NeuroImage 85 (2014) 694–701

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

Oscillatory correlates of memory in non-human primates

Michael J. Jutras [a,c], Elizabeth A. Buffalo [a,b,c,*]

[a] Yerkes National Primate Research Center, 954 Gatewood Road, Atlanta, GA 30329, USA
[b] Department of Neurology, Emory University School of Medicine, 1440 Clifton Road, Atlanta, GA, 30322, USA
[c] Department of Physiology and Biophysics and National Primate Center, University of Washington, Seattle, Washington 98195-7330, USA

ARTICLE INFO

Article history:
Accepted 3 July 2013
Available online 16 July 2013

Keywords:
Monkeys
Medial temporal lobe
Hippocampus
Gamma
Theta
Oscillations

ABSTRACT

The ability to navigate through our environment, explore with our senses, track the passage of time, and integrate these various components to form the experiences which make up our lives is shared among humans and animals. The use of animal models to study memory, coupled with electrophysiological techniques that permit the direct measurement of neural activity as memories are formed and retrieved, has provided a wealth of knowledge about these mechanisms. Here, we discuss current knowledge regarding the specific role of neural oscillations in memory, with particular emphasis on findings derived from non-human primates. Some of these findings provide evidence for the existence in the primate brain of mechanisms previously identified only in rodents and other lower mammals, while other findings suggest parallels between memory-related activity and processes observed in other cognitive modalities, including attention and sensory perception. Taken together, these results provide insight into how network activity may be organized to promote memory formation, and suggest that key aspects of this activity are similar across species, providing important information about the organization of human memory.

Contents

Introduction

The discovery, in 1957, that bilateral damage confined to the medial temporal lobes (MTL) of the human brain produced profound, selective impairment in the ability to form new declarative memories, i.e., the ability to remember facts and events (Scoville and Milner, 1957) ushered in a new era of memory research. Subsequently, a number of studies were able to replicate this memory loss in animal models, establishing that the neural correlates of at least some components of memory are likely conserved across species (Mishkin, 1982; Squire and Zola-Morgan, 1983). Through careful design of behavioral tasks and use of specific lesions in non-human primates, it has been possible to test competing theories of the nature of memory and the role of specific brain areas in different aspects of memory formation and retrieval. In particular, the similarities between the brains of humans and non-human primates, combined with the common sensory modalities generally employed among primate species in exploration and sensory input, have made studies with non-human primates invaluable in probing the neural correlates of memory. While a great deal of knowledge about the physiology of the hippocampus and other MTL areas has been derived from studies of non-primate species, including rodents, non-human primates have provided a way to bridge the gap between rodent and human studies, which has led to greater understanding of the common mechanisms employed across species. In particular, research over the last few years has led to a greater understanding of the role of neural

* Corresponding author at: Department of Physiology and Biophysics and National Primate Center, University of Washington, Seattle, Washington 98195-7330, USA
E-mail address: ebuffalo@uw.edu (E.A. Buffalo).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.07.011

oscillations in memory formation through the use of electrophysiological recording methods in multiple species, including rodents, non-human primates, and humans. Studies across multiple species inform each other and provide a richer understanding of the complex mechanisms underlying memory. This review will focus on the role of neural oscillations in several aspects of memory, with an emphasis on findings from recent studies in non-human primates.

Neural correlates of declarative memory

Declarative memory involves several different processes: the initial storage, or encoding, of information; the subsequent reactivation, or retrieval, of this memory trace; and, over time, a process of consolidation, through which the initially transient memory trace is converted into a longer lasting form. The brain regions essential for declarative memory in mammals include the hippocampus (comprised of the CA fields, the dentate gyrus, and the subiculum) and the surrounding entorhinal, perirhinal, and parahippocampal cortices. Lesion studies in humans, monkeys, and rodents have revealed that damage to these areas produces deficits in declarative memory (Eichenbaum, 1997; Mishkin, 1982; Schacter and Tulving, 1994; Squire and Zola-Morgan, 1991; Squire et al., 2004), suggesting that this ability is reliant on neuronal operations occurring in these areas. However, while declarative memory is critically dependent on processing within these regions, this ability is also thought to involve the concurrent, coordinated activation of ensembles of neurons that are distributed throughout the brain, including the medial temporal and frontal areas, as well as association cortices across various sensory modalities (Damasio, 1989; Mishkin, 1982; Rolls and Treves, 1994). In addition to mediating the initial acquisition of stored memories, such coordinated activity across brain regions is also thought to facilitate the consolidation of memories over time. The standard model of consolidation, which states that memory is initially stored in the hippocampus but gradually shifts to a purely cortical representation, is derived from evidence that damage limited to the hippocampus produces some memory loss for information acquired before the damage occurred (retrograde amnesia), with more recent memories often showing greater vulnerability to damage than more remote memories (McClelland et al., 1995; Squire and Alvarez, 1995). Because information that has become consolidated in memory is largely resistant to MTL damage, this suggests that the neural structures mediating the reactivation of consolidated memories gradually become independent of the areas critical for the initial memory formation, as hippocampal–cortical reactivations strengthen connections in the cortical network. An alternative account proposes that, while the cortex can support memory traces that are purely semantic in nature, the hippocampus is critical for the spatial and temporal context inherent in detailed autobiographical and episodic memories, regardless of how remote those memories are (Nadel and Moscovitch, 1997). Both theories are in agreement that declarative memories are encoded in hippocampal–cortical networks and that these memory traces are reorganized over time, as memories are reactivated (Frankland and Bontempi, 2005). In addition, because the process of memory formation does not occur in isolation but in concert with multiple other modes of cognition, including sensory perception and attentional selection, it is likely that certain principles of neuronal communication are common to these different modes of cognition. For instance, episodic memory involves the binding of multiple elements (e.g., time, place, and multiple physical elements integral to the memory) in the formation of the complete memory trace, much the way perception involves integrating multiple components of sensory information to form a coherent representation. It is possible that similar neuronal mechanisms may underlie both processes.

Non-human primates, including rhesus macaques and other related species, are important models for studying human memory for several reasons. Like humans, monkeys are predominantly visual, in that this is the primary modality utilized to gather information. The pathways that transmit information from the primary visual cortex to the regions essential for memory are remarkably conserved between monkeys and humans. Furthermore, monkeys have demonstrated the ability to remember complex visual stimuli over periods of time comparable to that of humans. In fact, even the quantitative performance (including measures such as reaction time) of monkeys on attentional and working memory tasks is comparable to that of humans (Witte et al., 1996). While recent years have seen an increasing number of electrophysiological studies performed in human epilepsy patients (Abbott, 2009; Engel et al., 2005; Jacobs and Kahana, 2010; Mukamel and Fried, 2012), one advantage of utilizing monkeys as research subjects is the ability to record activity at both the single neuron level and at the field potential level in any target brain region, without the constraint of only recording in clinically relevant areas. There are some challenges: for instance, monkeys do not verbalize their experiences, necessitating alternative strategies to assess memory. These usually involve explicit training in reward-based paradigms, or, alternatively, using more covert measures of memory based on free-viewing paradigms. In addition, there is a lack of direct evidence that monkeys have the capacity for episodic memory, which stores representations of one's own personal past experience, giving rise to the need for tasks which measure specific components thought to be essential for episodic memory function (e.g., associative memory, and the ability to track memories in specific instances of time). However, there is evidence that monkeys can reflect and report on their own memory states (Hampton, 2001) as well as recall information from memory that is not present at the time of testing (Basile and Hampton, 2011), suggesting that monkeys may possess at least some of the memory abilities that were traditionally thought to be specific to humans. Despite the challenges revolving around the use of monkeys as a model of human memory, a comprehensive picture of the brain mechanisms underlying memory formation is beginning to emerge, in large part through research utilizing monkeys as a model to study human memory.

The use of electrophysiology to study memory

Of the many methods employed to study the neural correlates of memory in awake, behaving animals, the use of electrophysiology has provided significant information about the role of the precise activity of neuronal circuits in memory processes. These methods, which utilize measurements obtained from electrodes placed within (or in proximity to) the region of interest, rely on the ability to detect the extracellular voltage fluctuations that result from neural activity. The signals commonly recorded within the brain consist of extracellular spikes, the rapid voltage fluctuations that represent neuronal action potentials, and local field potentials (LFPs), the slower voltage fluctuations that reflect the aggregate activity occurring in an area of surrounding neural tissue. Spikes, which are assigned to the neurons that are in local proximity to the recording electrode, represent rapid, direct communication between neurons, either in the same brain area or in different brain areas. LFPs, on the other hand, reflect a combination of multiple neuronal processes occurring among neurons within several hundred microns to several millimeters of the recording electrode (Kajikawa and Schroeder, 2011), and are thought to be associated with synaptic input to a region (Buchwald et al., 1966; Mitzdorf, 1985, 1987).

Oscillations during cognition represent activity of neural networks

Along with evoked potentials (the averaged LFP response to a stimulus or behavioral event), oscillatory rhythms in the brain are currently a focus of intense investigation. While long recognized as a prominent component of neural signals (Berger, 1929), recent years have seen a growing interest in characterizing neural oscillations and their association with behavior and cognition. During this time, a number of principles related to this association have come to light, many from studies of

neural physiology in monkeys. For example, oscillations in the gamma band, which encompasses frequencies in the approximate range of 30–120 Hz, have been suggested as a potential mechanism for synchronizing the activity of neuronal circuits within and across brain regions in order to promote sensory perception (Tallon-Baudry and Bertrand, 1999) and attention (Fell et al., 2003). By coordinating the formation of functional ensembles of neurons during cognition, activity in this frequency range may thus organize the representation of information in the brain (Engel and Singer, 2001; Fries, 2005; Singer and Gray, 1995; Womelsdorf et al., 2007). In addition, oscillations in the theta band (usually defined between 3 and 10 Hz, but sometimes as high as 12 Hz) are a hallmark of activity measured in the rodent hippocampus and surrounding neocortex (Buzsáki and Draguhn, 2004; Chrobak et al., 2000). The phase of theta-band oscillations not only organizes the firing of individual neurons in a manner that is relevant for spatial navigation (O'Keefe and Recce, 1993), but has also been shown to modulate the amplitude of gamma-band oscillations in rodents (Bragin et al., 1995; Colgin et al., 2009), monkeys (Lakatos et al., 2005), and humans (Canolty et al., 2006), possibly as a way of modulating inter-area communication (Fries, 2009; Jensen and Colgin, 2007).

How might these processes be relevant for memory? Because learning is thought to involve the modification of synaptic connections between neurons following repeated, correlated activation of one neuron by another through these connections, changes in the oscillatory power of field potentials, along with other measures such as phase synchronization, reflect network-level modulations that may be important for memory formation. One way in which gamma-band oscillations may promote these mechanisms is by organizing neuronal firing within a temporal window of approximately 10–20 ms (corresponding to half of a gamma-band cycle), which has been shown to be a critical window for the induction of spike timing-related plasticity (Bi and Poo, 1998; Markram et al., 1997). Enhanced gamma-band LFP power has been associated with successful memory formation in monkeys (Jutras et al., 2009) as well as humans (Sederberg et al., 2007a, 2007b).

Along with changes in the power of hippocampal gamma-band oscillations, enhanced gamma-band phase synchronization in the human (Fell et al., 2001) and monkey (Jutras et al., 2009) MTL has been associated with successful memory formation. Specifically, in Jutras et al. (2009), gamma-band synchrony was measured in the form of enhanced spike-field coherence, which likely reflects enhanced communication among neurons that are part of a functional network. This study used a variant of a recognition memory task, Visual Paired Comparison (VPC), which has consistently been shown to depend on the integrity of the hippocampus in primates (Bachevalier et al., 1993; McKee and Squire, 1993; Pascalis and Bachevalier, 1999; Zola et al., 2000). Primates possess an innate preference for novelty, as evidenced by the increased looking times for novel images presented in the VPC compared to the same images when they are familiar. In the variant used in Jutras et al. (2009), monkeys viewed a series of novel images over two presentations for each image, with a varying number of intervening stimuli between each presentation. Because increased looking times for repeated pictures is generally taken as evidence for forgetting in the VPC task, the images were ranked by the reduction in looking time from the first to the second presentation as a proportion of the initial looking time, with the assumption that this metric represents the strength of the memory. The activity of individual hippocampal neurons as well as hippocampal LFPs was recorded during task performance. Spike-field coherence, which provides a measure of the phase synchronization between spikes and LFPs as a function of frequency, was calculated for groups of images with similar recognition memory performance. Gamma-band coherence across neuron–LFP pairs in the hippocampus was found to be modulated during the initial period of novel image presentation in a manner that was predictive of subsequent recognition; i.e., higher coherence was measured during the encoding of images that were better remembered, as evidenced by a proportionally shorter looking time during the repeat presentation (Figs. 1a–c; Jutras et al., 2009). These results are similar to previous findings in human epilepsy patients, where gamma-band phase synchrony between the hippocampus and rhinal cortex increased over the same time-course, to a similar degree, during successful encoding (Fell et al., 2001). These studies illustrate separate, but similar, instances of gamma-band synchrony in the MTL. Jutras et al. demonstrated that activity of neural ensembles within the hippocampus is coordinated during memory formation, possibly representing communication of neurons involved in the creation of the intra-hippocampal memory trace. Similarly, the results of Fell et al. suggest that gamma-band synchrony also underlies the communication of feedforward and feedback signals between cortical MTL areas and the hippocampus. Together, these findings suggest that, similar to their role in associating elements during perception and attention, gamma-band oscillations in the MTL may promote the association of multiple components of a memory trace during encoding.

Changes in gamma-band power were also observed in the hippocampus during the delay period of a temporal-order memory task (Figs. 1d–e; Naya and Suzuki, 2011). Monkeys were presented with a sequence of two cue stimuli with a short delay between presentations, followed by a response phase in which the two cue stimuli were presented simultaneously with a third distractor stimulus. The monkeys were trained to indicate the order of presentation of the two cue stimuli by touching the cues in sequence while ignoring the distractor. This task elicited changes in multiple aspects of neuronal activity in the MTL, including the hippocampus and entorhinal/perirhinal cortices. These changes included “time cells”, whose firing rates reflected the relative time elapsing between, or order of, cue presentations, as well as “item cells”, which showed selectivity for the cue stimuli themselves. In addition, hippocampal LFPs showed evidence for an incremental timing signal, exhibiting increases in gamma-band power starting during the first cue presentation and persisting through the delay period and into the second cue presentation. Previous work in rodents has provided strong evidence for time-related signals in the hippocampus (Gill et al., 2011; Manns et al., 2007; Pastalkova et al., 2008). The study by Naya and Suzuki (2011) extends these findings to the primate brain, suggesting that the hippocampus provides similar capabilities for tracking temporal information across species, and furthermore that the primate MTL has the ability to integrate time and item information in a manner consistent with the theorized role of these structures in episodic memory (Eichenbaum and Fortin, 2003; Tulving, 2002).

Additional evidence supporting a common role of neural oscillations in memory across primate species comes from a recent study comparing neural activity in humans and monkeys performing an associative memory task (Hargreaves et al., 2012). The task was designed to measure neural activity in the MTL during the learning of new visuomotor associations. Each trial started with the presentation of an image (complex visual scenes for monkeys, and abstract kaleidoscopic images for humans) overlaid with 4 possible targets. After a delay, during which the image disappeared but the four targets remained on the screen, a cue signaled the subject to make a response to the appropriate target, with each image having a specific target consistently associated with it. The association between each stimulus and its corresponding target was learned over the course of multiple repeated presentations for each stimulus–target pair. Previous studies have revealed changes in hippocampal BOLD signals in humans (Law et al., 2005) and in medial temporal single-unit firing activity in monkeys (Wirth et al., 2003; Yanike et al., 2009) that reflect the learning of these visuomotor associations. In Hargreaves et al. (2012), changes in oscillatory power in several brain regions in the monkey were found to mirror changes in BOLD activation in the same areas in the human brain for several aspects of learning and memory, including stimulus novelty/familiarity and associative learning (Fig. 2). Specifically, beta- (10–25 Hz) and gamma-band (30–100 Hz) LFP power in the monkey MTL and BOLD activity in the human MTL were differentially influenced by correct versus

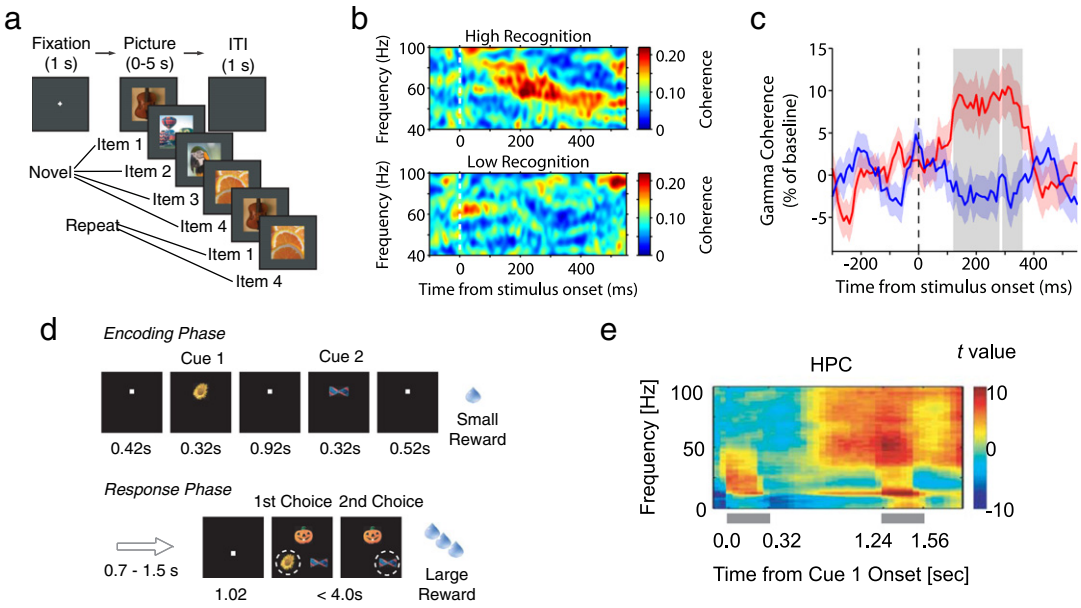

Fig. 1. Hippocampal gamma-band oscillations related to memory. (a) Visual Preferential Looking Task design from Jutras et al. (2009). Two-hundred unique stimuli were presented in each test session, with up to 8 trials intervening between the first and second presentations. Each trial began with a required 1 second fixation period and trials were separated by a 1 second inter-trial interval. (b) Spike-field coherence as a function of time and frequency for an example neuron–LFP pair, for high recognition (top) and low recognition (bottom) trials. Coherence (52–68 Hz) was significantly enhanced during the encoding of subsequently well-recognized stimuli. (c) Gamma-band spike-field coherence expressed as percentage of baseline averaged over 175 hippocampal recording pairs, during high recognition (red) and low recognition (blue) trials, as a function of time from stimulus onset. Red and blue shaded areas represent SEM. Gray shaded area represents time points at which gamma-band coherence was significantly different for the two conditions ($p < 0.01$). (d) Temporal-order task design from Naya and Suzuki (2011). A sequence of two cue stimuli was presented in the encoding phase. The two cue items and one distractor were presented at three different randomly-determined positions in the response phase. Monkeys were rewarded for touching the two cue items in the same temporal order as they were presented in the encoding phase. Dashed circles indicate correct targets. (e) Two-dimensional plot of the population average LFP spectrogram in the hippocampus ($n = 62$). Red pixels indicate time–frequency domains in which activity was stronger than that in the control period (lasting from 150 to 100 ms before cue 1 onset). Blue pixels indicate the opposite pattern. The differential activities were evaluated by t values (paired t test). Gray bars indicate times of cue presentation.

error trials, signals which have previously been attributed to the processes underlying the strengthening of correct associations and modification of incorrect associations during learning (Wirth et al., 2003).

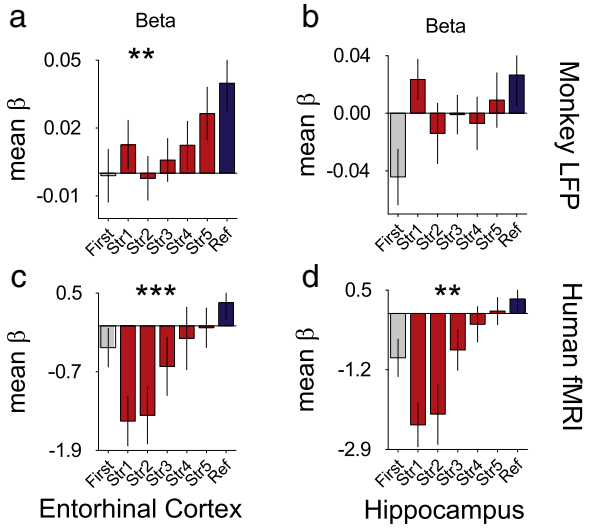

Fig. 2. Learning and immediate novelty signals of the monkey LFP and human fMRI (from Hargreaves et al., 2012). (a) Bar graphs depicting the results of the monkey entorhinal LFP multiple regression analyses comparing mean β values across different learning strengths (red), reference (blue), and initial presentation (gray) trials for the beta-band (10–25 Hz) spectra. (b) Same as (a), but for the monkey hippocampal LFP multiple regression analyses. (c) Results of the human entorhinal fMRI BOLD signal multiple regression analyses comparing mean β values across the different learning strengths (red), reference (blue), and initial presentation (gray) trials. (d) Same as (c), but for the human hippocampal fMRI BOLD signal multiple regression analyses. $^{**}p < 0.01$, $^{***}p < 0.0005$.

Neural activity was also modulated by the relative novelty and familiarity of task and reference stimuli. The latter finding is consistent with previous studies showing that the human MTL differentiates between novel and familiar stimuli during memory encoding and retrieval (Rutishauser et al., 2006; Schacter and Wagner, 1999), and with a previous study of hippocampal activity in monkeys (Jutras and Buffalo, 2010). Previous work in monkeys has also shown that the fMRI BOLD signal is correlated with higher gamma-band power in the LFP in the visual cortex (Logothetis et al., 2001). While it is unknown whether this principle applies to neural activity measured in the medial temporal lobe, it is possible that the medial temporal BOLD activation seen in memory studies indicates changes in oscillatory power in these brain regions; further studies exploring this hypothesis in non-human primates would be illuminating.

Network oscillations in the hippocampus may also emerge in the form of high frequency oscillations, or ripples, that are approximately 130–200 Hz in frequency and 50–100 ms in duration. In rodents, these oscillations, along with associated sharp waves, represent periods of time during which synchrony among hippocampal pyramidal neurons is at its highest (Buzsáki, 1989; Buzsàki et al., 1989). They are seen most frequently during periods of sleep or quiet wakefulness after periods of activity, and are associated with the reactivation of ensembles of hippocampal neurons that were active during the active period (Kudrimoti et al., 1999; Wilson and McNaughton, 1994). Because of this, hippocampal ripples are thought to reflect the coordinated firing of neurons involved with "replaying" a previously-encoded memory trace; this replaying of memory traces is an important component of prominent theories of memory consolidation in hippocampal–cortical networks (Frankland and Bontempi, 2005). Importantly, intracranial recordings from monkeys provide evidence that similar activity exists in the primate brain, and most likely promotes memory consolidation in a similar fashion. For example, electrophysiological recordings in multiple cortical regions (posterior parietal, motor, and somatosensory

cortices) in monkeys revealed the emergence of coordinated neural activity across distributed neural networks following a sequential reaching task (Hoffman and McNaughton, 2002). This activity represented the reactivation of previously coactive neural sequences, such that firing sequences that occurred among neurons that were co-active during task performance showed a tendency to re-emerge during the post-task rest period. More recently, multiple recordings were made in the monkey hippocampus to compare patterns of neural activity to those seen in rodent hippocampus during memory task performance and the following, behaviorally quiescent period (Skaggs et al., 2007). Similar to rodents, the primate hippocampus was found to exhibit sharp wave/ripple activity during periods of inactivity which, while seemingly less frequent than those appearing in rodents, show similar structure, location specificity, and behavioral correlates. Furthermore, these sharp waves coincided with higher firing rates of CA3 and CA1 neurons, as they do in rodents. Taken together, these results provide

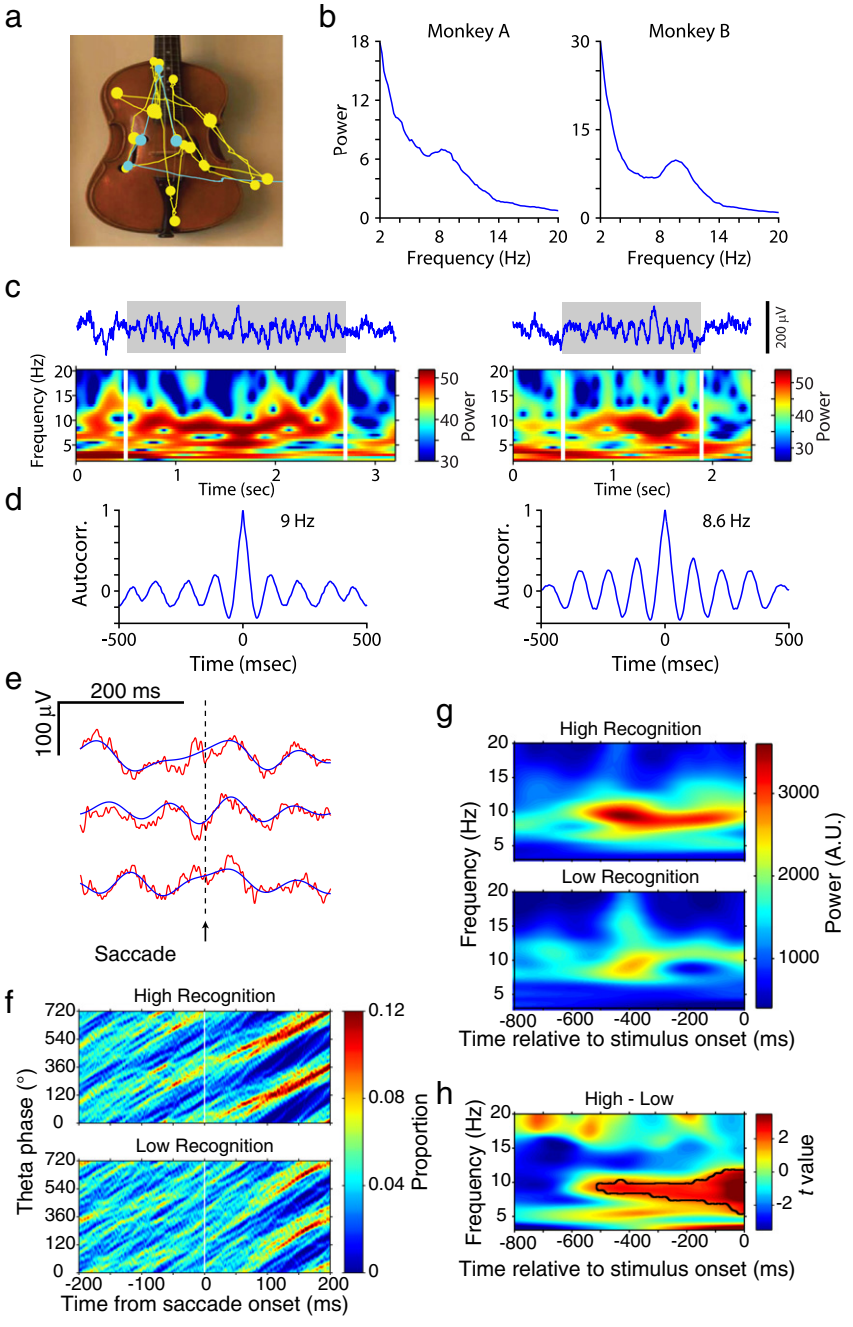

Fig. 3. Theta oscillations in the monkey hippocampus (from Jutras et al., 2013). (a) A representative example of one monkey's scan path from the Visual Preferential Looking Task, showing that the monkey spent more time looking at the image when it was novel (yellow) compared to when it was repeated (blue). Circles represent points of fixation between saccades, with the size of each circle proportional to the duration of the fixation period. (b) Power spectra for two example LFP channels across all VPLT blocks, showing peaks around 8–11 Hz. (c) Examples of theta bouts during VPLT performance. For each example, the theta bout in the raw LFP is marked by a gray square, and the power spectrogram of the LFP signal is presented below. (d) Autocorrelograms of each example LFP shown in (c), during the theta bout. (e) Raw (red) and theta (3–12 Hz) filtered segments (blue) from an example LFP, showing reset to a consistent phase following saccade onset. (f) Phase concentration for the 400-ms period centered on saccade onset for High and Low Recognition conditions, for an example LFP. (g) Power spectrograms from one example LFP, during the 800 ms time period immediately preceding stimulus presentation. (h) Modulation of theta power for High and Low Recognition trials across 114 LFPs. The area of significant power modulation across conditions is outlined in black.

evidence for a common neuronal mechanism across mammalian species underlying memory reactivation processes, possibly in the service of consolidation.

While well-characterized in the rodent hippocampus and entorhinal cortex, theta-band oscillations in the primate, along with their potential role in behavior and cognition, are much less well understood. Due to the association of theta-band activity in rodents with exploration and translation through space (Vanderwolf, 1969), the functions attributed to theta are usually tied to spatial navigation and memory (Buzsáki, 2005). However, while there are reports of theta oscillations in the human hippocampus (Ekstrom et al., 2005; Ekstrom et al., 2009; Lega et al., 2011), the story is complicated by a seeming lack of sustained theta oscillations in the electrical signal measured in the hippocampus of awake monkeys. This discrepancy has been attributed to the fact that recording methods in monkeys typically require immobile, head-affixed animals, in contrast to rodent studies using freely-moving animals (Skaggs et al., 2007). However, a recent study revealed the presence of theta in the hippocampus of bats as they explore their environment through echolocation, without locomotion (Ulanovsky and Moss, 2007). It may therefore be possible to address this discrepancy by considering the degree to which primates and rodents differ in their behaviors during exploration: while rodents generally rely on olfactory and somatosensory mechanisms to take in information about the proximal environment, primates mainly use eye movements to gather information about the surrounding visual world during exploration. Evidence for a close temporal relationship between hippocampal theta oscillations and running (McFarland et al., 1975), sniffing (Macrides et al., 1982), and whisking (Komisaruk, 1970; but see Berg et al., 2006) in the rodent suggests that in the primate, theta-like activity may occur in close association with visual exploration. This is consistent with recent theories concerning the relationship between motor behaviors associated with information gathering and "active sensing" processes in natural behavior (Schroeder et al., 2010), as well as recent evidence from rodents suggesting that multiple motor systems may coordinate their activity in the theta frequency range during exploration (Ranade et al., 2013).

A recent study revealed a link between theta-band LFP activity in the monkey hippocampus and saccadic eye movements (Jutras et al., 2013). Hippocampal LFPs exhibited theta-band oscillatory activity as monkeys freely explored novel images (Figs. 3a–d), and these oscillations underwent a phase reset with each saccade, similar to the theta phase reset seen in the hippocampus of rodents (Givens, 1996; Williams and Givens, 2003) and humans (Mormann et al., 2005; Rizzuto et al., 2003; Tesche and Karhu, 2000) with stimulus events during performance of memory tasks (Fig. 3e). In addition, the consistency of this phase reset was correlated with the strength of the memory, such that the post-saccade phase was more reliable when pictures were well remembered than when pictures were poorly remembered (Fig. 3f). This suggests that, like the visual cortex (Rajkai et al., 2008), the hippocampus goes from a "random" to a more "organized" state upon fixation onset to promote the successful processing (here, encoding) of sensory information. Because mechanisms of synaptic plasticity in the hippocampus, such as the induction of long-term potentiation, are preferential for particular phases of theta, as has been demonstrated in rodent hippocampus (Holscher et al., 1997; Huerta and Lisman, 1993, 1995; Hyman et al., 2003; McCartney et al., 2004), this finding has important implications for understanding the mechanisms of memory formation during exploration in primates. Along with these findings, pre-stimulus modulations in theta-band power were found to predict the strength of memory encoding; specifically, theta power was higher during the baseline fixation period preceding novel image presentation for stimuli that were later well remembered than for stimuli that were poorly remembered (Figs. 3g–h; Jutras et al., 2013). These results are in agreement with similar findings in the human medial temporal lobe (Addante et al., 2011; Fell et al., 2011; Guderian et al., 2009) and suggest that theta oscillations may provide a mechanism to bring the hippocampus into an "online" state (Buzsáki, 2002) in anticipation of the encoding of novel stimuli.

Conclusions

In conclusion, recent research in non-human primates has provided a way to bridge studies of memory-related signals from rodents to humans. In particular, recent studies of oscillatory activity have increased our understanding of how this activity may play a role in mediating and promoting the neuronal interactions underlying memory formation: encoding, retrieval, and consolidation. These studies, which have demonstrated changes in medial temporal lobe activity across multiple frequency ranges associated with memory encoding, stimulus novelty and familiarity, associative learning, temporal resolution, and memory reactivation, provide evidence that neural oscillations may influence interactions among neurons during learning to promote the formation of functional networks that may later be reactivated during retrieval or consolidation. Future studies of such phenomena in the non-human primate may further identify patterns of activity that, while homologous to neural activity described in the rodent brain, are closely linked to primate-specific behaviors, leading to a more comprehensive picture of the neural mechanisms specific to primate, and in particular human, memory ability.

Acknowledgments

Supported by grants from the National Institute of Mental Health, MH080007 and MH093807 (E.A.B.), and the National Center for Research Resources P51RR165 (currently the Office of Research Infrastructure Programs/OD P51OD11132).

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

References

Abbott, A., 2009. Neuroscience: opening up brain surgery. Nature 461, 866–868.
Addante, R.J., Watrous, A.J., Yonelinas, A.P., Ekstrom, A.D., Ranganath, C., 2011. Prestimulus theta activity predicts correct source memory retrieval. Proc. Natl. Acad. Sci. U. S. A. 108, 10702–10707.
Bachevalier, J., Brickson, M., Hagger, C., 1993. Limbic-dependent recognition memory in monkeys develops early in infancy. Neuroreport 4, 77–80.
Basile, Benjamin M., Hampton, Robert R., 2011. Monkeys recall and reproduce simple shapes from memory. Curr. Biol. 21, 774–778.
Berg, R.W., Whitmer, D., Kleinfeld, D., 2006. Exploratory whisking by rat is not phase locked to the hippocampal theta rhythm. J. Neurosci. 26, 6518–6522.
Berger, H., 1929. Über das Elektrenkephalogramm des Menschen. Arch. Psychiatr. Nervenkr. 87, 527–570.
Bi, G.Q., Poo, M.M., 1998. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. J. Neurosci. 18, 10464–10472.
Bragin, A., Jando, G., Nadasdy, Z., Hetke, J., Wise, K., Buzsaki, G., 1995. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. J. Neurosci. 15, 47–60.
Buchwald, J.S., Halas, E.S., Schramm, S., 1966. Relationships of neuronal spike populations and EEG activity in chronic cats. Electroencephalogr. Clin. Neurophysiol. 21, 227–238.
Buzsáki, G., 1989. Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31, 551–570.
Buzsáki, G., 2002. Theta oscillations in the hippocampus. Neuron 33, 325–340.
Buzsáki, G., 2005. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. Hippocampus 15, 827–840.
Buzsáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. Science 304, 1926–1929.
Buzsàki, G., Bickford, R.G., Ryan, L.J., Young, S., Prohaska, O., Mandel, R.J., Gage, F.H., 1989. Multisite recording of brain field potentials and unit activity in freely moving rats. J. Neurosci. Methods 28, 209–217.
Canolty, R.T., Edwards, E., Dalal, S.S., Soltani, M., Nagarajan, S.S., Kirsch, H.E., Berger, M.S., Barbaro, N.M., Knight, R.T., 2006. High gamma power is phase-locked to theta oscillations in human neocortex. Science 313, 1626–1628.
Chrobak, J.J., Lörincz, A., Buzsáki, G., 2000. Physiological patterns in the hippocampo-entorhinal cortex system. Hippocampus 10, 457–465.

Colgin, L.L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.B., Moser, E.I., 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462, 353–357.
Damasio, A.R., 1989. Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. Cognition 33, 25–62.
Eichenbaum, H., 1997. Declarative memory: insights from cognitive neurobiology. Annu. Rev. Psychol. 48, 547–572.
Eichenbaum, H., Fortin, N., 2003. Episodic memory and the hippocampus: it's about time. Curr. Dir. Psychol. Sci. 12, 53–57.
Ekstrom, A.D., Caplan, J.B., Ho, E., Shattuck, K., Fried, I., Kahana, M.J., 2005. Human hippocampal theta activity during virtual navigation. Hippocampus 15, 881–889.
Ekstrom, A., Suthana, N., Millett, D., Fried, I., Bookheimer, S., 2009. Correlation between BOLD fMRI and theta-band local field potentials in the human hippocampal area. J. Neurophysiol. 101, 2668–2678.
Engel, A.K., Singer, W., 2001. Temporal binding and the neural correlates of sensory awareness. Trends Cogn. Sci. 5, 16.
Engel, A.K., Moll, C.K.E., Fried, I., Ojemann, G.A., 2005. Invasive recordings from the human brain: clinical insights and beyond. Nat. Rev. Neurosci. 6, 35–47.
Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Schaller, C., Elger, C.E., Fernandez, G., 2001. Human memory formation is accompanied by rhinal–hippocampal coupling and decoupling. Nat. Neurosci. 4, 1259–1264.
Fell, J., Fernandez, G., Klaver, P., Elger, C.E., Fries, P., 2003. Is synchronized neuronal gamma activity relevant for selective attention? Brain Res. Brain Res. Rev. 42, 265–272.
Fell, J., Ludowig, E., Staresina, B.P., Wagner, T., Kranz, T., Elger, C.E., Axmacher, N., 2011. Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J. Neurosci. 31, 5392–5397.
Frankland, P.W., Bontempi, B., 2005. The organization of recent and remote memories. Nat. Rev. Neurosci. 6, 119–130.
Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9, 474–480.
Fries, P., 2009. The model- and the data-gamma. Neuron 64, 601–602.
Gill, P.R., Mizumori, S.J.Y., Smith, D.M., 2011. Hippocampal episode fields develop with learning. Hippocampus 21, 1240–1249.
Givens, B., 1996. Stimulus-evoked resetting of the dentate theta rhythm: relation to working memory. Neuroreport 8, 159–163.
Guderian, S., Schott, B.H., Richardson-Klavehn, A., Duzel, E., 2009. Medial temporal theta state before an event predicts episodic encoding success in humans. Proc. Natl. Acad. Sci. U. S. A. 106, 5365–5370.
Hampton, R.R., 2001. Rhesus monkeys know when they remember. Proc. Natl. Acad. Sci. 98, 5359–5362.
Hargreaves, Eric L., Mattfeld, Aaron T., Stark, Craig E.L., Suzuki, Wendy A., 2012. Conserved fMRI and LFP signals during new associative learning in the human and macaque monkey medial temporal lobe. Neuron 74, 743–752.
Hoffman, K.L., McNaughton, B.L., 2002. Coordinated reactivation of distributed memory traces in primate neocortex. Science 297, 2070–2073.
Holscher, C., Anwyl, R., Rowan, M.J., 1997. Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. J. Neurosci. 17, 6470–6477.
Huerta, P.T., Lisman, J.E., 1993. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 364, 723–725.
Huerta, P.T., Lisman, J.E., 1995. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 15, 1053–1063.
Hyman, J.M., Wyble, B.P., Goyal, V., Rossi, C.A., Hasselmo, M.E., 2003. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J. Neurosci. 23, 11725–11731.
Jacobs, J., Kahana, M.J., 2010. Direct brain recordings fuel advances in cognitive electrophysiology. Trends Cogn. Sci. 14, 162–171.
Jensen, O., Colgin, L.L., 2007. Cross-frequency coupling between neuronal oscillations. Trends Cogn. Sci. 11, 267–269.
Jutras, M.J., Buffalo, E.A., 2010. Recognition memory signals in the macaque hippocampus. Proc. Natl. Acad. Sci. U. S. A. 107, 401–406.
Jutras, M.J., Fries, P., Buffalo, E.A., 2009. Gamma-band synchronization in the macaque hippocampus and memory formation. J. Neurosci. 29, 12521–12531.
Jutras, M.J., Fries, P., Buffalo, E.A., 2013. Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. Proc. Natl. Acad. Sci. U. S. A. http://dx.doi.org/10.1073/pnas.1302351110 (Epub ahead of print 22 July 2013).
Kajikawa, Y., Schroeder, Charles E., 2011. How local is the local field potential? Neuron 72, 847–858.
Komisaruk, B.R., 1970. Synchrony between limbic system theta activity and rhythmical behavior in rats. J. Comp. Physiol. Psychol. 70, 482–492.
Kudrimoti, H.S., Barnes, C.A., McNaughton, B.L., 1999. Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J. Neurosci. 19, 4090–4101.
Lakatos, P., Shah, A.S., Knuth, K.H., Ulbert, I., Karmos, G., Schroeder, C.E., 2005. An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. J. Neurophysiol. 94, 1904–1911.
Law, J.R., Flanery, M.A., Wirth, S., Yanike, M., Smith, A.C., Frank, L.M., Suzuki, W.A., Brown, E.N., Stark, C.E.L., 2005. Functional magnetic resonance imaging activity during the gradual acquisition and expression of paired-associate memory. J. Neurosci. 25, 5720–5729.
Lega, B.C., Jacobs, J., Kahana, M., 2011. Human hippocampal theta oscillations and the formation of episodic memories. Hippocampus 22, 748–761.
Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412, 150–157.
Macrides, F., Eichenbaum, H.B., Forbes, W.B., 1982. Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. J. Neurosci. 2, 1705–1717.
Manns, J.R., Howard, M.W., Eichenbaum, H., 2007. Gradual changes in hippocampal activity support remembering the order of events. Neuron 56, 530–540.
Markram, H., Lubke, J., Frotscher, M., Sakmann, B., 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275, 213–215.
McCartney, H., Johnson, A.D., Weil, Z.M., Givens, B., 2004. Theta reset produces optimal conditions for long-term potentiation. Hippocampus 14, 684–687.
McClelland, J.L., McNaughton, B.L., O'Reilly, R.C., 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol. Rev. 102, 419–457.
McFarland, W.L., Teitelbaum, H., Hedges, E.K., 1975. Relationship between hippocampal theta activity and running speed in the rat. J. Comp. Physiol. Psychol. 88, 324–328.
McKee, R.D., Squire, L.R., 1993. On the development of declarative memory. J. Exp. Psychol. Learn. Mem. Cogn. 19, 397–404.
Mishkin, M., 1982. A memory system in the monkey. Philos. Trans. R. Soc. Lond. B Biol. Sci. 298, 83–95.
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.
Mitzdorf, U., 1987. Properties of the evoked potential generators: current source-density analysis of visually evoked potentials in the cat cortex. Int. J. Neurosci. 33, 33–59.
Mormann, F., Fell, J., Axmacher, N., Weber, B., Lehnertz, K., Elger, C.E., Fernández, G., 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.
Mukamel, R., Fried, I., 2012. Human intracranial recordings and cognitive neuroscience. Annu. Rev. Psychol. 63, 511–537.
Nadel, L., Moscovitch, M., 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr. Opin. Neurobiol. 7, 217–227.
Naya, Y., Suzuki, W.A., 2011. Integrating what and when across the primate medial temporal lobe. Science 333, 773–776.
O'Keefe, J., Recce, M.L., 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3, 317–330.
Pascalis, O., Bachevalier, J., 1999. Neonatal aspiration lesions of the hippocampal formation impair visual recognition memory when assessed by paired-comparison task but not by delayed nonmatching-to-sample task. Hippocampus 9, 609–616.
Pastalkova, E., Itskov, V., Amarasingham, A., Buzsáki, G., 2008. Internally generated cell assembly sequences in the rat hippocampus. Science 321, 1322–1327.
Rajkai, C., Lakatos, P., Chen, C.-M., Pincze, Z., Karmos, G., Schroeder, C.E., 2008. Transient cortical excitation at the onset of visual fixation. Cereb. Cortex 18, 200–209.
Ranade, S., Hangya, Kepecs, A., 2013. Multiple modes of phase locking between sniffing and whisking during active exploration. J. Neurosci. 33, 8250–8256.
Rizzuto, D.S., Madsen, J.R., Bromfield, E.B., Schulze-Bonhage, A., Seelig, D., Aschenbrenner-Scheibe, R., Kahana, M.J., 2003. Reset of human neocortical oscillations during a working memory task. Proc. Natl. Acad. Sci. U. S. A. 100, 7931–7936.
Rolls, E.T., Treves, A., 1994. Neural networks in the brain involved in memory and recall. In: Van Pelt, J., M.A.C.H.B.M.U., Silva, F.H.L.D. (Eds.), Progress in Brain Research. Elsevier, pp. 335–341.
Rutishauser, U., Mamelak, A.N., Schuman, E.M., 2006. Single-trial learning of novel stimuli by individual neurons of the human hippocampus–amygdala complex. Neuron 49, 805–813.
Schacter, D.L., Tulving, E., 1994. What are the memory systems of 1994? In: Schacter, D.L., Tulving, E. (Eds.), Memory Systems 1994. MIT Press, Cambridge, MA, pp. 1–38.
Schacter, D.L., Wagner, A.D., 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9, 7–24.
Schroeder, C.E., Wilson, D.A., Radman, T., Scharfman, H., Lakatos, P., 2010. Dynamics of active sensing and perceptual selection. Curr. Opin. Neurobiol. 20, 172–176.
Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurochem. 20, 11–21.
Sederberg, P.B., Schulze-Bonhage, A., Madsen, J.R., Bromfield, E.B., Litt, B., Brandt, A., Kahana, M.J., 2007a. Gamma oscillations distinguish true from false memories. Psychol. Sci. 18, 927–932.
Sederberg, P.B., Schulze-Bonhage, A., Madsen, J.R., Bromfield, E.B., McCarthy, D.C., Brandt, A., Tully, M.S., Kahana, M.J., 2007b. Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cereb. Cortex 17, 1190–1196.
Singer, W., Gray, C.M., 1995. Visual feature integration and the temporal correlation hypothesis. Annu. Rev. Neurosci. 18, 555–586.
Skaggs, W.E., McNaughton, B.L., Permenter, M., Archibeque, M., Vogt, J., Amaral, D.G., Barnes, C.A., 2007. EEG sharp waves and sparse ensemble unit activity in the macaque hippocampus. J. Neurophysiol. 98, 898–910.
Squire, L.R., Alvarez, P., 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol. 5, 169–177.
Squire, L.R., Zola-Morgan, S.M., 1983. The neurology of memory: the case for correspondence between the findings for human and nonhuman primate. In: Deutsch, J.A. (Ed.), The Physiological Basis of Memory. Academic Press, New York.
Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. Science 253, 1380–1386.
Squire, L.R., Stark, C.E.L., Clark, R.E., 2004. The medial temporal lobe. Annu. Rev. Neurosci. 27, 279–306.
Tallon-Baudry, C., Bertrand, O., 1999. Oscillatory gamma activity in humans and its role in object representation. Trends Cogn. Sci. 3, 151–162.
Tesche, C.D., Karhu, J., 2000. Theta oscillations index human hippocampal activation during a working memory task. Proc. Natl. Acad. Sci. U. S. A. 97, 919–924.

Tulving, E., 2002. Episodic memory: from mind to brain. Annu. Rev. Psychol. 53, 1–25.
Ulanovsky, N., Moss, C.F., 2007. Hippocampal cellular and network activity in freely moving echolocating bats. Nat. Neurosci. 10, 224–233.
Vanderwolf, C.H., 1969. Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr. Clin. Neurophysiol. 26, 407–418.
Williams, J.M., Givens, B., 2003. Stimulation-induced reset of hippocampal theta in the freely performing rat. Hippocampus 13, 109–116.
Wilson, M.A., McNaughton, B.L., 1994. Reactivation of hippocampal ensemble memories during sleep. Science 265, 676–679.
Wirth, S., Yanike, M., Frank, L.M., Smith, A.C., Brown, E.N., Suzuki, W.A., 2003. Single neurons in the monkey hippocampus and learning of new associations. Science 300, 1578–1581.
Witte, E.A., Villareal, M., Marrocco, R.T., 1996. Visual orienting and alerting in rhesus monkeys: comparison with humans. Behav. Brain Res. 82, 103–112.
Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., Fries, P., 2007. Modulation of neuronal interactions through neuronal synchronization. Science 316, 1609–1612.
Yanike, M., Wirth, S., Smith, A.C., Brown, E.N., Suzuki, W.A., 2009. Comparison of associative learning-related signals in the macaque perirhinal cortex and hippocampus. Cereb. Cortex 19, 1064–1078.
Zola, S.M., Squire, L.R., Teng, E., Stefanacci, L., Buffalo, E.A., Clark, R.E., 2000. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J. Neurosci. 20, 451–463.