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

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Abstract

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 translation from sensory information to memory remains unclear. Recordings from neurons within the brain in patients implanted with electrodes 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 BOLD measure in fMRI, or a measure of neuronal activity reflecting activity of large neuronal pools. Signals recorded from EEG and fMRI reflect several thousands to millions of neurons (for review see [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 of past events, freely arising wishes or desires. In particular

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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 medial temporal lobe (MTL, [2–4]). Other functions such as visual perception, however, do not depend on an intact MTL [5–6], although this has been debated to some extent (for review see [7–8]). In the current review, we summarize recent data afforded by key methodological advancements in human single neuron data acquisition and analysis (Figure 1, see Box 1). We show how the data obtained from single neurons within the MTL of neurosurgical patients implanted with intracranial electrodes for clinical reasons has yielded valuable information regarding neural mechanisms underlying conscious perception and recollection of experienced events.

Box 1

Technological advances in human single-neuron recordings

Microelectrode recordings in epilepsy patients undergoing clinical monitoring for curative neurosurgery have allowed for the extracellular recording of action potentials (i.e. spikes) from the human brain. However, spikes detected on a single microelectrode most likely 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 consist of several different types of cells such as principal pyramidal and interneurons, which have intrinsic differences in their electrophysiological properties and excitatory or inhibitory effects [9–11]. Fast and automated signal processing techniques have been developed in the past decade to extract single action potentials (i.e. spikes) from complex recording signals recorded from the human brain. Currently, efficient analysis techniques have automated the process of spike sorting to separate pyramidal vs. interneuron and single- vs. multi-unit types by comparing waveform characteristics (e.g. shape and amplitude) and inter-spike intervals distributions [12–16].

Real-time analysis and feedback of recorded brain activity has emerged as an extremely powerful tool in the field of human cognitive neurophysiology [17–18]. 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 [17, 19]. Real-time online spike sorting can now use data immediately acquired (during data acquisition) as feedback to adjust a given experiment in real-time [17].

In addition to spikes, microelectrodes can record LFPs, which are thought to largely reflect synaptic activity of several thousand neurons [20–21]. Simultaneous recordings of spikes and LFPs within the human brain have demonstrated the importance of phase relationships and coherence between LFP and spikes during memory [22] and provided insight into their relationship with each other and the fMRI BOLD signal [23–27].

MTL neurons and perception

The MTL receives multi-modality sensory input from wide areas of the cortex, thereby offering the possibility of convergence and integration of information [28]. The MTL itself consists of several smaller areas including the hippocampus, entorhinal, perirhinal, and parahippocampal cortices. 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; [29–30]). In order for the MTL to properly encode a given episode in time, 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 on the other hand require extensive training to do so, thus potentially altering existing or even recruiting different neuronal mechanisms.

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:

1. **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 [31–35]. For a simplified diagram illustrating a selective type of response see Figure 2.
2. **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 to the original stimulus [33]. 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 quite different in its visual properties than 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 independent of the sensory modality (visual image, audio, or written iconic representations) through which the stimulus was presented [36]. 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 as compared to the amygdala or parahippocampal cortex [36].

3. ***Responses are late.*** The selective and invariant responses described above are of relative long latencies often in the 300 msec - 500 msec 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 [35], but still with longer latencies than those observed in animal studies.
4. ***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 [37–38]. When varying the display time of an image between 33 to 256 msec, 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 msec. Conversely, if the subject reported no recognition of the image, the MTL neuron selective for that image is mostly silent [38].
5. ***Responses can be internally generated.*** The act of re-experiencing a previous episode can be internally 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 [39]. Subjects' ability to modulate these neurons was studied by Cerf and colleagues [17] 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 if 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 successfully control 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 whether externally or internally generated.

To summarize then, the neural code which 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 may 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, independent 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 [40–41].

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 possess 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 may 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 [41]. The human single neuron studies we have discussed thus far [17, 33–36, 38] often used stimuli that were highly familiar to the participant (e.g. a family member or famous person/landmark) and thus may to some extent reflect familiarity. 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 [34]. 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 [31, 42]. In addition, intracranial recording of LFPs have yielded important insights. Theta LFP oscillations (3–8 Hz) have been widely implicated in human memory (for review see [43–44]) and the strength of their amplitude measured in the MTL has been shown to predict the success of episodic encoding in humans [45–47]. Interestingly, the theta amplitude that predicted recall success was also strongly linked to the gamma oscillation (30–100 Hz; [45]). The phase of theta oscillations and their relationship to gamma oscillations in monkeys and humans have been related to memory performance [48–50]. There has been considerable interest in the relationship between the phase of theta oscillations and the timing of single neuronal spiking both in rodents [51] and humans [52]. It has been hypothesized that the theta-spiking relationship may reflect the cued recall of an upcoming item stored in memory [53–54]. A recent study in humans showed that the relationship between spiking and theta during encoding predicted memory success [22]. Single neuron activity was recorded while subjects made human/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; [22]). 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 an animal's recollection of a previously experienced event, since 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 (for review see [55]). Functional MRI studies from the human brain have shown increased BOLD activation within the MTL during both the learning and recall of memories [56–57]. 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 [58] designed a study where participants were able to freely report spontaneous recollections of a previously experienced episode while MTL neuron activity was recorded [58]; participants viewed various video clips representing episodes (e.g. Simpson's TV show clip) and later explicitly declared clips that "came to mind" (i.e. freely recalled). Interestingly, similar to the highly specific and 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 prior to the verbal report of recall of those very same episodes. While sustained selective responses during viewing of episodes was present in neurons of other brain regions such as amygdala and frontal cortex, the specific reactivation prior to reported recall was only present in the hippocampus and entorhinal cortex [58]. 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 [59]. These observations suggest a possible neural mechanism for binding of an episodic memory across time. Lastly, since electrical stimulation of the MTL circuit has been shown to evoke old memories or the feeling of déjà vu [60–62] and enhance hippocampal dependent memory [63], future studies may begin to unravel single neuron mechanisms of episodic recall whether naturally or electrically induced.

While free recall is thought to depend mainly on recollection, recognition tasks can be completed using mechanisms of recollection or familiarity (see glossary; [64–65]). The MTL is thought to support both recollection and familiarity, although it's specific role during familiarity is still a matter of debate [66–68]. Rutishauser and colleagues [69–70] 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 [69–70]. 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 [68]. It is important to note, however, that the responses in the previously discussed studies were not specific to individual stimuli and thus do not 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 (for review see [67]). Hippocampal and 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; [59]). 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 and not familiarity during free recall of specific memories. It has also been suggested that while the hippocampus supports only recollection, the perirhinal subregion of the MTL may alternatively support familiarity processes [67]. Since human single neuron studies to date have not recorded from perirhinal neurons, future studies are needed to investigate this dissociation between human hippocampal and perirhinal neurons and their involvement in recollection vs. 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 [71]. Place cells have been previously characterized in humans using single neuron recordings during virtual navigation of a novel spatial environment [72]. In addition directional cells reflecting clockwise versus counterclockwise navigation in circular mazes have been identified in the human entorhinal cortex [73]. However, several other types of cells have been found in rodents and non-human primates such as “grid cells”, “border cells”, “head-direction cells”, and “time” cells [74–78], which have not yet been characterized in humans. Furthermore in rodents, place cells can be modulated by goal, journey direction, and destination (79–82). Rodent and non-human primate studies have also shown place-selective neurons within the hippocampus can be modulated by the learning of an associated item [80, 83–84]. It has thus been hypothesized that spatially sensitive neurons may carry the contextual information related to the encoded episodic memory [85]. Given anatomical differences between the rodent and primate MTL [29–30], whether and where these types of cells 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 a rodent’s internal

memory of being in a particular location of an environment. Although numerous data from rodent studies show place cells reactivated during subsequent sleep ([86], for review see [87]), it is unknown whether these place cells are reactivated due to a replay of associated memories. Since it is impossible to measure a rodent's free recollection 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 persons 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 animal's environment. It has been suggested that the response pattern seen in humans are indeed "place cells" in a cognitive multidimensional space [31, 38]. Such notion is also supported by substantial data showing non-spatial correlates of memory in hippocampal neurons in non-human primates and in rodents [77–78, 84–85]. Future research will need to further address the relationship between rodent MTL physiology of space and animal physiology of memory, with 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 we experience is rarely static and is rather in constant flux with continuously changing stimuli, future studies will benefit from employment 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 [36]. 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 appear to respond to fewer persons or landmarks (come time only one) compared to neurons in other MTL regions [35]. 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 [88]. Neurons in the hippocampus and entorhinal cortex but not in the amygdala and parahippocampal cortex appear to be selectively reactivated prior to free recall of the same items they responded to during prior visual exposure [58]. 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 [59]. Studies have also shown that amygdala neurons will respond more often to whole versus partial face features [89], although a higher proportion of these neurons will respond to animals compared to persons, landmarks, or objects independent of arousal or emotional relevance [90]. 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 ([91], for review see [92]).

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 [29, 94]. The majority of human single neuron studies to date report recordings from the anterior and middle portion of the hippocampus and systematic anterior-posterior analysis in the hippocampal axis will have to 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. The dentate gyrus and CA fields 1–4 are differentially involved during the separation of similar overlapping spatial environments (for review see [94–95]). In-vivo visualization of the human brain, especially of MTL structures, has advanced in recent years to allow for the investigation of hippocampal subregional differences in fMRI BOLD activity during memory (for review see [96]). In fact, this technique has already been used to localize microelectrodes to hippocampal subregions in epilepsy patients [97]. Accurate electrode localization requires the alignment (i.e. registration) of CT images, visualizing the actual electrode with magnetic resonance images (MRI) and visualizing detailed brain anatomy. When registered to the electrode image, bundles of microelectrodes can be localized to areas as small as 1mm [97], 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 review 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 our ability to internally reactivate memories of events from our past. The neural code representing human experience as it is processed by MTL circuitry is selective and invariant, represents consciously perceived external information yet could be internally generated and modulated, and reactivated during imagery or free recall. Although the data presented are rare and limited by clinical opportunities, it offers exciting future avenues for

further exploration. With recent findings that DBS of the entorhinal area enhances human hippocampal-dependent memory [63] new opportunities have opened 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 (see Box 2). Ultimately the knowledge to be gained will altogether shed insight into clinical circumstances of memory disorders seen in neurological diseases such as Alzheimer's disease or temporal-lobe epilepsy.

Box 2

Future Directions

From single neurons to neuronal assemblies

In a given human microelectrode recording set up, such as in chronic epilepsy patient monitored with intracranial depth electrodes, the activity of less than 100 neurons are 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 deep brain stimulation (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 open new investigative opportunities to study the relationship 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—hippocampal subregions and temporal neocortex or MTL and frontal cortex, may open up avenues to new questions in human memory. These include questions such as 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 [60–62, 98–99]. Based on these observations Penfield surmised that “hidden in the temporal lobe there is a key to a mechanism that unlocks the past” [99]. These sporadic observations raise the possibility that more systematic stimulation of MTL circuitry may modify memory. Suthana and colleagues [63] 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 recall of the learned information later [63]. 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 [100] 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 perhaps better ways to ameliorate cognitive and memory disorders in neurological diseases.

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Glossary

Episodic memory

memory for events within a spatial and temporal context

Medial temporal lobe (MTL)

the MTL consists of the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex

Spikes

extracellularly recorded action potentials from single (single-unit) or multiple (multi-unit) neurons

Local field potentials (LFPs)

extracellular voltage changes reflective of dendritic currents and action potentials of populations of neurons

Recollection vs. 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

LFP Phase

Measurement in radians or degrees of the position within a cycle of an oscillatory waveform

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Figure 1.

Shown is an example experimental setup for intracranial single neuron recordings in humans. Participants are shown images on a laptop screen while continuous voltage data is 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. Bottom right shows 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 sec time window when the image was presented. Adapted from [17].

Figure 2.

(a) Simplified illustration of spiking activity (peristimulus time histogram or 'raster plot') of 3 theoretical neurons during the passive viewing of images each shown for 1 second. Single spikes are shown as purple lines. (b) Shown is a simplified illustration of a raster plot from neuron III during each of 6 image presentations. Illustration of an averaged histogram shows a selective response of this theoretical neuron to actress 'Josh Brolin'. Adapted with permission from [33,17] and from images created by Moran Cerf.

Figure 3.

(a) Shown are results from an example subject with a unit in the right hippocampus and a unit in the left parahippocampal cortex that were respectively selective for famous actors ‘Josh Brolin’ and ‘Marilyn Monroe’. Neuronal activity was recorded in real time and analyzed online to allow for the subject to control their recorded units to determine which 1 of a hybrid image of both actors would be displayed on the laptop screen. The example subject shown succeeded 7 out of 8 trials when instructed to display or ‘fade’ the image of Brolin onto the computer screen. (b) Shown is 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 [17].

Figure 4.

(a) Shown is the memory task in which participants viewed 100 images in a learning and recognition block. (b) Strength of the phase locking (i.e. spike-field coherence [SFC] percentage) of single neuron firing rate during learning is significantly higher for subsequently remembered versus forgotten images in the 2–10 Hz frequency band. (c) Shown is 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 [22].