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Memory: Theta Rhythm Couples Periodic Reactivation during Memory Retrieval

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Memory retrieval involves the reactivation of memory traces distributed throughout the brain. New research suggests that these memory reactivations have an oscillatory nature and that they are coupled to preferential stages of the hippocampal theta cycle.

Memory requires the separation of information from the external world that needs to be encoded as new from the information retrieved from internal circuits that must be treated as old. We have to be able to shift rapidly between the elements in our experience that are concerned with online perception and those that are brought to mind ‘offline’ from stored memory traces. Consider, for instance, the case of watching a new movie in which one of your most favourite actors is the star: it may be that, as you watch the new movie, seeing that actor triggers a recollection of an episode from another, previously watched, movie. Despite the vividness of these memories evoked as you watch the movie, in the future you can still distinguish memories of the new movie from the those of the one you watched earlier. How does the brain deal with the computational needs of continuously encoding new information and retrieving stored representations without interference between the two? In this issue of *Current Biology*, Kerrén et al. [1] report important evidence that, by alternating the encoding of novel information and the retrieval of stored memories, neural oscillatory activity provides a mechanism for solving the problem of parsing old and new information in the human brain.

An established view is that the hippocampus and neocortical areas interact during the formation and later retrieval of a memory [2]. At encoding, the hippocampus is thought to continuously store a sparse and non-overlapping index that points to ongoing activity patterns in the cortex. This hippocampal index can later be reactivated by a reminding cue and stimulate the reactivation of a previously stored memory pattern in the neocortex [3,4]. A putative mechanism by which functional hippocampal-neocortical integration takes place is through theta oscillations (4–8 Hz). Theta rhythms are thought to coordinate the precise timing of neurons in hippocampal and neocortical networks and thereby influence the representation and long-term coding of information [5,6]. This led Kerrén *et al.* [1] to make the intriguing hypothesis that memory recollection should be supported by a temporally evolved distribution of memory reactivations that fluctuate in the theta range.

To test this hypothesis, Kerrén *et al.* [1] asked 24 healthy participants to encode words that were each associated with a picture of either an animate or an inanimate object. Each of these words were later presented and memories for the associated picture were tested by asking the participants to indicate, by pressing a keyboard button, whether and when a complete image of the cued picture memory was brought to mind (Figure 1). The participants indicated that this occurred approximately three seconds after word onset and confirmed that the picture memory was recalled accurately as they successfully selected, thereafter, the correct semantic category of each of the pictures in >85% of the trials. This ingenious experimental design allowed the authors to investigate whether memory recollection of the pictures was preceded by instances of memory reactivations, and if so, whether they oscillated within the theta range. Addressing this question empirically poses a methodological challenge, however, as one might need to identify, with very fine-grained temporal resolution, patterns of neural reactivations that may be widely distributed throughout different cortical regions.

To address this issue, Kerrén *et al.* [1] non-invasively acquired the participants’ whole-head brain activity through scalp electroencephalographic recordings (EEG) during the task. The very large sampling space of the EEG is ideal for detecting the widely distributed patterns of cortical activity expected to be seen during memory reactivation. The authors applied a pattern classifier approach to the EEG data to quantify, at a sub-second level, the extent to which words evoked distinct patterns of neural activity as a function of whether the associated picture belonged to an animate or an inanimate object category. The use of pattern classifiers has already been used in electrophysiological studies in humans in a time-resolved manner and showed its usefulness to uncover neural mechanisms associated with rapid memory reactivations during memory processing [7].

In most of the previous studies, the decoding approach was used to provide a discrete classification of whether a specific neural pattern belonged to a pre-defined category or class. For example, for a two-class classification problem one can visualize the operation of a classifier as splitting a high-dimensional input space with a hyperplane: all points on one side of the hyperplane are classified as belonging to one category, while the others are classified as belonging to the other (Figure 1). By setting a given threshold, classifier accuracy is obtained by calculating the number of cases that the

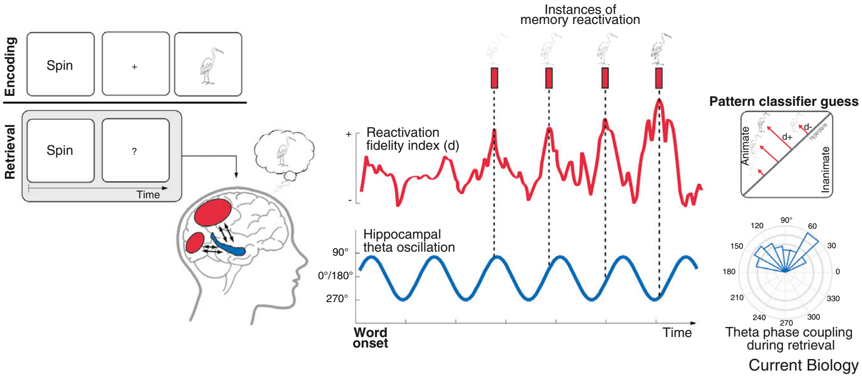

Figure 1. Schematic of experimental design and results.

Participants were asked to encode words that were each associated with a picture of either an animate or an inanimate object. In a subsequent test, participants had to indicate whether and when a complete image of the cued picture memory was brought to mind. A time-resolved parametric index of reactivation 'fidelity' of the recalled memory was obtained from pattern classification analysis on scalp EEG data. This index fluctuated at the theta rhythm (7–9 Hz) and it was coupled to the phase of the hippocampal 8 Hz oscillation.

classifier's guesses are correct. In the context of memory research, however, this approach is complicated by the possibility that different gradients of memory reactivation strength play a role during retrieval, as would be the case, for instance, when similar reactivation strength of targeted and competing memories interferes with successful memory recollection [8].

To resolve this important issue, a novel fine-grained temporal metric sensitive to gradients of classifier accuracy is needed, providing a continuous measure of the degree of reactivation 'fidelity' of a targeted memory. Kerrén *et al.* [1] offer such a metric: in their investigation, they took the distance from the hyperplane (d value) that optimally separated the two classes of retrieved objects (animate versus inanimate), and their time-courses served as a time-resolved parametric index of reactivation 'fidelity' of the targeted memory (Figure 1). Congruent with the idea that memory reactivation should precede memory recollection, the authors found that this index fluctuated rhythmically during the retrieval period preceding memory recollection at the theta frequency range (7–9 Hz). These findings suggest that memory retrieval engages a theta-based oscillatory mechanism in which instances of memory reactivation wax and wane, thereby supporting the notion of the existence of temporally defined time windows at which cortical reinstatement may lead to successful recollection.

Based on the observation that the hippocampus and the entorhinal cortex, the major source of cortical projections to the hippocampus, interact in different theta phases, Hasselmo *et al.* [9] suggested that the theta rhythm may, in fact, set the dynamics for alternating 'optimal' phases of encoding and retrieval. At the trough of the hippocampal theta rhythm, synaptic transmission arising from entorhinal cortex is strong and more susceptible to long-term potentiation [10], so this input is likely associated with encoding. At the opposite phase (at the peak of the theta cycle), synaptic transmission arising from entorhinal cortex is relatively weak, but synaptic transmission arising from region CA3 subfield of the hippocampus is strong, allowing effective retrieval of previously encoded memory. At this phase, synapses undergo long-term depression [10], which may suppress information storage during memory retrieval. As a result, hippocampal networks could regulate encoding and retrieval as a function of task demands.

Are, then, the theta-modulated memory reactivations during retrieval observed by Kerrén *et al.* [1] phase-coupled to the ongoing hippocampal theta rhythm, as would be predicted by the existence of an optimal 'theta state' that coordinates hippocampal–neocortical interactions during memory processing? Kerrén *et al.* [1] examined this possibility by projecting the raw EEG data into a source space and computed a phase-amplitude coupling analysis between the ongoing 8 Hz phase of the hippocampus extracted from the virtual channels and the classifier fidelity index obtained during the retrieval period. This analysis revealed strong theta phase coupling, indicating that fidelity of the retrieval classifier was modulated by the phase of the hippocampal 8 Hz oscillation (Figure 1). Notably, by repeating a similar analysis during encoding, the authors found strong hippocampal theta phase coupling with the classifier fidelity index, but shifted by $\sim 180^{\circ}$. Together, these findings are important evidence in humans supporting theoretical predictions of the existence of optimal hippocampal theta phase states associated with memory encoding and retrieval [9].

Arguably, if instances of memory reactivations are triggered by theta-modulated excitability in cortical areas projecting to and receiving from the hippocampus, theta phase consistency should be observed surrounding these time points. Consistent with this idea, Kerrén *et al.* [1] found a significant phase alignment at a 7–8 Hz frequency range in different brain regions, including the medial temporal lobe and parietal cortex, preceding the time points of memory reactivation during retrieval by approximately 200–300 ms. These findings align well with previous studies using invasive cortical electrophysiological recordings in humans that showed that the onset of encoding and retrieval during a working memory task was accompanied by a phase reset of the ongoing theta oscillations [11], and that this reset induced states of preferential theta phase consistency that differed between the study and the test [12].

Kerrén *et al.* [1] interpret their findings in line with the idea the reactivation of a memory is triggered at a consistent phase of a hippocampal theta oscillation followed by memory reinstatement in a broader range of neocortical regions. Alternatively, however, theta synchrony preceding memory reactivations could also be explained by fluctuations in cortical networks engaged during periods of 'sustained' attentional states [13,14] that could perhaps promote an increase in representational acuity in a distributed cortical network leading to vivid memory recollection. In fact, neuroimaging studies in humans have provided intriguing links between memory and attention, describing how these two cognitive processes interact in the brain during memory formation [15] and retrieval [16].

The extent to which models of attention and memory can be integrated and linked to brain theta oscillations may, thus, be an interesting topic for future research.

The study of the brain electrophysiological dynamics underlying human memory has been a topic of research for the last 30 years. A resurgence of this interest seems to have been taking place over the past few years with the incorporation of machine learning techniques, which allow the uncovering of temporal fine-grained mechanistic principles by which memory representations are accounted for by the human brain. This research may also provide fundamental insights to test mechanistic predictions derived from computational and animal work, thereby contributing to establishing similarities and differences across species. While much of the research in humans remains to be done, studies such as that by Kerrén *et al.* [1] illuminate the path towards inspiring, fruitful and exciting research in the upcoming years.

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Cell Biology: Functional Conservation, Structural Divergence, and Surprising Convergence in the MICOS Complex of Trypanosomes

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The MICOS complex is conserved across eukaryotes, but little is known about it outside the group that comprises animals and fungi. A new study finds that mitochondria of trypanosomatid parasites bear a divergent MICOS with both ancestral and derived subunits, but with conserved functions in crista development and membrane contact-site formation.

If you ever need a reminder that evolution does not create perfect forms, just look at the mitochondrial genome of trypanosomatid parasites. *Trypanosoma brucei*, the cause of sleeping sickness in humans, has a dense mass of DNA inside its single mitochondrion called the kinetoplast, which is the defining feature of kinetoplastids. In the kinetoplast, the