Synchronous Neural Activity and Memory Formation

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Summary

Accumulating evidence suggests that the synchronization of neuronal activity plays an important role in memory formation. In particular, several recent studies have demonstrated that enhanced synchronous activity within and among medial temporal lobe structures is correlated with increased memory performance in humans and animals. Modulations in rhythmic synchronization in the gamma- (30–100 Hz) and theta-frequency (4–8 Hz) bands have been related to memory performance, and interesting relationships have been described between these oscillations that suggest a mechanism for inter-areal coupling. Neuronal synchronization has also been linked to spike timing-dependent plasticity, a cellular mechanism thought to underlie learning and memory. The available evidence suggests that neuronal synchronization modulates memory performance as well as potential cellular mechanisms of memory storage.

Introduction

Ever since Donald Hebb formulated the theory that changes in the strength of neuronal connectivity follow from the correlated activation of multiple neurons [1] the study of memory has been closely tied to the study of synchronous activity in the brain. The discovery that concurrent activation of presynaptic and postsynaptic neurons can lead to long-lasting changes in signal transmission [2] has produced an entire field of study. Central to these studies is the concept that the precise synchronization of neuronal activity is one of the underlying mechanisms by which information is stored in neural tissue. This phenomenon has been well-characterized at the level of single neurons, and growing evidence suggests that precisely timed neuronal activity at the network level can be linked to improved memory performance.

As documented in a recent review [3], significant advances have been made in our understanding of spike timing-dependent plasticity (STDP), which involves changes in synaptic connectivity induced by the precise timing of spiking activity of multiple neurons in relation to one another. The ability of synchronized activity between two neurons to induce long-term potentiation (LTP) or long-term depression (LTD) of the synapse(s) connecting those neurons depends on whether the activity falls within a particular critical window (10–20 ms), as well as whether the presynaptic spike precedes or follows the postsynaptic spike within

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this window [4–8]. The size of the window varies depending on the cell type as well as the dendritic location of intercellular connections [9–12]. Because LTP and LTD can lead to long-lasting changes in neuronal properties, including receptor trafficking and spine motility, these studies provide a direct link between synchronous neuronal firing and the modifications that may underlie memory formation in the brain.

In this article we review evidence, gathered over the past two years, that synchronization of neuronal activity in the brain can affect memory formation. The results from these studies have furthered the idea that gamma- (30–100 Hz) and theta- frequency (4–8 Hz) synchronization, and the interaction between these two rhythms, may engender the critical conditions by which synchrony among neural networks can support the specific processes underlying learning at the cellular level in the brain.

Gamma-band oscillations link memory formation to cellular mechanisms of learning

Neuronal ensembles often synchronize their activity at particular frequencies, producing oscillations that can be measured either noninvasively or with subdural arrays or electrodes planted deep within the brain. Modulations in oscillatory activity are often seen as humans and animals engage in cognitive tasks. Gamma-band oscillations, in particular, have been associated with neuronal processing when the brain is in an "active" state, such as during attentional or mnemonic processing [13–15]. In the hippocampus, gamma-band oscillations rely on interactions between inhibitory networks and local collaterals of pyramidal cells providing excitatory signals to the network ([16]; see [17] for a recent review on the generation of gamma-band oscillations in hippocampal area CA3). Gamma-band synchronization may affect signal transmission by two distinct mechanisms. First, gamma-band synchronization may provide input gain modulation through the influence of rhythmic network inhibition on local principal cells. Because these oscillations arise from strong, perisomatic inhibition from networks of local interneurons [17–18], the efficacy of excitatory input to neurons within the oscillating network is highest when this input arrives out of phase with this rhythmic inhibition. In this way, gamma-band oscillations can align rhythmic inhibition among neuronal groups, ensuring that the interactions between groups are the strongest when their phases are well-aligned with each other [19;Figure 1]. Second, neurons under the common influence of gamma-band oscillation will tend to fire within 10 ms of each other (roughly the equivalent of a gamma-band half-cycle). This synchronization may enhance the impact of multiple excitatory neurons to downstream areas, where they converge on a common target. This feedforward coincidence detection may involve increased temporal summation of excitatory postsynaptic potentials, resulting in an increased likelihood that downstream neurons will fire. In this way, gamma-band oscillations may serve to enhance the impact of projection neurons [20–22]. As mentioned above, correlated activity within this time window (10–20 ms) is a necessary condition for STDP. Accordingly, gamma-band oscillations may promote interactions among neurons that bring about the synaptic changes thought to be necessary for memory formation.

Although much research has focused on the role of gamma-band synchronization in selective attention [23–26], many recent studies have observed synchronous activity in the medial temporal lobe (MTL) during performance of memory tasks in rodents [27–29], humans [14, 30–39], and most recently in monkeys [40]. Changes in neuronal activity have been observed, with respect to memory formation, in oscillatory power, which reflects the energy per unit time within a particular frequency range, and coherence, which is a measure of linear predictability that captures phase and amplitude correlations. In particular, studies of intracranial electroencephalography (iEEG) signals in human epileptic patients have shown that when subjects study lists of words and are subsequently asked to freely recall as many words as possible, gamma-band power in the MTL is higher during the encoding of subsequently

recalled words then unrecalled words [39]. Using a similar task, others showed that gamma-band coherence between iEEG signals in the hippocampus and the rhinal cortex also predicts successful memory encoding [14,32].

Recently, the relationship between gamma-band synchronization and memory formation was extended to single hippocampal neurons. Monkeys were shown a series of novel pictures which were repeated after a variable delay, and recognition for the pictures was inferred based on the time spent looking at pictures during the repeated presentation relative to the initial presentation. Hippocampal neurons showed enhanced gamma-band coherence with each other and with simultaneously-recorded local field potentials (LFPs) during stimulus encoding in a manner that predicted the degree of subsequent recognition [40]. The time-course of this enhancement was extremely similar in monkeys and humans, using different behavioral paradigms, suggesting that gamma-band synchronization may reflect a basic mechanism for the neuronal interactions that are critical for successful memory encoding (Figure 1).

Coupling between gamma-band and theta-band oscillations

Modulations in gamma-band oscillations are often observed with respect to the phase of slower oscillations. This has primarily been observed in the theta-frequency band [41–43], but instances of cross-frequency coupling with the alpha-frequency (8–13 Hz) band have also been noted [44]. For example, Canolty and colleagues found that power in the fast gamma-frequency (80–150 Hz) band was highest at the trough of the theta-band oscillation in the human electrocorticogram [42]. Cross-frequency coupling may represent a mechanism for inter-areal communication. In support of this idea, it was recently observed that gamma-band oscillations in hippocampal area CA1 of the rat hippocampus can be divided into fast and slow components, each occurring at a particular phase of the theta-band oscillation, and each associated with a different source of afferent input to CA1 [45]. Slow (~25–50) gamma-band oscillations in CA1 were most prominent during the descending phase of the theta-band oscillation and were synchronous with slow gamma-band oscillations in CA3, while fast (~65–150) gamma-band oscillations in CA1 peaked during the trough of the theta-band oscillation and synchronized with fast gamma-band oscillations in medial entorhinal cortex. These results suggest that hippocampal theta-band oscillations may play a role in regulating information flow from entorhinal cortex and CA3 to CA1 in a way that optimizes memory encoding and retrieval. Also, similar to results obtained in monkey hippocampus for gamma-band synchronization [40], spike-field coherence in the theta-band is enhanced during the encoding of visual stimuli in human hippocampus (A Rutishauser *et al.*, abstract in *Soc Neurosci Abstr* 2009, 622.4). The hippocampal theta-band oscillation has been shown to exert an influence over activity in other areas of the cortex, as well. In one recent study, neurons in primary sensory cortices and the medial prefrontal cortex were transiently coherent with locally-generated gamma-band oscillations during exploration or REM sleep, and "bursts" of gamma-band oscillations as well as with theta-band oscillations generated in the hippocampus [46]. Taken together, these findings support the idea that rhythmic modulation in the gamma- and theta-frequency bands interact in support of memory formation and that theta-band phase can convey important information about the flow of information in the MTL during encoding processes [47].

Phase resetting as a mechanism of processing during memory formation

Because the phase of the theta-band oscillation can have important implications for gamma-band oscillations, gamma-band coherence, and thus memory formation, it is important to consider behavioral factors that may influence theta-band phase at any given moment. During working memory tasks, stimulus presentation induces shifts in the phase of the hippocampal theta-band oscillation [48–49]. Such phase-resetting has recently been studied in monkey visual and auditory cortices [50–51], where it appears to play a role in modulating neuronal

responses to incoming sensory stimuli. Particularly noteworthy in this regard is the finding that oscillations in monkey primary auditory cortex undergo phase-reset upon somatosensory stimulation [51]. This modulation affected the neuronal response to auditory stimuli such that auditory inputs arriving at a specific phase of the low-frequency oscillation produced an amplified neuronal response. Interestingly, similar effects have been seen in monkey primary visual cortex with respect to eye movements. Theta-band phase reset occurs upon fixation onset when monkeys make saccades in complete darkness, and the oscillatory phase at stimulus onset determines the strength of the subsequent neural response [50]. Such phenomena are thought to represent a mechanism by which salient events (e.g. saccades or microsaccades [50,52]) trigger a reset in ongoing oscillatory activity to an "ideal phase" in order to optimize the processing of incoming information. Similarly, theta-band oscillations in the monkey hippocampus undergo phase reset upon stimulus presentation as well as fixation onset (MJ Jutras & EA Buffalo, abstract in *Soc Neurosci Abstr* 2009, 480.2). If theta-band phase influences the patterns of signaling in the MTL through modulations in the power of gamma-band oscillatory activity, as seen in other systems [41–42], then resetting to an ideal phase upon salient environmental or behavioral events may set different regions of the MTL to the optimum state of synchronization for memory formation and retrieval. Because LTP is optimally induced at particular phases of the theta-band oscillation in the hippocampus [53–55], hippocampal theta-band phase-resetting may also have important implications for memory formation through enhanced plasticity. These various mechanisms associated with theta-band oscillations, and their proposed role in memory formation, are summarized in Box 1. Interestingly, other recent evidence indicates that the amplitude of theta-band oscillations in the human MTL even before stimulus encoding can predict subsequent recognition [38], suggesting that oscillatory activity may play an important functional role in generating a cognitive state associated with successful memory formation.

Conclusion

In conclusion, there have been a number of recent advances in our understanding of the role of synchronized neuronal activity in memory formation. Several recent studies have shown gamma-band neuronal synchronization during the encoding of sensory information, and that subsequent memory formation can be predicted by in the magnitude of this synchronization, both within and between regions of the medial temporal lobe. There have been clear demonstrations of interactions across frequency bands, particularly between the theta- and gamma-frequency bands, and an important topic of future research will be to further elucidate the functional implications of these interactions. Intriguing new findings have provided evidence for behavioral conditions that can control oscillatory phase-resetting, thereby modulating neuronal synchronization as well as sensory processing. However, the behavioral outcome of this kind of modulation has yet to be demonstrated. For the most part, findings regarding the functional implications of enhanced synchronization are still correlational, and future studies that may involve experimentally enhancing or reducing synchronization, perhaps by taking advantage of modulations in phase resetting, will be critical for advancing our understanding of the role of synchronous neuronal activity in learning and memory.

Acknowledgments

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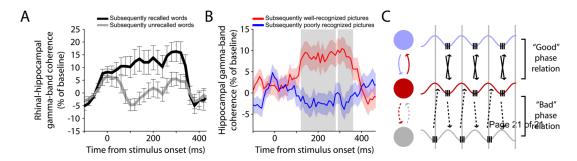
Figure 1. Gamma-band synchronization in the medial temporal lobe during memory encoding is associated with the degree of subsequent recognition
(A) Gamma-band phase synchronization (coherence) between the human hippocampus and the rhinal cortex during word study, as a function of time from stimulus onset. Coherence was significantly higher during the encoding of words that are subsequently recalled (black) than for words that were not later recalled (gray). Error bars indicate SEM. Modified from [14].
(B) Gamma-band spike-field coherence in the monkey hippocampus during the encoding of pictures, as a function of time from stimulus onset. Coherence was significantly higher for stimuli which monkeys subsequently showed a high degree of recognition (red) than for stimuli which were not well recognized (blue). 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 ($p < 0.01$). Modified from [**40]. **(C)** Schematic illustration of oscillatory activity (LFP oscillations with spikes in troughs) for three groups of neurons. Phase alignment among rhythmically-active neuronal ensembles promotes effective communication between these ensembles (top) while misalignment results in less effective communication (bottom). [19].

Box 1

Memory-related mechanisms associated with theta-band oscillatory activity

Process associated with theta phase:	Outcome:	Role in memory formation:
LTP/LTD induction [53–55]	Stimulation at peak of theta in rodent hippocampus produces LTP; stimulation at trough produces LTD.	Hippocampal theta-band oscillations provide a background for regulating the processing of input from sensory areas.
Gamma-band oscillations [41–42,45–46]	Slow gamma-band amplitude in monkey auditory cortex is highest at falling phase of theta [41]; fast gamma-band power in human cortex is highest at trough of theta [42]; slow gamma-band synchronization between rodent CA3 and CA1 occurs at falling phase of CA1 theta while fast gamma synchronizes entorhinal cortex and CA1 at trough of CA1 theta [45]; gamma-band bursts in rodent neocortex and hippocampus occur preferentially at peak and falling phase of hippocampal theta, respectively [46].	Gamma-band oscillations are modulated by the phase of theta, providing a foundation for patterns of signaling between brain regions that may be important for memory encoding and retrieval

Process eliciting phase reset:	Outcome:	Role in memory formation:
Stimulus onset [48–51]; Jutras & Buffalo, abstract, 2009	Phase reset in hippocampal theta occurs in rodents [48] and humans [49] during performance of a working memory task and in monkeys during a recognition memory task (Jutras & Buffalo, abstract, 2009); theta-band phase resets in monkey auditory cortex upon somatosensory stimulation, allowing incoming auditory stimuli to elicit amplified neuronal responses depending on resulting theta-band phase [51].	Phase resetting of theta-band oscillations with stimulus and fixation onset may ensure that sensory input occurs at an "ideal phase" of the oscillation; this may have important implications for mechanisms of plasticity thought to underlie memory formation.
Fixation onset [50]; Jutras & Buffalo, abstract, 2009	Theta-band phase reset occurs in monkey primary visual cortex upon fixation onset in the dark, and theta-band phase upon stimulus onset determines amplitude of evoked neural response [50]; reset of hippocampal theta-band oscillation in monkeys upon fixation onset shows phase synchronization with single-unit activity (Jutras & Buffalo, abstract, 2009).	