

Review

Modulating Human Memory via Entrainment of Brain Oscillations

Simon Hanslmayr,^{1,*} Nikolai Axmacher,² and Cory S. Inman³

In the human brain, oscillations occur during neural processes that are relevant for memory. This has been demonstrated by a plethora of studies relating memory processes to specific oscillatory signatures. Several recent studies have gone beyond such correlative approaches and provided evidence supporting the idea that modulating oscillations via frequency-specific entrainment can alter memory functions. Such causal evidence is important because it allows distinguishing mechanisms directly related to memory from mere epiphenomenal oscillatory signatures of memory. This review provides an overview of stimulation studies using different approaches to entrain brain oscillations for modulating human memory. We argue that these studies demonstrate a causal link between brain oscillations and memory, speaking against an epiphenomenal perspective of brain oscillations.

Brain Oscillations and Memory

Brain oscillations (see [Glossary](#)) arise from synchronized interactions between neural populations [1]. Memories are thought to primarily rely on changes in synaptic connectivity, which – among other factors – depend on the level of synchrony between neurons [2]. Therefore, brain oscillations arguably are centrally important for memory processes. Classically, oscillations are divided into different frequency bands including delta, theta, alpha, beta, and gamma oscillations (from slow to fast). It is important to note that all these frequencies, and not only the more commonly discussed theta and gamma bands, have been linked to memory processes. Furthermore, brain oscillations are not exclusively linked to memory, and are linked to many other cognitive processes. These seemingly nonspecific relationships raise a fundamental question – what are the mechanisms that oscillations implement, and how do they serve memory? Current theories argue that oscillations carry out basic or canonical neural computations on different temporal and spatial scales [3]. These basic computations can each serve several different cognitive processes, with memory being one of them [4,5]. Thus, even if time-frequency oscillatory patterns cannot ultimately be specifically linked to individual cognitive processes, one could envisage them as ‘indexing’ basic computations, such as maintenance of information, neural communication, and spike timing-dependent plasticity, as has been elaborated in previous reviews (e.g., [4–7]). A major goal of modern cognitive neuroscience is to determine what these computations are.

Before one can uncover these oscillatory mechanisms, however, it is important to clarify the nature of the relationship between a cognitive process, namely memory, and brain oscillations. More specifically, is the relationship between oscillations and memory of a **causal** nature, or is it of an epiphenomenal nature?

If oscillations are causally linked to memory processes, then one can sensibly hope to uncover their specific mechanistic roles in memory. However, it is important to keep in mind that any cognitive function (e.g., memory) may have several underlying causes. An observable effect on memory enhancement therefore may be due to various different cognitive processes (e.g., enhanced

Highlights

Brain oscillations in various frequency bands have been linked to memory processes.

Oscillatory entrainment refers to the modulation of neural oscillations that in the human brain can be achieved via three rhythmic stimulation approaches: sensory stimulation, noninvasive electric/magnetic stimulation, and invasive electrical stimulation.

Studies using different techniques of entrainment lend support to the idea that brain oscillations can modulate human memory, and suggest that oscillations are causally relevant for memory processes

¹Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham, UK

²Department of Neuropsychology, Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

³Department of Neurosurgery, Emory University, 1365 Clifton Road North East, Atlanta, GA 30322, USA

*Correspondence:
s.hanslmayr@bham.ac.uk
(S. Hanslmayr).

attention, saliency, or deeper processing) that can each, in turn, be based on various basic computational mechanisms and their putative corresponding oscillatory correlates. In other words, although oscillatory mechanisms may be sufficient conditions for a given cognitive function, they may not be necessary for this function because it could also be accomplished via other mechanisms.

A causal role for oscillations in memory can be tested by experiments which modulate oscillations and assess whether such modulation has consequences for behavioral measures of memory. Modulation of oscillations can be achieved via **entrainment** (Box 1). Entrainment modifies naturally occurring oscillations, and thus probes the causal relevance of a natural physiologically occurring state. This is not to be confused with methods that induce atypical rhythmic activity, in other words activity that is not naturally present in the stimulated area (e.g., as in electroconvulsive therapy), which also can have cognitive consequences that would more likely take the form of an impairment or a negligible effect on the memory behavior of interest. In the human brain, oscillations can be entrained broadly via three different stimulation approaches: (i) sensory entrainment, (ii) noninvasive electric/magnetic entrainment, and (iii) invasive electric entrainment. These entrainment approaches are increasingly used in basic neuroscience studies to ask specific questions about the mechanistic role of oscillations and memory, as well as in applied studies where the goal is to improve memory functions in the healthy and nonhealthy brain. In the following we review these results, focusing on studies examining possible effects of oscillatory entrainment on memory performance in **working memory** (WM) and **episodic memory** tasks. With this specific focus on memory, this review differs from some previous reviews [8–10]. As discussed in more detail later, sample-size considerations are an important theme in this context, and an overview of the key studies under discussion, together with their respective sample sizes, can be found in Table 1.

Sensory Entrainment – The Poor Man’s Optogenetics

The idea of inducing oscillatory rhythms via sensory entrainment (Box 2) so as to modulate memory performance is not new [11]. Williams [12] found that the recognition performance of subjects increased when items during encoding followed a ‘flicker’ at 10 Hz (i.e., alpha) compared with a nonflicker condition, as well as compared with slower and faster control frequencies. Similar findings have been obtained using auditory rhythmic stimulation, where memory performance increased after binaural beat stimulation in the beta frequency range [13]. Interestingly, recent studies in a mouse model of Alzheimer’s disease showed that driving hippocampal neurons at gamma frequency (40 Hz) reduces the level of β -amyloid plaques [14,15]. This suppressive effect on β -amyloid plaques was present with invasive (optogenetics) stimulation as well as with noninvasive sensory flicker, suggesting that sensory entrainment indeed affects activity (and brain structure) in the hippocampus. Becher and colleagues [16] were able to confirm that sensory rhythmic stimulation affects synchronization levels in human medial temporal lobe regions. Based on these findings it appears feasible to use sensory rhythmic stimulation to control the degree of synchronization between neural assemblies processing a given stimulus, and this in turn should affect memory. Specifically, in such a scenario two elements of an associative stimulus (i.e., a sound and a video) can be modulated separately such that they are synchronized in one condition and asynchronous in another condition. If neural synchronization indeed plays a role in modulating synaptic plasticity, then such a manipulation should impact on memory.

Following this idea, Clouter and colleagues [17] presented multisensory audiovisual stimuli in an episodic memory paradigm where subjects remembered sound–video associations. The experiments were inspired by physiological studies suggesting that the phase of a theta oscillation represents windows for long-term potentiation (LTP) and long-term depression (LTD) [18–20]. One can extrapolate from these studies that conditions which bias neurons to fire in the same

Glossary

Brain oscillations: the rhythmic activity of a population of neurons within a given frequency band. Brain oscillations can be measured at different spatial scales ranging from below a millimeter in case of local field potentials to about 1 cm for intracranial electroencephalography (iEEG), 1–2 cm for magnetoencephalography (MEG), and several centimeters in the case of EEG.

Causality: two variables x and y are causally related if a manipulation of x (e.g., oscillations) causes a change in y (e.g., memory).

Entrainment: ‘[...] is the process whereby two interacting oscillating systems, which have different periods when they function independently, assume a common period.’ (https://en.wikipedia.org/wiki/Injection_locking#Entrainment). In neuroscience, the two oscillating systems are (i) a rhythmic stimulator (i.e., flickering stimulus, electrical pulses, current sine wave, etc.) and (ii) the stimulated neural population.

Entrainment echoes: a narrow band neural response to entrainment which is phase-locked to the entraining stimulus and outlasts stimulation by at least two oscillatory cycles (Box 1).

Episodic memory: memory for specific experiences, often from an autobiographical perspective, in which the time, place, and other contextual information can be explicitly stated or internally conjured.

Working memory (WM): the process by which information is maintained and manipulated across a short time-interval (typically a few seconds). WM has a limited capacity of only a few items but allows their direct access.

Box 1. Entrainment of Neural Oscillations

Entrainment occurs if a population of neurons in a stimulated region adopts the phase of an entraining stimulus (Figure 1A). The entraining stimulus has two effects on population activity: (i) an increase in signal intensity (or power) as more and more neurons become phase aligned to the entraining stimulus, and (ii) phase alignment of the population activity to the entraining stimulus. Crucially, entrainment does not take place instantaneously but takes time [86], depending on stimulation intensity [87,88]. This introduces a progression of states which a neural population must go through during entrainment. Initially, the neural population is at a baseline state, where neurons are moderately synchronized. Such a baseline state can take various forms, from 'resting state' (e.g., to produce alpha oscillations) to experimentally controlled settings (e.g., visual gratings to produce gamma oscillations, or spatial navigation to produce theta). The important point is that the 'to-be-entrained' oscillation is visible in the population before entrainment starts (i.e., a deviation from the $1/f$ spectrum [89,90]). Accordingly, a neural system which lacks oscillations at the appropriate band cannot be entrained. The second stage is the build-up phase where the neural population begins to pick up on the entraining stimulus. During this stage the phase of the population activity begins to move towards the phase of the entraining stimulus. The third stage is the fully entrained state where the neural population is maximally entrained. During this stage the phase-lag between the neural population and the entraining stimulus is zero. After termination of the entraining stimulus, the neural population slowly reverts to the baseline state, giving rise to an entrainment echo [40,41,91].

There are several ways to measure entrainment. One way is to measure the power and phase of a stimulated region during entrainment. However, this is not trivial given stimulation artifacts or superimposed event-related responses (event-related potentials, ERPs). Entrainment echoes, on the other hand, allow a relatively straightforward assessment of entrainment, which is only limited by the temporal 'smearing' of the filters applied (if any). Another way to measure entrainment is the so-called Arnold tongue (Figure 1B), which requires plotting the strength of entrainment against stimulation intensity at different frequencies. The Arnold tongue describes the phenomenon that low intensities will only entrain internally present (i.e., resonant) frequencies. With increasing stimulation intensity, frequencies that are not present in the system can also be artificially induced [88,92].

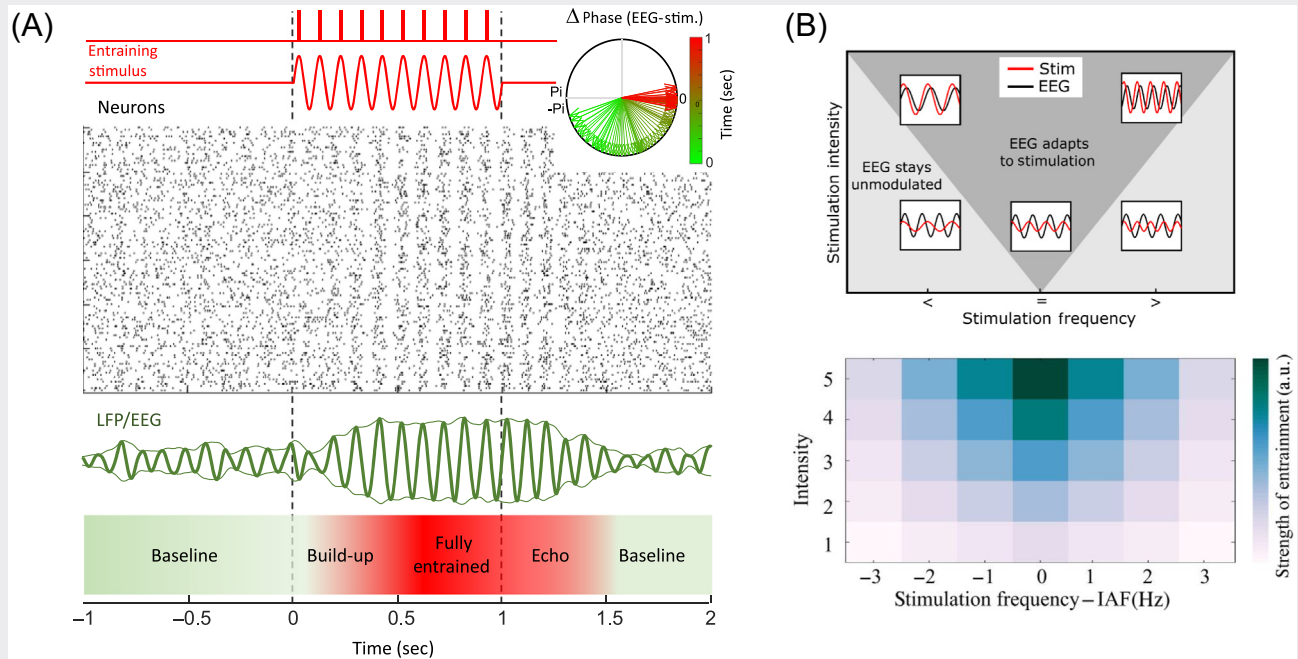


Figure 1. Basic Principles of Neural Entrainment and Ways to Measure It. (A) A population of neurons is entrained either via a continuous stimulus (sine wave) or via pulses of stimuli. A raster plot shows simulated spiking activity in a neural population, the local field potential (LFP)/EEG (electroencephalography) shows the population level activity. The difference in phase between the entraining stimulus and the population activity is shown on the upper right, with the colors indicating time from the start (green) to the end (red) of entrainment. (B) The Arnold tongue. The intensity of stimulation (y axis) is plotted against internal frequency (x axis). Low stimulation intensities will only cause entrainment if the stimulation frequency matches the internal frequency (IAF). Figure adapted, with permission, from [88,92]. Abbreviations: a.u., arbitrary units; stim., stimulation.

LTP-inducing theta phase should lead to better memory compared with conditions which bias neurons to fire in different (LTP- and LTD-inducing) theta phases. A different, but not mutually exclusive framework, links theta oscillations to 'active sensing', in particular in the visual and auditory domains [21]. Within this framework the internal rhythms would be entrained to allow an optimal flow of sensory information. Building on these assumptions, Clouter and colleagues showed that synchronized presentation of auditory and visual stimuli leads to better memory

Table 1. An Overview of the Reviewed Entrainment Studies Showing an Effect on Memory Performance^{a,b}

Number of subjects ^c	Entrainment method	Entrainment measured during stimulation	Entrainment measured after stimulation	Refs
24/24/9/24	Sens. entr.	+ SSSEP	–	Clouter <i>et al.</i> [17]
24	Sens. entr.	+ SSSEP	–	Wang <i>et al.</i> [22]
50/40	Sens. entr.	+ Power	+ EEG power	Roberts <i>et al.</i> [23]
11	Sens. entr.	+ ERP, power	–	Ngo <i>et al.</i> [26]
13	CL sens. entr.	+ ERP, power	–	Papalambros <i>et al.</i> [28]
16	CL sens. entr.	+ ERP, power	–	Ong <i>et al.</i> [29]
13	tES	–	+ EEG power	Marshall <i>et al.</i> [32]
17	rTMS	+ EEG power, ITPC	+ EEG power, ITPC	Albouy <i>et al.</i> [40]
18	tES	–	–	Polania <i>et al.</i> [42]
10/24	tES	+ BOLD connecton	–	Violante <i>et al.</i> [43]
16/14/15	tES	–	+ EEG phase connectivity	Alekseichuk <i>et al.</i> [47]
72	tES	–	–	Lara <i>et al.</i> [48]
33	tES	–	+ EEG power	Vosskhi <i>et al.</i> [50]
32	tES	–	–	Wolinski <i>et al.</i> [51]
7/13	rTMS	–	–	Sauseng <i>et al.</i> [55]
25/25	tES	–	–	Borghini <i>et al.</i> [56]
19	rTMS	–	+ ITPC	Hanslmayr <i>et al.</i> [41]
14	DBS	–	+ iEEG PAC	Inman <i>et al.</i> [64]
4	DBS	–	+ iEEG phase connectivity	Kim <i>et al.</i> [76]

^aThe table lists sample sizes, and shows whether physiological measures of entrainment were obtained (+, yes; –, no), and how entrainment was measured

^bAbbreviations: BOLD, blood oxygen level-dependent; CL, closed loop; DBS, deep brain stimulation; EEG, electroencephalography; ERP, event-related potential; iEEG, intracranial EEG; ITPC, intertrial phase connectivity; PAC, phase–amplitude coupling; rTMS, repetitive transcranial magnetic stimulation; sens. entr., sensory entrainment; SSSEP, sensory steady-state evoked potential; tES, transcranial electric stimulation.

^cIf a study included several experiments the *N* values are given per experiment (i.e., 24/9).

versus asynchronously presented stimuli (Figure 1A). This memory advantage for synchronous over asynchronous conditions was specific to the theta rhythm (4 Hz), compared with slower (1.7 Hz) and faster (10.5 Hz) rhythms. Intriguingly, synchronizing stimuli at 4 Hz led to better memory compared not only with asynchronous but also to natural stimuli (i.e., unmodulated movie–sound pairs). These findings were replicated and extended, demonstrating that, in human participants, the degree to which auditory and visual brain regions followed the entrainment on a single-trial level predicted later memory [22]. On a single trial increased synchrony between auditory and visual brain regions in the theta range led to better memory. Finally, a study by Roberts and colleagues demonstrated that audiovisual entrainment of theta oscillations between study and test improves retention of context memory [23]. Together, these studies underline the specific importance of theta synchronization for human memory, and suggest that they play a causal role in the formation of associative memory.

Brain oscillations can be entrained not only in the awake brain but also during sleep, for example, via auditory rhythmic stimulation [24–27]. This approach allows targeting of oscillatory signatures that are specific to sleep, and testing of their causal role in memory consolidation processes. Such entrainment during sleep is particularly attractive because the participant is unaware of the stimulation, therefore excluding trivial explanations of any ensuing behavioral effects. Using closed-loop auditory stimulation, Ngo and colleagues [26] demonstrated that auditory stimulation, timed to the endogenous slow-wave activity, enhances both slow-wave activity and memory

Box 2. Three Different Entrainment Approaches**Entrainment via Sensory Stimulation**

Neuronal assemblies, particularly in sensory regions corresponding to the modality of a sensory input, closely follow the temporal dynamics of externally presented stimuli [93–95]. Therefore, presenting stimuli containing a regular rhythmic component is an effective way to entrain oscillatory activity, including in the human brain. Of note, these rhythms are not exclusively induced in sensory regions but are also transmitted to downstream regions, for instance the hippocampus [14,16].

Entrainment via tES/rTMS

Transcranial electric stimulation (tES) is a technique whereby weak electrical currents are applied to the scalp via electrodes. tES describes in fact a family of stimulation protocols ranging from transcranial direct current stimulation (tDCS), where a static current with no rhythmic component is applied, to transcranial alternating current stimulation (tACS), where a waveform oscillates around 0, or a combination of the two where a waveform oscillates between a positive value and 0 [32,34,35]. Repetitive transcranial magnetic stimulation (rTMS) induces current flow in neural tissue by applying short-lasting magnetic pulses (Figure 2). An advantage of rTMS is its focality, namely the ability to target specific brain regions at specific rhythms. This is ideal for testing the causal role of oscillations in local networks. Bifocal stimulation (i.e., stimulating with two rTMS coils) allows causal testing of oscillations at the network level [96]. tES, by contrast, has lower spatial resolution, which is often seen as a disadvantage, but, depending on the goal of the study, can actually be beneficial, for instance when one wants to probe the causal role of oscillations at a broad network level [82]. Another difference between rTMS and tES is that rTMS can induce action potentials (i.e., suprathreshold) whereas tES typically affects only the local field potential (i.e., subthreshold). This is an important difference in the context of entrainment because rTMS in principle allows induction of 'artificial' neural activity, whereas tES can only modulate ongoing activity through resonance [87]. Therefore, tES effects can be expected to be more subtle, but also allow a more direct test of entrainment.

Entrainment via Invasive Electrical Stimulation

Deep brain stimulation (DBS) is the direct electric stimulation of brain tissue in neurological or psychiatric patients undergoing invasive recording and/or stimulation protocols (e.g., epilepsy patients). This clinical context lends the opportunity to both record from and stimulate many different regions of interest throughout the brain, using various stimulation parameters such as location, amplitude, frequency, and timing relative to external stimuli or internal brain states. Targets of stimulation include cortical areas as well as deeper structures, such as the hippocampus, and also several efferent and afferent medial temporal lobe pathways including the entorhinal cortex, medial septum, fornix, lateral temporal lobe, and basolateral amygdala (Figure 3). The exact physiological and behavioral effects of invasive stimulation are still not fully understood [97,98]. Directly stimulating cortical and subcortical areas is thought to induce a complex summation effect of inhibition and excitation of the stimulated area itself, as well as of remote areas via axonal connections to the stimulated area [97,99,100].

consolidation (Figure 1B). These effects were replicated in older adults [28] and in young healthy students taking a nap [29]. However, auditory stimulation during sleep in general elicits slow oscillations and spindles [25,30], and this makes it difficult to ascertain whether any changes in memory performance are due to changes in slow-wave or spindle activity. Another issue is that these studies could not disentangle direct effects of stimulation on the neural processes of memory consolidation, from an indirect improvement of conditions that are conducive for memory consolidation (e.g., clearance of toxic metabolites [31]). Nevertheless, these studies suggest that sensory entrainment of oscillations during sleep can increase memory performance.

Noninvasive Electrical (tES) and Electro-Magnetic (rTMS) Entrainment

Additional ways to entrain oscillations noninvasively are transcranial stimulation methods such as transcranial electric stimulation (tES) or repetitive transcranial magnetic stimulation (rTMS; Box 2). In the following we group entrainment studies by the targeted frequencies, starting with slow (delta) oscillations. We also specifically focus on studies which modulate oscillations at the time these processes are assumed to be active (i.e., online stimulation studies), and emphasize studies which, in addition to behavior, provide physiological data suggesting that oscillations have indeed been entrained (Table 1).

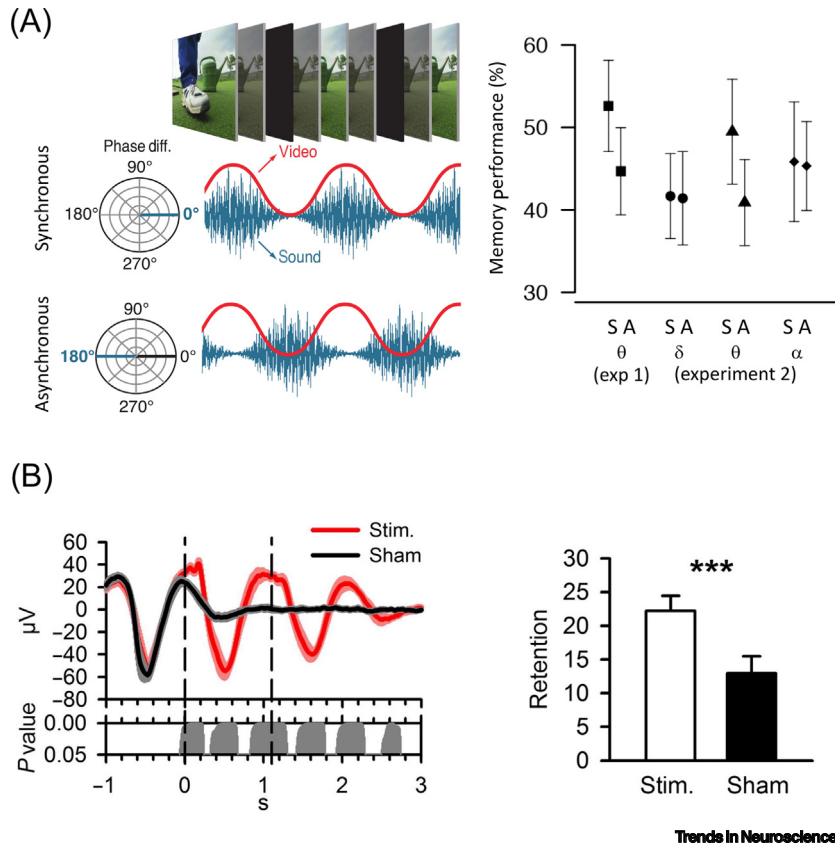


Figure 1. Modulating Memory via Sensory Entrainment of Oscillations during Wakefulness (A) and Sleep (B) in Humans. (A) An audiovisual video clip was presented for 3 s. The video (red) and the audio (blue) were luminance/amplitude-modulated, respectively, with a sine wave at a theta (4 Hz) frequency. The video and sound were modulated during the memory-encoding phase such that the corresponding brain regions would be either in-phase (synchronous condition) or out-of-phase (asynchronous condition). Associative memory recall (right panel) was better for synchronous (S) compared with asynchronous stimuli (A). This effect is specific to theta (4 Hz) and was not obtained using slower (delta, 1.6 Hz) or faster (alpha, 10.4 Hz) entrainment frequencies. (B) Auditory stimulation phase locked to slow oscillations during sleep via closed-loop stimulation entrains slow oscillations as measured via event-related potentials (ERPs) time-locked to the first auditory stimulus (left panel). The red trace shows the ERP for the stimulation condition, the black trace shows the ERP for the sham condition (events marked but no stimulation applied). Auditory closed-loop stimulation improved memory consolidation (right panel). Panels in (A) reproduced, with permission, from [17], panels in (B) reproduced, with permission, from [26]. Abbreviations: phase diff., phase difference; stim., stimulation.

The first evidence (to our knowledge) that slow-wave sleep is causally relevant for human memory consolidation (in the context of entrainment studies) comes from Marshall *et al.* [32], who injected a low-intensity current in sleeping participants at 0.75 Hz [with concurrent transcranial direct current stimulation (tDCS); Box 2]. This stimulation increased slow-wave activity, thus showing evidence for entrainment, and also induced better memory performance, suggesting a causal role for slow-wave oscillations in memory consolidation. Interestingly, induction of slow oscillations during wakefulness had similar beneficial effects on memory, and enhanced theta and beta electroencephalography (EEG) activity [33]. However, these studies have been criticized on two fronts. First, recent studies failed to replicate the behavioral improvement following slow-wave induction via tES [34,35]. Second, another study failed to find any effects of slow-wave tES on intracranially recorded EEG [24], presumably because the electrical current induced by tES was too weak to affect the internally generated slow oscillations which have a 10-fold

higher magnitude. At this point it remains unclear how to resolve these discrepancies. With the invention of closed-loop stimulation, where the phase of tES is timed to the phase of the internal oscillator [36], it might be possible to resolve these issues. This is because closed-loop stimulation renders the notoriously weak currents induced by tES more effective in enhancing slow-wave activity during sleep.

WM strongly relies on the coordinated interplay between brain regions, as mediated by brain oscillations [37]. Theta oscillations in particular are assumed to play a crucial role in WM by organizing neural assemblies into a sequential code, thus maintaining the temporal relationships between items held in WM [37,38]. A recent study in primates showed that theta synchronization between prefrontal and parietal neural assemblies allows efficient read-out of information held in WM [39]. It seems logical to conclude that entraining theta oscillations in parietal and prefrontal regions should benefit WM performance. Indeed, evidence in support of this hypothesis was provided by Albouy and colleagues [40] who stimulated the left intraparietal sulcus (IPS) using rTMS at 5 Hz, and showed that such theta stimulation increases WM performance specifically in a task that requires maintenance of the serial order of the items (Figure 2A). Simultaneous EEG recordings additionally showed that 5 Hz rTMS not only enhances theta oscillations during stimulation but also that these induced oscillations persisted after stimulation has ended. The latter result provides particularly firm evidence that rTMS indeed affected an internal oscillator that is visible as an entrainment echo (Box 1) [41]. The authors also demonstrated that 5 Hz stimulation of

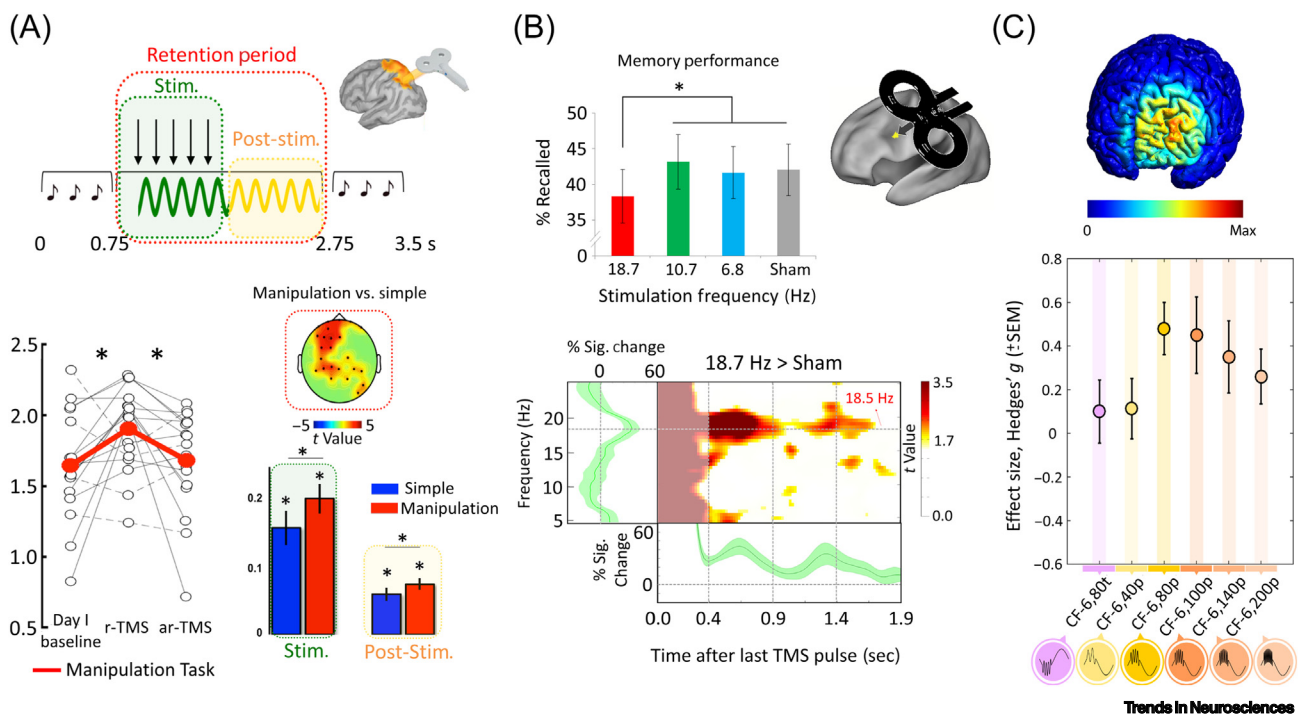


Figure 2. Memory Effects via Noninvasive Electric/Magnetic Entrainment of Brain Oscillations. (A) Stimulating the left intraparietal sulcus during a working memory (WM) task in humans improves performance compared with baseline and arrhythmic transcranial magnetic stimulation (ar-TMS). Phase-locked electroencephalography (EEG) responses to the transcranial magnetic stimulation (TMS) pulses outlasted the stimulation period by approximately 5 cycles (post-stim.; lower right). (B) Stimulation of the left inferior frontal gyrus at beta selectively impairs memory encoding of verbal material (words). EEG data showed a band limited phase-locked response to the stimulation frequency (18.7 Hz) which outlasted the stimulation by ~ 1.5 s. (C) Theta-to-gamma cross-frequency coupling stimulation via transcranial alternating current stimulation (tACS) of the left dorsolateral prefrontal cortex (DLPFC) modulates WM performance. WM performance is most improved for stimulation conditions where an 80 Hz oscillation is coupled to the theta peak (bright yellow) as opposed to the theta trough (purple). Panels in (A), (B), and (C) are reproduced, with permission, from [40,41,47], respectively. Abbreviation: Sig., Signal. Asterisks indicate statistically significant differences between conditions ($p < 0.05$).

parietal regions increased theta-frequency functional connectivity to the prefrontal cortex, thus showing effects of local stimulation on a frontoparietal theta network. Two transcranial alternating current stimulation (tACS) studies [42,43] attempted to directly test the causal relevance of such prefrontal to parietal theta connectivity by stimulating prefrontal and parietal areas such that theta phases are aligned (i.e., zero-phase locked) or continuously opposing (i.e., 180° apart). Indeed both studies found that WM performance was enhanced during the 'synchronizing' (i.e., zero phase lag) stimulation compared with the 'asynchronous' (i.e., 180° phase lag) stimulation. In addition, it was reported [43] that synchronous (zero phase lag) stimulation increased functional connectivity between parietal and frontal regions as measured with functional magnetic resonance imaging (fMRI). An important limitation in these studies refers to the chosen electrode montage, which may have been suboptimal and likely introduced other confounding factors (i.e., different brain regions might be stimulated in the in-phase versus out-of-phase conditions [44]). Future studies should make use of more optimized protocols [44,45]. Despite these issues, the studies reviewed above do suggest a causal role for frontoparietal theta oscillations in the maintenance of items in WM.

Oscillations may temporally organize information in WM via nested gamma oscillations [38]. In particular, individual gamma cycles may code for individual items. A sequence of items can then be coded via multiple gamma cycles nested within a theta cycle [46]. This theory predicts that external induction of gamma oscillations at the peak or trough of theta cycles may differentially affect WM capacity. Alekseichuk and colleagues [47] tested this hypothesis by stimulating the left prefrontal cortex (PFC) with complex theta-gamma waveforms during a spatial WM task. Stimulating with gamma oscillations nested in the theta peak improved WM performance, whereas stimulating with gamma oscillations nested in the theta trough did not (Figure 2C). Interestingly, stimulating with gamma oscillations coupled to the trough of theta impaired verbal long-term memory encoding [48]. Another prediction that follows from the theta-gamma WM model [38,46] is that slowing down the frequency of theta allows more gamma cycles to be nested, and this should then increase WM capacity [49]. Conversely, speeding up theta frequency should decrease the number of gamma cycles and consequently decrease WM capacity. This prediction was confirmed by two recent tACS studies showing that stimulating at lower theta frequencies increases WM capacity [50,51]. Wolinski and colleagues [51] further demonstrated that stimulation at faster theta frequencies reduced WM capacity. Together, these two studies provide causal evidence for nesting of gamma oscillations in theta cycles, and that this determines the amount of items one can maintain in WM.

Alpha and beta oscillations have been implicated in various cognitive and neurobiological processes, with one prominent view suggesting that they reflect functional inhibition of cortical areas [52,53]. Accordingly, in WM tasks involving visual stimuli, increases in alpha oscillations during WM maintenance have been interpreted to reflect functional inhibition of visual processing regions. Such functional inhibition may protect the internal maintenance of information by blocking processing of potentially interfering visual information [54]. An rTMS study supports such a causal protective role of alpha oscillations by showing that stimulating parietal regions ipsilateral to the to-be-maintained information at 10 Hz increased WM performance, whereas the same stimulation of contralateral regions decreased WM performance [55]. Similar evidence comes from a tACS study showing that WM performance improves in elderly subjects during parietal 10 Hz stimulation [56]. Concerning episodic memory, decreases in alpha and beta oscillations have been linked to memory formation [5,57]. Memory formation of verbal material in particular is correlated with beta power decreases in the left inferior frontal gyrus [58]. Evidence for this relationship being causal was provided by an rTMS study showing that synchronizing the left inferior prefrontal cortex specifically at beta frequency (~18.5 Hz; Figure 2B) impaired verbal

memory formation [41]. The authors further showed that the entrained beta oscillations persisted for ~1.5 s after the stimulation stopped, in other words an **entrainment echo**. This echo was modulated by whether the individual beta frequency matched the stimulated frequency or not, which suggests that an internal beta rhythm was driven by the stimulation. Together, the abovementioned studies support a causal role of alpha and beta oscillations in WM and long-term memory. In contrast to theta and gamma oscillations, however, a desynchronization of alpha and beta in the regions that are actively processing the to-be-remembered information seems to be beneficial for memory. Given the assumed inhibitory function of alpha and beta oscillations, entrainment of alpha and beta would be beneficial for memory when used to silence areas which would otherwise potentially interfere with memory processing. One important open question for future studies concerns whether stimulating alpha and theta differentially impacts on memory performance, as has been shown for gamma and beta oscillations in a visual search paradigm [59].

Invasive Electrical Entrainment via Deep Brain Stimulation (DBS)

Recent years have seen a prominent increase in the use of oscillatory patterns of invasive stimulation in studies pertaining to memory modulation. Although some studies applied sine waves at 40 Hz (between rhinal cortex and hippocampus [60]), others used low-frequency stimulation (5 Hz [61]) or theta-bursts, namely the application of several stimuli at high frequency that rhythmically alternated (in the theta range) with periods devoid of stimulation [62–64]. Theta-burst stimulation constitutes a very efficient stimulation scheme for inducing LTP in rodents [65,66], and can be conceived of as mimicking physiologically occurring EEG patterns of phase–amplitude coupling [49,67]. Both features of burst stimulation overall have motivated initial adoption of theta-burst stimulation in several papers. For instance, Miller and colleagues [63] performed theta-burst stimulation of the human fornix on half of the trials as patients completed a battery of neuropsychological tests. They found that theta-burst stimulation of the fornix was associated with an improvement of immediate and delayed memory performance on a visuospatial learning task. In another study using theta-burst stimulation to enhance memory, Titiz and colleagues [62] performed microstimulation via a 100 μm diameter electrode of the perforant path between the entorhinal cortex and hippocampus. Theta-burst microstimulation to the right entorhinal white matter improved subsequent memory specificity for portraits. It should be noted that the findings from some of these early studies of rhythmic stimulation for modulating memory have been called into question given the lack of large sample sizes (i.e., [63]) because data collection was from fairly rare patient populations at single epilepsy centers. Recent studies [68,69] have collected data across much larger epilepsy datasets on modulation of memory by DBS (>200 patients), and this involved data collection by a consortium of eight epilepsy centers across the USA over a period of 4 years [the Defense Advanced Research Projects Agency (DARPA) Restoring Active Memory Project [68]], but these studies did not aim to entrain specific brain oscillations with rhythmic DBS. Finally, in relation to the definition of entrainment put forth in the current article, although some studies show an improvement of memory after theta-burst DBS, few studies to date have examined actual oscillatory changes in response to theta-burst DBS.

Unfortunately, most DBS studies on memory enhancement were unable to evaluate changes in oscillatory activity during the stimulation because of electrical artifacts at the site of stimulation. As an alternative method to assess possible entrainment effects indirectly, some invasive stimulation studies analyzed the change in neural activity from pre- to post-stimulation periods; however, these studies often did not focus on examining the entrainment of oscillations based on the delivered frequency of stimulation [68–75]. For instance, Kucewicz and colleagues [72] showed that 50 Hz stimulation modulated high gamma (62–118 Hz) activity induced as patients encoded individual words from pre- to post-stimulation during word presentation, but this

broadband increase in power does not specifically reflect entrainment of the delivered 50 Hz stimulation. Other studies have examined oscillatory changes for stimulated and nonstimulated items during a later period of time that is divorced from the stimulation period [64]. To the best of our knowledge, only two studies thus far have employed stimulation parameters that target intrinsic oscillatory activities relevant to memory processes and also examined a form of entrainment after the stimulation period [64,76].

Kim and colleagues [76] used a network-based brain stimulation approach to select stimulation targets in an attempt to modulate memory in a spatiotemporal memory encoding and retrieval paradigm. Specifically, they directly stimulated two functional hubs based on single-trial pairwise phase-consistency measures and graph theory centrality metrics (i.e., node degree) to test the necessity and selectivity of theta phase coherence in memory retrieval. In a prestimulation session they identified network hub regions that exhibited strong theta phase coherence for either 'spatial' or 'temporal' retrieval conditions [77]. Behaviorally, they found that theta-burst stimulation (four bursts of 50 Hz stimulation in 1 s at 4 or 5 mA) to the two network nodes impaired spatial retrieval but did not affect temporal retrieval. They found that theta phase coherence throughout these networks was initially increased during the first 400 ms after stimulation, but then became decoupled across the network ~500 ms after stimulation. These findings suggest a more complex relationship between the entrainment of oscillatory activity via invasive stimulation in which initial entrainment gives way to decoupled activity shortly after the termination of stimulation.

Inman and colleagues [64] tested whether theta-burst stimulation to the basolateral amygdala could enhance recognition memory for neutral objects. In this paradigm, neutral objects were presented during encoding. A randomized half of the objects were immediately followed by amygdala stimulation (eight bursts of 50 Hz stimulation for 1 s at 0.5 mA; Figure 3). Recognition memory for each object was tested at an immediate and 1 day delay after encoding. Amygdala stimulation reliably improved later object-recognition memory at the 1 day delay. Although stimulation artifacts precluded any analysis of immediate entrainment after amygdala stimulation, the authors tested whether there were any reliable changes in electrophysiological activity in the medial temporal lobe (i.e., amygdala, perirhinal cortex, anterior hippocampus) during the accurate recognition of previously stimulated objects versus nonstimulated objects (Figure 3A–C). Interestingly, they found an increase in perirhinal 30–55 Hz gamma power that occurred at specific phases of 6–8 Hz theta activity in the amygdala (i.e., phase–amplitude coupling; Figure 3D–F). These findings suggest that stimulation has entrained a theta-modulated gamma pattern in this amygdala–hippocampus–perirhinal network at encoding that, after a period of synaptic plasticity and consolidation, replayed accurate recognition of the previously stimulated neutral objects. In conclusion, the studies reviewed above suggest that intracranial electrical stimulation is a useful means to entrain brain oscillations, especially theta and gamma, and thus causally modulates memory performance. As evidenced by these studies, there is an outstanding need to use invasive stimulation parameters that are inspired by the intrinsic oscillatory activity of specific brain regions during memory processing periods, rather than using nonoscillatory stimulation parameters (pure 50 or 130 Hz stimulation). With that in mind, recent evidence suggests that even nonoscillatory stimulation can induce slower oscillatory activity across many regions of the brain [78]. Overall, it seems reasonable to recommend that future studies of invasive stimulation approaches should deliver stimulation at frequency patterns that match the endogenous frequencies of neural oscillations for a given brain region, and examine the neural and behavioral consequences of invasively stimulating at these endogenous, behaviorally relevant frequencies.

Future Directions and Limitations

The studies reviewed above suggest that targeting specific oscillations via invasive and noninvasive entrainment techniques is a promising avenue to modulate memory performance. However,

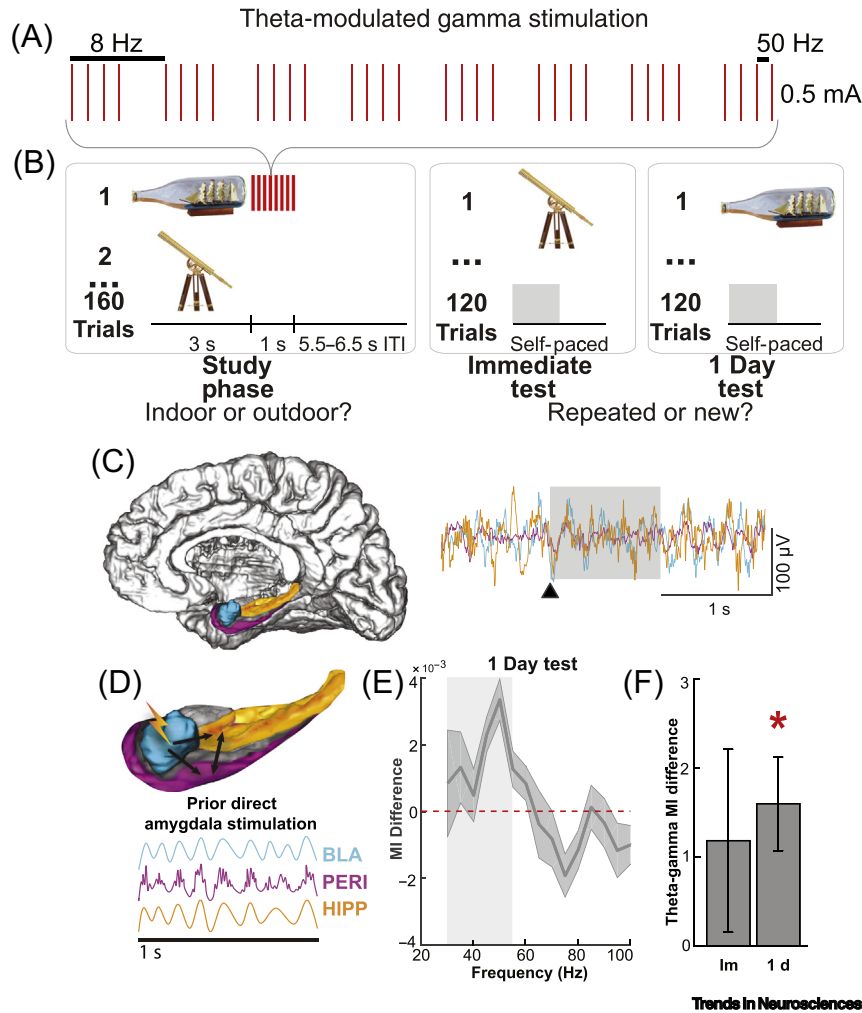


Figure 3. Entrainment Effects of Amygdala Deep Brain Stimulation (DBS). (A) Schematic of the 1 s stimulation pulse sequence to the human amygdala (each pulse is a 500 μ s biphasic square wave; pulse frequency, 50 Hz; train frequency, 8 Hz). (B) Schematic of recognition memory task in which the amygdala was stimulated following a random half of the objects in the study phase, and recognition memory was tested on unique subsets of images immediately and 1 day after the study phase. The grey shaded region corresponds to the first 0.5 s after picture onset during the recognition tests, as also depicted in the right side of panel (C). Behavioral results showed that brief electrical stimulation to the amygdala in humans enhanced subsequent declarative memory without eliciting an emotional response ([64] for full results). Abbreviation: ITI, intertrial interval. (C) Illustration of the basolateral amygdala (BLA), hippocampus (HIPP), and perirhinal cortex (PERI), and a representative local field potential (LFP) from each region during a recognition test trial (black triangle indicates image onset; the grey shaded region corresponds to the shaded region in panel B during recognition tests). 3D brain model adapted with permission from Albany Medical College (AMC) Virtual Brain Model (<http://www.amc.edu/academic/software>). (D) Schematic representation of oscillatory activity during the 1 day recognition test in the BLA, HIPP, and PERI for objects in the stimulation condition. The oscillations depict increased theta interactions between the three regions and gamma power in perirhinal cortex modulated by those theta oscillations. (E) Modulation index (MI) differences between stimulation and no stimulation conditions by spectral frequency in the perirhinal cortex during the 1 day test. The shaded region denotes the gamma band of 30–55 Hz. (F) Cumulative MI difference between stimulation – no-stimulation conditions for the gamma range in perirhinal cortex. During the 1 day (1 d) test, MI was increased for remembered images in the stimulation condition relative to remembered images in the no-stimulation condition (Im, immediate test). All error bars and bands represent the standard error of the mean (SEM). Asterisks indicate statistically significant differences between conditions ($p < 0.05$). Figure adapted, with permission, from [64].

a cautionary note is warranted because there are important methodological limitations that apply to most of the above studies. In particular, the majority of studies reviewed here, including our own, use fairly low sample sizes per experiment (Table 1) which creates the problem of overestimating effect sizes as a result of publication bias and the risk of false positives [79]. A recent tDCS study used a considerably large sample size of 75 subjects [80] and estimated the effect size to be 0.45, implying that even this study was slightly underpowered. This highlights the importance of using appropriately powered large-scale studies and the necessity to revisit the findings described throughout this article in replication attempts. In addition, we hope to see more stimulation studies in the future making use of preregistration, which will increase the transparency and replicability of the results [81].

It would also be important to advance our understanding of the mechanics behind entrainment and how specifically they affect memory. For that, it would be crucial to collect physiological measurements alongside behavior to gain a better understanding of whether and how the targeted oscillations are affected by entrainment (Table 1). Indeed, most of the studies reviewed here used some form of physiological measurement to test whether rhythmic stimulation affected oscillations or not. However, better methods need to be developed that allow robust measurements of oscillatory activity during the stimulation period, free of stimulation artifacts. Furthermore, it is becoming increasingly clear that stimulation parameters should be adjusted to the internal network dynamics, and not arbitrarily determined, especially if the goal is to increase (rather than interfere with) memory performance [82]. Intuitively, there are many more ways to interfere with neural activity than to constructively shape endogenous processes, and this could explain why memory-boosting stimulation protocols are particularly challenging to develop. Closed-loop stimulation setups, where the phase, frequency, and waveform of the entraining stimulus are matched to the internal dynamics, and stimulation methods which operate at a network level [82], are the most promising developments in that respect [36].

The different properties of invasive versus noninvasive stimulations (e.g., regarding the spatial resolution of the recorded oscillations and the locality of stimulation effects) may yield crucially different outcomes which should be systematically compared in the future. Although invasive stimulation may be more effective when aiming to target specific brain areas, the more global effects of noninvasive stimulation may result in more distributed effects on multiple memory-related systems [82]. Thus, future studies should also attempt to pair invasive recording techniques with each stimulation technique to elucidate and reconcile the mechanistic underpinnings of both noninvasive and invasive stimulation, as well as to optimize memory-enhancement effects. For instance, it is possible that modulation of local oscillations, rather than global entrainment, is crucial to achieve enhanced memory. Future studies should also combine invasive recordings with noninvasive stimulation (i.e., tES) to better understand how the more global noninvasive entrainment effects impact on local oscillations [83]. Furthermore, closed-loop stimulation in which the stimulation parameters are adjusted to neural oscillations in real-time have high promise to dissociate between different oscillatory mechanisms in the service of memory [71]. Finally, it is also now possible to pair invasive stimulation with noninvasive recording methodologies [84] to gain traction on understanding the broad neural effects that are more commonly and readily studied in healthy participant samples.

A better understanding of the complex neurophysiological effects of entrainment on cellular circuits is needed. More studies that combine single-unit recordings and optogenetic stimulation (in animal models) and/or electrical stimulation (in humans or animal models) will be necessary to address this limitation. Computational neural network modeling work will also be essential because it can offer testable predictions and help to translate between empirical results at the single-unit and macroscopic levels [85].

Concluding Remarks

This paper set out with the question of whether neural oscillations are of causal relevance for memory or whether they are more of an epiphenomenon. In our view, the studies reviewed here, which use various forms of entraining oscillations, lend support to the former view, namely that brain oscillations do in fact implement specific neural mechanisms subserving the formation, maintenance, consolidation, and retrieval of memories. Although much needs to be done in terms of unraveling how neural entrainment specifically affects memory (see Outstanding Questions), we can now begin to unpack the specific mechanisms that brain oscillations implement during memory. This is crucial for the development of effective treatments for memory-related disorders.

Acknowledgements

The authors would like to thank Jürgen Fell and Hong Viet Ngo for helpful comments in preparing this manuscript. S.H. is supported by grants from the European Research Council (grant agreement N°647954), the Economic and Social Research Council (ESRC grant agreement N°ES/R010072/1), and the Wolfson Society and Royal Society. N.A. received funding by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 316803389 – SFB 1280 as well as via Projektnummer 122679504 – SFB 874.

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Outstanding Questions

What are the neural and computational mechanisms that brain oscillations in different frequency bands implement? How do these mechanisms subserve the formation, maintenance, consolidation, and retrieval of memories?

How does neural entrainment affect neural circuit dynamics and structure?

How can one increase the efficacy of 'weak' stimulation approaches such as tACS?

What are the effects of oscillatory DBS on large-scale brain networks, both during stimulation and afterwards?

How does oscillatory DBS affect noninvasive measures of brain activity more commonly used in healthy individuals (fMRI, scalp EEG, autonomic psychophysiology)?

The effects of oscillatory entrainment on memory have often been tested using stimuli such as images and words. What are the effects of sensory, noninvasive, and invasive stimulation approaches on memory in paradigms employing more natural stimuli such as movies, augmented reality, and virtual reality?

What is the therapeutic potential of entrainment?

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