespective of the varying details of the pictures used, and even to the person's written or spoken name); and (3) are not modulated by context (see below). Several studies have further characterized the properties of these neurons, and it has been proposed that they are involved in declarative memory (Quian Quiroga, 2012), in line with the well-established role of the MTL for this function (Squire and Zola-Morgan, 1991). This is supported by the facts that (1) concept cells have a relatively late latency of responses (~300 ms; Mormann et al., 2008), much later than what would be expected for sensory processing; (2) they fire to personally relevant concepts (Viskontas et al., 2009; namely, those that tend to be stored in memory); (3) they show a high degree of invariance (Quian Quiroga et al., 2009, 2005), which is in agreement with the fact that we tend to conceptualize and forget irrelevant details; (4) they have high selectivity (Quian Quiroga et al., 2007), which, as shown by theoretical studies, is ideal for memory functions, such as creating new associations (Marr, 1971); (5) their function is beyond sensory processing because their firing can be triggered by different stimulus modalities (Quian Quiroga et al., 2009) or internal processes in the absence of external stimulation (Gelbard-Sagiv et al., 2008); and (6) they respond to the subjective attribution of meaning by the subjects (i.e., how they will eventually store in memory what they believe they saw), mostly with all-or-none responses, irrespective of the sensory features of the stimuli (Quian Quiroga et al., 2014, 2008).

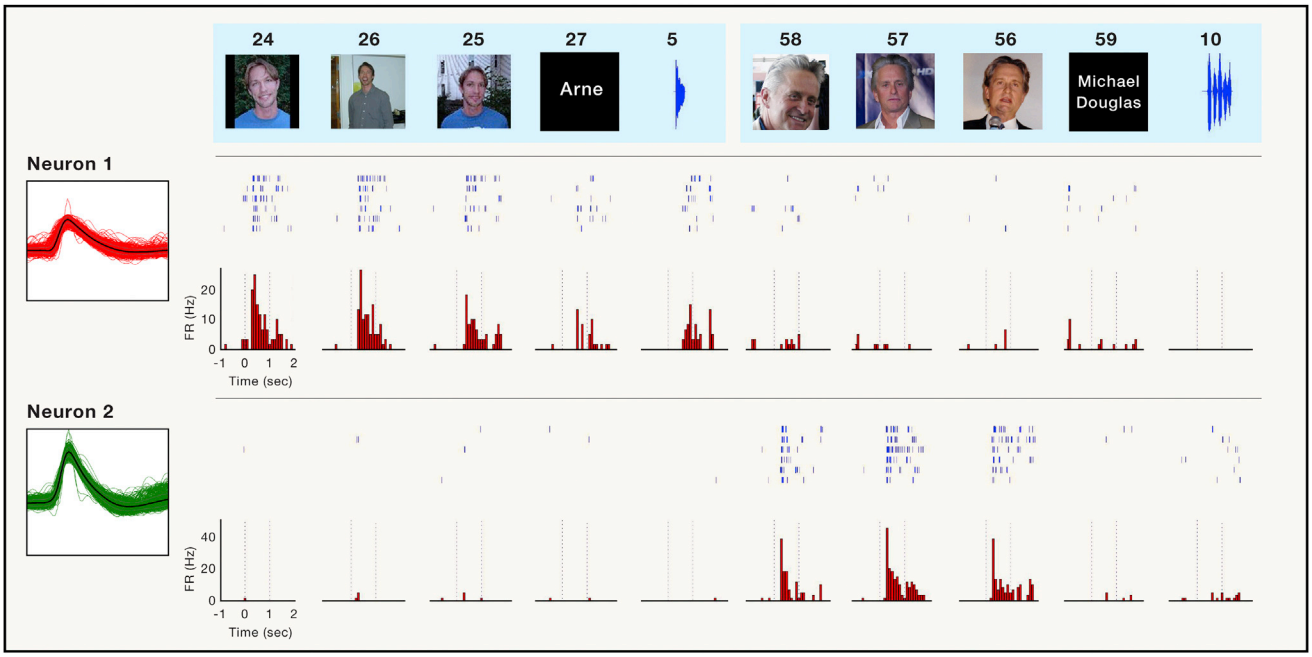

Figure 4. Concept Cells

Two neurons identified from a microwire in the amygdala of a patient after spike sorting. The first neuron (top) responded to 3 different pictures of one of the researchers performing experiments with the patient and to his name (Arne) written on the screen (stim 27) and pronounced by a synthetized voice (sound waveform of stim 5). The second neuron (bottom) responded to the pictures of actor Michael Douglas. In this case, there were no strong responses to his written (stim 59) and pronounced name (stim 10). The neurons did not respond to any of the other 90 pictures and names presented in this experiment.

Spatial Memory

Since the discovery of neurons that fire at specific locations (''place cells'') in the rodent hippocampus (O'Keefe and Dostrovsky, 1971), many studies have described spatially tuned neurons, including grid cells in the medial entorhinal cortex (Hafting et al., 2005), and have suggested a crucial role of the hippocampal formation in spatial navigation (Moser et al., 2017).

The exquisitely complex structure of the hippocampus is similar in rodents and humans (Strange et al., 2014), and a large number of fMRI studies have also shown the involvement of the human hippocampus in spatial navigation (e.g., Burgess et al. [2002] and Maguire et al. [2000], among many others). Moreover, using a virtual navigation task with human single-neuron recordings, it has been shown that place cells are present in the human hippocampus as well (Ekstrom et al., 2003). Imaging studies (Doeller et al., 2010) and iEEG recordings analyzing activity in the theta frequency band (Kunz et al., 2019) have also reported a 6-fold rotational symmetry in the entorhinal cortex, as expected from the geometrical structure of grid cells, and single-neuron recordings with epileptic patients later confirmed that grid cells are also present in the human entorhinal cortex as well as in the cingulate cortex and the hippocampus (Jacobs et al., 2013).

A General Framework for MTL Memory Function

Several different functions have been attributed to the hippocampal formation, and one may wonder whether we are perhaps asking too much of this area and most findings could be explained as different manifestations of the same general principle. Within this view, how could we reconcile the finding of spatially tuned neurons in rodents (and humans) with the episodic memory function attributed to this area? Several studies have shown that place cells in rodents remap following physical changes in the environment and that they are also modulated by non-spatial factors according to the specific task performed by the animal (Eichenbaum and Cohen, 2014; Eichenbaum et al., 1999; Moser et al., 2017), indicating that the role of these neurons goes beyond spatial processing. Although grid cells also realign with physical changes in the environment (Fyhn et al., 2007), the geometrical structure of their fields has been considered to provide a more invariant spatial representation (Moser et al., 2017). However, more recent studies have shown that grid cells encode cognitive aspects as well, with their precise place of firing being modulated by reward location (Boccara et al., 2019; Butler et al., 2019; Quian Quiroga, 2019).

The modulations produced by cognitive factors of the spatial representations by place and grid cells provide contextual information about the experience of the animals in the environment, which is in line with the memory function attributed to this area based on human studies. Therefore, to merge the rodent and human literature regarding the function of the hippocampal formation, it has been argued that this area has a general ''relational memory'' role, linking together the elements of experiences (Eichenbaum and Cohen, 2014; Eichenbaum et al., 1999). Within this framework, spatial location is one of several components that constitute a memory. This spatial representation is behaviorally critical in rodents because of the importance of knowing their precise location and routes to reach safety–hence the prevalence of spatially tuned neurons in their hippocampal formation. Furthermore, rodents acquire information about the environment

through exploration, whereas primates rely mainly on vision and eye movements to explore and navigate their surroundings (Ekstrom, 2015; Rolls and Wirth, 2018). However, although they may be represented differently at the neuronal level (Discussion), rodents also have notions of concepts (e.g., cat, cheese, etc.), and humans also have spatial representations that enrich their memories and help avoid interference; for example, the context of my office helps me remember a conversation I had there with a colleague, which I do not confuse with another one we have had at a conference dinner. A particular location in space, represented by place cells or by other spatially tuned neurons, can then be seen as a concept that is associated with different experiences.

Novel stimuli activate a relatively large proportion of neurons. These responses tend to be weaker compared with the ones to familiar stimuli (Quian Quiroga et al., 2007), suggesting that the initial modulations in response to novel stimuli may get stronger for stimuli that become familiar. For example, a set of neurons will fire to a group of persons we meet for the first time at a party, but only a few of them will consolidate a more stable representation of one of these persons that we happen to meet often again and get to know better. More generally, we can postulate a similar mechanism for the observation of hippocampal activations in declarative memory tasks. MTL neurons that are not already recruited in strong assemblies may offer a temporary and malleable representation to perform these tasks. For example, if a subject is asked to remember a set of faces, words, or images, as in standard recognition memory paradigms, these stimuli will modulate the activity of MTL neurons, producing an activation that could be observed non-invasively with fMRI and EEG (Paller and Wagner, 2002). However, the representation of these stimuli is labile, and the involved neurons could soon be recruited to encode something else after the experiments are done, unless the stimuli is rehearsed over and over again, becoming familiar and triggering specific memories (e.g., the memory of doing the experiment). This simple mechanism can offer an adaptive and temporary code that is able to deal with different hippocampus-dependent tasks and form long-term representations.

Coding of Associations in the Human MTL

Episodic memory relies on the fast formation of associations (Eichenbaum, 2004; Quian Quiroga, 2012; Wallenstein et al., 1998); for example, the memory of seeing a *celebrity* in the *subway* involves making a link between these concepts. Concept cells represent familiar concepts (Viskontas et al., 2009)—concepts we form memories about—to encode meaningful associations. Moreover, a very sparse representation, as the one by concept cells, is ideal for the fast encoding of new associations required for episodic memory (Marr, 1971; McClelland et al., 1995). Furthermore, we tend to forget irrelevant details and remember concepts, which is exactly the type of information encoded by these neurons.

Encoding of New Associations

The hypothesis that concept cells are involved in memory was tested using a pair association task, in which, for each person to whom a neuron initially responded (as determined from previous screening sessions), an association with an arbitrary place was created by showing an artificial image (created with Photoshop) of the person in the place. Neurons initially firing to a person showed a significant increase in firing to the presentation of the associated place (without the person) but not to other places that were associated with other persons (the associations also worked the other way around; neurons initially firing to a place started firing to the person associated with it and not to other persons) (Ison et al., 2015). Figure 5A shows the normalized responses of these neurons, which, for the preferred stimulus (the one the neurons originally fired to), showed a decrease after learning due to repetition suppression, as described in previous studies (Pedreira et al., 2010; Rey et al., 2015a). In contrast, for the non-preferred associated stimulus, there was a marked increase in the neurons' responses after learning. Moreover, Figure 5B shows that, after learning, the responses to the associated stimuli were similar in different tasks and conditions. When aligning trials to the time of learning, we observed that the increase in the response to the non-preferred associated stimulus was relatively abrupt and happened at the exact time of learning the associations, which sometimes was after a single presentation (Figure 5C). The fact that such rapid learning was observed is very relevant because episodic memories, like remembering seeing a person in a place, are typically formed by single unique experiences.

Long-Term Coding of Associations

A somewhat puzzling result from the previous study was the fact that about 40% of the neurons initially firing to a concept expanded their tuning to start firing to the associated one (Ison et al., 2015). The problem is that, with such a high probability of firing to associated concepts, the neurons should end up responding to most concepts (because, directly or indirectly, they are all somehow related to each other), which is incompatible with the very high selectivity of these neurons (Quian Quiroga et al., 2007). It could, however, be the case that many neurons encode the associations during the task but only a few of them will continue to do so afterward if the associations remain relevant and are later remembered.

What, then, is the chance of neurons encoding such associations in the long term? This issue was addressed by evaluating the probability of the neurons to respond to associated concepts in the screening sessions (De Falco et al., 2016), in which no memory task was performed, and the neurons' activities reflected what they code for rather than temporary task-related activations. For this, after performing the experiments, the patients were asked to rank how much the concepts eliciting responses (and other concepts for comparison) were related to each other. The left bars in Figure 5D show that, as illustrated in Figure 3 with the example of a neuron firing to 3 related actors, when neurons fired to more than one concept, these concepts tended to be associated. In other words, these neurons encode long-term associations; associations that were already meaningful to the subject and were not created by the task (passive viewing of the pictures), supporting the notion of a permanent role of the MTL in encoding of episodic memories, as proposed by the multiple trace theory (Nadel and Moscovitch, 1997).

Because it is not possible to ask patients to rank how much each of the ~100 concepts presented are associated with each other (which would give about 5,000 comparisons), a

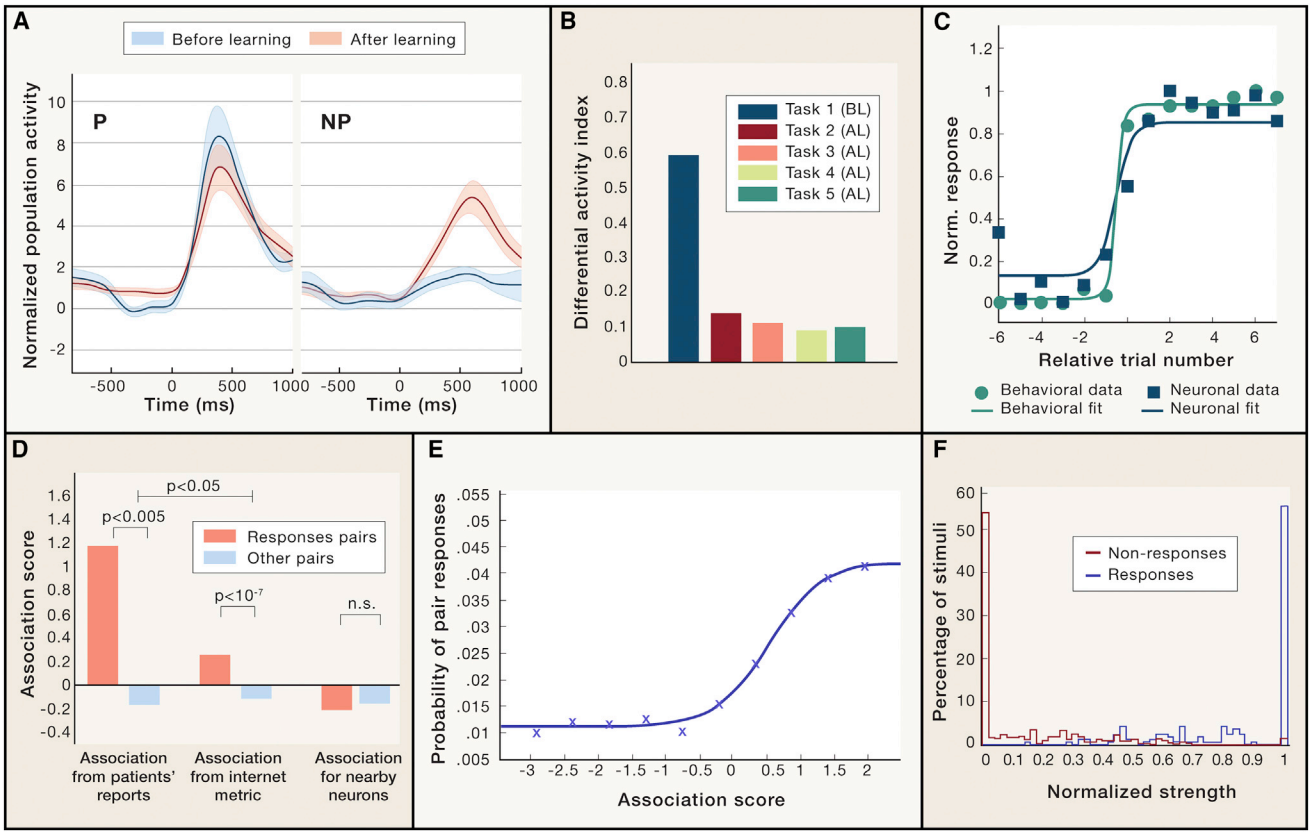

Figure 5. Formation and Long-Term Coding of Associations in the Human Hippocampal Formation

(A) Average responses to the preferred (P) pictures and the associated non-preferred (NP) pictures before and after learning a pair association. Shaded areas represent SEM. The preferred pictures show a decrease in response because of repetition suppression, whereas the non-preferred ones show an increase after learning, encoding the association.

(B) Differential activity index (that is, the normalized difference between the P and NP responses) before learning (BL; task 1) and after learning (AL; tasks 2–5). A clear difference between preferred and non-preferred responses was present before learning, which was reduced by a factor of 5.5, on average after learning ($p < 10^{-6}$), because of the increase of the non-preferred responses. After learning, there were no significant differences in the differential activity index between tasks 2–5, suggesting that (after learning), the responses were not task dependent. Task 1/2, picture presentations before/after learning; task 3, testing of the associations; task 4, recall; task 5, final passive viewing of the pictures without a memory task.

(C) Normalized learning (behavioral) curve and neural responses to the associated pictures, aligned to the time of learning (trial 0). Note the correlation between both curves and the step increase in the neural responses (and behavior) at the time of learning the associations.

(D) Mean association score for pairs of pictures to which the neuron fired and other picture pairs, based on the patients' scores (left) and on an internet search association metric (middle), and mean association score between pictures eliciting responses in nearby neurons, showing a non-topographic organization (right). Values are *Z* score normalized.

(E) Probability of responses to pairs of pictures as a function of their degree of association using the internet search metric. Error bars show SEM.

(F) Normalized activation for responsive and non-responsive neurons (0 corresponds to baseline activity and 1 to the maximum response for each neuron), showing a nearly binary code.

(A)–(C) were adapted from Ison et al. (2015). (D) and (E) were adapted from De Falco et al. (2016). (F) was adapted from Rey et al. (2018).

metric of association was used based on the number of hits obtained when doing an internet search of each pair of concepts together, normalized by the number of hits obtained when searching for each concept on its own (De Falco et al., 2016); e.g., a Google search for "Bill Clinton" and "Hillary Clinton" gives many more hits than a search for "Bill Clinton" and "Jennifer Aniston," because the first two are more related to each other. The middle bars in Figure 5D show the result obtained using this association metric, where we again observe that the neurons tend to encode meaningful associations. However, this tendency was not as large as when asking the patients for their own association scores, which are based on subjective evaluations that are not necessarily shared by other web users. In other words, the neurons reflect idiosyncratic rather than universal associations, suggesting that they encode episodic memories from personal experiences. In line with this view, the coding of associations was specific to particular concepts (e.g., an actor and a place) and not to other concepts corresponding to the same broad semantic categories (other actors and other places) (De Falco et al., 2016). Moreover, when having a response to a concept, the probability of finding a response to another one was calculated as a function of its association with the first. Figure 5E shows that, as expected, the probability of finding a second response increased with the degree of association with the first but saturated at about 4% for highly associated concepts, ten times less than the 40% probability when learning

new associations, showing that only a fraction of the neurons consolidate the associations in the long term.

Non-topographic Organization

In Figure 4, we show two nearby neurons that fired to allegedly unrelated concepts: Arne and Michael Douglas. This observation was quantified by evaluating the association metric for concepts to which nearby neurons (separated after spike sorting) fired, and it was found that the things nearby neurons fired to were not related to each other (right bars in Figure 5D). Contrasting with the topographically organized information in visual neocortical areas—i.e., with nearby neurons firing to similar things (Tanaka, 1996; see section 3.1 in Quian Quiroga, 2016)—MTL neurons show a non-topographic organization, as found with place cells in the rat hippocampus (Muller et al., 1987; Redish et al., 2001). Such lack of spatial organization is ideal for episodic memory, to quickly form associations between any two items (of any category) without the need of establishing connections between distant areas.

Binary Responses

In Figure 5A the response to the associated pictures was not as large as the one to the preferred pictures to which the neurons originally fired. It is therefore possible that MTL neurons preferentially encode one concept and respond less strongly to others according to their similarity (or degree of association) with the first. Alternatively, the difference in the neurons' responses to the preferred and associated pictures may only be present during learning but not in the long term. To address this issue, the pictures eliciting the neurons' firing (as determined from the screening sessions) were shown several times, and, for neurons responding to more than one picture, the responses to them was compared. In most cases (~80%), it was not possible to distinguish the pictures eliciting responses from the neuron's firing (Rey et al., 2018). Interestingly, the 20% of cases where the differences were significant corresponded to less-associated concepts; that is, associations that were not well consolidated, as those studied in the pair association learning task described above (Ison et al., 2015). So, differences in the neurons' responses are observed for less consolidated (temporary) associations and tend not to be present for the most consolidated ones. In line with this, and in contrast to the graded tuning typically found in the neocortex (Tanaka, 1996), Figure 5E shows that responses were mostly binary. That is, if the neuron responded to a set of pictures, it did so with the same strength, and if it did not respond, the firing was mostly indistinguishable from baseline (Rey et al., 2018). The finding of such binary coding shows that (associated) concepts can only be distinguished from each other at the assembly level. Moreover, such binary coding also has implications for memory functions, increasing the network capacity, robustness to noise, ease of readout, and avoidance of interference (Treves and Rolls, 1994).

A Simple Memory Model with Concept Cells

Having reviewed concept cells, let us now discuss how these neurons encode episodic memories. Concept cells do not act in isolation but are part of cell assemblies representing familiar concepts (Quian Quiroga, 2012). Each of these assemblies, on its own, does not represent any particular memory or context, but the associations between these assemblies encode specific memories, which may be further enriched by representations in the neocortex. For example, we may have an assembly of concept cells encoding a particular friend and another one encoding our favorite café in town, and the memory of meeting our friend at the café is given by having an association between both assemblies (and perhaps some others related to this encounter), which produces a coactivation of both concept representations when retrieving the memory. We therefore propose that the main function of concept cells is to (1) form and retrieve meaningful associations and (2) point to and coactivate neocortical sensory representations.

Coding of Associations with Partially Overlapping Assemblies

Following the example presented in Figure 3A, let us consider a hippocampal cell assembly representing Kris Kristofferson (Figure 6). Different pictures of him activate similar (but different) representations in the neocortex that initially ignite different subsets of the MTL cell assembly but then rapidly activate most of the assembly representing Kristofferson through pattern completion. This activation of the same assembly (or most of it) by different pictures of a person is the neural substrate underlying the "unitization" observed at the behavioral level; i.e., the fact that different pictures of the same concept convey the same meaning for memory functions (Graf and Schacter, 1989).

A first function of this assembly of concept cells is to act as a pointer to coactivate neocortical representations related to Kristofferson (Teyler and DiScenna, 1986) (solid blue arrows in Figure 6), such as how his face looks, the sound of his voice, etc., as well as related semantic information; e.g., the fact that he is a country singer and an actor. A second function is to bring about related information coded by associated MTL assemblies (filled arrows in Figure 6), such as the fact that he acted with Mel Gibson in the film *Payback* or that he sang a song with his wife, Rita Coolidge. The association between two concepts in the MTL is encoded with neurons firing to both of them, thus having a partial overlap of their assemblies (as described above, of about 4%), which is low enough to distinguish the concepts from each other but, at the same time, large enough to encode meaningful associations that may eventually lead to temporary coactivations (or sequential activations to go from one concept to the other, as in the flow of consciousness). The firing to an associated concept can be generated very rapidly (Ison et al., 2015) through Hebbian synaptic plasticity (Hebb, 1949), considering that there are many instances in which the related concepts appear or are recalled together (e.g., when watching or remembering the movie or a song), thus generating the overlap. Given the finding of binary responses at the single-neuron level, the degree of overlap between the assemblies gives a distance metric of how associated with each other two concepts are.

We can then argue that these associations between concepts constitute the skeleton of episodic memories; the association between Kristofferson and Gibson (together with a few other ones) may provide a rough representation of having watched the movie *Payback*, whereas the one with Coolidge will be the substrate of the memory of having heard them sing a country song. Furthermore, memories are also enriched by details encoded in neocortical representations that MTL

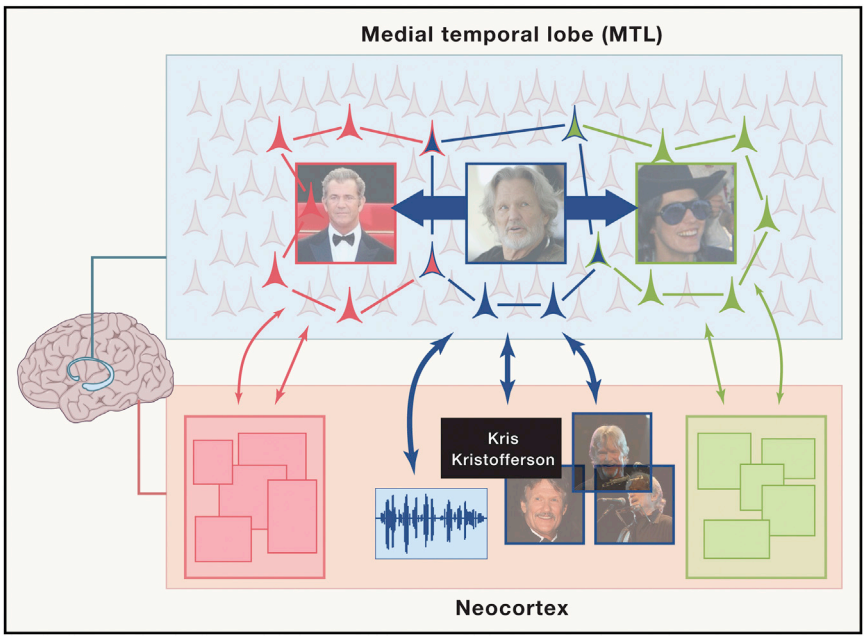

Figure 6. Coding of Associations with Concept Cells

Shown is the encoding of associations via partially overlapping assemblies. An assembly of concept cells in the MTL responding, for example, to actor Kris Kristofferson (neurons joined with blue lines) is activated by neocortical inputs (curved blue arrows) triggered by sensory representations of him. A first function of this assembly is to link and coactivate different neocortical sensory representations related to the actor, creating a rich memory content. A second function is to encode associations between concepts in the MTL. For this, some of the neurons firing to Kristofferson also fire to Mel Gibson (neurons in blue/orange), who faced him in the movie *Payback*. Another assembly representing Rita Coolidge, his ex-wife, with whom he sang country songs, also shares neurons with Kristofferson (neurons in blue/pink). Context is given by the coactivation of associated assemblies: the coactivation of Kristofferson's with Gibson's assemblies (among other related ones) gives the context of Kristofferson in a movie, whereas the coactivation of Kristofferson's and Coolidge's assemblies gives the context of Kristofferson singing a country song. The encoding of associations via partially overlapping assemblies can also sustain the flow of thoughts in the MTL: the initial activation of an assembly leads to the activation of an associated one (filled arrows) via pattern completion from the initial activation of the overlapping neurons encoding both concepts.

assemblies coactivate, such as some scenes of the movie or the sound of Kristofferson's song.

Associations and Context

Converging evidence has shown that context modulates hippocampal responses to facilitate the discrimination between different memories (Stark et al., 2018). Within the model presented above, we argue that in the MTL context is provided by the coactivation of associated assemblies, including spatial representations. We previously postulated that spatial locations can be seen as concepts that enrich memories. For example, I may remember the location of a cinema where I watched Kristofferson's movie during a holiday in Paris, I may remember the Eiffel Tower, which I visited during this trip, etc. Context is also enriched by other non-spatial factors, such as the memory of a friend I met in Paris, the fact that I often had steak tartare, etc. All of these concepts constitute the context of my holiday in Paris and are associated through partially overlapping assemblies, which, when coactivated, may evoke memories I have had during this trip, like watching this movie, because the assemblies of Kristofferson and Gibson are both associated with the concepts constituting this context. Likewise, I may have heard Kristofferson's song on my sofa, and when thinking of Kristofferson on the sofa, I may remember Rita Coolidge and not Mel Gibson.

Episodic and Semantic Memory—MTL and Neocortical Representations

The role of the neocortex and MTL in episodic and semantic memory has been widely discussed in the literature (Moscovitch et al., 2005; Sekeres et al., 2018; Squire et al., 2015). However, the distinction between these two types of memory is not clear. For example, it has been argued that personal semantics (namely, factual information related to one's own past) may lie between these two extremes and may sometimes be seen as episodic and sometimes as semantic memory (Renoult et al., 2012).

We have shown that there is a non-topographic organization of the responses in the MTL (Figure 5D), which facilitates establishing associations between any arbitrary concepts and not just those corresponding to the same category, and that the high selectivity of concept cells is ideal for the fast encoding of associations characteristic of episodic memory (Marr, 1971). This is precisely what was found in the pair association study, in which we observed that neurons could rapidly encode arbitrary associations (of any person with any place) (Ison et al., 2015). Further support for the role of concept cells in episodic memory is given by the fact that MTL neuron responses matched specific and personal association judgements by the subjects based on their own experiences rather than broad semantic categories (Figure 5D; De Falco et al., 2016). On the contrary, the topographic organization observed in the neocortex, together with a more distributed population coding, is better suited to encode organized information and hierarchical structures that are characteristic of semantic memory and that can typically support relatively slow learning, so that the encoding of new associations does not disrupt established hierarchies and the organization of semantic information (McClelland et al., 1995; Quian Quiroga, 2016). But even with a slow learning rate, some disparate associations may not fit within such hierarchical organization, and, therefore, we have the complementary hippocampal system to encode them.

In spite of all the evidence mentioned above, it is difficult to discern whether the associations encoded by concept cells represent pure episodic experiences, semantic information, personal semantics, or a mixture of these. Does the association between Kristofferson and Gibson represent a fact, a personal

experience, or both? In our view, and based on the data presented above, it might be more plausible to argue that the MTL is the substrate to form and encode disparate associations that mainly support episodic memory, in contrast with more ordered and topographically organized associations supporting semantic memory in the neocortex. Such associations in the MTL would then constitute the skeleton of long-term episodic memories, in line with the multiple memory trace theory and the dramatic effect on episodic memory produced by lesions in this area (Moscovitch et al., 2005). With this framework, the long-term coding of disparate associations by the MTL allows "jumps" in a memory narrative, like the transitions between scenes in a movie, and, not surprisingly, it has been reported that patients with MTL lesions are quite limited in their recall and imagination and are able to provide only fractional accounts that are supported by neocortical structures (Hassabis et al., 2007), as when remembering a few isolated scenes from a movie but not the movie plot—the details of the scenes are encoded in the neocortex and the link between them in the MTL.

Memory Formation, Consolidation, and Forgetting

MTL neurons that are already recruited in consolidated assemblies represent concepts that are very relevant to the subject. But memories are far from stable representations or engravings in a wax tablet, as Plato saw them, and can be formed, consolidated, and, to a large extent, forgotten (Hardt et al., 2013; Richards and Frankland, 2017). At the neuronal level, we could argue that the stability of the assemblies representing specific concepts is maintained by the coactivation of the neurons that form them if the concepts are revisited frequently enough. If this is not the case, then the assemblies become labile, and their neurons can be recruited to encode other memories that may become more relevant.

The largest proportion of MTL neuron responses was to experimenters who were initially unknown to the patients and performed recordings with them (Figure 4A; Viskontas et al., 2009). For the patients, the experimenters were recently known but, at the same time, very salient because they interacted with them very frequently while they remained in the hospital during the intracranial recordings. However, the experimenters kept no contact with the patients afterward, and although we cannot track the neurons over long periods of time, it is reasonable to assume that, after some time without contact, these neurons are now encoding other concepts.

Memories "fight" to recruit MTL neurons. Novel concepts initially recruit neurons with relatively labile responses. As familiarity increases, these responses get stronger, and neurons representing a new concept connect with each other, forming a stable assembly. But as the concept becomes more familiar, it has more associations related to it, thus recruiting neurons initially responding to other concepts that start firing to the first one, which explains the tendency to find responses to very familiar items (Viskontas et al., 2009). Memories that are periodically revisited form relatively stable assemblies, whereas those that are not have more labile representations with neurons that have weaker connections with each other and that can be easily co-opted to encode new memories. This simple competition mechanism may be the neural basis of forgetting episodic information. Going back to the example of the responses to experimenters, it may be the case that, after a few years, the patient will still recognize them or feel that they are familiar. But recognition is performed in the neocortex, not in the hippocampus, and the lack of a hippocampal representation would mean that the subject has forgotten episodic memories related to them.

When creating a new association, about 40% of the neurons encoding a concept initially respond to the associated one, but only about 4% of the neurons may consolidate this information and keep encoding the association in the long term, if the association is further revisited and it is well established and remembered. Unfortunately, we could not directly track this consolidation process (responses to the associated items remained at the same levels after learning), but such a decay in the encoding of associated items was, in fact, observed in another study in which the neurons started firing in anticipation of the presentation of a stimulus triggering their responses after about a dozen trials, but—probably because of a weaker association established by showing a sequence of consecutive pictures compared with showing simultaneously a pair of items (a person in a place), as in Ison et al. (2015)—this anticipatory associative response gradually decreased over time as the session progressed (Reddy et al., 2015).

Comparison with Other Species

Although neurons representing high-level features have been described in monkeys and rodents, neurons like concept cells have so far not been reported in other animals. In this section, we describe key differences compared with findings in other species—based on the level of abstraction and multimodal invariance of these neurons, the latency of their responses, and their context-independent representation—and postulate that concept cells may support our unique memory and cognitive abilities.

Multimodal Invariance

Along the monkey ventral visual pathway, there is an increase in selectivity to complex features and visual invariance (Logothetis and Sheinberg, 1996; Tanaka, 1996). At the end of this sensory processing pathway, neurons in the anterior medial face patch (AM) in the monkey temporal lobe respond to relatively few faces (Tsao et al., 2006), apparently showing a coding similar to the one of concept cells. However, a recent study demonstrated that these neurons, rather than being activated by specific individuals, respond to complex visual features, according to the projection of the faces onto specific feature axes (Chang and Tsao, 2017). Another study in the monkey hippocampus replicated the protocol used to find concept cells—showing very familiar faces, such as those of other monkeys in the colony, pictures of researchers interacting with the animals, etc.—but did not find neurons with such a degree of selectivity and multimodal invariance (Sliwa et al., 2016). Likewise, another study performed recordings in the rat hippocampus while the animals interacted with other rats and showed that, although the presence of conspecifics altered the firing of hippocampal neurons, no cell responded selectively to individual rats (von Heimendahl et al., 2012).

Response Latencies

Neurons in high-level visual areas in monkeys (see Table 1 in Mormann et al. 2008) and humans (Davidesco et al., 2014;

Jacques et al., 2016; Liu et al., 2009) have similar response latencies, about 100–150 ms after stimulus onset. From high-level visual areas, there are direct connections to the MTL (Suzuki, 1996), and although the latency of hippocampal responses in monkeys is about 150 ms (Jutras and Buffalo, 2010; Rolls et al., 1989, 2005; Yanike et al., 2004), in humans it is about 300 ms (Mormann et al., 2008; Quian Quiroga et al., 2009; Rey et al., 2018). So, the MTL response latencies in monkeys have the values expected from direct feedforward inputs from visual areas (Thorpe and Fabre-Thorpe, 2001) but in humans are about double and shortly preceded by a theta LFP deflection (Rey et al., 2014, 2018). This longer latency in humans could be attributed to much further neocortical processing—possibly involving the prefrontal cortex to sustain specific stimulus-induced activations (Goldman-Rakic, 1995) according to the context and task at hand (Eichenbaum, 2017; Fletcher and Henson, 2001)—to merge information from different sensory modalities and extract a high-level "conceptual meaning" of the stimulus (Quian Quiroga, 2012); for example, to abstract that a glass of water should be taken as "water" irrespective of the glass.

Context Modulations

The responses of neurons in the monkey hippocampus are, to a large extent, modulated by the task (Baraduc et al., 2019; Cahusac et al., 1989; Miyashita et al., 1989; Rolls and Wirth, 2018; Rolls et al., 2005), whereas in humans, concept cells show a more abstract, context-independent representation. For example, a concept cell fires to a particular person irrespective of whether the subject is passively looking at pictures of the person in a screening session, seeing morphed versions of it (Quian Quiroga et al., 2014), performing a pair association task, seeing the person on his/her own or in a specific location, or when recalling him/her (Figure 5C; Ison et al., 2015; Quian Quiroga, 2019).

In the rodent hippocampal formation, there are neurons encoding the spatial location of the animals, most notably place cells in the hippocampus and grid cells in the entorhinal cortex (Moser et al., 2017). These neurons also show some degree of abstraction because, in open arenas, they fire to specific locations irrespective of the trajectory of the animal. However, a key difference from concept cells is that, as in the monkey hippocampus, these neurons tend to remap and be modulated by context; that is, they change their firing when cues in the environment or the specific tasks performed by the animal are altered (Eichenbaum and Cohen, 2014; Eichenbaum et al., 1999; Moser et al., 2017). Therefore, both in the rodent and the monkey hippocampus, neurons show a "conjunctive coding," being modulated by the task and context, which can be seen as a logical "AND" function; the firing of the neurons is triggered by a particular location (or an object) AND in a particular task. This representation tends to orthogonalize memories and might be ideal to avoid interference if enough neurons are available. This might be the case for animals raised in the lab, performing just a handful of tasks in their life, but it might not apply to the richness of human memory. On the contrary, human hippocampal responses seem to be better described by an "OR" function because they fire in the same way to a particular concept in one OR another condition or task. This gives an explicit representation of the meaning of the stimulus, devoid of context and details, that facilitates establishing high-level relationships between concepts and might be ideal for generalization and fast learning when changing context, building associations in a high-level conceptual space that is also supported by neocortical activations.

Back to the example of Figure 6, in the MTL, the context of Kristofferson as an actor in the movie *Payback* is given by coactivation of the assembly firing to Mel Gibson (among other associations), and the context of Kristofferson as a country singer is given by coactivation of the assembly coding Rita Coolidge. The key difference with rodents and monkeys is that the "Kristofferson neurons" fire in the same way in both contexts. In other words, the coding of specific associations and context, likely enforced by activations of the prefrontal cortex (Eichenbaum, 2017), is not represented at the single-neuron level but given by the coactivation of invariant assemblies representing the concepts that are part of a specific memory. Episodic memory, then, seems to be implemented with different coding strategies in rodents, monkeys, and humans—something that could also be attributed to different types of neocortical inputs, considering the larger neocortex in humans and the much longer time for processing incoming stimuli before reaching the hippocampus.

Are Concept Cells Uniquely Human?

Animals clearly have notions of concepts. For a rat, a cat is a cat, no matter what: seen in front view, in profile, or even when hearing its meow. What seems to be lacking though, is an explicit and context-independent representation of such concepts at the single-neuron level in memory areas. This abstract representation has so far not been found in animals. Why?

One can first argue that more experiments are needed to rule out that other species, and particularly monkeys, lack concept cells. In particular, the way animals are trained and the fact that animals in the lab perform only a few tasks and have relatively limited experiences may impose conjunctive representations, whereas real-life experiences force generalizations and perhaps other type of coding. Future experiments could indeed show that neurons like concept cells may also exist to some extent in monkeys but perhaps not with the same level of abstraction as in humans. One could also argue that the abstract representations by concept cells are just the end result of elaborated processing in the much larger and refined human neocortex. Besides this, a major obvious difference between humans and other species is our refined use of language. Language allow us to exchange information and communicate elaborate thoughts, to talk about our past and plan our future (without language, we can only refer to things at hand in our immediate present). Language facilitates shared knowledge and culture, but another key advantage of language is that it reinforces abstractions—to think in terms of concepts detached of meaningless details and circumstances. Every noun, every verb, and every adjective is in itself an abstraction, a representation of meaning upon which we construct our high-level thoughts. It therefore seems reasonable to postulate that, after tens and perhaps hundreds of thousands of years of evolution, concept cells may have developed together with language, reinforcing abstractions and providing the machinery to facilitate our cognitive abilities.

Conclusions and Future Challenges

Single-neuron recordings in the human MTL give unique insights into memory function, allowing the possibility of asking subjects about their thoughts and recollections while directly recording

from neurons involved in these tasks. These recordings have, however, several limitations because of the availability of patients, limitations in covering the areas involved in these functions, the number of recorded neurons, the stability of the recordings, etc. Therefore, they should not be seen as a replacement technique but, rather, as complementary to the findings of non-invasive studies in humans and invasive studies in animals. Future developments may, however, overcome some of these limitations. In particular, optimal spike-sorting algorithms and new electrode designs (considering that these have remained basically unchanged for decades) should facilitate recording from hundreds of neurons simultaneously, which would not only increase the yield of responsive neurons but also encourage population analyses to further understand complex brain processes. Moreover, the use of continuous 24/7 recordings will permit tracking neurons across days to evaluate the stability and plasticity of the neural representations and study consolidation processes and the activity of neurons during sleep. In addition, although the coverage of single-neuron recordings is relatively limited, further studies may provide a better understanding of the relationship between single-neuron, LFP, and iEEG activity; for example, to use high-frequency activity as a proxy of neural firing and complement MTL single-neuron findings with those inferred from high-frequency patterns measured in the neocortex.

Compared with non-invasive human studies, single-neuron recordings can validate and complement these works and give information that it is not possible to obtain with non-invasive tools, such as the finding of sparsely firing neurons like concept cells (Figures 1, 2, 3, and 4), or an understanding of the neuronal activity underlying the scene-selective responses observed with fMRI recordings (Figure 2A). A better understanding of what can and cannot be done with each recording technique should lead to a better and more comprehensive interpretation of results with different recordings. In particular, the finding of context modulations of MTL responses with fMRI recordings in humans (Stark et al., 2018) is a description at the population level that does not imply context modulations at the single-neuron level, as found in other species. In fact, we have argued that human MTL neurons are largely context-independent and that context is provided by coactivation of different assemblies (which can give different fMRI responses).

We have described how single-neuron recordings allow the study of memory mechanisms, showing that associations are encoded by partially overlapping assemblies of concept cells in the MTL, which can be formed very rapidly to link initially disparate concepts. We postulated that this simple model constitutes the basis of episodic memories, which are further enriched by the coactivation of more detailed and hierarchically organized information in the neocortex. We have further argued that episodic and semantic memories could be seen as the coding of disparate (episodic) and organized (semantic) associations that interact to store our memories. We have also proposed a unified framework explaining responses to novel items, spatial representations, and specific concepts, linking the rodent and human literature about the function of the hippocampal formation in spatial navigation and memory.

The study of the different aspects that encode our experiences requires new experimental paradigms that may give further insights into the role of the MTL and neocortex in memory formation, consolidation, storage, and recall. Performing experiments with humans, and particularly being able to record the neurons' activity directly while the subjects perform memory tasks, cries out for a paradigm shift, focusing on ''real-life'' memory experiments, exploiting to the maximum the possibility of obtaining complex and detailed behavioral feedback that can be correlated with the neuronal responses.

Research lines of particular interest are those that tap into human brain mechanisms and may explain our unique cognitive abilities. Compared with other animals, there are some similarities, such as the finding of responses to familiar and relatively complex items (e.g., particular faces or places) and the coding of associations in the hippocampal formation. However, some key differences are also noticeable: the highly selective, invariant, and multimodal responses by concept cells have so far been found only in humans; response latencies in the human MTL are about double compared with monkeys, showing further neocortical processing before reaching this area; and, in contrast to what is found in rodents and monkeys, responses in the human MTL seem to be mostly context independent, which highlights the interesting possibility that a completely different coding principle may underlie human thoughts and memories. Future work, ideally developed in parallel in humans and other animals, should provide a better characterization of the neuronal machinery storing memories in different species; a major goal of this discussion is to encourage animal physiologists to further seek this type of neuron and better characterize whether and to what degree animals may have analogous explicit abstract representations. Modeling studies may also offer further mechanistic insights into the advantages and caveats a representation such as the one by concept cells may have for memory and cognitive functions.

There is no doubt that other animals, and particularly monkeys, our closest relatives, are very intelligent, but they do not solve integrals or wonder about the origin of the universe. It is currently unclear what key component of the human brain gives rise to the unique intelligence of our species. In this respect, we postulate that the explicit abstract representation by concept cells may provide the machinery to facilitate high-level thoughts, which may have evolved together with the abstractions facilitated by the use of language.

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