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Review

Rhythmic sensory stimulation as a noninvasive tool to study plasticity mechanisms in human episodic memory

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In recent years, research in animals has increasingly focused on understanding the role of precise neural timing in inducing synaptic plasticity (the strengthening or weakening of synaptic connections). Human episodic memory is thought to depend on such plasticity. Animal studies have provided valuable insights into mechanisms such as spike-timing-dependent plasticity and theta-phase-dependent plasticity, highlighting the importance of coordinated timing between neural inputs for synaptic changes to occur. Building upon these findings, recent studies employing rhythmic sensory stimulation and electromagnetic stimulation in humans have attempted to link these mechanisms to episodic memory formation. These studies have revealed that memory consolidation relies on the precise co-ordination of timing between neural inputs, particularly in the gamma and theta frequency ranges. This body of work represents a crucial bridge between our understanding of cellular-level mechanisms in animal models and the complex processes underlying human memory.

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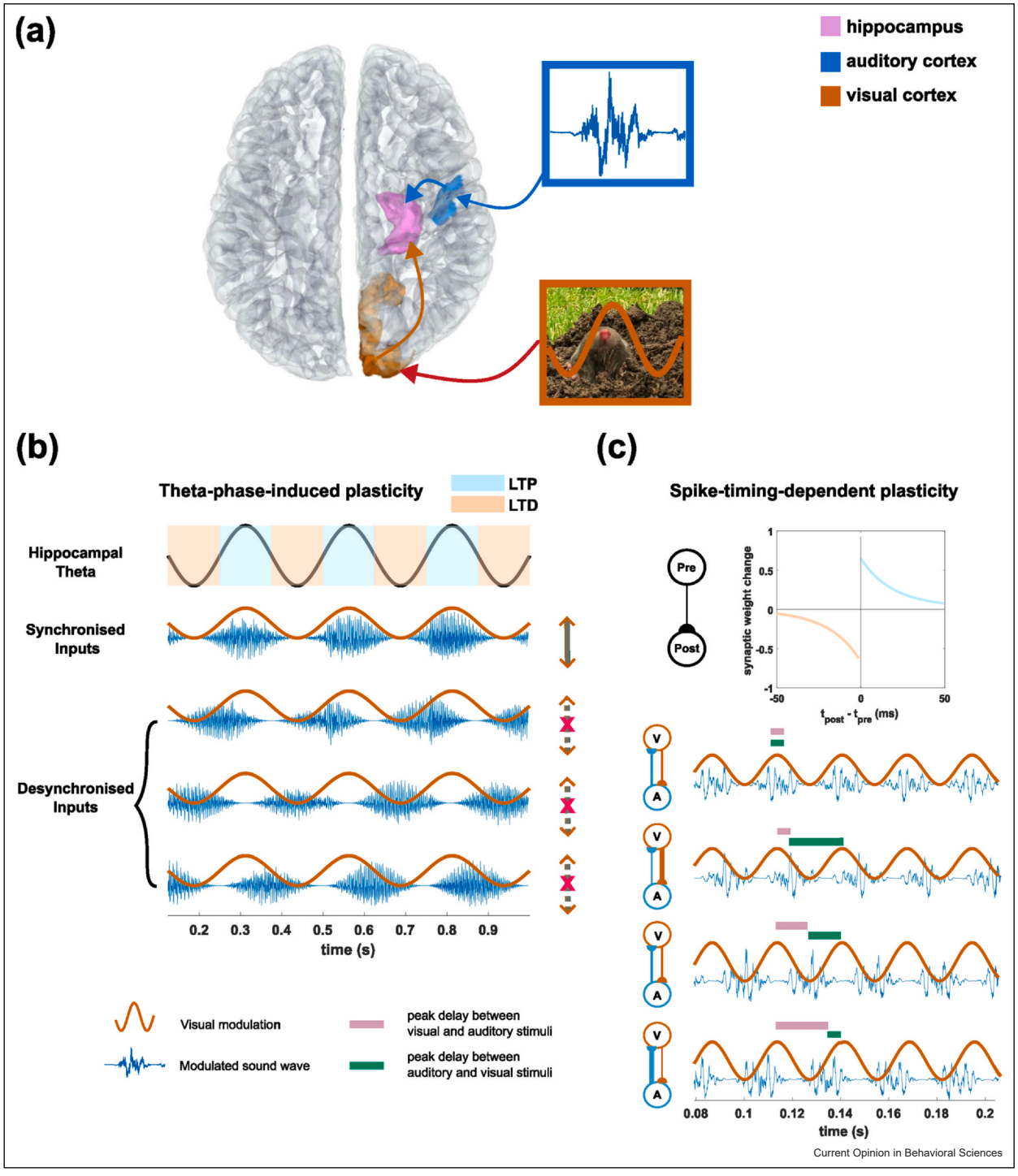
Introduction

Episodic memory allows one to mentally travel back in time to re-experience often rich multisensory events, such as a concert you have seen. Binding multisensory elements into a coherent memory representation is one of the characteristics of episodic memory. Importantly, forming such episodic representations is rapid and occurs almost instantly. The hippocampus, a region that receives multimodal inputs from corresponding neocortical areas, is suggested to be the location where binding occurs [1]. Long-term potentiation (LTP) and long-term depression (LTD) are two forms of activity-induced synaptic modifications that occur in hippocampal synapses. LTP involves the strengthening of synaptic connections between neurons, making them more efficient at transmitting signals. On the other hand, LTD results in the weakening of synaptic connections, leading to a decrease in signal transmission efficiency. The facts that these synaptic modifications are thought to be fundamental mechanisms underlying learning and memory processes and that hippocampal synapses are more likely to undergo activity-induced synaptic modifications (LTP and LTD) makes the region a prime candidate for rapidly forming episodic memories [2,3]. In his seminal book, Donald Hebb proposed the neuronal basis for learning and memory as 'Neurons that fire together wire together' [4]. The discovery of LTP and LTD in the hippocampus *in vitro*, as well as *in vivo*, has supported Hebb's theory [5–8]. However, direct evidence for a contribution of synaptic plasticity to human episodic memory is scarce due to the difficulty of linking the cellular to the behavioural level using noninvasive techniques in healthy humans.

Both rodent studies and computational models suggest that synaptic plasticity is influenced by the timing of neural activity relative to ongoing hippocampal theta oscillations [9–12]. Inspired by these findings, researchers have sought to study synaptic plasticity in humans noninvasively by synchronising neural inputs with the frequency of hippocampal theta oscillations (the rhythmic neural activity in the hippocampus that has been associated with processes such as memory formation). This synchronisation has been achieved through two main techniques: rhythmic sensory stimulation (RSS; Figure 1a) and transcranial magnetic stimulation (TMS)/transcranial electrical stimulation (TES).

Figure 1



Schematic of the RSS paradigm and the theta-phase-induced plasticity and STDP. **(a)** Sensory regions receive inputs from auditory and visual stimuli. Sensory information arrives in the hippocampus in-phase or out-of-phase depending on the phase offsets between the modulated auditory and visual stimuli. **(b)** Framework of theta-phase-induced plasticity. LTP and LTD occur at opposing theta phases in the hippocampus. Thus, associations are more likely to be encoded when sensory inputs are synchronised than when inputs are desynchronised. **(c)** The STDP framework. Synaptic modification depends on spike timing between a presynaptic neuron and a postsynaptic neuron. Associations are formed asymmetrically depending on the length of delay from one modality to the other modality. Pink bars represent delays between a video and a sound. Teal bars represent delays from the sound to the video. When the pink bar is shorter than the teal bar, then associations from visual to auditory modalities are stronger than associations from the auditory modality to the visual, and vice versa.

In this article, we review recent evidence on the role of synaptic plasticity in human learning and memory using these noninvasive tools. We focus on two distinct mechanisms of synaptic plasticity: theta-phase-dependent plasticity and spike-timing-dependent plasticity (STDP). Theta-phase-dependent plasticity (Figure 1b) suggests that the direction and magnitude of synaptic changes are modulated by the phase of hippocampal theta oscillations [10]. This mechanism provides a potential link between the rhythmic activity of the hippocampus and the encoding of memories in the brain. STDP (Figure 1c) proposes that the timing of action potentials, or spikes, between pre- and post-synaptic neurons determines the strength of synaptic connections [13]. This mechanism highlights the importance of precise temporal relationships between neuronal activity for synaptic plasticity to occur.

By exploring these two mechanisms, we aim to elucidate how neural activity and synaptic plasticity contribute to human learning and memory processes, shedding light on the underlying mechanisms of episodic memory formation.

Synaptic plasticity in rodents and humans

In both the human hippocampus and neocortex, synaptic modifications have been observed bidirectionally using stimulation protocols similar to those employed in rodent studies, indicating shared features between species [6,14–16].

Theta-rhythmic oscillations are characteristic of the cyclic periods of excitation and inhibition in the hippocampus [17]. These hippocampal theta oscillations are implicated in LTP induction (e.g. [18–20]), modulating plasticity (e.g. [21–27]), memory formation (e.g. [28,29]) and providing temporal windows to bind information from different brain regions (e.g. [30–33]).

Theta-frequency electrical stimulation of CA1 pyramidal neurons has been shown to optimally induce LTP in the dentate gyrus and CA1 regions of the hippocampus [18–20,34–37]. This induction of LTP can occur with a single burst of electrical stimulation, resembling the one-shot mechanism thought to underlie hippocampal memory formation. Priming stimulation delivered at theta-frequency timing (typically around 200 ms before the burst) enhances the effectiveness of LTP induction, highlighting the importance of temporal co-ordination in synaptic plasticity processes.

The phase of hippocampal theta oscillations plays a critical role in facilitating one-shot memory formation by providing the necessary depolarisation for synaptic plasticity induction [10,33,38–40]. Optimal induction of LTP in the hippocampus relies on the precise timing of neural inputs relative to the phase of theta oscillations. Studies have shown that short bursts of electrical stimulation can effectively induce LTP when they coincide with the peak of depolarization during the theta phase, whereas the same bursts lead to LTD when they align with the trough of the theta cycle [10,38]. However, it is essential to note that there is a 180-degree phase reversal of theta oscillations within different regions of the hippocampus, meaning that the relationship between LTP induction and theta phase may vary depending on the recording site [33]. Consequently, the phase relationship between incoming neural inputs and the ongoing hippocampal theta oscillation is crucial for determining the success of LTP induction *in situ*. Understanding and manipulating this phase relationship can provide valuable insights into the mechanisms underlying synaptic plasticity and memory formation within the hippocampus.

Rodent studies on STDP have revealed that the timing and interval between pre- and post-synaptic spikes are crucial determinants of synaptic modification [13,41,42]. Specifically, LTP occurs when the presynaptic neuron fires before the postsynaptic neuron while reversing this order results in LTD. This temporal window for synaptic modification typically spans around 40–60 ms in rodents. However, studies conducted in the human hippocampus have indicated a wider time window for LTP induction compared with rodents [5,43]. Notably, research involving hippocampal tissues from patients spanning a wide age range (20–66 years) suggests that the classic STDP rule observed in juvenile rats may not fully apply to adult humans [43,44]. Verhoog et al. [44] conducted a comparative analysis of STDP in adult humans and rats, revealing similarities in the broader time window for LTP induction, implying a potential age-related variation in STDP mechanisms [16,41,45].

In human research, paired associative stimulation (PAS) studies have provided valuable insights into STDP mechanisms in the healthy brain. PAS protocols typically involve pairing TMS pulses with afferent inputs generated by peripheral nerve stimulation [46]. The timing relationship between TMS delivery to the motor cortex and the afferent input activation modulates the amplitude of motor evoked potentials (MEPs), resembling the principles of STDP [47,48]: asynchronous TMS delivery following afferent input activation has been shown to increase MEP amplitude, with the relative timing between stimuli determining the polarity and magnitude of MEP responses.

A variant of the PAS protocol, termed cortico-cortical paired associative stimulation (ccPAS), has been developed to induce plasticity changes in cortico-cortical pathways, replicating the patterns observed in STDP [49]. Studies employing the ccPAS protocol have

demonstrated task-related alterations in network oscillatory activity across distinct frequency bands, as well as changes in network oscillatory coherence during rest periods [50,51]. For instance, Sel et al. [50] reported that ccPAS induced discernible modifications in network communication and connectivity, as evidenced by the observed shifts in oscillatory activity patterns [52,53].

Investigations into the behavioural consequences of STDP have utilised paired-sensory-stimulation paradigms, wherein repeated presentation of stimulus A before stimulus B induces perceptual shifts favouring stimulus B. Notably, reversing the order of stimulus presentation results in a corresponding reversal of the perceptual shift [54–56]. This underscores the critical role of temporal intervals between stimulus presentations, with the optimal time window for inducing perceptual shifts typically falling within 40 ms, mirroring the time window associated with cortical STDP mechanisms.

Beyond potential variations in the time windows of plasticity induction between humans and rodents, these neurostimulation protocols have suggested a higher degree of complexity in the plasticity patterns of the human brain [43,57,58]. These studies have described concomitant antithetical forms of human STDP and the capacity of dynamically transitioning between Hebbian and anti-Hebbian plasticity (i.e. correlated activation in the pre- and post-synaptic neurons leading to a weakening of their connection [13]). This transitioning appears to be influenced by various factors, including the engagement of distinct neuronal populations by different stimulation parameters (e.g. TMS coil orientation [57]), the activity state of the targeted areas [13,57] and interhemispheric interactions [58]. However, the use of different experimental approaches complicates the comparisons between findings in humans and other species. Further investigation and comparative studies are needed to elucidate the precise mechanisms involved and better characterise plasticity in the human brain.

Recent studies of brain stimulation on human learning and episodic memory

Invasive deep brain stimulation (DBS) using theta-burst microstimulation to the human entorhinal cortex has been suggested to improve episodic memory [59], which is consistent with the findings from rodents that LTP can be induced by theta-burst [19]. Moreover, human noninvasive Magnetoencephalography/Electroencephalography and invasive intracranial EEG (iEEG) and single-neuron recording studies all suggest a key role of precise timing relative to ongoing oscillations in successful episodic memory [60]. Closed-loop auditory stimulation and DBS to the specific phase of slow-wave activity during sleep enhance memory consolidation [61,62], which proves a causal role of synchronised input relative to ongoing oscillations in human episodic memory. Studies on DBS and auditory stimulation of sleep oscillations in human memory have been reviewed deeply elsewhere [63–67] and are not the focus of the current review. Instead, we focus on the noninvasive rhythmic stimulation studies and how they modulate human episodic memory via synaptic plasticity.

Motivated by the idea that hippocampal theta oscillations provide a temporal reference for inducing LTP and LTD, Clouter et al. [68] conducted a behavioural experiment to test the causal role of theta phase synchronisation in forming associative memories in humans. Significantly enhanced recall performance was found when the phase offset between 4 Hz (theta) modulated video and sound clips (Figure 1) was 0°, compared with out-of-phase conditions. This phase synchrony-induced memory effect was specific to theta-modulated stimuli, not to delta (1.65 Hz) or alpha (10.47 Hz). The effect has been replicated by the authors from the same group [69], who also demonstrated that trial-by-trial variability in phase differences between visual and auditory theta activity predicts subsequent success of the association of a video–sound pair. Visuo-auditory RSS has also been used to modulate the retrieval orientation conducive for later successful source monitoring. Roberts et al. [70] showed that theta (5.5 Hz) flickers (lights) and flutters (tones) between encoding and retrieval phases enhanced source memory and endogenous theta power over frontal electrodes, compared with control, nontheta frequency stimulation conditions. Such a memory enhancement has also been shown by flickering object images on a monitor at individualised theta frequency (3–8 Hz) compared with alpha frequency (8–13 Hz) [71]. The subsequently remembered items showed increases in theta–gamma power amplitude coupling (PAC), compared with the subsequently forgotten ones, which provides further evidence that theta oscillations provide an optimal time window for LTP occurring at a slower time scale. On a similar note, theta–gamma PAC can be mimicked by applying gamma bursts within a theta cycle. Noninvasive theta-burst TMS that is applied to the parietal cortex has been shown to increase episodic memory retrieval, as well as episodic encoding-related hippocampal activity. Such memory advantage was specific to theta-burst stimulation and predicted by the hippocampal connectivity with other cortical regions [72,73]. Together, these findings suggest that noninvasive theta-rhythmic stimulations entrain the hippocampal endogenous activity, which provides optimal time windows for synaptic plasticity, thus improving episodic memory performance and aligning with the findings that theta-frequency burst stimulation produces maximal LTP in the rodents' hippocampus (e.g. [18–20]).

Using multimodal RSS, Plog et al. [74] showed in a fear-conditioning task that theta phase synchronisation enhances contingency knowledge between a conditioned stimulus (CS) and an aversive unconditioned stimulus

(US) and affective rating on the CS. The same group [75] further replicated the findings by a web-based online study with large samples (N = 182). Although they showed that the phase synchronisation effect was not specific to theta-modulated stimuli, as the enhancement in CS-US contingency knowledge was also present for delta (1.67 Hz) in-phase groups. It is still unclear to what extent the large sample size is able to account for the interindividual or intertrial variability in the environment, hardware or software that can influence participants' attention and temporal precision of the stimulus delivery.

To connect the findings in humans to theta-phase-dependent plasticity in rodents, Wang et al. [76] constructed a computational model with theta-phase-dependent and STDP rules (Figure 2a). They reproduce findings from the rodent *in vitro* experiment by Huerta and Lisman [10] and the human associative memory experiments by Clouter et al. [68] and Wang et al. [69] (Figure 2b). If STDP learning is switched off, the model failed to reproduce the hockey-stick pattern shown in Clouter et al. [68] and Wang et al. [69], showing that recall accuracy was better in the 0° condition than in the 90°, 180° and 270° conditions, while learning in the three out-of-phase conditions did not differ, suggesting that STDP indeed is involved. To investigate this possibility explicitly, Wang et al. [77] used visual and auditory RSS at 37.5 Hz with 0°, 90°, 180° and 270° phase offsets. An STDP model suggests that learning is better from the visual group to the auditory group in the 90° condition (shortest delay, 6.67 ms) than from the auditory group to the visual group (longest delay, 20 ms). The pattern is reversed in the 270° condition with empirical results confirming a role of STDP in multisensory episodic memory (Figure 2c).

Two iEEG studies showed that multisensory flickers at a similar frequency ~40 Hz entrain brain areas related to higher cognitive functions, such as the hippocampus [78,79]. Converging evidence has been shown in Wang et al. [77] with EEG source analysis, suggesting that the maximum difference in 37.5 Hz phase-locking during the RSS between subsequently remembered and forgotten trials is localised in the hippocampus (Figure 2d). This was linked with the hippocampal STDP model simulated results (Figure 2e). Therefore, the degree to which RSS propagates from lower to higher brain regions is modulated by cognitive states, which make memory formation more or less likely (like attention).

Another study [80] attempted to induce synchronisation between sensory cortices by entraining the visual cortex with 4 Hz transcranial alternating current stimulation (tACS). To this end, the sounds were presented at 4 Hz as before, but the visual stimuli were not modulated; instead, the visual cortex was electrically stimulated at 4 Hz. Surprisingly, the results failed to replicate the previous findings, raising questions about whether tACS is capable of entraining the occipital cortex in a way relevant to this paradigm (i.e. assuming downstream propagation of the signal to the hippocampus) [81–83].

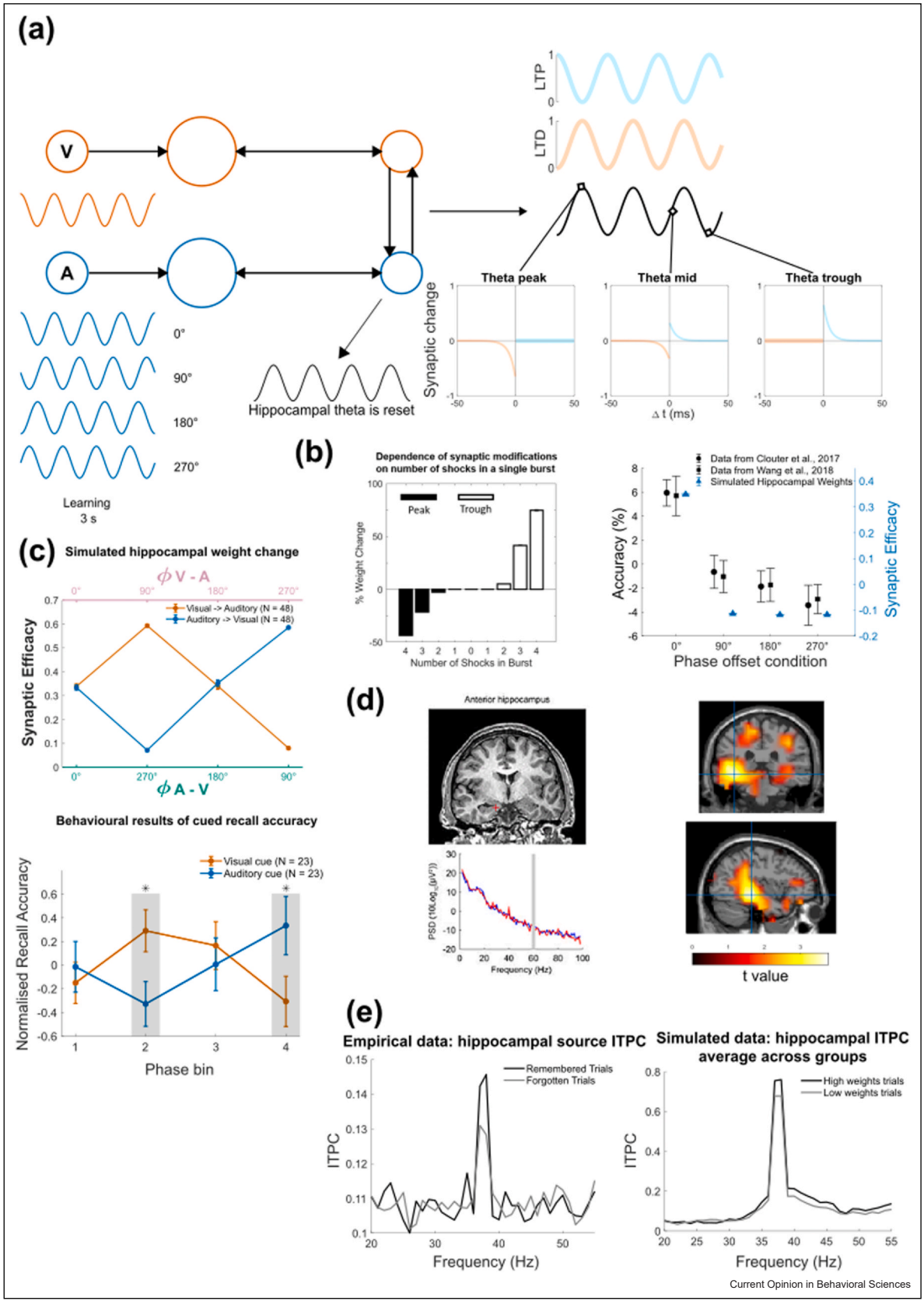
Implications and future directions

Boundary conditions in terms of RSS frequency specificity have been tested by Clouter et al. [68], which suggests the importance of synchronising the inputs to the range of hippocampal endogenous frequency. Another boundary condition to be tested is if the memory effect is specific to multimodal RSS. Using unimodal 37.5 Hz RSS, Chen et al. [84] showed no memory effect for phase offsets between videos, which were flickered at left and right hemifields. Response of ~40 Hz multisensory RSS has been found to be in a broader brain network, including the hippocampus than is seen in unisensory RSS [78,79]. It could be that the 37.5 Hz unimodal RSS in the visual cortex fails to influence the downstream targets of hippocampal neurons (but see Ref. [85]). Recently, Griffiths et al. [86,87] showed that visual RSS at 32.5 Hz and 65 Hz during memory retrieval enhances associative memory via entraining the endogenous 32.5 Hz activity. Slow gamma (~25 to 50 Hz) is suggested to influence memory retrieval via coupling with hippocampal CA3 slow gamma activity [88,89]. Therefore, whether ~40 Hz unimodal RSS during memory encoding can boost episodic memory via the hippocampal synaptic plasticity such as STDP is not clear. Future research with other modalities or other frequencies, and neuroimaging techniques with higher spatial resolution will help disentangle the involvement of hippocampal STDP in the memory effect.

The brain's response to a repetitive stimulus can vary under the influence of multiple factors. The ongoing activity at the time of the stimulation, as well as the intrinsic variability in brain oscillations both across individuals and within the same individual over time, contribute to this variability [90–92]. In turn, this may explain the presence of variability in the results and suggests that 4 Hz might not be the optimal stimulation frequency for every individual. Notably, hippocampal theta oscillations are slower in humans compared with rodents and manifest as short, infrequent episodes spanning a broader range of frequencies [93,94]. Therefore, dynamically adjusting the stimulation parameters to the ongoing oscillatory properties of the participant may be a more effective approach (e.g. see Ref. [95]). Growing evidence supports such brain-informed approaches, which have so far shown promising results (for a review, see Ref. [96]).

Finally, we suggest another important avenue for future research is the role of neuromodulators, for example,

Figure 2


(a)
V
A
0°
90°
180°
270°
Learning
3 s
Hippocampal theta is reset
LTP
LTD
Theta peak
Theta mid
Theta trough
Synaptic change
Δ t (ms)
(b)
Dependence of synaptic modifications on number of shocks in a single burst
Peak
Trough
% Weight Change
Number of Shocks in Burst
Data from Clouter et al., 2017
Data from Wang et al., 2018
Simulated Hippocampal Weights
Accuracy (%)
Synaptic Efficacy
Phase offset condition
(c)
Simulated hippocampal weight change
ϕ V - A
Visual -> Auditory (N = 48)
Auditory -> Visual (N = 48)
Synaptic Efficacy
ϕ A - V
Behavioural results of cued recall accuracy
Visual cue (N = 23)
Auditory cue (N = 23)
Normalised Recall Accuracy
Phase bin
(d)
Anterior hippocampus
PSD (10·log10(μV²))
Frequency (Hz)
t value
(e)
Empirical data: hippocampal source ITPC
Remembered Trials
Forgotten Trials
ITPC
Frequency (Hz)
Simulated data: hippocampal ITPC average across groups
High weights trials
Low weights trials
ITPC
Frequency (Hz)
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Summary of the findings of the impact of RSS on human episodic memory. **(a)** Computational model that implements theta-phase-induced plasticity and STDP. Two subgroups of neurons in the neocortex receive inputs from visual and auditory stimuli. The hippocampal neurons receive the corresponding inputs and ongoing theta oscillations (4 Hz). STDP is modulated by the theta oscillations, resulting in LTP and LTD at opposing phases. The human experiments from Clouter et al. [68] are simulated by feeding two 4 Hz cosine waves into the neocortical neurons, with phase offsets between the two cosine waves being 0°, 90°, 180° or 270°. Hippocampal theta phase is reset with a 180° offset from the cosine wave that represents visual stimulus after stimulus onset. **(b)** Simulated hippocampal weight change reproduces the findings from Left: Huerta and Lisman [10]; and Right: Clouter et al. [68] and Wang et al. [69]. **(c)** Top: simulated hippocampal weight changes between two groups of neurons simulated by the model that only implements the STDP learning. Bottom: results of the human episodic memory experiments using 37.5 Hz multisensory RSS. The actual phase differences between visual and auditory activity were 0°, 90°, 180° and 270° in phase bin 1, 2, 3 and 4, respectively. Recall accuracy in phase bin 2 was significantly better when memory was cued with a visual stimulus than cued with an auditory stimulus. The pattern was reversed in phase bin 4, which is consistent with the pattern simulated by the STDP model. **(d)** Left top: An example coronal MRI image from Chan et al. [79], before implanting electrodes to the patient. Left bottom: The power spectral density of the iEEG from a patient with medically intractable epilepsy. The red plus sign represents the approximate location of the depth electrode contact. The blue line represents the baseline condition that the visuo-auditory stimulation was at 0 dB. The red line represents the 40 Hz visual-auditory stimulation condition. Right: Source localised differences in intertrial-phase-coherence (ITPC, a phase-locking measure) of the EEG data between subsequently remembered and forgotten trials. MNI coordinates: –40, –31, and –10. **(e)** Left: the ITPC at the left hippocampus as a function of frequency. Right: the ITPC of the simulated hippocampal LFP data of high weights trials and low weights trials. All error bars represent the standard error of the mean (SE). (EEG), Electroencephalography.
(d) Adapted from Chan et al. [79].

acetylcholine or monoamines, in the above-described memory effects. A considerable number of studies in animal models reveals strong effects of neuromodulation on the strength and shape of STDP (reviewed in Ref. [97]), which has been suggested to link fast-acting plasticity mechanisms (such as STDP and theta-phase-dependent plasticity) to more behaviourally relevant time scales.

Conclusions

The exact mechanism and the neuronal changes responsible for the memory-enhancing effects produced by RSS have yet to be clarified. Based on our findings, we propose a co-ordination between STDP and theta-phase-dependent plasticity in the human hippocampus. Our model suggests that a theta-phase reset occurs in the hippocampus in response to the stimuli to be encoded from sensory cortices. This reset aligns incoming information in a manner that enhances the likelihood of inducing LTP and, consequently, the formation of a new memory trace [76]. This interpretation is consistent with a recent human single-neuron study, showing that nested theta–gamma coupling predicted co-firing of neurons at short time delays and subsequent successful memory [98]. Research on this question is important not only because it links basic neuroscience findings in animals with human behaviour but also because driving the human brain at specific frequencies could be a potential noninvasive treatment for patients with memory problems. For instance, recent investigations in Alzheimer's disease (AD) mouse models [99,100] and patients with AD [79] reported structural changes in the hippocampus following 40 Hz audio-visual stimulation, with consequent effects on hippocampal-related cognitive tasks. Notwithstanding the current debate on the effectiveness of such treatments (see Refs. [101–104]), RSS may offer an opportunity for the development of noninvasive therapeutic interventions in clinical populations with impaired hippocampal function.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

S.H. and A.C. act as scientific advisers to Clarity Technologies Inc., potentially benefiting from this review. However, we affirm that this affiliation did not influence the study's design or interpretation. The research maintains objectivity and adherence to scientific standards, and we believe the disclosed conflict of interest does not compromise the integrity of the presented findings.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Moscovitch M: **The hippocampus as a "stupid," domain-specific module: implications for theories of recent and remote memory, and of imagination**. *Can J Exp Psychol Rev Can De Psychol expérimentale* 2008, **62**:62-79.
2. Neves G, Cooke SF, Bliss TVP: **Synaptic plasticity, memory and the hippocampus: a neural network approach to causality**. *Nat Rev Neurosci* 2008, **9**:65-75.
3. Burgess N, Oapos, Keefe J, Morris RGM, Frey U: **Hippocampal synaptic plasticity: role in spatial learning or the automatic recording of attended experience?** *Philos Trans R Soc Lond Ser B Biol Sci* 1997, **352**:1489-1503.
4. Hebb DO: **The Organization of Behavior; a Neuropsychological Theory**. Wiley; 1949.
5. Bi G, Poo M: **Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type**. *J Neurosci* 1998, **18**:10464-10472.
6. Bliss TVP, Lømo T: **Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path**. *J Physiol* 1973, **232**:331-356.

7. Nabavi S, Fox R, Proulx CD, Lin JY, Tsien RY, Malinow R: **Engineering a memory with LTD and LTP**. *Nature* 2014, **511**:348-352.

8. Whitlock JR, Heynen AJ, Shuler MG, Bear MF: **Learning induces long-term potentiation in the hippocampus**. *Science* 2006, **313**:1093-1097.

9. Hasselmo ME: **What is the function of hippocampal theta rhythm? — Linking behavioral data to phasic properties of field potential and unit recording data**. *Hippocampus* 2005, **15**:936-949.

10. Huerta PT, Lisman JE: **Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro**. *Neuron* 1995, **15**:1053-1063.

11. Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME: **Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough**. *J Neurosci* 2003, **23**:11725-11731.

12. Parish G, Hanslmayr S, Bowman H: **The sync/desync model: how a synchronized hippocampus and a desynchronized neocortex code memories**. *J Neurosci* 2018, **38**:3428-3440.

13. Feldman DE: **The spike-timing dependence of plasticity**. *Neuron* 2012, **75**:556-571.

14. Beck H, Goussakov IV, Lie A, Helmstaedter C, Elger CE: **Synaptic plasticity in the human dentate gyrus**. *J Neurosci* 2000, **20**:7080-7086.

15. Chen WR, Lee S, Kato K, Spencer DD, Shepherd GM, Williamson A: **Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex**. *Proc Natl Acad Sci USA* 1996, **93**:8011-8015.

16. • Mansvelder HD, Verhoog MB, Goriounova NA: **Synaptic plasticity in human cortical circuits: cellular mechanisms of learning and memory in the human brain?** *Curr Opin Neurobiol* 2019, **54**:186-193.

This review paper summarises and compares recent studies on synaptic plasticity in the animal and human brains *in vitro* and *in vivo* and links synaptic plasticity to behaviours of learning and memory.

17. Arnolds DEAT, Lopes Da Silva FH, Aitink JW, Kamp A, Boeijinga P: **The spectral properties of hippocampal EEG related to behaviour in man**. *Electroencephalogr Clin Neurophysiol* 1980, **50**:324-328.

18. Larson J, Lynch G: **Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events**. *Science* 1986, **232**:985-988.

19. Larson J, Wong D, Lynch G: **Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation**. *Brain Res* 1986, **368**:347-350.

20. Rose GM, Dunwiddie TV: **Induction of hippocampal long-term potentiation using physiologically patterned stimulation**. *Neurosci Lett* 1986, **69**:244-248.

21. Buzsáki G: **Theta oscillations in the hippocampus**. *Neuron* 2002, **33**:325-340.

22. Buzsáki G: **Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory**. *Hippocampus* 2005, **15**:827-840.

23. Dragoi G, Harris KD, Buzsáki G: **Place representation within hippocampal networks is modified by long-term potentiation**. *Neuron* 2003, **39**:843-853.

24. Dragoi G, Buzsáki G: **Temporal encoding of place sequences by hippocampal cell assemblies**. *Neuron* 2006, **50**:145-157.

25. Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsáki G: **Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm**. *Neuron* 2008, **60**:683-697.

26. Tort ABL, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ: **Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task**. *Proc Natl Acad Sci* 2008, **105**:20517-20522.

27. Mizuseki K, Sirota A, Pastalkova E, Buzsáki G: **Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop**. *Neuron* 2009, **64**:267-280.

28. Griffin AL, Asaka Y, Darling RD, Berry SD: **Theta-contingent trial presentation accelerates learning rate and enhances hippocampal plasticity during trace eyeblink conditioning**. *Behav Neurosci* 2004, **118**:403-411.

29. Lega BC, Jacobs J, Kahana M: **Human hippocampal theta oscillations and the formation of episodic memories**. *Hippocampus* 2012, **22**:748-761.

30. Vertes RP, Albo Z, Di Prisco GV: **Theta-rhythmically firing neurons in the anterior thalamus: implications for mnemonic functions of Papez's circuit**. *Neuroscience* 2001, **104**:619-625.

31. Vertes RP: **Hippocampal theta rhythm: a tag for short-term memory**. *Hippocampus* 2005, **15**:923-935.

32. Hasselmo ME: **Arc length coding by interference of theta frequency oscillations may underlie context-dependent hippocampal unit data and episodic memory function**. *Learn Mem* 2007, **14**:782-794.

33. Hyman JM, Zilli EA, Paley AM, Hasselmo ME: **Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior**. *Hippocampus* 2005, **15**:739-749.

34. Davies CH, Starkey SJ, Pozza MF, Collingridge GL: **GABAB autoreceptors regulate the induction of LTP**. *Nature* 1991, **349**:609-611.

35. Mott DD, Lewis DV: **Facilitation of the induction of long-term potentiation by GABAB receptors**. *Science* 1991, **252**:1718-1720.

36. Mott DD, Lewis DV: **GABAB receptors mediate disinhibition and facilitate long-term potentiation in the dentate gyrus**. *Epilepsy Res Suppl* 1992, **7**:119-134.

37. Larson J, Munkácsy E: **Theta-burst LTP**. *Brain Res* 2015, **1621**:38-50.

38. Huerta PT, Lisman JE: **Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state**. *Nature* 1993, **364**:723-725.

39. Hölscher C, Anwyl R, Rowan MJ: **Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo**. *J Neurosci* 1997, **17**:6470-6477.

40. Pavlides C, Greenstein YJ, Grudman M, Winson J: **Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of θ-rhythm**. *Brain Res* 1988, **439**:383-387.

41. Caporale N, Dan Y: **Spike timing–dependent plasticity: a Hebbian learning rule**. *Annu Rev Neurosci* 2008, **31**:25-46.

42. Dan Y, Poo M-M: **Spike timing-dependent plasticity: from synapse to perception**. *Physiol Rev* 2006, **86**:1033-1048.

43. Silva G, Verhoog M, Goriounova N, Loebel A, Hjorth J, Baayen J, De Kock C, Mansvelder H: **Human synapses show a wide temporal window for spike-timing-dependent plasticity**. *Front Synaptic Neurosci* 2010, **2**:12.

44. Verhoog MB, Goriounova NA, Obermayer J, Stroeder J, Hjorth JJJ, Testa-Silva G, Baayen JC, de Kock CPJ, Meredith RM, Mansvelder HD: **Mechanisms underlying the rules for associative plasticity at adult human neocortical synapses**. *J Neurosci* 2013, **33**:17197-17208.

45. Csemer A, Kovács A, Maamrah B, Pocsai K, Korpás K, Klekner Á, Szücs P, Nánási PP, Pál B: **Astrocyte- and NMDA receptor-dependent slow inward currents differently contribute to synaptic plasticity in an age-dependent manner in mouse and human neocortex**. *Aging Cell* 2023, **22**:e13939.

46. Müller-Dahlhaus: **Plasticity resembling spike-timing dependent synaptic plasticity: the evidence in human cortex**. *Front*

Synaptic Neurosci 2010, **2**:34, https://doi.org/10.3389/fnsyn.2010.00034

47. Stefan K: **Induction of plasticity in the human motor cortex by paired associative stimulation**. *Brain* 2000, **123**:572-584.

48. Wolters A, Schmidt A, Schramm A, Zeller D, Naumann M, Kunesch E, Benecke R, Reiners K, Classen J: **Timing-dependent plasticity in human primary somatosensory cortex: timing-dependent plasticity in human somatosensory cortex**. *J Physiol* 2005, **565**:1039-1052.

49. Rizzo V, Siebner HS, Morgante F, Mastroeni C, Girlanda P, Quartarone A: **Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a Hebbian Mechanism**. *Cereb Cortex* 2009, **19**:907-915.

50. •• Sel A, Verhagen L, Angerer K, David R, Klein-Flügge MC, Rushworth MFS: **Increasing and decreasing interregional brain coupling increases and decreases oscillatory activity in the human brain**. *Proc Natl Acad Sci* 2021, **118**:e2100652118.
This elegant TMS study shows that ccPAS modulates oscillatory networks connectivity as predicted by STDP.

51. • Trajkovic J, Romei V, Rushworth MFS, Sel A: **Changing connectivity between premotor and motor cortex changes inter-areal communication in the human brain**. *Prog Neurobiol* 2023, **228**:102487.
This study shows that ccPAS induces STDP-like changes in oscillatory phase synchrony, which is also predictive of subsequent oscillatory power during motor behaviour

52. Andrade-Talavera Y, Fisahn A, Rodríguez-Moreno A: **Timing to be precise? An overview of spike timing-dependent plasticity, brain rhythmicity, and glial cells interplay within neuronal circuits**. *Mol Psychiatry* 2023, **28**:2177-2188, https://doi.org/10.1038/s41380-023-02027-w

53. Veniero D, Ponzo V, Koch G: **Paired associative stimulation enforces the communication between interconnected areas**. *J Neurosci* 2013, **33**:13773-13783.

54. Fu Y-X, Djupsund K, Gao H, Hayden B, Shen K, Dan Y: **Temporal specificity in the cortical plasticity of visual space representation**. *Science* 2002, **296**:1999-2003.

55. McMahon DBT, Leopold DA: **Stimulus timing-dependent plasticity in high-level vision**. *Curr Biol* 2012, **22**:332-337.

56. Yao H, Dan Y: **Stimulus timing-dependent plasticity in cortical processing of orientation**. *Neuron* 2001, **32**:315-323.

57. Koch G, Ponzo V, Lorenzo FD, Caltagirone C, Veniero D: **Hebbian and anti-hebbian spike-timing-dependent plasticity of human cortico-cortical connections**. *J Neurosci* 2013, **33**:9725-9733.

58. Conde V, Vollmann H, Taubert M, Sehm B, Cohen LG, Villringer A, Ragert P: **Reversed timing-dependent associative plasticity in the human brain through interhemispheric interactions**. *J Neurophysiol* 2013, **109**:2260-2271.

59. Titiz AS, Hill MRH, Mankin EA, Aghajan ZM, Eliashiv D, Tchemodanov N, Maoz U, Stern J, Tran ME, Schuette P, *et al*.: **Theta-burst microstimulation in the human entorhinal area improves memory specificity**. *eLife* 2017, **6**:e29515.

60. Fell J, Axmacher N: **The role of phase synchronization in memory processes**. *Nat Rev Neurosci* 2011, **12**:105-118.

61. Geva-Sagiv M, Mankin EA, Eliashiv D, Epstein S, Cherry N, Kalender G, Tchemodanov N, Nir Y, Fried I: **Augmenting hippocampal–prefrontal neuronal synchrony during sleep enhances memory consolidation in humans**. *Nat Neurosci* 2023, **26**:1-11.

62. Ngo H-VV, Martinetz T, Born J, Mölle M: **Auditory closed-loop stimulation of the sleep slow oscillation enhances memory**. *Neuron* 2013, **78**:545-553.

63. Esfahani MJ, Farboud S, Ngo H-VV, Schneider J, Weber FD, Talamini LM, Dresler M: **Closed-loop auditory stimulation of sleep slow oscillations: basic principles and best practices**. *Neurosci Biobehav Rev* 2023, **153**:105379.

64. Hanslmayr S, Axmacher N, Inman CS: **Modulating human memory via entrainment of brain oscillations**. *Trends Neurosci* 2019, **42**:485-499.

65. Kucewicz MT, Worrell GA, Axmacher N: **Direct electrical brain stimulation of human memory: lessons learnt and future perspectives**. *Brain* 2023, **146**:2214-2226.

66. Mankin EA, Fried I: **Modulation of human memory by deep brain stimulation of the entorhinal-hippocampal circuitry**. *Neuron* 2020, **106**:218-235.

67. Staresina BP: **Coupled sleep rhythms for memory consolidation**. *Trends Cogn Sci* 2024, **0**:339-351.

68. •• Clouter A, Shapiro KL, Hanslmayr S: **Theta phase synchronization is the glue that binds human associative memory**. *Curr Biol* 2017, **27**:3143-3148.e6.
This is the first study to show that multisensory synchronization specifically at theta modulates episodic memory.

69. Wang D, Clouter A, Chen Q, Shapiro KL, Hanslmayr S: **Single-trial phase entrainment of theta oscillations in sensory regions predicts human associative memory performance**. *J Neurosci* 2018, **38**:6299-6309.

70. Roberts BM, Clarke A, Addante RJ, Ranganath C: **Entrainment enhances theta oscillations and improves episodic memory**. *Cogn Neurosci* 2018, **9**:181-193.

71. Köster M, Martens U, Gruber T: **Memory entrainment by visually evoked theta-gamma coupling**. *NeuroImage* 2019, **188**:181-187.

72. Hermiller MS, VanHaerents S, Raij T, Voss JL: **Frequency-specific noninvasive modulation of memory retrieval and its relationship with hippocampal network connectivity**. *Hippocampus* 2019, **29**:595-609.

73. Hermiller MS, Chen YF, Parrish TB, Voss JL: **Evidence for immediate enhancement of hippocampal memory encoding by network-targeted theta-burst stimulation during concurrent fMRI**. *J Neurosci* 2020, **40**:7155-7168.

74. •• Plog E, Antov MI, Bierwirth P, Keil A, Stockhorst U: **Phase-synchronized stimulus presentation augments contingency knowledge and affective evaluation in a fear-conditioning task**. *eNeuro* 2022, **9**:1-19 ENEURO.0538-20.2021.
This is the first study to demonstrate that multisensory synchronization at theta modulates fear memory.

75. Plog E, Antov MI, Bierwirth P, Stockhorst U: **Effects of phase synchronization and frequency specificity in the encoding of conditioned fear — a web-based fear conditioning study**. *PLoS One* 2023, **18**:e0281644.

76. Wang D, Parish G, Shapiro KL, Hanslmayr S: **Interaction between theta phase and spike timing-dependent plasticity simulates theta-induced memory effects**. *eNeuro* 2023, **10**:1-18.

77. •• Wang D, Shapiro KL, Hanslmayr S: **Altering stimulus timing via fast rhythmic sensory stimulation induces STDP-like recall performance in human episodic memory**. *Curr Biol* 2023, **33**:3279-3288.e7.
This is the first study to show behavioural evidence for STDP in human episodic memory.

78. LT Blanpain, E Chen, J Park, MY Walelign, RE Gross, BT Cabaniss, JT. Willie, AC Singer : Multisensory Flicker Modulates Widespread Brain Networks and Reduces Interictal Epileptiform Discharges in Humans; 2023. doi: 10.1101/2023.03.14.23286691.

79. Chan D, Suk H-J, Jackson BL, Milman NP, Stark D, Klerman EB, Kitchener E, Avalos VSF, de Weck G, Banerjee A, *et al*.: **Gamma frequency sensory stimulation in mild probable Alzheimer's dementia patients: results of feasibility and pilot studies**. *PLoS One* 2022, **17**:e0278412.

80. van der Plas M, Wang D, Brittain J-S, Hanslmayr S: **Investigating the role of phase-synchrony during encoding of episodic memories using electrical stimulation**. *Cortex* 2020, **133**:37-47.

81. Brignani D, Ruzzoli M, Mauri P, Miniussi C: **Is transcranial alternating current stimulation effective in modulating brain oscillations?** *PLoS One* 2013, **8**:e56589.

82. Héroux ME, Loo CK, Taylor JL, Gandevia SC: **Questionable science and reproducibility in electrical brain stimulation research**. *PLoS One* 2017, **12**:e0175635.

83. Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, Opitz A, Mehta A, Pack CC, Krekelberg B, *et al.*: **Immediate neurophysiological effects of transcranial electrical stimulation**. *Nat Commun* 2018, **9**:5092.

84. Chen Q, Wang D, Shapiro KL, Hanslmayr S: **Using fast visual rhythmic stimulation to control inter-hemispheric phase offsets in visual areas**. *Neuropsychologia* 2021, **157**:107863.

85. Adaikkan C, Middleton SJ, Marco A, Pao P-C, Mathys H, Kim DN-W, Gao F, Young JZ, Suk H-J, Boyden ES, *et al.*: **Gamma entrainment binds higher-order brain regions and offers neuroprotection**. *Neuron* 2019, **102**:929-943.e8.

86. Griffiths BJ, Jensen O: **Gamma oscillations and episodic memory**. *Trends Neurosci* 2023, **0**:832-846.

87. Griffiths BJ, Weinert DE, Jensen O, Staudigl T: Imperceptible Gamma-Band Sensory Stimulation Enhances Episodic Memory Retrieval; 2023. ⟨doi:10.1101/2023.07.21.550057⟩.

88. Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser M-B, Moser EI: **Frequency of gamma oscillations routes flow of information in the hippocampus**. *Nature* 2009, **462**:353-357.

89. Griffiths BJ, Parish G, Roux F, Michelmann S, van der Plas M, Kolibius LD, Chelvarajah R, Rollings DT, Sawlani V, Hamer H, *et al.*: **Directional coupling of slow and fast hippocampal gamma with neocortical alpha/beta oscillations in human episodic memory**. *Proc Natl Acad Sci* 2019, **116**:21834-21842.

90. Arieli A, Sterkin A, Grinvald A, Aertsen A: **Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses**. *Science* 1996, **273**:1868-1871.

91. Bergmann TO, Mölle M, Schmidt MA, Lindner C, Marshall L, Born J, Siebner HR: **EEG-guided transcranial magnetic stimulation reveals rapid shifts in motor cortical excitability during the human sleep slow oscillation**. *J Neurosci* 2012, **32**:243-253.

92. Donoghue T, Schaworonkow N, Voytek B: **Methodological considerations for studying neural oscillations**. *Eur J Neurosci* 2022, **55**:3502-3527.

93. Jacobs J: **Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory**. *Philos Trans R Soc B Biol Sci* 2014, **369**:20130304.

94. Qasim SE, Fried I, Jacobs J: **Phase precession in the human hippocampus and entorhinal cortex**. *Cell* 2021, **184**:3242-3255.e10.

95. Thut G, Bergmann TO, Fröhlich F, Soekadar SR, Brittain J-S, Valero-Cabré A, Sack AT, Miniussi C, Antal A, Siebner HR, *et al.*: **Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: a position paper**. *Clin Neurophysiol* 2017, **128**:843-857.

96. Zrenner C, Ziemann U: **Closed-loop brain stimulation**. *Biol Psychiatry* 2023, **0**:545-552.

97. Brzosko Z, Mierau SB, Paulsen O: **Neuromodulation of spike-timing-dependent plasticity: past, present, and future**. *Neuron* 2019, **103**:563-581.

98. Roux F, Parish G, Chelvarajah R, Rollings DT, Sawlani V, Hamer H, Gollwitzer S, Kreiselmeyer G, ter Wal MJ, Kolibius L, *et al.*: **Oscillations support short latency co-firing of neurons during human episodic memory formation**. *eLife* 2022, **11**:e78109.

99. Adaikkan C, Tsai L-H: **Gamma entrainment: impact on neurocircuits, glia, and therapeutic opportunities**. *Trends Neurosci* 2020, **43**:24-41.

100. •• Martorell AJ, Paulson AL, Suk H-J, Abdurrob F, Drummond GT, Guan W, Young JZ, Kim DN-W, Kritskiy O, Barker SJ, *et al.*: **Multi-sensory gamma stimulation ameliorates Alzheimer's-associated pathology and improves cognition**. *Cell* 2019, **177**:256-271.e22.

The study shows that 40 Hz auditory and multisensory stimulation to the AD mouse models entrained both the sensory cortex and the hippocampus. AD pathology in the sensory cortex and areas involving higher cognitive functions, such as the hippocampus and medial prefrontal cortex, was significantly reduced. Learning and memory performance have also been improved.

101. Soula M, Martín-Ávila A, Zhang Y, Dhingra A, Nitzan N, Sadowski MJ, Gan W-B, Buzsáki G: **Forty-hertz light stimulation does not entrain native gamma oscillations in Alzheimer's disease model mice**. *Nat Neurosci* 2023, **26**:570-578.

102. Schneider M, Tzanou A, Uran C, Vinck M: **Cell-type-specific propagation of visual flicker**. *Cell Rep* 2023, **42**:112492.

103. Kahn M, Chan D, Wang D, Geigenmuller U, Blanco-Duque C, Murdock MH, Suk H-J, Jackson B, Jakkamsetti V, Niederst E, et al.: Gamma Sensory Stimulation and Effects on the Brain; 2023. ⟨doi:10.1101/2023.10.30.564197⟩.

104. Carstensen M, Pedersen JT, Carstensen J: Unexpected Contribution to the Prevailing Trend of Positive Results for 40 Hz Light Flicker; 2023. ⟨doi:10.1101/2023.10.27.564342⟩.