Synchronicity: when you're gone I'm lost without a trace?

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Recordings from the human medial temporal lobe suggest that synchronization of oscillations between rhinal cortex and hippocampus may contribute to building declarative memories.

Conscious memory for everyday events depends on learning mechanisms in the medial temporal lobe[1,2], where neocortical inputs converge on the hippocampus by way of rhinal cortex. A key to understanding medial temporal contributions to learning is determining how these regions interact during the building of memories. One proposed mechanism for functional integration across different brain regions is gamma-band phase synchronization, in which distinct populations of neurons fire at around 40 Hz and in synchrony[3,4]. In this issue, Fell and colleagues[5] report that intracranial electroencephalograms from human rhinal cortex and hippocampus tend to demonstrate greater synchrony while subjects learn words later remembered than words later forgotten. This brain–behavior correlation suggests that rhinal-hippocampal interactions may contribute to effective memory formation.

Lesion evidence from humans and experimental animals indicates that the medial temporal lobe circuit is necessary for declarative memory. It is well established that damage to these regions decreases the ability to consciously remember events that occur after the neural insult[1,2]. Moreover, recent functional imaging and electroencephalographic (EEG) studies in humans implicate medial temporal lobe computations in mnemonic encoding[6]. For example, the degree of rhinal, posterior parahippocampal and hippocampal activation during the encoding of an experience correlates with whether the experience will be later remembered or forgotten[7], with these subsequent memory effects emerging in the rhinal cortex before the hippocampus. Although considerable insights into medial temporal lobe function have emerged from these and related studies, evidence regarding the nature of human rhinal–hippocampal interactions during encoding and their relationship to effective learning has been lacking.

Fell and colleagues recorded field potentials from the seizure-free rhinal (perirhinal and entorhinal) and hippocampal regions of patients with intractable epilepsy while the patients were attempting to learn individually presented words (**Fig. 1**). After encoding, the patients were asked to freely recall the words that had been studied, and EEG data acquired during learning were sorted by whether the words were subsequently recalled or forgotten. Rhinal–hippocampal interactions were indexed separately for later remembered and later forgotten trials by assessing the phase synchronization of gamma-frequency oscillations in the EEG signals from these regions. Critically, Fell and colleagues observed that the constancy of the phase lag between rhinal and hippocampal gamma oscillations differed depending on whether the words were later remembered or forgotten. Gamma synchronicity was initially greater for remembered words from 100 to 300 ms and from 500 to 600 ms following word onset. These changes reflected a decrease in the phase differences between rhinal and hippocampal oscillations during these periods (**Fig. 1**). Later during stimulus processing, decreased synchronicity was observed from 1,000 to 1,100 ms after the onset of subsequently recalled words. These synchronization differences partially overlapped in time with transient reductions in gamma power in both rhinal and hippocampal regions during effective encoding trials.

Due to the correlational nature of these results, we cannot conclude that early rhinal–hippocampal gamma synchronization, later desynchronization, or decreased gamma power in these regions is necessary for declarative memory formation. Nevertheless, these novel findings suggest that more effective encoding may emerge when rhinal and hippocampal neurons synchronously oscillate and then desynchronize, and further suggest that decreased gamma power in these regions during encoding may aid learning. Fell and colleagues propose that increased gamma phase coupling may reflect a change in the functional connectivity between rhinal and hippocampal regions that is important for initiating encoding, for instance by facilitating the transmission of information between these regions. Subsequent desynchronization may mark termination of these regional interactions following information transfer. The authors further suggest that the negative correlation between gamma power and effective encoding may reflect adverse consequences of noise-like ambient gamma activity that could interfere with stimulus-specific activity and thus encoding. Alternatively, they suggest that decreases in gamma could reflect the suppression of components of the rhinal–hippocampal circuit and that failure of such suppression may hinder encoding. Although these interpretations are speculative, they provide important directions for further investigation that undoubtedly will continue to unravel the mysteries of memory formation in the medial temporal lobe.

Fell and colleagues results raise a number of fundamental questions regarding rhinal–hippocampal synchronization. First, how do these changes in synchrony emerge? One possibility is that they emerge directly through the dynamics of the medial temporal circuit. However, it is also possible that an attentional signal beyond the medial temporal lobe may serve as a 'pacemaker' through inputs that entrain rhinal and hippocampal neurons. Functional MRI studies of encoding consistently show greater prefrontal cortical activation during learning trials that are later better remembered[7,8]. A number of theorists have posited that encoding depends on interactions among prefrontal, posterior neocortical and medial temporal computations, with prefrontal cortex initiating a cascade of events that can modulate effective trace

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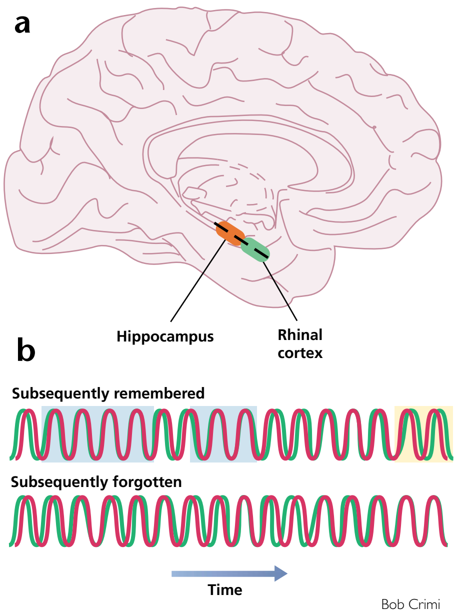

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Fig. 1. EEG recordings from human medial temporal lobe revealed greater gamma phase synchronization and desynchronization during the encoding of words later remembered compared to words later forgotten. (**a**) Approximate location of Fell and colleagues' recordings from rhinal cortex and hippocampus. The dashed black line represents the angle of electrode insertion along the long axis of the hippocampus. (**b**) Relationship between rhinal–hippocampal coupling and subsequent memory performance. Encoding of events that were subsequently remembered first evoked increased gamma-phase synchronization between rhinal and hippocampal regions (blue shading) and then decreased synchronization (yellow shading) relative to the encoding of events later forgotten. (Note that, for visualization purposes, the presently rendered oscillations are slower than the observed gamma frequency.)

formation[8,9,10]. Fell and colleagues propose that the early onset of increased rhinal–hippocampal synchronization may preclude a prefrontal source, perhaps pointing to thalamic modulation of the circuit. However, given the hypothesized role of prefrontal cortex in representing goal states—representations that may be on-line before stimulus presentation—and in biasing posterior processes in favor of task-relevant codes and pathways[11], assessment of prefrontal contributions to the emergence of rhinal–hippocampal synchrony would appear to be a promising direction for further investigation.

Second, is subsequent memory selectively associated with changes in rhinal–hippocampal synchronization in the gamma range? Fell and colleagues do not specify whether changes in frequency bands outside of gamma were associated with memory performance. Prior intracranial EEG recordings in humans have shown theta (4–8 Hz) oscillations during spatial navigation[12]. These results converge with animal studies that demonstrate a relationship between theta rhythm and hippocampal place codes, with theta modulation being associated with processing stages that may strengthen memory representations[13]. To fully appreciate the role of gamma-band synchronization, it may be critical to determine whether memory-related rhinal–hippocampal coupling is selective to this oscillatory frequency or derives from broader coupling.

Third, what form of declarative memory emerges from rhinal–hippocampal coupling? Memory for a previously encountered stimulus, such as a person you recently met at a conference, can be based on recollection of specific details about the past encounter with the stimulus or on a general sense of stimulus familiarity. For example, when subsequently encountering the person, you may recall her name or professional affiliation or you may simply have the subjective sensation that the face is familiar and, hence, that you must have met her before. Recently, extensive attention has focused on whether rhinal and hippocampal subregions differentially subserve recollection and familiarity. From one perspective, the hippocampus is thought to specifically mediate processes that underlie subsequent conscious recollection of event details[13,14]. Within this framework, hippocampally derived traces do not subserve memory based on item familiarity in the absence of recollection. Rather, perirhinal cortex is posited to subserve the acquisition of item traces that support subsequent familiarity-based memory[14]. Fell and colleagues assessed subsequent memory using a free recall test. Thus, their results demonstrate that synchronous rhinal–hippocampal activity is correlated with subsequent recollection. However, these findings need not imply that rhinal and hippocampal structures subserve the same form of declarative memory. That is, although rhinal inputs to the hippocampus are likely important for successful hippocampal formation of traces that ultimately yield recollection, within rhinal cortex the resultant traces may simply support subsequent item memory. It should prove informative in future investigations to derive separate behavioral measures of recollection and familiarity, and to examine the relationship between each of these forms of declarative memory and rhinal–hippocampal synchronization (and gamma power).

Although questions remain regarding how the medial temporal lobe circuit supports declarative memory formation, the results of Fell and colleagues mark a significant advance in understanding the temporal dynamics of activity within these regions and their relationship to memory formation. Moreover, their study highlights the leverage that can be gained by assessing temporal characteristics of neuronal responses, both within and across distinct structures. This investigation may prove to be the first of many influential efforts to specify how neural coupling across brain regions affects memory behavior. Such future efforts may also emerge from the integration of scalp-recorded magnetoencephalography or EEG with fMRI. The findings by Fell and colleagues[5] may well stand as a landmark along the road to specifying the neurocognitive processes that allow us to remember our past.

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