Review

Percepts to recollections: insights from single neuron recordings in the human brain

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Transformation of experience into memories that can guide future behavior is a common ability across species. However, only humans can declare their perceptions and memories of experienced events (episodes). The medial temporal lobe (MTL) is central to episodic memory, yet the neuronal code underlying the translation from sensory information to memory remains unclear. Recordings from neurons within the brain in patients who have electrodes implanted for clinical reasons provide an opportunity to bridge physiology with cognitive theories. Recent evidence illustrates several striking response properties of MTL neurons. Responses are selective yet invariant, associated with conscious perception, can be internally generated and modulated, and spontaneously retrieved. Representation of information by these neurons is highly explicit, suggesting abstraction of information for future conscious recall.

Recording from single neurons in humans

Clinical circumstances that allow for direct recordings from individual neurons within the human brain provide a rare opportunity to investigate single cell mechanisms underlying cognition. Other methods in cognitive neuroscience often provide either an indirect measure of neuronal activity, such as the blood oxygen-level dependent (BOLD) measure in functional MRI (fMRI), or a measure of neuronal activity reflecting activity of large neuronal pools. Signals recorded from electroencephalogram (EEG) and fMRI reflect several thousands to millions of neurons (reviewed in [1]). Neurophysiological studies in laboratory animals do provide single neuron resolution, but are limited by the report that animals can provide and, thus, cannot address fundamental questions of human cognition, such as spontaneous recollection (see Glossary) of past events, or freely arising wishes or desires. In particular, the study of declarative memory, or memory for recent facts and events, is best studied in subjects who can declare their recollections.

The ability to form new episodic memories, which can later be consciously accessed, relies on an intact hippocampus and surrounding MTL [2–4]. However, other functions, such as visual perception, do not depend on an intact MTL [5,6], although this has been debated to some extent (reviewed in [7,8]). In this review, we summarize recent data afforded by key methodological advancements in human single neuron data acquisition and analysis (Figure 1; Box 1). We show how the data obtained from single neurons within the MTL of neurosurgical patients implanted with intracranial electrodes for clinical reasons have yielded valuable information regarding neural mechanisms underlying conscious perception and recollection of experienced events.

MTL neurons and perception

The MTL receives multimodality sensory input from wide areas of the cortex, thereby offering the possibility of convergence and integration of information [9]. The MTL itself comprises several smaller areas, including the hippocampus, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and amygdala. Within the MTL, the hippocampus is positioned at the top of a multisensory hierarchy, receiving converging incoming sensory information through the entorhinal cortex that is either object identifying (via perirhinal cortex) or spatially informative (via parahippocampal cortex; [10,11]). For the MTL to encode a given episode in time properly, the event must be first perceived and processed in upstream sensory cortices. In studying neural mechanisms of perception, intracranial human studies benefit from the fact that humans can easily report whether they consciously perceive an external event or stimulus, whereas animals require extensive training to do so, thus potentially altering existing or even recruiting different neuronal mechanisms.

Glossary

Episodic memory: memory for events within a spatial and temporal context.
LFP phase: measurement in radians or degrees of the position within a cycle of an oscillatory waveform.
Local field potentials (LFPs): extracellular voltage changes reflective of dendritic currents and action potentials of populations of neurons.
Medial temporal lobe (MTL): the MTL comprises the hippocampus, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and amygdala.
Recollection versus familiarity: recollection refers to being able to link a given memory to a specific place in time, whereas familiarity refers to having a given memory without being able to assign its origin.
Spikes: extracellularly recorded action potentials from single (single-unit) or multiple (multi-unit) neurons.

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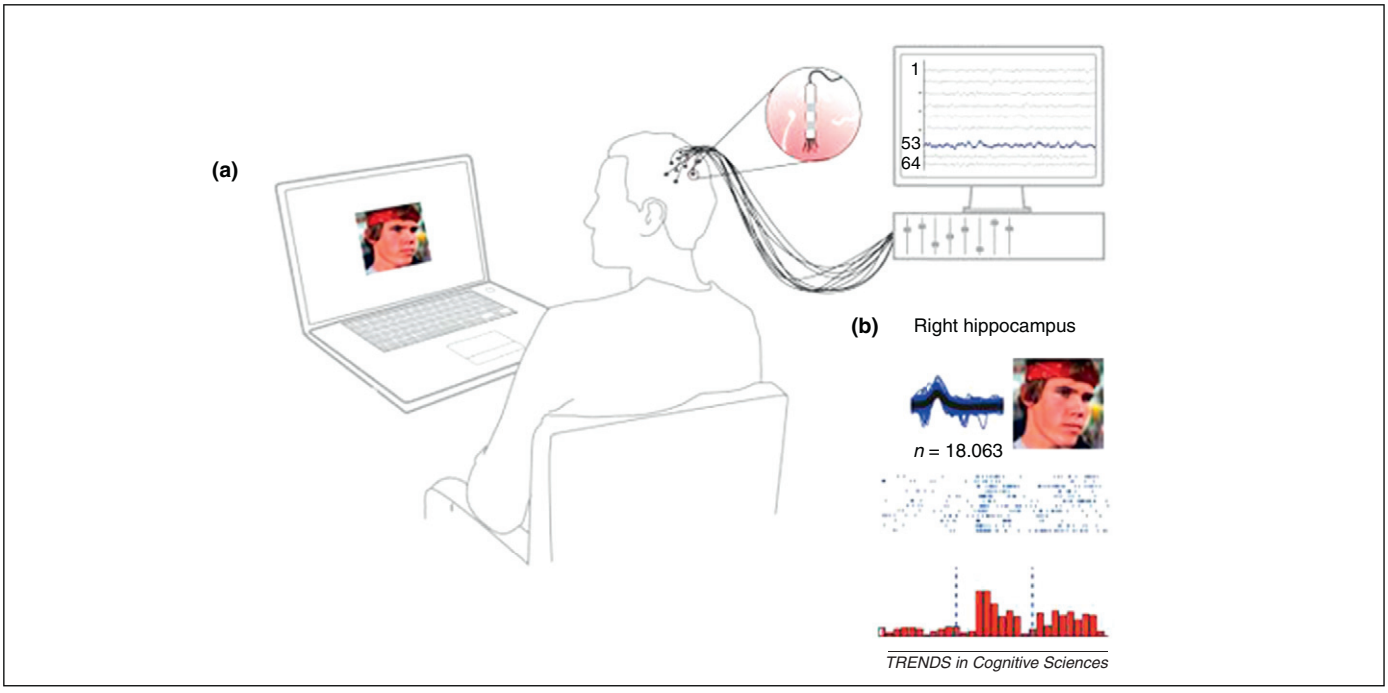

Figure 1. An example experimental setup for intracranial single neuron recordings in humans. **(a)** Participants are shown images on a laptop screen while continuous voltage data are recorded. Spike sorting can then either be done on- or off-line to determine single unit and local field potential activity during viewing of stimuli. **(b)** An example single unit (blue traces are single spike waveforms) recorded from the right hippocampus. Single spikes (blue dots) for each trial (line) and averaged firing rate (red bars) across trials significantly increased during the viewing of the image of actor 'Josh Brolin'. Dotted blue vertical lines show the 1-s time window when the image was presented. Adapted from [21].

The responses of single neurons in the MTL reflect the transformation that the stimulus undergoes as it is processed upstream in the sensory hierarchy. That transformation is, in essence, the neural code that governs information processing in the temporal lobe. Intracranial recordings in humans over the past decade have found that single MTL neurons have distinct response properties. These can be summarized as follows:

(i) Responses are selective. MTL neurons can respond to particular stimulus categories (e.g. faces, outdoor scenes, animals, etc.) or to individual stimuli (e.g. a family member, a famous individual, or a particular landmark) during the passive viewing of visual stimuli [12–16]. For a simplified diagram illustrating a selective type of response, see Figure 2.

(ii) Responses are invariant. An MTL neuron may respond to a particular stimulus, such as a particular face or landmark, but in addition it will also respond to other stimuli representing that particular face or landmark, even if these stimuli are distinctly different in stimulus features compared with the original stimulus [14]. Thus, a neuron may respond to a picture of the Sydney Opera House and exhibit no response to 50 other landmarks, yet also respond to many permutations and physically different representations of the Sydney Opera House, seen in color, in black and white, or from different angles. In fact, the neuron may also respond to the iconic representation, namely the words 'Sydney Opera', which is obviously different in its visual properties compared with the image of this landmark. Recently, it was shown that this invariance crosses modalities, meaning that MTL neurons may exhibit a selective and 'invariant' response to a particular stimulus out of 100 images and do so independently of the sensory modality (visual image, audio, or written iconic representations) through which the stimulus was presented [17]. Results were consistent with the anatomical hierarchy within the MTL; the highest percentage of neurons with modality-independent invariant responses was found in the hippocampus and entorhinal cortex, compared with the amygdala or parahippocampal cortex [17].

(iii) Responses are late. The selective and invariant responses described above are of relative long latencies, often in the 300–500 ms range. Interestingly and consistent with the anatomical hierarchy, responses in the parahippocampal cortex are significantly shorter than those in the hippocampus, amygdala, and entorhinal cortex [16], but still with longer latencies than those observed in animal studies.

(iv) Responses are associated with conscious perception. Using flash suppression and backward masking paradigms, it has been shown that selective MTL responses are mainly triggered when accompanied by the participants' conscious perception or recognition of the stimulus [18,19]. When varying the display time of an image between 33 and 256 m, MTL neurons selective for an image significantly increase in firing rate only if the image is recognized by the subject, even if the image is presented for as briefly as 33 ms. Conversely, if the subject reported no recognition of the image, the MTL neuron selective for that image is mostly silent [19].

(v) Responses can be internally generated. The act of re-experiencing a previous episode can be internally

Box 1. Technological advances in human single neuron recordings

Microelectrode recordings in patients with epilepsy undergoing clinical monitoring for curative neurosurgery have enabled the extracellular recording of action potentials (i.e. spikes) from the human brain. However, spikes detected on a single microelectrode probably originate from several neighboring neurons, especially within brain areas that have densely packed cellular structures, such as the hippocampus. Furthermore, a small region within the MTL can comprise several different types of cells, such as principal pyramidal and interneurons, which have intrinsic differences in their electrophysiological properties and excitatory or inhibitory effects [80–82]. Fast and automated signal-processing techniques have been developed over the past decade to extract single spikes from complex recording signals recorded from the human brain. Currently, efficient analysis techniques have automated the process of spike sorting to separate pyramidal versus interneuron and single- versus multi-unit types by comparing waveform characteristics (e.g. shape and amplitude) and inter-spike interval distributions [51,81–84].

Real-time analysis and feedback of recorded brain activity has emerged as a powerful tool in the field of human cognitive neurophysiology [21,85]. Given the rare opportunity to record during clinical circumstances and the high value of data from the human brain, intracranial recording studies can now benefit from real-time online spike-sorting algorithms [21,86]. Real-time online spike sorting can now use data immediately acquired (during data acquisition) as feedback to adjust a given experiment in real time [21].

In addition to spikes, microelectrodes can record LFPs, which are thought to reflect largely synaptic activity of several thousand neurons [87,88]. Simultaneous recordings of spikes and LFPs within the human brain have demonstrated the importance of phase relations and coherence between LFP and spikes during memory [37], and have provided insight into their relation with each other and the fMRI BOLD signal [89–93].

generated or cued by an external percept within the environment. Generating an internal percept of a stimulus through imagery in the absence of an external visual stimulus, recruits the same MTL neuron activated during viewing of the stimulus itself [20]. Subjects' ability to modulate these neurons was studied by Cerf and colleagues [21], who investigated the competition between responses to external information and responses that are internally generated. Using on-line real-time analysis and feedback of neuron activity, they sought to determine whether participants could consciously modulate the activity of their own MTL neurons. Subjects were told to try and control which of two competing images would be projected on an external display; the displayed images were controlled by the firing rate of recorded MTL neurons selective for the two images. Subjects were able to control successfully which image was projected by altering the firing rate of two independently selective neurons independent of the visual input of the stimulus on the screen (Figure 3). These results highlight the power of internal representation to override sensory input. They also illustrate how human single neuron recordings can illuminate mechanisms of conscious perception, regardless of whether they are externally or internally generated.

Therefore, the neural code that characterizes the representation of external stimuli in the MTL is expressed in the responses of individual neurons, which appear to be highly specific, yet invariant, suggesting that neurons respond in an explicit fashion to concepts such as a particular person or landmark. These responses appear to be preserved (i.e. invariant) through multiple representations of the same stimulus independent of physical features or of modality of sensory presentation and, in fact, present even in the absence of the stimulus altogether, such as in imagery responses. Obviously, a particular concept is not represented by a single cell alone, although the coding is ultra sparse [22,23].

Why are these responses present in the MTL, and in the hippocampus and entorhinal cortex in particular? Given the critical role of these regions in episodic memory, we posit that these responses are central in the transformation of novel stimuli to representations that can be later consciously retrieved as episodic memories. As such, these representations need to have detail but also abstraction (i.e. the loss of detail), so that they can be later summoned by internal as well as external cues. It is also possible that consciously perceived familiar stimuli trigger the recollection of an associated memory and, thus, reactivate MTL neurons.

MTL neurons and episodic memory

Although patients with damage to the MTL can no longer form new episodic memories, their visual perceptual function remains intact [5,6]. The correlation of single neuron responses in the MTL with specific conscious percepts does not imply that these regions are necessary for conscious percepts, yet these responses may reflect the link between conscious percepts and episodic memories that can be later consciously accessed [23]. The human single neuron studies we have discussed so far [14–17,19,21] often used stimuli that were highly familiar to the participant (e.g. a family member or famous person and/or landmark) and so may reflect familiarity to some extent. Yet these responses were also often rapidly formed to novel stimuli. For instance, MTL neurons responding to particular individuals participating in administering the experimental paradigms were formed over a few hours or days [15]. Furthermore, these responses were present with passive viewing or when subjects made perceptual judgments without overt memory demands. What is the evidence then that single neuron activity in the human MTL is directly related to memory performance?

Human intracranial studies have shown that the spiking rate of single hippocampal neurons predicts whether a recently learned item will be remembered [12,24]. In addition, intracranial recording of local field potentials (LFPs) have yielded important insights. Theta LFP oscillations (3–8 Hz) have been widely implicated in human memory (reviewed in [25,26]) and the strength of their amplitude measured in the MTL has been shown to predict the success of episodic encoding in humans [27–29]. Interestingly, the theta amplitude that predicted recall success was also strongly linked to the gamma oscillation (30–100 Hz; [27]). The phase of theta oscillations and their relationship to gamma oscillations in monkeys and humans have been related to memory performance [30–32]. There has been considerable interest in the

Figure 2. Selectivity in MTL (medial temporal lobe) neurons. **(a)** Simplified illustration of spiking activity (peristimulus time histogram or 'raster plot') of three theoretical neurons during the passive viewing of images each shown for 1 s. Single spikes are shown as purple lines. **(b)** Simplified illustration of a raster plot from neuron III during each of six image presentations. Illustration of an averaged histogram shows a selective response of this theoretical neuron to the actor 'Josh Brolin'. Adapted, with permission, from [14,21] and from images created by Moran Cerf.

relation between the phase of theta oscillations and the timing of single neuronal spiking both in rodents [33] and humans [34]. It has been hypothesized that the theta-spiking relation may reflect the cued recall of an upcoming item stored in memory [35,36]. A recent study in humans showed that the relation between spiking and theta during encoding predicted memory success [37]. Single neuron activity was recorded while subjects made human and/or non-human judgments for 100 images of people, animals, and objects, and then completed a recognition memory test (Figure 4a). During the memory test, subjects were shown a new set of 100 images (50 old and 50 new stimuli) and were asked to report whether they had seen a presented image before. A tighter coordination between hippocampal single neuron spiking and the simultaneously recorded theta LFP oscillation during initial viewing of the image predicted the success of the formed memory for that image (Figure 4; [37]). These results implicate a direct role for theta-linked spiking activity in episodic memory. Altogether, intracranial studies in humans affording simultaneous LFP and single neuron recordings have begun to link potential mechanisms by which the theta and gamma oscillations, together with single neuron activity, may support successful episodic memory. Insight into how these neurophysiological signals work together to support the encoding and free recall of individual episodic memories will be an exciting area of future intracranial research.

Investigating questions of episodic memory in animal studies relies on creative indirect ways to probe the recollection by an animal of a previously experienced event, given that animals cannot verbally report their episodic memories. In humans, researchers can directly instruct a participant to retrieve an explicit memory by using either tests of recognition or free recall. Several functional neuroimaging studies in humans have shown that the same brain areas activated during encoding of new information can be reactivated during recall of the encoded information (reviewed in [38]). fMRI studies from the human brain have shown increased BOLD activation within the MTL during both the learning and recall of memories [39,40]. However, is global reactivation of the entire MTL reflected in single neurons or just in coherent populations of neurons recruited during recall? Gelbard-Sagiv and colleagues [41] designed a study where participants were able to freely report spontaneous recollections of a previously experienced episode while MTL neuron activity was recorded [41]; participants viewed various video clips representing episodes (e.g. a clip of the TV show 'The Simpsons') and later explicitly declared clips that 'came to mind' (i.e. freely recalled). Interestingly, similar to the highly specific and

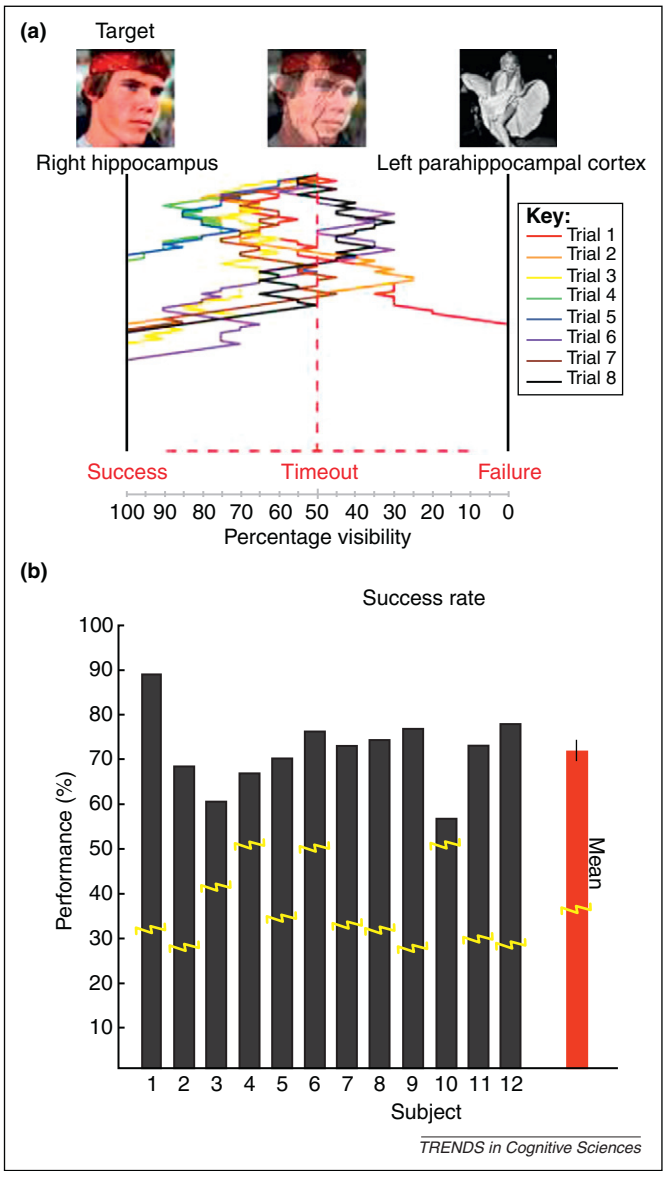

Figure 3. Internal modulation of MTL (medial temporal lobe) neurons. **(a)** Results from an example subject with a unit in the right hippocampus and a unit in the left parahippocampal cortex that were selective, respectively, for the famous actors 'Josh Brolin' and 'Marilyn Monroe'. Neuronal activity was recorded in real time and analyzed online to enable the subject to control their recorded units to determine which one of a hybrid image of both actors would be displayed on the laptop screen. The example subject shown succeeded in seven out of eight trials when instructed to display or 'fade' the image of Brolin onto the computer screen. **(b)** The percentage of trials in which each of the 12 subjects successfully controlled the activity of units and faded to the target image. Adapted from [21].

invariant responses to individual persons and landmarks reported before, sustained responses specific to distinct episodes were observed. Strikingly, hippocampal and entorhinal neurons that were selectively active during the initial viewing of distinct episodes were similarly reactivated just before the verbal report of recall of those very same episodes. Although sustained selective responses during viewing of episodes was present in neurons of other brain regions, such as amygdala and frontal cortex, the specific reactivation before reported recall was only present in the hippocampus and entorhinal cortex [41]. The highly specific reactivation was observed with a single free recall report, highlighting the robustness of this phenomenon that could be observed in a single trial in a single neuron under complex recording conditions in a hospital ward. Furthermore, the degree of correlation of hippocampal neuronal firing rate across successive time points within an episode increased over subsequent repetitions of the same episode, and predicted subjects' future recall performance [42]. These observations suggest a neural mechanism for binding of an episodic memory across time. Lastly, given that electrical stimulation of the MTL circuit has been shown to evoke old memories or the feeling of déjà vu [43–45] and enhance hippocampal-dependent memory [46], future studies may begin to unravel single neuron mechanisms of episodic recall, regardless of whether they are naturally or electrically induced.

Whereas free recall is thought to depend mainly on recollection, recognition tasks can be completed using mechanisms of recollection or familiarity [47,48]. The MTL is thought to support both recollection and familiarity, although its specific role during familiarity is still a matter of debate [3,49,50]. Rutishauser and colleagues [51,52] investigated hippocampal and amygdala single neuron mechanisms underlying recognition using an overt recognition memory paradigm. Subjects were shown novel images during learning and told to remember where each one had been positioned on the screen (i.e. left up, left bottom, right up, and right bottom). During a proceeding recognition block, subjects had to recognize old images in addition to where they were placed on the screen, allowing for behavioral measurements of both recollection (recognized as 'old' with spatial position correctly recalled) and familiarity (recognized as 'old' but with spatial position incorrectly recalled). Results showed that single hippocampal neurons recorded during recognition could distinguish between novel (new) versus recognized (old) stimuli independent of whether spatial position was recalled, and even after a single trial [51,52]. These results are consistent with the view that the hippocampus does not differentiate between recollected versus familiar items in memory; rather, it relates to the strength of the memory [50]. However, it is important to note that the responses in the previously discussed studies were not specific to individual stimuli and, thus, do no necessarily represent single memories. Rather, the hippocampal and amygdala neurons may reflect the judgment of recognition independent of recollection or familiarity of individual items. Neurons with activity reflecting recognition judgment have also been recorded in monkeys and rats (reviewed in [3]). Hippocampal but not other MTL neurons show evidence for linking specific events across time (i.e. activity of a single neuron during a given time segment is correlated with, and can predict, its activity during the following time segment; [42]). These findings suggest a unique role for the hippocampus in recollection, which requires the ability to link events across time. Further studies will determine whether the hippocampus specifically supports recollection rather than familiarity during free recall of specific memories. It has also been suggested that, although the hippocampus supports only recollection, the perirhinal subregion of the MTL alternatively supports familiarity processes [3]. Given that human single neuron studies to date have not recorded from perirhinal neurons, future

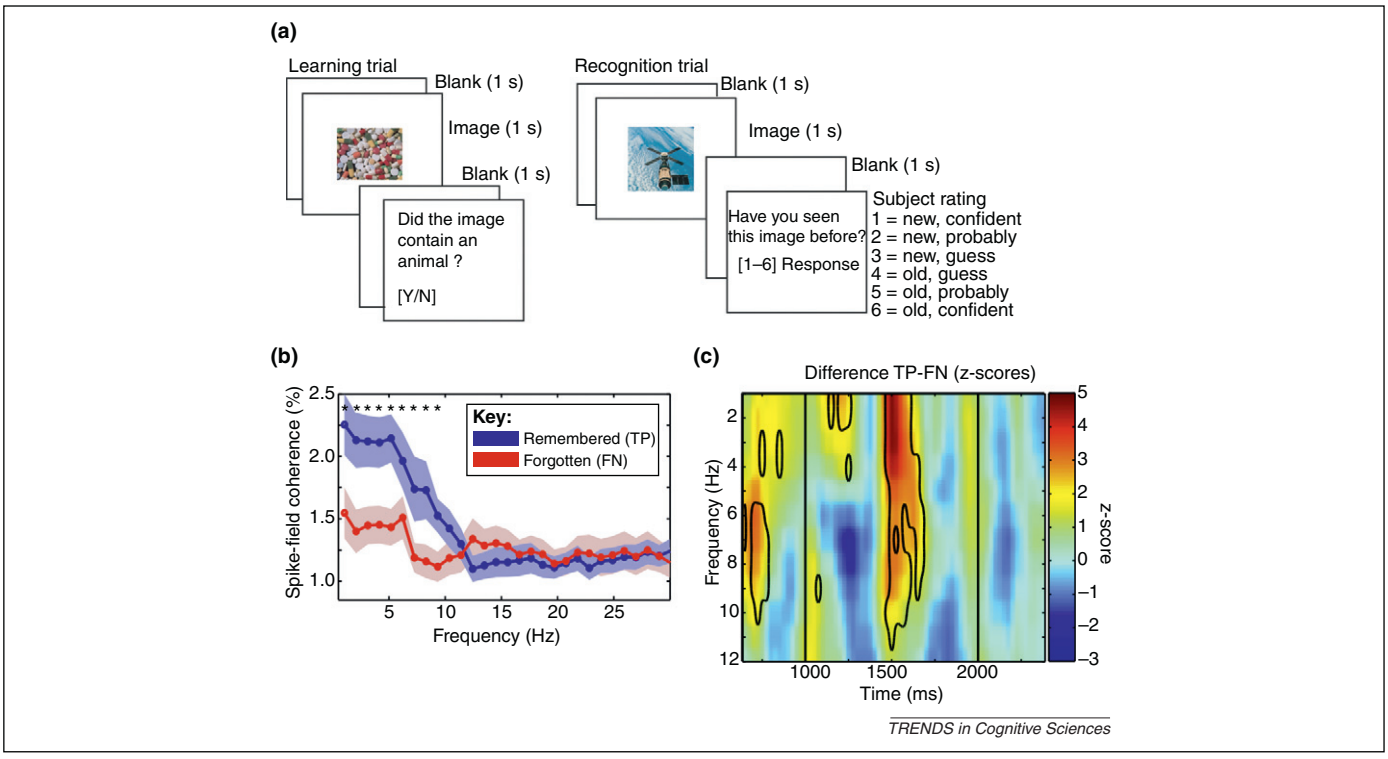

Figure 4. MTL (medial temporal lobe) spike-theta coordination predicts memory. **(a)** A memory task in which participants viewed 100 images in a learning and recognition block. **(b)** The strength of the phase locking [i.e. spike-field coherence (SFC) percentage] of the single neuron firing rate during learning is significantly higher for subsequently remembered versus forgotten images in the 2–10-Hz frequency band. **(c)** The time course of the significant difference in SFC between remembered true positive (TP) versus forgotten false negative (FN) images. Images were shown between 1000 and 2000 ms. Adapted, with permission, from [37].

studies are needed to investigate this dissociation between human hippocampal and perirhinal neurons and their involvement in recollection versus familiarity.

Future directions

Convergence with animal studies

Electrophysiological recordings in rodents have identified 'place cells' within the hippocampus, which increase in firing rate when an animal is in a specific location within an environment [53]. Place cells have been previously characterized in humans using single neuron recordings during virtual navigation of a novel spatial environment [54]. In addition, directional cells reflecting clockwise versus counterclockwise navigation in circular mazes have been identified in the human entorhinal cortex [55]. However, several other types of cell have been found in rodents and non-human primates, such as 'grid cells', 'border cells', 'head-direction cells', and 'time' cells [56–60], which have not yet been characterized in humans. Furthermore, in rodents, place cells can be modulated by goal, journey direction, and destination [61–64]. Rodent and non-human primate studies have also shown that place-selective neurons within the hippocampus can be modulated by the learning of an associated item [62,65,66]. Thus, it has been hypothesized that spatially sensitive neurons may carry the contextual information related to the encoded episodic memory [67]. Given the anatomical differences between the rodent and primate MTL [10,11], whether and where these types of cell exist in humans is important for understanding the role of these cells in memory as well as for future translational research. The exact role of spatially sensitive cells in episodic memory remains unclear; it is difficult to directly probe the internal memory of a rodent of being in a particular location of an environment. Although numerous data from rodent studies show place cells reactivated during subsequent sleep ([68], reviewed in [69]), it is unknown whether these place cells are reactivated due to a replay of associated memories. Given that it is impossible to measure the free recollection by a rodent of a particular experience, human single neuron recording studies uniquely allow for the direct investigation of the role of place cells during episodic recall. Future studies may provide insight into potential reactivation of place cells during recall of human episodic memories within a spatial context. Also, tracking the activity of human place cells during multiple paradigms on a given testing day may help determine how neurons act during navigation versus recollection of a non-spatial episodic memory.

Place cells and grid cells in rodents reflect spatial invariances in the neuronal representation of space in the MTL. The invariant responses to individual people and landmarks observed in the human MTL may be compared to the striking place fields in rodents, which appear to encode particular locations in the environment of the animal. It has been suggested that the response pattern seen in humans is indeed 'place cells' in a cognitive multidimensional space [12,19]. Such a notion is also supported by substantial data showing non-spatial correlates of memory in hippocampal neurons in non-human primates and in rodents [59,60,66,67]. Future research will need to address further the relation between rodent MTL physiology of

space and animal physiology of memory, and human MTL physiology of episodic memory.

Due to the obvious invasive nature of single neuron recordings, studies are done only in special circumstances where electrodes are placed in the brain for specific clinical reasons. These often involve closely monitored patients limited to their hospital room who cannot navigate a real environment during recordings. However, because the world that humans experience is rarely static, but instead in constant flux with continuously changing stimuli, future studies will benefit from the use of 'real-world' tasks rather than those presented on a stationary screen. These can be achieved with development of better virtual-reality technology, as well as from the development of wireless and miniaturized recording technology, so that neuronal recordings may be possible during less-constrained environment (e.g. during spatial navigation).

Regional differences in MTL responses of single neurons

To date, human single neuron studies of the MTL have identified several regional differences in neuronal responses to various stimuli or tasks. Responses in the human hippocampus and entorhinal cortex exhibit the highest degree of multimodal invariance in the MTL [17]. At the same time, these responses appear to be highly specific to particular stimulus identity (or concept) so that a neuron in these two regions appears to respond to fewer people or landmarks (come time only one) compared with neurons in other MTL regions [16]. In response to repeated trials of the same image, neurons within the hippocampus and entorhinal cortex (but not parahippocampal cortex) decrease in their response peak latencies [70]. Neurons in the hippocampus and entorhinal cortex, but not in the amygdala and parahippocampal cortex, appear to be selectively reactivated before free recall of the same items that they responded to during previous visual exposure [41]. Additionally, the activity of single hippocampal, but not amygdala or entorhinal, neurons increases in its correlation between successive time segments during encoding of a subsequently recalled episode [42]. Studies have also shown that amygdala neurons will respond more often to whole versus partial face features [71], although a higher proportion of amygdala neurons will respond to animals compared with people, landmarks, or objects independent of arousal or emotional relevance [72]. Outside the MTL, lateral temporal neocortex neurons have been identified with differential responses to perceptual changes during the viewing of faces and encoding of verbal material ([73], reviewed in [74]).

Anatomical as well as neuroimaging studies have shown structural and functional dissociations along the anterior–posterior axis of the MTL. For example, the posterior portion of the hippocampus receives spatially relevant information from the parahippocampal cortex via the posterior portion of the entorhinal cortex. Conversely, the anterior portion of the hippocampus is thought to receive object-related information from the perirhinal cortex via the anterior portion of the entorhinal cortex [10,75]. Most human single neuron studies to date report recordings from the anterior and middle portion of the hippocampus; therefore, systematic anterior–posterior analysis in the hippocampal axis await future studies with larger neuronal samples.

As regards to hippocampal subfields, single unit studies in rodents suggest there are subregional differences in hippocampal neurons in terms of their specificity of firing.

Box 2. Future directions

From single neurons to neuronal assemblies

In a given human microelectrode recording set up, such as in a patient with chronic epilepsy being monitored with intracranial depth electrodes, the activity of less than 100 neurons is simultaneously recorded, and these neurons may be distributed across several brain areas, which need to be clinically sampled. Other clinical settings where single unit recordings may be feasible include DBS procedures, where microelectrode recordings are helpful in identifying clinically relevant brain targets. Of particular interest is the development of neuroprosthetic devices based on brain–machine interfaces using brain signals obtained from multichannel arrays of microelectrodes to interact directly with external devices in closed-loop paradigms. Development of electrode construction technology as well as recording technology may enable recording from much larger neuronal pools, perhaps thousands of neurons simultaneously. This will provide new investigative opportunities to study the relation between representation at the single neuron level and at the level of neuronal assemblies in the human brain. Furthermore, extensive and simultaneous recordings in different regions (e.g. hippocampal subregions and temporal neocortex or MTL and frontal cortex) may open avenues to new questions in human memory, such as those relating to the transfer of information between the hippocampus and neocortex during awake and sleep stages in humans, or the influence of frontal lobe networks on episodic memory processing in MTL.

From correlation to causation: stimulation of specific neuronal networks

Since the pioneering observations of Wilder Penfield, focal electrical stimulation of MTL circuits has been shown to evoke old memories or the feeling of déjà vu [43–45,94,95]. Based on these observations, Penfield surmised that 'hidden in the temporal lobe there is a key to a mechanism that unlocks the past' [95]. These sporadic observations suggest that more systematic stimulation of MTL circuitry modifies memory. Suthana and colleagues [46] have recently shown that stimulation of the entorhinal white matter area, but not the hippocampus itself, enhances memory. In the study, it was the application of stimulation during the learning phase of a spatial navigation task that enhanced later recall of the learned information [46]. Interestingly, stimulation of the entorhinal area reset the phase of the theta rhythm in the hippocampus, providing a possible mechanism for memory enhancement. Future studies using microstimulation techniques may be able to dissect in better detail the local networks in the MTL participating in the complex processes of encoding, retention, and retrieval in humans. In this respect, using the foundations provided by rodent and nonhuman primate physiology, including microstimulation, microrecordings, and examining the relationship between single neuron activity and LFP oscillations, may provide further insight into the neuronal basis of episodic memory. A particularly tantalizing example is the use of optogenetic techniques to study memory, such as the recent study by Liu and colleagues [96], where optogenetic stimulation of specific hippocampal neurons reactivated fear memory recall. The ability to extend these approaches to appropriate and safe clinical situations may provide not only further insight into the neurobiology of memory, but also perhaps better ways to ameliorate cognitive and memory disorders in neurological diseases.

The dentate gyrus and CA fields 1–4 are differentially involved during the separation of similar overlapping spatial environments (reviewed in [76,77]). *In vivo* visualization of the human brain, especially of MTL structures, has advanced in recent years to enable the investigation of hippocampal subregional differences in fMRI BOLD activity during memory (reviewed in [78]). In fact, this technique has already been used to localize microelectrodes to hippocampal subregions in patients with epilepsy [79]. Accurate electrode localization requires the alignment (i.e. registration) of CT images, visualizing the actual electrode with MRI and visualizing detailed brain anatomy. When registered to the electrode image, bundles of microelectrodes can be localized to areas as small as 1 mm [79], although separation of a single microelectrode from its bundled neighboring electrodes is still a challenge. Recent and future advances in the ability to localize intracranial microelectrodes will facilitate single neuron studies in humans aimed at investigating hippocampal subregional roles in memory. In particular, the role of specific neurons in differentiating similar overlapping memories can be investigated at a more comparable resolution to animal studies.

Concluding remarks

In this article, we have reviewed recent results from direct recordings of single neurons from the human brain. Based on recent findings, we explore the idea that MTL neurons are intimately involved in one's ability to reactivate internal memories of events from one's past. The neural code representing human experience as it is processed by MTL circuitry is selective and invariant, represents consciously perceived external information, yet can be internally generated and modulated, and reactivated during imagery or free recall. Although the data presented are rare and limited by clinical opportunities, they offer exciting avenues for further exploration. With recent findings that deep brain stimulation of the entorhinal area enhances human hippocampal-dependent memory [46], new opportunities have arisen to study how MTL neuronal activity (both action potentials and LFPs) may be modulated to affect memory. Human brain recordings combined with recent and future technological advancements, such as those provided by microstimulation or optogenetic stimulation, may provide exciting new opportunities for research aimed at deciphering the neural code underlying uniquely human behaviors (Box 2). Ultimately, the knowledge to be gained will shed insight into clinical circumstances of memory disorders seen in neurological diseases such as Alzheimer's disease or temporal-lobe epilepsy.

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References

1 Ekstrom, A. (2010) How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. *Brain Res. Rev.* 62, 233–244
2 Scoville, W.B. and Milner, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21
3 Eichenbaum, H. *et al.* (2007) The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152
4 Squire, L.R. *et al.* (2004) The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 6748–6753
5 Milner, B. *et al.* (1968) Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologica* 6, 215–234
6 Corkin, S. (1984) Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. *Semin. Neurol.* 4, 249–258
7 Suzuki, W.A. and Baxter, M.G. (2009) Memory, perception, and the medial temporal lobe: a synthesis of opinions. *Neuron* 61, 678–679
8 Suzuki, W.A. (2010) Untangling memory from perception in the medial temporal lobe. *Trends Cogn. Sci.* 1, 195–200
9 Felleman, D. and Van Essen, D. (1991) Distributed hierarchical processing in primate cerebral cortex. *Cereb. Cortex* 1, 1–47
10 Suzuki, W.A. and Amaral, D.G. (1994) Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J. Neurosci.* 14, 1856–1877
11 Saleem, K.S. and Tanaka, K. (1996) Divergent projections from the anterior inferotemporal area TE to the perirhinal and entorhinal cortices in the macaque monkey. *J. Neurosci.* 16, 4757–4775
12 Fried, I. *et al.* (1997) Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 18, 753–765
13 Kreiman, G. *et al.* (2000) Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat. Neurosci.* 3, 946–953
14 Quiroga, R.Q. *et al.* (2005) Invariant visual representation by single neurons in the human brain. *Nature* 435, 1102–1107
15 Viskontas, I.V. *et al.* (2009) Human medial temporal lobe neurons respond preferentially to personally relevant images. *Proc. Natl. Acad. Sci. U.S.A.* 106, 21329–21334
16 Mormann, F. *et al.* (2008) Latency and selectivity of single neurons indicate hierarchical processing in the human medial temporal lobe. *J. Neurosci.* 28, 8865–8872
17 Quiroga, R.Q. *et al.* (2009) Explicit encoding of multimodal percepts by single neurons in the human brain. *Curr. Biol.* 19, 1308–1313
18 Kreiman, G. *et al.* (2002) Single-neuron correlates of subjective vision in the human medial temporal lobe. *Proc. Natl. Acad. Sci. U.S.A.* 99, 8378–8383
19 Quiroga, R.Q. *et al.* (2008) Human single-neuron responses at the threshold of conscious recognition. *Proc. Natl. Acad. Sci. U.S.A.* 105, 3599–3604
20 Kreiman, G. *et al.* (2000) Imagery neurons in the human brain. *Nature* 408, 357–361
21 Cerf, M. *et al.* (2010) On-line, voluntary control of human temporal lobe neurons. *Nature* 467, 1104–1108
22 Waydo, S. *et al.* (2006) Sparse representation in the human medial temporal lobe. *J. Neurosci.* 26, 10232–10234
23 Quiroga, R.Q. *et al.* (2008) Sparse but not 'grandmother-cell' coding in the medial temporal lobe. *Trends Cogn. Sci.* 12, 87–91
24 Cameron, K.A. *et al.* (2001) Human hippocampal neurons predict how well word pairs will be remembered. *Neuron* 30, 289–298
25 Buzsáki, G. (2005) Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* 15, 827–840
26 Kahana, M.J. *et al.* (2001) Theta returns. *Curr. Opin. Neurobiol.* 11, 739–744
27 Lega, B.C. *et al.* (2012) Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus* 22, 748–761
28 Guderian, S. *et al.* (2009) Medial temporal theta state before an event predicts episodic encoding success in humans. *Proc. Natl. Acad. Sci. U.S.A.* 106, 5365–5370
29 Sederberg, P.B. *et al.* (2003) Theta and gamma oscillations during encoding predict subsequent recall. *J. Neurosci.* 23, 10809–10814
30 Mormann, F. *et al.* (2005) Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. *Hippocampus* 15, 890–900
31 Canolty, R.T. and Knight, R.T. (2010) The functional role of cross-frequency coupling. *Trends Cogn. Sci.* 14, 506–515

32 Jutras, M.J. and Buffalo, E.A. (2010) Synchronous neural activity and memory formation. *Curr. Opin. Neurobiol.* 20, 150–155
33 O'Keefe, J. and Recce, M.L. (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330
34 Jacobs, J. *et al.* (2007) Brain oscillations control timing of single-neuron activity in humans. *J. Neurosci.* 27, 3839–3844
35 Jensen, O. and Lisman, J.E. (1996) Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. *Learn. Mem.* 3, 279–287
36 Tsodyks, M.V. *et al.* (1996) Population dynamics and theta rhythm phase precession of hippocampal place cell firing: a spiking neuron model. *Hippocampus* 6, 271–280
37 Rutishauser, U. *et al.* (2010) Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature* 464, 903–907
38 Danker, J.F. and Anderson, J.R. (2010) The ghosts of brain states past: remembering reactivates the brains regions engaged during encoding. *Psychol. Bull.* 136, 87–102
39 Schacter, D.L. and Wagner, A.D. (1999) Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus* 9, 7–24
40 Zeineh, M.M. *et al.* (2003) Dynamics of the hippocampus during encoding and retrieval of face–name pairs. *Science* 299, 577–580
41 Gelbard-Sagiv, H. *et al.* (2008) Internally generated reactivation of single neurons in human hippocampus during free recall. *Science* 322, 96–101
42 Paz, R. *et al.* (2010) *A* neural substrate in the human hippocampus for linking successive events. *Proc. Natl. Acad. Sci. U.S.A.* 107, 6046–6051
43 Gloor, P. (1990) Experiential phenomena of temporal lobe epilepsy. Facts and hypotheses. *Brain* 113, 1673–1694
44 Hamani, C. *et al.* (2008) Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann. Neurol.* 63, 119–123
45 Jacobs, J. *et al.* (2012) Explaining how brain stimulation can evoke memories. *J. Cogn. Neurosci.* 24, 553–563
46 Suthana, N. *et al.* (2012) Memory enhancement and deep-brain stimulation of the entorhinal area. *N. Engl. J. Med.* 366, 502–510
47 Atkinson, R.C. and Juola, J.F. (1974) Search and decision processes in recognition memory. In *Contemporary Developments in Mathematical Psychology* (Krantz, D.H. *et al.*, eds), pp. 243–290, Freeman
48 Squire, L.R. and Wixted, J.T. (2011) The cognitive neuroscience of human memory since H.M. *Annu. Rev. Neurosci.* 34, 259–288
49 Brown, T. and Aggleton, J.P. (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61
50 Wixted, J.T. and Squire, L.R. (2010) The role of the human hippocampus in familiarity-based and recollection-based recognition memory. *Behav. Brain Res.* 215, 197–208
51 Rutishauser, U. *et al.* (2006) Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. *Neuron* 49, 805–813
52 Rutishauser, U. *et al.* (2008) Activity of human hippocampal and amygdala neurons during retrieval of declarative memories. *Proc. Natl. Acad. Sci. U.S.A.* 105, 329–334
53 O'Keefe, J. and Conway, D.H. (1978) Hippocampal place units in the freely moving rat: why they fire where they fire. *Exp. Brain Res.* 31, 573–590
54 Ekstrom, A.D. *et al.* (2003) Cellular networks underlying human spatial navigation. *Nature* 425, 184–187
55 Jacobs, J. *et al.* (2010) A sense of direction in human entorhinal cortex. *Proc. Natl. Acad. Sci. U.S.A.* 107, 6487–6492
56 Hafting, T. *et al.* (2005) Microstructure of a spatial map in the entorhinal cortex. *Nature* 436, 801–806
57 Taube, J.S. *et al.* (1990) Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *J. Neurosci.* 10, 420–435
58 Solstad, T. *et al.* (2008) Representation of geometric borders in the entorhinal cortex. *Science* 322, 1865–1868
59 MacDonald, C.J. *et al.* (2011) Hippocampal 'time cells' bridge the gap in memory for discontiguous events. *Neuron* 71, 737–749
60 Naya, Y. and Suzuki, W.A. (2011) Integrating what and when across the primate medial temporal lobe. *Science* 333, 773–776
61 Ferbinteanu, J. *et al.* (2011) Memory modulates journey-dependent coding in the rat hippocampus. *J. Neurosci.* 31, 9135–9146
62 Wood, E.R. *et al.* (2000) Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27, 623–633
63 Ferbinteanu, J. and Shapiro, M.L. (2003) Prospective and retrospective memory coding in the hippocampus. *Neuron* 40, 1227–1239
64 Smith, D.M. and Mizumori, S.J. (2006) Learning-related development of context specific neuronal responses to places and events: the hippocampal role in context processing. *J. Neurosci.* 26, 3154–3163
65 Moita, M.A.P. *et al.* (2003) Hippocampal place cells acquire location specific responses to the conditioned stimulus during auditory fear conditioning. *Neuron* 37, 485–497
66 Wirth, S. *et al.* (2003) Single neurons in the monkey hippocampus and learning of new associations. *Science* 300, 1578–1581
67 Eichenbaum, H. (2004) Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron* 44, 109–120
68 Pavlides, C. and Winson, J. (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *J. Neurosci.* 9, 2907–2918
69 Carr, M.F. *et al.* (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat. Neurosci.* 14, 147–153
70 Pedreira, C. *et al.* (2010) Responses of human medial temporal lobe neurons are modulated by stimulus repetition. *J. Neurophysiol.* 103, 97–107
71 Rutishauser, U. *et al.* (2011) Single-unit responses selective for whole faces in the human amygdala. *Curr. Biol.* 21, 1654–1660
72 Mormann, F. *et al.* (2011) A category-specific response to animals in the right human amygdala. *Nat. Neurosci.* 14, 1247–1249
73 Ojemann, G.A. *et al.* (2009) The roles of human lateral temporal cortical neuronal activity in recent verbal memory encoding. *Cereb. Cortex* 19, 197–205
74 Engel, A.K. *et al.* (2005) Invasive recordings from the human brain: clinical insights and beyond. *Nat. Rev. Neurosci.* 6, 35–47
75 Colombo, M. *et al.* (1998) Functional differentiation along the anterior-posterior axis of the hippocampus in monkeys. *J. Neurophysiol.* 80, 1002–1005
76 Yassa, M.A. and Stark, C.E. (2011) Pattern separation in the hippocampus. *Trends Neurosci.* 34, 515–525
77 Guzowski, J.F. *et al.* (2004) Ensemble dynamics of hippocampal regions CA3 and CA1. *Neuron* 44, 581–584
78 Carr, V.A. *et al.* (2010) Imaging the human medial temporal lobe with high-resolution fMRI. *Neuron* 65, 298–308
79 Ekstrom, A. *et al.* (2008) High-resolution depth electrode localization and imaging in patients with pharmacologically intractable epilepsy. *J. Neurosurg.* 108, 812–815
80 Csicsvari, J. *et al.* (1999) Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat. *J. Neurosci.* 19, 274–287
81 Viskontas, I.V. *et al.* (2007) Characterizing interneuron and pyramidal cells in the human medial temporal lobe in vivo using extracellular recordings. *Hippocampus* 17, 49–57
82 Ison, M.J. *et al.* (2011) Selectivity of pyramidal cells and interneurons in the human medial temporal lobe. *J. Neurophysiol.* 106, 1713–1721
83 Quiroga, R.Q. *et al.* (2004) Unsupervised spike detection and sorting with wavelets and superparamagnetic clustering. *Neural Comput.* 16, 1661–1687
84 Tankus, A. *et al.* (2009) An automatic measure for classifying clusters of suspected spikes into single cells versus multiunits. *J. Neural. Eng.* 6, 056001
85 Hochberg, L.R. *et al.* (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 442, 164–171
86 Rutishauser, U. *et al.* (2006) Online detection and sorting of extracellularly recorded action potentials in human medial temporal lobe recordings, in vivo. *J. Neurosci. Methods* 154, 204–224
87 Mitzdorf, U. (1985) Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiol. Rev.* 65, 37–100
88 Logothetis, N.K. (2003) The underpinnings of the BOLD functional magnetic resonance imaging signal. *J. Neurosci.* 23, 3963–3971
89 Mukamel, R. *et al.* (2005) Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. *Science* 309, 951–954

90 Nir, Y. *et al.* (2007) Coupling between neuronal firing rate, gamma LFP, and BOLD fMRI is related to interneuronal correlations. *Curr. Biol.* 17, 1275–1285
91 Ekstrom, A. *et al.* (2009) Correlation between BOLD fMRI and theta-band local field potentials in the human hippocampal area. *J. Neurophysiol.* 101, 2668–2678
92 Ojemann, G.A. *et al.* (2010) Neuronal correlates of functional magnetic resonance imaging in human temporal cortex. *Brain* 133, 46–59
93 Ekstrom, A. *et al.* (2007) Contrasting roles of neural firing rate and local field potentials in human memory. *Hippocampus* 17, 606–617
94 Penfield, W. and Perot, P. (1963) The brain's record of auditory and visual experience. A final summary and discussion. *Brain* 86, 595–696
95 Penfield, W. (1958) Some mechanisms of consciousness discovered during electrical stimulation of the brain. *Proc. Natl. Acad. Sci. U.S.A.* 44, 51–66
96 Liu, X. *et al.* (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484, 381–385