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 non-invasively 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).
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.
which RSS propagates from lower to higher brain regions simulated results (Figure 2e). Therefore, the degree to this was linked with the hippocampal STDP model goten trials is localised in the hippocampus (Figure 2d). 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] (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 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,
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 hippocampal 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 is consistent with the pattern simulated by the STDP model. (d) 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.

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 benefitting 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


This review paper summarizes and compares recent studies on synaptic plasticity in the animal and human brains. It discusses the role of hippocampal theta rhythm in learning and memory, and how this rhythm may be linked to behavioral data and phasic properties of field potential and unit recording data.

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Episodic memory and plasticity in humans

Wang et al. 9


This elegant TMS study shows that ccPAS modulates oscillatory network connectivity as predicted by STDP.


This study shows that ccPAS induces STDP-like changes in oscillatory phase synchrony, which is also predictive of subsequent oscillatory power during motor behaviour.


This is the first study to show that multisensory synchronization specifically at theta modulates episodic memory.


This is the first study to demonstrate that multisensory synchronization at theta modulates fear memory.


This is the first study to show behavioural evidence for STDP in human episodic memory.


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.


