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Modulating human memory via entrainment of brain oscillations

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Abstract

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. A number of recent studies went 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 on brain oscillations.

Brain oscillations and memory

Brain oscillations 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 like delta, theta, alpha, beta and gamma oscillations (from slow to fast). It is important to note that all of these frequencies, and not just the more commonly discussed theta and gamma bands, have been linked to memory processes. Furthermore, brain oscillations are not exclusively linked to memory, but to many other cognitive processes. These seemingly non-specific relationships raise the fundamental question of 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 a number of 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 envision 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 figure out 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, i.e. 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 (see Glossary for our definition of causality) then one can sensibly hope to uncover their specific mechanistic roles in memory. It is important to keep in mind though that any cognitive function (e.g., memory) can have not one but several underlying causes. An observable effect on memory enhancement therefore may be due to various different cognitive processes (e.g., enhanced 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, even though 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 behavioural measures of memory. Modulation of oscillations can be achieved via entrainment (see 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 which induce atypical rhythmic activity, i.e. activity that is not naturally present in the stimulated area (like for instance 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 behaviour of interest. In the human brain, oscillations can be entrained broadly via three different stimulation approaches: (i) sensory entrainment, (ii) non-invasive electric/magnetic entrainment, (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, and in applied studies where the goal is to improve memory functions in the healthy and non-healthy brain. In the following we will review these results, focusing on studies examining possible effects of oscillatory entrainment on memory performance in working memory and episodic memory tasks. With this specific focus on memory, this review differs from some of the previous reviews [8-10]. As discussed in more detail later, sample-sizes considerations are an important theme in this context, and an overview of the key studies being discussed, along 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) in order to modulate memory performance is not new [11]. Williams [12] found that subjects' recognition performance was increased when items during encoding followed a 'flicker' at 10 Hz (i.e. alpha) compared to a non-flicker condition as well as compared to 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 expression of beta-amyloid plaques [14, 15]. This suppressive effect on beta-amyloid plaques was present with invasive (optogenetics) stimulation as well as with non-invasive 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, which 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 multi-sensory audio-visual 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 LTP and LTD [18-20]. One can extrapolate from these studies that conditions which bias neurons to fire in the same LTP inducing theta phase should lead to better memory compared to 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 domain [21]. Within this framework the internal rhythms would be entrained to allow for 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 over asynchronously presented stimuli (Figure 1A). This memory advantage for synchronous over asynchronous conditions was specific to the theta rhythm (4 Hz), compared to a slower (1.7 Hz,) and a faster (10.5 Hz) rhythm. Intriguingly, synchronizing stimuli at 4 Hz led to better memory compared not only to asynchronous but also natural stimuli (i.e. unmodulated movie-sound pairs). These findings were replicated and extended in 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]. The more synchronized auditory and visual regions were in theta on a single trial, the better the resulting memory. Finally, a study by Roberts and colleagues demonstrated that audio-visual 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 associative memory formation.

Brain oscillations can not only be entrained in the awake brain, but also during sleep, e.g. via auditory rhythmic stimulation [24-27]. This approach allows for targeting oscillatory signatures that are specific to sleep, and test their causal role in memory consolidation processes. Such entrainment during sleep is particularly attractive since the participant is unaware of the stimulation, which excludes trivial explanations of any ensuing behavioural effects. Using closed-loop auditory stimulation Ngo and colleagues [26] demonstrated that auditory stimulation, timed to the endogenous slow wave activity, enhances slow wave activity and memory 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], which makes it difficult to ascertain whether changes in memory performance were 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.

Non-invasive electrical (tES) and electro-magnetic (rTMS) entrainment

Additional ways to entrain oscillations non-invasively are transcranial stimulation methods like transcranial electric stimulation (tES) or repetitive transcranial magnetic stimulation (rTMS; see 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 behaviour provide physiological data suggesting that oscillations have indeed been entrained (see Table 1).

First evidence (to our knowledge) for slow wave sleep being 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 tDCS; see 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 EEG activity [33]. However, these studies have been criticized on two fronts. First, recent studies failed to replicate the behavioural improvement following slow wave induction via tES [34, 35]. Second, another study failed to find 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 comparably 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], these issues might get resolved. This is because closed loop stimulation renders the notoriously weak currents induced with tES more effective in enhancing slow wave activity during sleep.

Working memory (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 critical role in WM by organizing neural assemblies into a sequential code, and thus maintaining the temporal relationships between items held in working memory [37, 38]. A recent study in primates showed that theta synchronization between prefrontal and parietal neural assemblies allows for 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 that these induced oscillations persisted after stimulation has ended. The latter result provides particularly firm evidence that rTMS indeed affected an internal oscillator, visible in an 'entrainment echo' (see Box 1; [41]). The authors also demonstrated that 5 Hz stimulation of parietal regions increased functional connectivity in theta to the prefrontal cortex, thus showing effects of local stimulation on a fronto-parietal theta network. Two 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 degrees apart). Indeed both studies found that WM performance was enhanced during the "synchronizing" (i.e. zero phase lag) stimulation compared to the "asynchronous" (i.e. 180 degree phase lag) stimulation. In addition, [43] demonstrated that synchronous (zero phase lag) stimulation increased functional connectivity between parietal and frontal regions as measured with 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 stimulated in the in-phase versus out-of-phase conditions; see [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 fronto-parietal 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 which are 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 via stimulating the left 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 for more gamma cycles to be nested which then should 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 the nesting of gamma oscillations in theta cycles, which 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 in showing that stimulating parietal regions ipsilateral to the to-be-maintained information at 10 Hz increased WM performance, whereas the same stimulation contralateral 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 which showed that synchronizing the left inferior prefrontal cortex specifically at beta (~18.5 Hz; Figure 2B) impaired verbal memory formation [41]. The authors further showed that the entrained beta oscillations persisted for ~1.5 seconds after the stimulation has stopped, i.e. 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 working memory 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 done in an attempt to silence areas, which would otherwise potentially interfere with memory processing. One important open question for future studies is 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. While some studies applied sine waves at 40Hz (between rhinal cortex and hippocampus [60]), others used low-frequency stimulation (5Hz: [61] or theta-bursts, i.e. 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 an 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 visuo-spatial learning task. In another study using theta-burst stimulation to enhance memory, Titiz and colleages [62] performed microstimulation on a 100 µm diameter electrode to 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 the modulation of memory have been called into question for the lack of large sample sizes (i.e. [63]) due to data collection from fairly rare patient populations at single epilepsy centres. Recent studies [68, 69] have collected data across much larger epilepsy datasets on the modulation of memory from DBS (>200 patients), which required a consortium of 8 epilepsy centres across the U.S. to collect over 4 years (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, while some studies show an improvement of memory after theta-burst DBS, studies that have examined actual oscillatory changes in response to the theta-burst DBS are rare to date.

Unfortunately, most studies DBS studies on memory enhancement could not evaluate changes in oscillatory activity during the stimulation due to electrical artefacts at the site of stimulation. As an alternative method to assess possible entrainment effects indirectly, some invasive stimulation studies have analysed the change in neural activity from pre- to post-stimulation periods, however, often these studies do 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 non-stimulated 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 chosen stimulation parameters targeting intrinsic oscillatory activities relevant to memory processes *and* 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 pre-stimulation session they identified network hub regions that exhibited strong theta phase coherence for either “spatial” or “temporal” retrieval conditions [77]. Behaviourally, they found that theta-burst stimulation (4 bursts of 50 Hz stimulation in 1 second at 4 or 5 mA) to the two network nodes impaired spatial retrieval while not affecting 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 around 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 (8 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 artefacts 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 vs non-stimulated objects (Figure 3A-C). Interestingly, they found an increase in

perirhinal 30-55 Hz gamma power that occurred at specific phases of the amygdala's 6-8 Hz theta activity (i.e., phase-amplitude coupling; Figure 3D-F). These findings suggest that stimulation has entrained a theta-modulated gamma pattern in this amygdala-hippocampal-perirhinal network at encoding that, after a period of synaptic plasticity and consolidation, replayed upon 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 non-oscillatory stimulation parameters (pure 50 or 130 Hz stimulation). With that in mind, recent evidence suggests that even non-oscillatory 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 behavioural consequences of invasively stimulating at these endogenous, behaviourally-relevant frequencies.

Future directions and limitations

The studies reviewed above suggest that targeting specific oscillations via invasive and non-invasive entrainment techniques is a promising avenue to modulate memory performance. However, a cautionary note is warranted as 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 (see Table 1) which creates the problem of overestimating effect sizes due to publication bias and a risk of false positives [79]. A recent tDCS study used a considerably large sample size of 75 subjects [80] and estimated the effect size at 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. Additionally, we hope to see more stimulation studies in the future making use of pre-registration, which will increase 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 behaviour to gain a better understanding of whether and how the targeted oscillations are affected by entrainment (see 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 robustly measuring oscillatory activity during the stimulation period, free of stimulation artefacts. 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, which 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 work on a network level [82] are most promising developments in that respect [36].

The different properties of invasive vs. non-invasive stimulations (e.g., regarding the spatial resolution of the recorded oscillations and the locality of stimulation effects) may yield critically

different outcomes which should be systematically compared in the future. While invasive stimulation may be more effective when aiming to target specific brain areas, the more global effects of non-invasive 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 non-invasive and invasive stimulation, and to optimize memory enhancement effects. For instance, it is possible that modulation of local oscillations, rather than global entrainment, is critical to achieve enhanced memory. Future studies should also combine invasive recordings with non-invasive stimulation (i.e. TES) in order to better understand how the more global non-invasive entrainment effects impact on local oscillations [83]. Furthermore, closed-loop stimulation, where 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 non-invasive recording methodologies [84] to gain traction on understanding the broad neural effects that are more commonly and readily studied in healthy participant samples.

There is a need for better understanding of the complex neurophysiological effects of entrainment on cellular circuits. More studies that combine single unit recordings and optogenetic stimulation (in animal models) and/or electrical stimulation (in humans or animal models) are needed to address this limitation. Computational neural network modelling work will also be essential, by offering testable predictions and helping translate between empirical results at the single unit level and the macroscopic level [85].

Concluding remarks

This paper set out with the question as to 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, i.e., 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 unravelling *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 of memory related disorders.

Boxes

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 I-A). 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. Critically, entrainment does not happen instantaneously but takes time [86], depending on stimulation intensity [87, 88]. This introduces a certain progression of states which a neural population has to 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 goes back into the baseline state, giving rise to an entrainment echo [40, 41, 91].

There are several ways to measure entrainment. One way is to measure power and phase of a stimulated region during entrainment. However, this is not trivial given the stimulation artefacts or superimposed event-related responses (ERPs). Entrainment echoes, on the other hand, allow for 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 I-B), 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, also frequencies that are not present in the system can be artificially induced [88, 92].

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 of entraining oscillatory activity, including in the human brain. Of note, these rhythms are not exclusively induced in sensory regions but are also transmitted to down-stream 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 DC stimulation (tDCS) where a static current with no rhythmic component is applied, to 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]. Rhythmic 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, i.e. the ability to target specific brain regions at specific rhythms. This is ideal for testing the causal role of oscillations in local networks. Bi-focal stimulation (i.e. stimulating with two rTMS coils) allows for a causal testing of oscillations on the network level [96]. tES, by contrast, has lower spatial resolution, which is often seen as a disadvantage, but depending on the study's goal, can actually be beneficial, for instance when one wants to probe the causal role of oscillations on a broad network level [82]. Another difference between rTMS and tES is that rTMS can induce action potentials (i.e. supra-threshold) whereas tES typically affects only the local field potential (i.e. sub-threshold). This is an important difference in the context of entrainment, since rTMS in principle allows for *inducing* '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 for a more direct test of entrainment.

Entrainment via invasive electrical stimulation: Deep brain stimulation 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, like the hippocampus, as well as 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 behavioural 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, and of remote areas via axonal connections to the stimulated area [97, 99, 100].

Glossary:

Entrainment: "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.

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 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 (see Box 1).

Brain oscillations: Rhythmic activity of a population of neurons within a given frequency band. Brain oscillation can be measured at different spatial scales ranging from below a millimeter in case of local field potentials to about 1 centimeter for intracranial EEG, 1-2 centimeters for MEG, and several centimeters in case of EEG.

Working Memory: Process during which information is maintained and manipulated across a short time interval (typically a few seconds). Working memory has a limited capacity of only a few items but allows for their direct access.

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.

Tables

Table 1. An overview of the reviewed entrainment studies showing an effect on memory performance. The table lists sample size, and shows whether physiological measures of entrainment were obtained (+ = yes / - = no), and how entrainment was measured.

	Number of Subjects	Entrainment Method	Entrainment measured during stimulation	Entrainment measured post stimulation
Clouter et al [17]	24 / 24 / 9 / 24	Sens. Entr.	+ SSSEP	-
Wang et al. [22]	24	Sens. Entr.	+ SSSEP	-
Roberts et al. [23]	50 / 40	Sens. Entr.	+ Power	+ EEG Power
Ngo et al. [26]	11	Sens. Entr.	+ ERP, Power	-
Papalambros et al. [28]	13	CL sens. Entr.	+ ERP, Power	-
Ong et al [29]	16	CL sens. Entr.	+ ERP, Power	-
Marshall et al. [32]	13	tES	-	+ EEG Power
Albouy et al. [40]	17	rTMS	+ EEG Power, ITPC	+ EEG Power, ITPC
Polania et al. [42]	18	tES	-	-
Violante et al. [43]	10 / 24	tES	+ BOLD Connect.	-
Alekseichuk et al. [47]	16 / 14 / 15	tES	-	+ EEG Phase Connect.
Lara et al. [48]	72	tES	-	-
Vosskhl et al. [50]	33	tES	-	+ EEG Power
Wolinski et al. [51]	32	tES	-	-
Sauseng et al. [55]	7 / 13	rTMS	-	-
Borghini et al. [56]	25 / 25	tES	-	-
Hanslmayr et al. [41]	19	rTMS	-	+ ITPC
Inman et al. [64]	14	DBS	-	+ iEEG PAC
Kim et al. [76]	4	DBS	-	+ iEEG Phase Connect.

Abbreviations: Sens. Entr. = Sensory Entrainment; CL = Closed Loop; SSSEP = Sensory Steady State Evoked Potentials; ERP = Event Related Potentials; Connect. = Connectivity; ITPC = Inter Trial Phase Connectivity; iEEG = intracranial EEG; PAC = Phase-Amplitude Coupling). If a study included several experiments N are given per experiment (i.e. 24 / 9).

Figure Legends

Figure 1. Modulating memory via sensory entrainment of oscillations during wakefulness (A) and sleep (B) in humans. (A) An audio-visual video clip was presented for 3 seconds. 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 to 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 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].

Figure 2. Memory effects via non-invasive electric/magnetic entrainment of brain oscillations. (A) Stimulating the left intraparietal sulcus during a working memory task in humans improves performance compared to baseline and a-rhythmic TMS (ar-TMS). Phase locked EEG responses to the 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 seconds. (C) Theta-to-gamma cross-frequency coupling stimulation via tACS of the left DLPFC modulates working memory 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) reproduced with permission from [40], [41], and [47], respectively.

Figure 3. Entrainment effects of amygdala deep brain stimulation. (A) Schematic of the 1-s stimulation pulse sequence to the human amygdala (each pulse = 500 μs 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 one-day after the study phase. Gray shaded region corresponds to the first 0.5 seconds after picture onset during the recognition tests, as also depicted in the right side of panel C. Behavioural results showed that brief electrical stimulation to the amygdala in humans enhanced subsequent declarative memory, without eliciting an emotional response (see [64] for full results). (C) Illustration of the basolateral amygdala (BLA), hippocampus (HIPP), and perirhinal cortex (PERI) and a representative LFP from each region during a recognition test trial (black triangle indicates image onset; gray shaded region corresponds to shaded region in panel B during recognition tests). 3D brain model adapted with permission from AMC Virtual Brain Model (http://www.amc.edu/academic/software). (D) Schematic representation of oscillatory activity during the one-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) MI Differences between stimulation and no stimulation conditions by spectral frequency in the perirhinal cortex during the one-day test. Shaded region denotes gamma band between 30-55 Hz. (F) Cumulative MI difference between stimulation – no stimulation conditions for the gamma range in perirhinal cortex. During the one-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). Figure adapted with permission from [64].

Figure I (for Box 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 LFP/EEG 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 colours indicating time from start (green) to end (red) of entrainment. (B) The Arnold Tongue. Intensity of stimulation (y-axis) is plotted against internal frequency (x-axis). Low stimulation intensities will only entrain if stimulation frequency matches the internal frequency (IAF). Figure reproduced with permission from [88, 92].

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Figure 1.

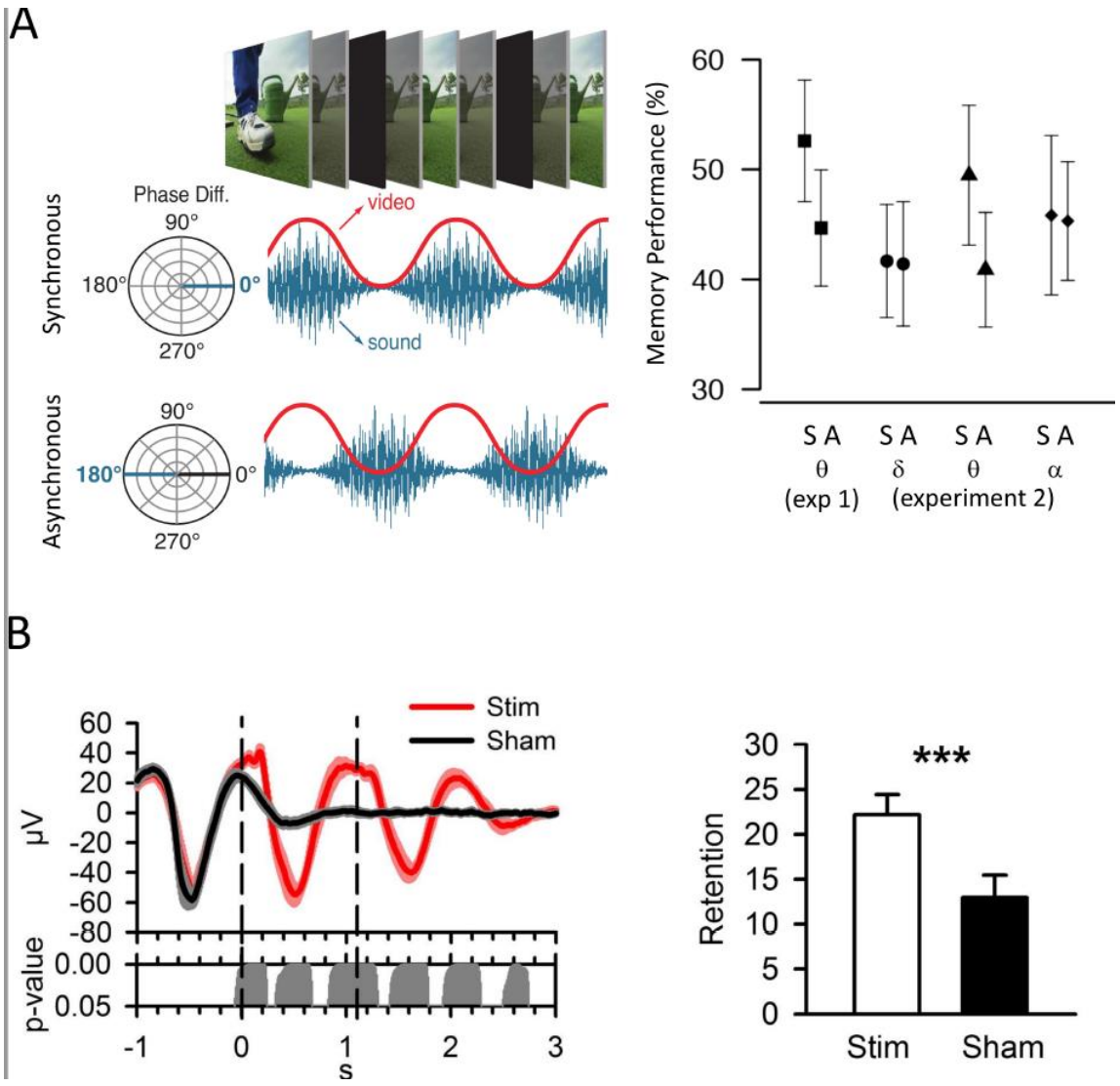
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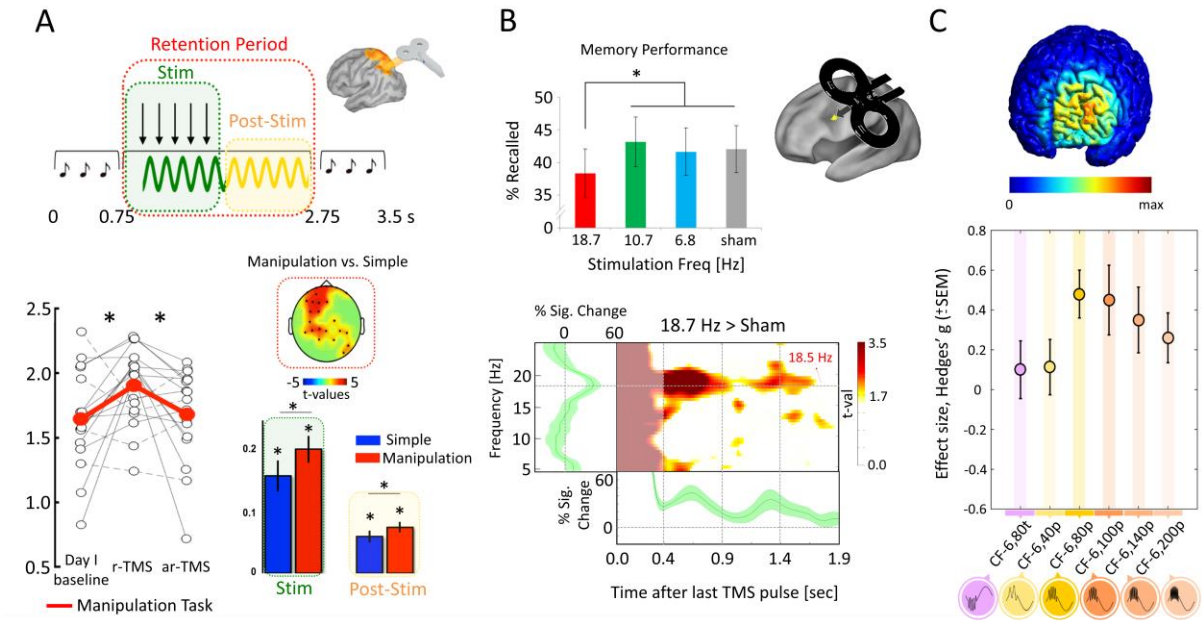
Figure 2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CF-6,80p
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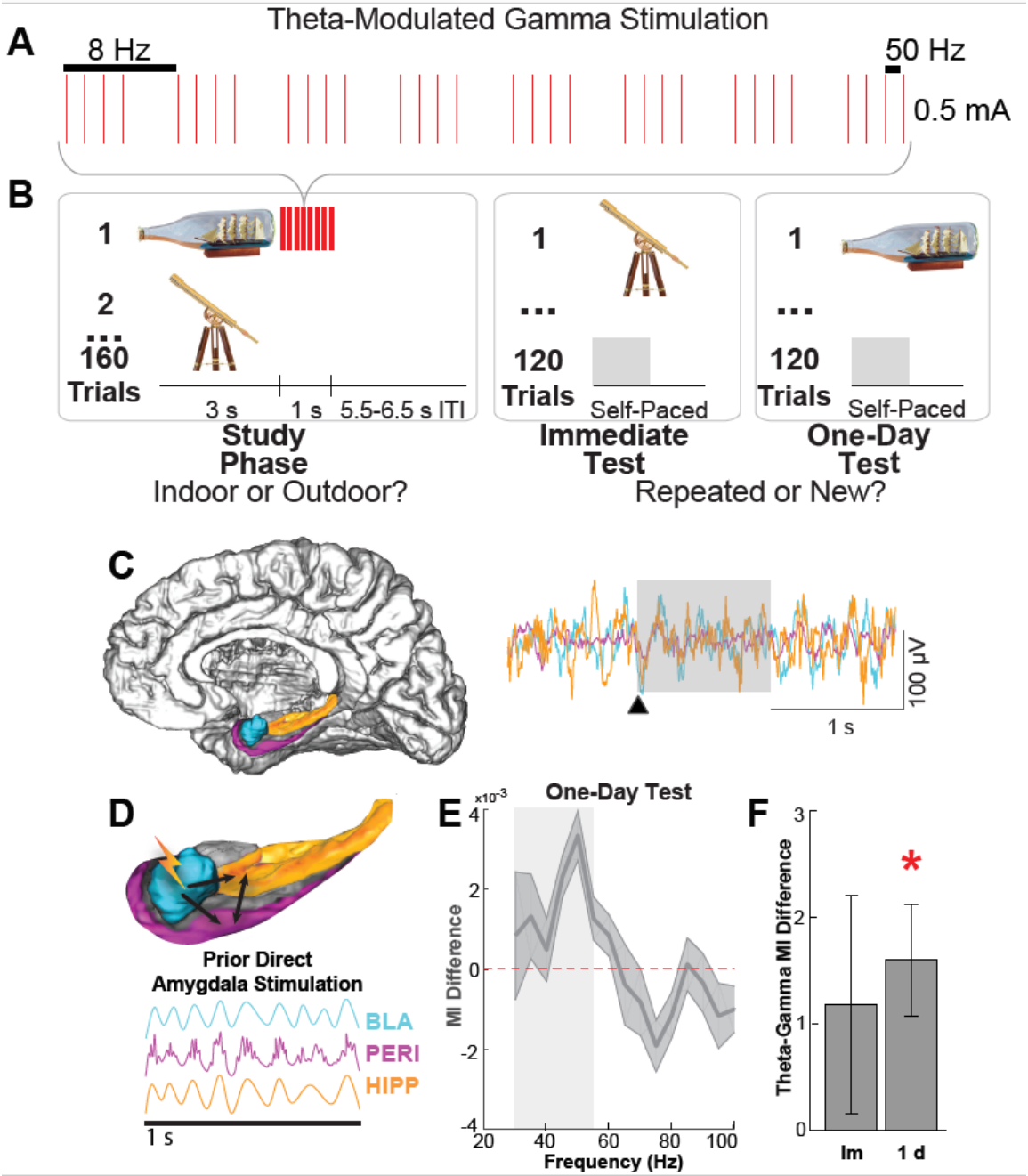
CF-6,140p
CF-6,200p

Figure 3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120
Trials
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Box 1 Figure 1