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Brain oscillations and memory

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Oscillatory fluctuations of local field potentials (LFPs) in the theta (4–8 Hz) and gamma (25–140 Hz) band are held to play a mechanistic role in various aspects of memory including the representation and off-line maintenance of events and sequences of events, the assessment of novelty, the induction of plasticity during encoding, as well as the consolidation and the retrieval of stored memories. Recent findings indicate that theta and gamma related mechanisms identified in rodent studies have significant parallels in the neurophysiology of human and non-human primate memory. This correspondence between species opens new perspectives for a mechanistic investigation of human memory function.

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Oscillations in the theta and gamma range can be measured at different anatomical scales, ranging from invasive recordings of small neuronal populations in animals (e.g. [1^{••},2]) and humans (e.g. [3–5]) to non-invasive recordings of large cortical assemblies from the surface of the scalp using electroencephalography (EEG) and magnetoencephalography (MEG) (e.g. [6–14]). Both types of oscillation, and the phase relationships between them (e.g. [15–17,18^{••},19,20]), appear to contribute to memory-relevant coding of information ranging from objects (e.g. [21^{••}]) to environmental locations (e.g. [1^{••}]). In addition, theta and gamma oscillations may help to coordinate the interactions between regions required by some mnemonic processing (e.g. [18^{••},22–24]) while high frequency ‘ripples’ in the hippocampus may contribute to consolidation (e.g. [25–28]). Furthermore, by

regulating the precise timing of presynaptic and postsynaptic neurons, theta and gamma oscillations also modulate spike-time dependent plasticity [29], a prerequisite for both short-term and long-term memory processes.

Rhythmic activity in the rodent hippocampal formation underlying spatial representation, memory and consolidation

The systems neurophysiology underlying brain oscillations and their relationship to memory has been extensively studied using chronically implanted electrodes in freely moving rodents. In this research there has been a focus on the hippocampal formation, because of its central role in memory, and also a focus on spatial representation, because of the interesting spatial correlates of neural firing found in and around the hippocampus, such as the ‘place cells’ (e.g. [28]).

The theta rhythm and spatial representation

In freely moving rodents, the hippocampal LFP is dominated by the theta rhythm whenever the animal is in translational motion. This motion-related theta rhythm increases in frequency with both age and running speed, falling into a range from around 5 Hz to around 11 Hz. During motion, power is also seen sporadically in the gamma frequency band, with high (60–140 Hz) and low (25–50 Hz) frequency gamma being associated with different phases of theta [18^{••}]. During immobility the LFP shows ‘large irregular activity’ characterized by the appearance of high frequency (200 Hz) ‘ripples’ or ‘sharp waves’ (See [15,28] for reviews). Interestingly, there are signs that human spatial navigation in virtual environments is also accompanied by the presence of theta rhythmicity in intracranial recordings (e.g. [3]) and MEG [12].

The hippocampal theta rhythm depends on a circuit including the medial septum, hippocampus and entorhinal cortex and the projections between them. Lesions to the medial septum both abolish movement related theta and impair spatial memory while generators of theta are also present in the hippocampus and entorhinal cortex (see [15,28] for reviews). Consistent with the dominant role of theta, the firing of the majority of neurons in the hippocampal formation is modulated in the theta band. However, the firing of hippocampal place cells shows a systematic phase relationship to the LFP theta rhythm. Individual place cells fire whenever the animal enters a specific part of its environment, so that together the place cells encode the location of the animal relative to its environment. However, the firing of place cells is modulated at a slightly higher frequency than the LFP theta

frequency so that their firing phase shifts from late to early phases as the animal moves through the firing field [1**]. This ‘theta phase precession’ provides a phase code for location, independent of the firing rate code which also codes for location, but can be modulated by other factors such as the objects, odors or actions occurring at the location of the firing field [2].

Theta phase precession has also been observed in the firing of ‘grid cells’ in the medial entorhinal cortex [30] – one of the main neocortical inputs to the hippocampus. It is possible that the regular spatial firing pattern of grid cells [31] results from interference between theta band membrane potential oscillations [32,33], and that the increase in theta frequency with running speed relates to the temporal firing pattern of these cells [34]. Interestingly, there is evidence that similar spatial representations exist in human entorhinal cortex, and that they contribute to spatial memory performance in virtual environments [35].

Oscillatory coordination of processing in multiple regions

As well as providing a phase code for location within the hippocampal formation, hippocampal theta also appears to coordinate activity in other regions during the performance of spatial tasks by rats. Thus, during spatial memory tasks, theta activity coherent with that in hippocampus is seen in prefrontal cortex [23,36,37] and in ventral striatum [38].

The high and low frequency gamma in CA1 that occurs at specific phases of theta may coordinate flows of information within the hippocampal formation [18**]: high frequency gamma in CA1 is synchronized with high frequency gamma in entorhinal cortex while low frequency gamma in CA1 is synchronized with low frequency gamma in CA3. Thus the inputs to CA1 from memory-related recurrent processing in CA3 may occur at one phase of theta and be characterized by low frequency gamma coherence, while sensory-related input from entorhinal cortex may occur at a different phase of theta and be characterized by high frequency gamma. This would be consistent with the idea that CA1 acts as a novelty detector (by comparing mnemonic and perceptual information (e.g. [19,39]), and with the idea that encoding and retrieval occur at different phases of the theta rhythm [40]. It also supports the idea that theta and gamma oscillations in the hippocampal formation work together to support memory [20]. Interestingly, there is evidence from intracranial recordings in humans, that phase coherence between rhinal (i.e. entorhinal and perirhinal) and hippocampal cortices in both gamma and theta bands is predictive of subsequent memory performance [4,41], see below.

Oscillatory coordination of reactivation/consolidation

It has long been thought that episodic information might be rapidly stored within the recurrent connections of

hippocampal region CA3 and then incorporated into neocortical stores of long-term semantic memory [42]. One specific proposed mechanism is that the information encoded during motion-related theta is transmitted to neocortex by the coherent spiking of large populations of hippocampal neurons during the sharp waves/ripples occurring during subsequent immobility and slow wave sleep, reviewed in [43]. Much subsequent research has been consistent with this hypothesis: the activation patterns of populations of place cells seen during awake movement through an environment appear to be reiterated on a faster timescale during the ripples/sharp wave complexes of slow wave sleep (e.g. [25,26]). During periods of awake immobility, it is possible to observe both forward ‘preplay’ of the place cell representation of upcoming locations and backward replay of recently visited locations during ripple/sharp wave complexes (e.g. [27,44]). Recent experiments have shown that selective disruption of sharp wave/ripple complexes following training in a spatial memory task impairs learning in rats (e.g. [45]). In addition, there is evidence from intracranial recording in humans that ripple-like oscillations at 80–140 Hz occur in both hippocampal and rhinal cortices, and that the number recorded during resting (but not necessarily sleeping) after encoding lists of pictures correlates with subsequent memory for the pictures [46].

Brain oscillations and memory maintenance

Active short-term maintenance

Active short-term maintenance allows information from transient events to persist in the brain as active representations. This enables goal-directed decision making and learning to utilize and manipulate information beyond its transient sensory availability. Slow oscillations in the delta (1–3 Hz) and theta as well as faster oscillations in the beta (12–25 Hz) and gamma ranges have been associated with two major contributions during maintenance; coordinating distributed cortical representations [14] and representing encoded stimuli and their sequence of occurrence [21].

Theta networks of maintenance

Patients with bilateral hippocampal lesions are impaired in their ability to maintain associative forms of information even over short delays of a few seconds, while performing normally for non-associative information. After a brief presentation of a scene, for example, these patients are unable to keep in mind the configural/relational association of multiple features in the scene even for very short periods of just a few seconds (e.g. [14,47]). A recent MEG study showed that theta-synchrony between occipital and temporal brain regions accompanied maintenance of configural/relational (CR) information about photographs depicting natural indoor or outdoor scenes, and was absent in patients with bilateral hippocampal sclerosis [14]. Occipito-temporal theta-synchrony may indicate the coordination of cortical representations along the visual ventral stream processing hierarchy, integrating anterior repres-

entations of complex conjunctions of scene elements with more posterior representations of the component features. This study is consistent with the coordination of cortical activity by hippocampal theta seen in rodents [22,23,36] and with the observation that neural firing of visual area V4 in monkeys is patterned by the local theta phase during delay maintenance of images [24].

Stimulus coding and replay during maintenance

The maintenance of sequential information by hippocampal theta and gamma oscillations has been a focus of some computational approaches [20]. Specifically, groups of neurons that represent single items may fire on each theta cycle, but only in a given gamma subcycle. During maintenance, sequential items are active in sequential gamma subcycles, thereby encoding sequence order and achieving a temporal compression of the naturally occurring timing of item separation into one that is suitable for active maintenance. This model is intriguing because the timing and interaction of theta and gamma cycles may capture behavioral properties of short-term memory such as its limited capacity.

Evidence that oscillatory synchrony mediates a phase-dependent coding of items during maintenance comes from recent studies in non-human primates [21^{••},24]. In one study [21^{••}] monkeys were required to maintain both the identity and the order of two objects over a delay of 1 s. There was prefrontal spike-LFP synchronization at 32 Hz during the delay interval. This synchronization improved object decoding compared to spike-rate alone. Also, maximal information in spikes about the identity of the first presented object was found in an earlier phase of the 32 Hz LFP cycle than information about the second object. This was accompanied by a significant modulation of the amplitude of 32 Hz oscillations by the phase of delta (3 Hz) oscillations.

In humans, the active maintenance of single item non-configural visual information enhances theta-synchrony between right frontal and parietal regions (e.g. [14,48]). As expected, given that there is no sequence learning involved, this network is functionally intact in patients with bilateral hippocampal sclerosis [14]. Increasing the number of items to be retained during maintenance, without requiring sequence memory, appears to be associated with increased theta-coupling of bilateral frontal and temporal regions [14,49] as well as regions in the visual ventral processing hierarchy [50]. Gamma oscillations have also been implicated in nonconfigural delay maintenance in humans [51,52,53] and delayed-response tasks in non-human primates [54], and theta-gamma coherence has been correlated with successful nonconfigural maintenance [55^{*}]. More recently, hippocampal theta-gamma coupling has also been related to non-configural multi-item maintenance in humans [56]. However, it is currently unclear whether nonconfigural high load maintenance,

and the cortical theta and gamma oscillations that accompany it are compromised by bilateral hippocampal lesions in humans when sequence memory is required.

Theta-coupled replay during maintenance

The investigation of phase-coupled representation, or replay, of object-information during maintenance has been recently boosted by the application of multivariate pattern classifier (MVPC) decoding algorithms to EEG/MEG (e.g. [57]). This could potentially enable non-invasive decoding of large-scale neural activity with high temporal resolution. In one MEG study, MVPC analysis detected replay of encoded stimulus features during maintenance [57]. Replay was specific to whether the maintained stimulus depicted an indoor or an outdoor scene and whether maintenance centred on configural associations of scene elements or just single scene elements. The periodicity of replay events was phase-coupled to theta oscillations and correlated with the ability to identify the matching image at the end of configural maintenance [57]. These findings, together with data from invasive recordings in humans showing that neuronal spiking tends to be phase-locked to specific phases of delta, theta and gamma oscillations [5], are compatible with a role of oscillations in active maintenance [20,21^{••}].

Theta-coupled periodic replay is likely to interact with another neural mechanism of active maintenance which cannot be directly measured using MEG or scalp EEG, namely the persistence of neural firing from stimulus processing into maintenance. Persistent firing has been observed in medial temporal, prefrontal and parietal regions (for a discussion see [58]). It is possible that persistent firing and theta periodic activity could interact to sustain each other [58]. Through such interaction, persistent firing coding multimodal stimulus-attributes [59], or task-related information such as goals and cognitive control signals, could sustain periodic replay of stimulus-specific information. An interesting avenue to study this interaction during maintenance in humans would be to combine recordings of slow-potentials or DC-potentials [60] with analyses of oscillatory rhythms.

Brain oscillations and novelty, memory encoding and retrieval

The aforementioned observations in rodent studies that theta states modulate long-term plasticity have two interesting implications. First, the baseline theta state present when a stimulus is encountered may affect stimulus encoding and second, contextual aspects of the encounter such as novelty may affect the theta state so as to promote stimulus encoding.

Baseline theta states

Findings in rodents show that the amplitude of hippocampal theta even before stimulus-onset is associated

with enhanced learning in classical conditioning (e.g. [61]). Because the hippocampus and surrounding MTL structures are also critical for episodic memory encoding in humans, elevated prestimulus amplitudes of MTL theta might also lead to effective episodic memory encoding. This possibility was recently confirmed in human free recall [13] (for a prestimulus oscillatory modulation of subsequent word-stem completion priming see [62]). In an MEG word list learning and free recall experiment, the amplitudes of theta oscillations 200 ms preceding the onsets of words were higher for later recalled than for later forgotten words. Furthermore, single-trial analyses revealed that recall rate increased as a function of increasing prestimulus theta amplitude within subjects. This positive correlation was independent of whether participants were preparing for semantic or phonemic word processing, thus probably signifying a specific memory-related theta state rather than a preparatory task set. Source analysis located this theta state to the MTL. Such data raise the possibility that memory might be improved by timing stimulus presentation to optimal theta states and that this may be trainable via neurofeedback.

Novelty and theta

Lesion data in humans and recordings in rodents indicate that the hippocampus proper [63,64] and specifically region CA1 [64] play a role in novelty detection (see [19,39]). Placing a rat into a novel environment causes a decrease in hippocampal theta frequency [63], and increases the preferred phase of CA1 neuronal firing when compared to firing in the familiar environment. This shift is correlated with hippocampal plasticity (remapping) in response to the new environment [64]. These findings are compatible with the idea that encoding and retrieval in CA1 occur at different theta phases [40] that correspond to input from entorhinal cortex and CA3 respectively [18^{**}]. Comparable findings in human are still missing.

Successful encoding

The relationship between theta/gamma power and successful encoding appears to be complex. Words that are successfully recalled in a later free recall test elicit lower amplitudes of induced theta at encoding than words that are later forgotten [13,65]. However, another study used pictures instead of words and reported an increase in theta amplitude as a function of encoding success as measured using recognition memory [66]. Similarly, encoding-related induced gamma oscillations in the hippocampus, prefrontal cortex, and left temporal lobe have been reported to show an increase in amplitude with successful encoding in humans [65,66] and the hippocampus of non-human primates [67], while the reverse relationship has also been reported in the hippocampus and rhinal cortex [4]. It is currently unclear whether these discrepancies relate to stimulus material (words vs. pictures) or the type of memory test used to probe successful memory (recall vs. recognition).

One intriguing possibility is that poststimulus decreases in theta or gamma amplitude reflect improved tuning or neuronal response specificity during encoding which is made possible by improved preparatory tuning before stimulus-onset. In the case of prestimulus theta, this tuning may relate to the contextual details that accompany stimulus presentation. Such a possibility is supported by the observation that the decrease of theta oscillations as a function of successful encoding tends to correlate with the increase in theta amplitude in the baseline preceding stimulus-onset [13] (for a discussion of a related mechanism for priming see [62]).

Memory retrieval: recollection versus familiarity

Cognitive models of recognition memory (e.g. [68]) distinguish between recollection-based recognition, or 'remembering,' accompanied by contextual information about the episode in which an item was encountered, versus familiarity-based recognition, or 'knowing,' which is devoid of such information. A hallmark of recollection is that different types of information such as time, location and sensory information need to be bound together despite their likely distribution across disparate brain regions. The widespread interconnections of MTL regions provide support for its role as a convergence zone for such distributed information (e.g. [42]), and theta and gamma oscillations may play a key role in coordinating the long-range interactions (e.g. [22–24]) required during recollection.

Compatible with such a possibility, theta oscillations have been reported to be higher in amplitude during recollection than during familiarity [9,11]. Source analysis results suggested that, for associations between faces and scenes, this 'induced' theta activity increase is generated in a distributed synchronous theta network including prefrontal, MTL and visual areas [11]. Microelectrode recordings from the human entorhinal cortex in the MTL during autobiographic memory retrieval indeed showed that theta oscillations were dominant in cortically projecting layers and were accompanied by prefrontal and temporal theta oscillations [69]. In addition to enabling long-range interaction (also see [70^{*}]), theta oscillations may also be related to making recognition decisions [71]. Aside from long-range interactions, there is also evidence for spreading of activity from the hippocampus to cortical regions, as demonstrated for invasively recorded gamma oscillations in self-cued free recall [72].

Conclusions and outlook

Recent animal recordings suggest that the hippocampus may actively control the transfer of cortical information to the hippocampus itself via theta phase biasing of neocortical network dynamics [22,23,36,37]. Such a 'master-slave' relationship between the hippocampus and cortical regions could potentially be detected in humans using dynamic causal modeling (DCM) for phase-coupling

[73], or similar methods. These models, based on a weakly coupled oscillator framework, allow using EEG and MEG data to make inferences about how synchronized states arise. A DCM based comparison involving the hippocampus, prefrontal cortex and visual areas indeed showed that master-slave models are more compatible with delay activity during configural maintenance than models which involve partial or total mutual entrainment [73].

Pattern classification algorithms may allow non-invasive investigation of reactivation of memories [57] based on high density whole-head recordings (using MEG or EEG). The very large sampling space of these methods seems ideal for detecting the widely distributed patterns of activity expected to be seen during reactivation. By contrast, focal, anatomically targeted, intracranial recordings, offer complementary insight into how single neurons and small neuronal populations contribute to network behavior. Hence, the combination of high density MEG/EEG with focal intracranial recordings seems particularly suited to understanding how reactivations are coordinated across and within neuronal ensembles.

A number of pharmacological and lesion studies in humans and animals show that cholinergic neuromodulation arising from the basal forebrain (medial septal nucleus, diagonal Band of Broca and Nucleus Basalis of Meynert) [74] is not only critical for recognition memory (e.g. [75]) and active maintenance [76] but also regulates theta amplitude (for reviews see [15,28]). Dopamine may interact with cholinergic mechanisms of theta generation [77,78]. Since both neurotransmitters play a role in age-related decline in memory [74,79] it will be of clinical importance to understand how the theta and gamma dependent mechanisms outlined here depend on cholinergic and dopaminergic neurotransmission.

Recent success in intracellular recording from awake behaving rodents performing virtual reality navigation opens a window onto the neurophysiological mechanisms underlying brain rhythms and neuronal coding [80••]. This work shows that the theta phase precession effect results from an intrinsic membrane potential oscillation that has slightly higher frequency than the surrounding LFP. This avenue of research and its combination with pharmacological and genetic manipulations and optic imaging promises to have profound implications for the basic neurophysiology of cognition in behaving animals. And these in turn are likely to have significant parallels for human cognitive neurophysiology, as demonstrated by the close correspondences between the species described above.

Conflicts of interest

The authors have no conflicts of interest to declare.

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