

targets of imprinting, long-term effects of early-life experiences might be reversed and/or masked by exposure to more potent imprinting environmental conditions later in life.

Altogether, these results provide valuable insight into the perseverance and/or reversibility of imprinted behavior and establish a basis for future studies aiming to further advance our understanding of an animal's adaptability to its environment and, as Marcel Proust elaborated on, to the memory of things past.

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# Theta Rhythm: Temporal Glue for Episodic Memory

Sam C. Berens and Aidan J. Horner\*

Department of Psychology, University of York, York YO10 5DD, UK

\*Correspondence: [aidan.horner@york.ac.uk](mailto:aidan.horner@york.ac.uk)

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The low frequency theta rhythm is thought to promote the formation of long-term multimodal memories in the hippocampus by orchestrating input from multiple cortical sources. New research has demonstrated a causal association between the timing of experimentally induced theta rhythms and episodic memory formation in humans.

The complex neural symphony of the brain is thought to be supported by cortical oscillations, or 'brain rhythms'. Oscillations act like musical conductors, orchestrating the timing of neural firing across the brain. Without them, our brain's complex temporal firing patterns would lack coherence, resulting in a neural cacophony. This orchestration may support communication between distant brain regions, ensuring they are talking to each other at the right time. Further, the

temporal organisation of neural firing is thought to be critical for the formation of long-term memories in the hippocampus. A new study by Clouter *et al.* [1], reported in this issue of *Current Biology*, sheds light on the role of the low-frequency theta rhythm (4–8 Hz) in the formation of long-term multimodal memories.

Theta rhythms are found throughout the brain, and dominate the local field potential in the hippocampus; a region known to be critically involved in episodic

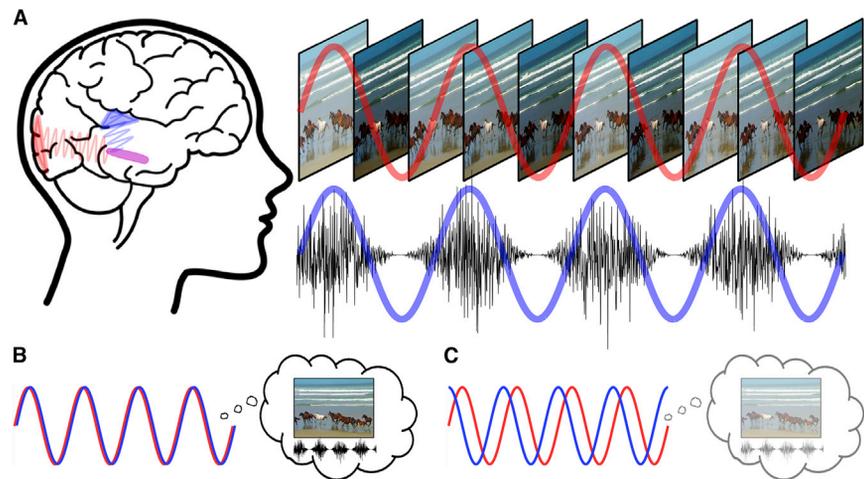
memory [2]. Given this association with the hippocampus, it has long been speculated that theta plays a role in coordinating activity during memory encoding [3,4]. However, the specific function of hippocampal theta is not clear. In rodents, theta is predominantly associated with translational movement through an environment [5]. Further, hippocampal place cells, which signal an animal's location with respect to the environment, are known to fire at different

phases of the theta rhythm depending on an animal's location in the environment, a phenomenon known as 'theta phase precession' [6,7]. This constitutes a form of phase coding that can be used to anticipate locations ahead of the animal and plan trajectories to particular goals [8]. These observations support a role for the theta rhythm in spatial navigation.

Animal studies also, however, suggest that theta plays a key role in memory. Disrupting hippocampal theta in rodents abolishes spatial learning in the Morris water maze, which can be restored by stimulation at theta frequency [9]. Furthermore, theta power — that is, the strength of the oscillations — during conditioning paradigms has been positively associated with the rate of learning [10,11]. Computational models have been formulated which indicate that theta phase could play a role in differentiating encoding and retrieval states in the hippocampus [12].

In humans, theta has been associated with both working memory and long-term episodic memory function [13]. In relation to episodic memory, theta power at encoding has been shown to predict subsequent word recall [14], and memory for word–video associations [15]. However, these studies are inherently correlative in nature, and focus primarily on theta *power*, as opposed to the synchrony of hippocampal inputs as a function of theta *phase*. Indeed, the lack of agreement in the literature with regards to whether increases [15] or decreases [16] in theta power predict subsequent memory may be an indicator of the relative importance of theta phase relative to power.

Experimental evidence in rodents demonstrates the critical role played by theta phase in long-term potentiation (LTP), the likely neural basis of long-term memory formation. For example, short pulses of excitation to the hippocampus during the peak of the theta rhythm induce LTP, whereas excitation during the trough does not [3]. Moreover, Hebbian learning is known to rely on the precise timing of spikes in pre- and postsynaptic neurons (on the order of tens of milliseconds) [17]. Theta may therefore be involved in the formation of long-term multimodal memories, coordinating



**Figure 1. The theta-induced memory effect (TIME).**

(A) An audio-visual stimulus is modulated at theta frequency (4 Hz). The luminance of the video (red) and amplitude of the audio (blue) are modulated independently, and both independently induce theta oscillations in their respective primary sensory cortices. This is thought to ensure the timing of inputs into the hippocampus (purple) are synchronised, allowing for the formation of a multimodal association. (B) When the phases of the two theta-modulated stimuli are synchronous at encoding, subsequent memory performance increases. (C) But when the phases are asynchronous at encoding, subsequent memory performance is similar to baseline levels.

inputs from multiple cortical sources to ensure that this precise timing is achieved.

Clouter *et al.* [1] set out to provide direct evidence that episodic memory formation in humans relies on synchronisation of inputs in the theta band (Figure 1). They presented audio-visual movie clips to participants, modulating the luminance (video) and amplitude (sound) independently in a rhythmic fashion to induce entrained oscillations in primary sensory cortices. The videos and sounds were semantically unrelated, and participants had to remember which video was associated with which sound in a subsequent memory test. In their first experiment, all video and sound clips were modulated at theta frequency (4 Hz) and presented either 'synchronously', such that the theta modulation of the video and sound were in phase; or 'asynchronously', such that they were out of phase by 90° or 180°.

Using electroencephalography (EEG), the authors showed that the theta modulation of sensory input induces appropriate theta rhythms in both primary visual and auditory regions. The phase of the entrained theta rhythms in these sensory regions matched the sensory input, such that theta phase in the two

regions was synchronous when the sensory inputs were synchronous. The key question is whether this synchronous entrainment led to improvements in memory relative to asynchronous input.

Clouter *et al.* [1] found better memory for the video-sound clips if they were presented synchronously relative to asynchronously. The results also showed that this memory effect is specific to the theta band — it was not seen when the clips were modulated in either the delta (1.7 Hz) or alpha (10.5 Hz) bands. Importantly, this memory enhancement was not seen when the stimuli were not modulated. Hence, coherent modulation of audio-visual clips at theta frequency improves memory performance above baseline levels. They called this experimental finding the 'theta induced memory effect' (TIME).

In demonstrating that associative encoding is facilitated for stimuli that are modulated by a synchronous theta rhythm, Clouter *et al.* [1] provide causal evidence for a role of theta frequency oscillations in episodic memory formation. The results support the proposal that theta phase synchrony plays a key role in the encoding of long-term multimodal memories,

critically extending such accounts to humans.

Naturally, the findings raise further important questions. First, does the theta modulation of the audio-visual clips disrupt perception of the stimuli in subtle ways that have a knock-on memory effect? This seems unlikely, as Clouter *et al.* [1] show that memory in the synchronous condition is better than when the stimuli aren't modulated, and perception is presumably unaffected. Second, do the theta rhythms induced by these experimental stimuli actually propagate to the hippocampus? Source-localised EEG or MEG, or invasive electrophysiological recordings from the hippocampus, would be ideal to answer this important question. It would also be interesting to know whether the memory effect was specific to memory for multimodal associations that critically rely on the hippocampus [18], relative to memory for individual unimodal items.

Finally, do the theta-modulated stimuli facilitate memory encoding by inducing a 'theta state' in the hippocampus? The *timing* of inputs may not be critical *per se*, but rather synchronous modulation of cortical inputs might enhance hippocampal theta power in general, increasing the likelihood of successful encoding. While possible, Clouter *et al.* [1] rightly point out that their asynchronous conditions ( $\pm 90^\circ$  or  $180^\circ$ ) showed similar levels of memory performance. If the stimuli merely served to enhance hippocampal theta power, a phase difference of  $90^\circ$  should entrain hippocampal theta rhythms to a greater extent than a phase difference of  $180^\circ$ . As there was no detectable difference in memory performance between these two conditions, the data do not support this possibility; at least if one assumes a linear relationship between memory performance and the summed signal across theta modulated stimuli. Of course, the theta synchrony effect is not necessarily driven by a single neural mechanism, and both induced theta power and theta phase synchrony may play roles in the successful encoding of long-term memories.

As well as the important theoretical insight provided by the study [1], this effect may have therapeutic value, being used to improve memory encoding in

patients with memory difficulties such as those associated with Alzheimer's disease. Although it may not be feasible to continuously theta-modulate sensory input for such patients, the technique could be used to increase the likelihood of encoding new, important pieces of information. For example, if a patient had to move home and wanted to learn their new address or the name of a new carer.

Finally, the results potentially provide further evidence that hippocampal encoding can be modulated by long-range non-invasive external input. Previous research has shown that sustained transcranial magnetic stimulation (TMS) over a parietal region known to be functionally coupled to the hippocampus increases post-stimulation memory performance [19]. Thus, long-range *offline* stimulation modifies hippocampal memory encoding. In the work of Clouter *et al.* [1], theta-modulated sensory stimuli appear to modify memory encoding in a long-range, but *online*, manner. Alongside more invasive brain stimulation methods [20], the variety of techniques with which to potentially *non-invasively* promote hippocampal-based episodic memory opens exciting avenues for the future development of therapeutic interventions in patients with memory impairments.

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