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Investigating the cortico-hippocampal dynamics involved in human episodic memory with neural stimulation

By

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Abstract

The human episodic memory system depends on specific interactions between the hippocampus and neocortex. The three studies performed as part of this doctoral thesis each sought to improve our understanding of the cortico-hippocampal system in the context of episodic memory. Each study used a different approach to directly manipulate neural activity with the aim of revealing causal relationships between certain patterns of neural activity and behaviour.

In the first study the cortico-hippocampal network was investigated by using occipital transcranial alternating current stimulation (tACS) and auditory sensory stimulation with the aim of altering memory performance during an audio-visual association task. The electrical stimulation was hypothesized to interact with the auditory sensory stimulation after propagating from the neocortex to the hippocampus. This study was unsuccessful in modulating behaviour through stimulation.

In the second study, the left Dorsolateral Prefrontal Cortex (DLPFC) was targeted using 1 Hz repetitive transcranial magnetic stimulation (rTMS) over the course of two experiments, during a set of list learning tasks. This study found a beneficial effect on memory performance when stimulation occurred over the left DLPFC compared to stimulation over the vertex (control site). This behavioural effect was further characterized by a beta-power decrease over parietal sensors as measured by electroencephalography (EEG).

The third study probed the cortico-hippocampal network by directly stimulating the hippocampus and the neocortex, by applying direct electrical stimulation through implanted electrodes in human subjects. This study used measures of population activity as well as single neuron activity to monitor how the brain responds to direct stimulation. This study found that direct stimulation throughout the network produces a neural response that is characterized by short, intense excitation and prolonged follow-up inhibition which has the potential to travel throughout the brain. The ability of the response to travel between the neocortex and hippocampus was leveraged to measure a transduction delay of ~140 ms between the two regions.

Together these findings have advanced our understanding on how different stimulation methods can be used to manipulate neural activity and consequently affect the episodic memory system. Through these methods we might one day be able to aid persons suffering from cognitive impairments or related pathologies.

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Acknowledgments

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Chapter 1 : General Introduction

Methods such as electroencephalography (EEG), magnetoencephalography (MEG), intracranial EEG (iEEG), and functional Magnetic Resonance Imaging (fMRI) provide us with little windows that allow us to peek into our heads. For example, we might want to know what happens when we remember the last time we experienced a particular event in our life. By looking through those windows, we get to see which areas of the brain are involved and how they communicate with one another, as we remember the event. This observational approach has given us many great insights and allowed for the creation of a wealth of theories and hypotheses on how cognitive systems, like our memory system, are implemented in the brain. Unfortunately, the possible inferences of such methods are limited to the correlation realm. We might suspect that a specific brain pattern is associated with a behavioural outcome and would want to show that the pattern plays an important role in causing a predictable change in behaviour. With the previously mentioned methods, we can only confirm that this observed pattern is involved, not whether it is necessary. As it were, we can look through the windows, but cannot change what we see directly. To show that a given pattern of neural activity is actually necessary for a particular cognitive process, one would want to see that the behavioural outcome changes when the pattern is manipulated directly. In other words, methods that allow for causal inferences are vital to further our understanding of the brain by confirming observed relationships.

Brain stimulation methods, such as transcranial alternating current stimulation (tACS), transcranial magnetic stimulation (TMS), and direct electrical stimulation, allow us to make causal inferences by directly manipulating ongoing brain activity (Bergmann & Hartwigsen, 2020; Thut et al., 2012). This thesis focusses on the application of such methods in the pursuit of understanding the human episodic memory system. The first chapter will provide context for the following chapters, by introducing core concepts and describing the general methods that were used. The following chapters of this thesis will each present findings from studies that manipulated brain activity to allow for causal inferences in the context of episodic memory and its mechanisms. The three different studies each targeted neural activity in the neocortex or hippocampus, by using one of the above-mentioned stimulation methods. The last chapter will summarize and synthesize the findings of all the preceding chapters, while discussing the implications of the studies within the wider literature.

1. Episodic Memory

Not all memories are created equal. Some memories relate to our conscious (declarative) knowledge, such as facts and events in our life, while others relate to implicit (non-declarative) knowledge, which can be activated without conscious memory, such as specific skills (Squire & Zola, 1996). Early lesion studies have revealed that declarative memory can be further divided into separate sub-categories (Scoville & Milner, 1957). One of these categories is episodic memory, as it was first coined by Tulving in 1972, which is separated from another declarative memory category named semantic memory (Tulving, 1972). Episodic memory specifically refers to our ability to mentally travel back to past personal experiences while retaining at least some awareness of the present. This is opposed to semantic memory, which encompasses memories of abstract knowledge that do not contain this experiential and temporal dimension.

To illustrate the difference with an example: the knowledge that Birmingham was voted the UK's ugliest city is a fact that does not rely on any experiential knowledge and is therefore categorized as a semantic memory ('Birmingham Named UK's Ugliest City', 2011). When remembering such a general fact, one does not think back to the moment this knowledge was first acquired, apart from the trivial awareness that this fact was at some point learnt in the past. Rather, that moment in time is not actively re-experienced when thinking of such a fact. In contrast to this, remembering the breath-taking sights, sounds, and smells, of a sunny day in Birmingham would constitute an episodic memory, as it relates to a unique self-centred personal experience that is specific to a particular point in space and time. This separates it from all other experiences in one's life. It is important to highlight that remembering an episodic memory is a distinct experience from perception or imagination in this framework (Wheeler et al., 1997).

Initially, the previously mentioned lesion studies mainly implicated the hippocampus as necessary for episodic memory (Scoville & Milner, 1957). Subsequent research revealed that the whole medial temporal lobe (MTL), with a variety of neocortical and subcortical areas, plays an important role in our ability to form and retrieve episodic memories (Dickerson & Eichenbaum, 2010; Squire et al., 2004). While the exact roles of the hippocampus and surrounding neocortex are still under investigation, the most influential frameworks in the field of memory, are in agreement that the hippocampus and neocortex require close communication with one another to encode and retrieve episodic memories

(McClelland et al., 1995; Nadel et al., 2000; O'Reilly et al., 2014; Teyler & DiScenna, 1986; Teyler & Rudy, 2007).

The Complementary Learning Systems (CLS) framework is a particularly important framework when talking about episodic memories. It presents the hippocampus and neocortex as two parts of a highly overlapping distributed system (McClelland et al., 1995). In this system the hippocampus first creates a signature during encoding that it can later retrieve and keep it separate from other already established signatures. It is able to do this due to its unique neural architecture. This architecture allows the hippocampus to perform both one-shot and statistical learning (O'Reilly et al., 2014; Schapiro et al., 2017). The neocortex on the other hand is limited by its architecture in this respect and can only perform slow statistical learning over time. However, the memories stored here are also more robust, as the neocortex is less susceptible to short-term changes. After a memory has been formed in the hippocampus, the hippocampus subsequently is assumed to make the neocortex replay the memory by repeatedly reactivating neocortical assemblies tied to the specific memory. This replay is thought to occur during sleep as well as every single time a memory is retrieved. As the hippocampus trains the neocortex through replay, the neocortex integrates and consolidates the memory (using statistical learning) without having to overwrite old memories. This framework has been refined over the years and has become the overarching framework for many other models of the episodic memory system.

2. Brain signals

2.1. Neural Oscillations

Our brain is never at rest. Even when idle, neurons in the brain appear to have a certain level of baseline firing. Each action-potential contributes a slight change in electrical potential within the surrounding cerebrospinal fluid (CSF) (Buzsáki et al., 2016). The fluctuating accumulation of firing can then be measured by using electrodes. Typically, when this signal is recorded from the scalp it is referred to as the electroencephalogram (EEG), while if it is recorded from within the brain it is referred to as intracranial EEG (iEEG), electrocorticogram (ECoG) (when iEEG is recorded on the cortical surface), or Local Field Potential (LFP) depending on the electrode sizes, impedances and arrangements.

It has been observed that with certain ongoing processes some neurons are more likely to fire synchronously. This synchronous firing manifests itself as waves in the electrophysiological data; the activity waxes and wanes as populations of neurons fire and

rest in synchrony. These patterns are also known as neural oscillations. These neural oscillations are characterized by the frequency at which they occur. Multiple neural oscillations can co-exist and be superimposed on each other as long as they occur at separate frequencies. Interestingly, while these oscillations arise from neural spiking, they can in turn also have the ability to influence neural firing themselves (Anastassiou et al., 2011; Fröhlich & McCormick, 2010).

An important feature of oscillations is that they are stationary and occur at a narrow frequency (Donoghue et al., 2021). This is important, since oscillatory activity is not the only type of activity visible in the frequency spectrum. The frequency spectrum can be separated in periodic activity (aka 'true' oscillations) and aperiodic activity (also commonly referred to as fractal or '1/f' activity). The aperiodic activity consists of the non-oscillatory contributions to the data. Neural oscillations are super-imposed on this scaffold of aperiodic activity. Since the aperiodic activity is the most prominent activity in the data, changes in aperiodic activity may falsely appear as oscillatory changes. Therefore, it is important to disentangle the periodic from the aperiodic activity (Donoghue et al., 2020; Wen & Liu, 2016).

2.2. The Sync-Desync model

Neural oscillations have been implicated in many cognitive processes (Buzsaki, 2006). They are of particular interest in the field of memory since it has been observed that co-firing neurons will strengthen their connectivity to each other at the level of the synapse (Hebb, 1949). Such a mechanism is a prime candidate for providing a low-level process of how different concepts would be associated with one another. Thus, synchronized activity could reflect such a mechanism at the population level. Indeed, gamma band activity (30-100 Hz) in the hippocampus has been associated with increases in synaptic changes that are beneficial for memory (Fell & Axmacher, 2011). Synchronized activity in the theta frequency band (3-8 Hz) has also been found to play a crucial role in the episodic memory system (Buzsáki, 2002; Düzel et al., 2010; Jacobs, 2014; B. C. Lega et al., 2012). Activity at these two frequency bands seems to interact in a way where the gamma band activity is dependent on the phase of theta activity (J. E. Lisman & Jensen, 2013). Thus, theta is assumed to help the hippocampus organize the information that is processed when the signal synchronizes in the gamma band by restricting processing to specific time-windows.

Increases in synchrony are not the only oscillatory process associated with the memory system. Synchronization decreases in alpha/beta (8-30 Hz) frequency bands have been shown to enable memory processes as well (Hanslmayr, Staudigl, et al., 2012). This observation has been used as the foundation for the sync-desync framework, which provides an oscillatory framework within the wider CLS framework for how information is processed and communicated in the cortico-hippocampal network (Hanslmayr et al., 2016; Parish et al., 2018).

According to this model, the baseline activity of the cortico-hippocampal network is a low overall firing rate (and therefore also low gamma band synchronization) accompanied by high alpha band power in the neocortex. This pattern of activity is seen as a consequence of ongoing inhibitory firing (Jensen & Mazaheri, 2010). At the same time the corresponding hippocampal activity at baseline is characterized by low firing rates and low power in gamma and theta frequencies, as the hippocampus does receive much input from the neocortex and therefore has little information to process.

As information is being processed in the neocortex during memory encoding, firing rates go up as different stimuli are being processed simultaneously. With increased firing rates, the ongoing inhibition decreases, as a result of neural assemblies processing information in parallel (Jensen & Mazaheri, 2010). This manifest itself as alpha/beta power decreases (Haegens et al., 2011; Hanslmayr et al., 2009; Hanslmayr, Gross, et al., 2011; Esther B Meeuwissen et al., 2011; Noh et al., 2014). The information from neocortical processing is subsequently transmitted to the hippocampus. The hippocampus binds the information it receives from the various neocortical areas together (Staresina & Davachi, 2009). Hippocampal theta is thought to serve as a mechanism to organize the incoming information from the many different neocortical areas and incorporate them into a memory. This manifests itself as gamma power increases in the theta up-states, which in turn leads to an increase in theta power and theta-gamma coupling during encoding (B. Lega et al., 2016; Long et al., 2014; Rutishauser et al., 2010; Staudigl & Hanslmayr, 2013; Tort et al., 2009). A computational implementation of this model has shown that this can manifest itself as either theta power increases or decreases, depending on the amount of input the hippocampus receives (Parish et al., 2018).

At memory recall this pattern is assumed to reverse. In this case increased hippocampal theta synchronized firing is assumed to drive the relevant neurons in the neocortex to reinstate the pattern first encountered during encoding (Burke et al., 2014). This would once again results

in an alpha/beta band decrease in the neocortex as the firing rate goes up (Khader et al., 2010; Michelmann et al., 2016; Waldhauser et al., 2012).

3. Stimulation methods

This section will introduce the stimulation methods that were in the studies performed as part of this thesis

3.1. Sensory Stimulation

Sensory stimulation encompasses any type of presentation of brief sensory stimuli or sinusoidally modulated stimuli, with the intention of altering ongoing neural activity. The rationale is that the presentation of a perceptual stimulus will induce neural firing in the relevant low-level sensory regions. A rhythmic application of sensory stimuli should be able to entrain the neural activity according to the stimulated frequency (Haegens & Golumbic, 2018; Notbohm et al., 2016). Entrainment in this context refers to the process of coupling the ongoing neural oscillations to an external phase and frequency (Lakatos et al., 2019; Pikovsky et al., 2003).

The visual system was the first modality where rhythmic presentation of sensory stimuli was observed to have the potential for rhythmically modulating neural responses (Adrian & Matthews, 1934; Brenner et al., 1975; Norcia et al., 2015). However, sensory stimulation in different modalities has since been shown to also have the ability to modulate neural activity, such as for example the auditory (Pantev et al., 1996; Picton et al., 2003) and the somatosensory system (Brenner et al., 1978; Onishi et al., 2010).

3.2. tACS

tACS is a non-invasive electrical stimulation method that is intended to directly entrain ongoing neural oscillations (Antal et al., 2008; Antal & Paulus, 2013). It is usually implemented by applying an alternating current at a specific frequency through at least two (or more) electrodes placed directly on the scalp. The switching current then induces polarity changes in the underlying brain area at the applied frequency. The resulting electric field is very weak, as it is not possible to make the field strong enough to induce action potentials. This is due to the fact that electric fields of such a magnitude would cause sever discomfort in the subject (Antal et al., 2017; Vöröslakos et al., 2018). While the induced polarity changes do not induce neural firing per se, they bias neural activity to occur within specific time-windows, since the polarity changes make it more or less likely for a neuron to pass the threshold for an action potential. This means that tACS is assumed to change the timing of neural firing independent of the firing rate. This is reminiscent of how oscillations have the

ability to influence neural spiking (Fröhlich & McCormick, 2010). This also constitutes the major advantage of tACS over other non-invasive stimulation methods, as it merely allows to manipulate the phase of ongoing activity without artificially inducing action potentials, making it ideally suited to study the causality of brain oscillations. This also means that entrainment is only possible to frequencies close to naturally occurring frequencies in a given area.

tACS has been shown to be able to entrain single neurons in animal models and humans (Alekseichuk et al., 2019; Huang et al., 2017; Krause et al., 2019; Vieira et al., 2020). Despite this, there have been many null effects and failures to replicate positive results using this method. This has brought about much scepticism about the methods effectiveness in consistently bringing about behavioural changes (Asamoah et al., 2019a; Haberbosch et al., 2019; Lafon et al., 2017; Liu et al., 2018). It appears that many older studies have used parameters that are not able to affect neural firing at all due to insufficient field strength, no modelling of the electric field, or inability to disentangle neural from sensory effects (Asamoah et al., 2019b; Saturnino et al., 2017; Vöröslakos et al., 2018). This makes it very difficult to assess the exact level of effectiveness tACS has in various applications.

3.3. TMS

TMS leverages the principle of electromagnetic induction to induce electrical fields in a targeted brain region (Barker et al., 1985). The basic principle is that a brief electrical current is produced in a coil placed perpendicularly to the brain. This current in turn induces a short but intense magnetic field pulse that runs perpendicular to the originally produced electric field. This magnetic field in turn, induces an electric field in the brain, where the current in the induced field travels parallel to, but in the opposite direction of, the original electric field (Terao & Ugawa, 2002). These induced electrical fields then drive neuronal activity in the targeted region, with a bias for neurons that run perpendicular to the electrical field (which are more likely to by pyramidal neurons due to their size and numerosity throughout the brain) (V. Di Lazzaro et al., 2012; Vincenzo Di Lazzaro & Ziemann, 2013; Murphy et al., 2016). The area of effect of this field can be very focal (Romero et al., 2019).

TMS can be administered with a wide array of parameters and is not limited to single pulses. When administered as long pulse train (also named repetitive TMS/rTMS), TMS has the potential to entrain ongoing activity and change cortical excitability (Gerschlager et al., 2001; Lakatos et al., 2019; Wassermann, 1998). Specifically, low frequency rTMS (~1 Hz)

has been observed to have a decrease in cortical excitability (Casula et al., 2014; Chen et al., 1997; Todd et al., 2006). Higher frequency stimulation (~20 Hz) has been associated with increases in cortical excitability (Pascual-Leone et al., 1998; Quartarone et al., 2005). This allows rTMS to be used to boost or reduce neural activity in targeted brain areas to confirm their involvement in specific cognitive processes.

The major advantage of TMS over electrically based stimulation is that it is non-invasive and can therefore be used on healthy subjects without as much preparation. Additionally, TMS is able to stimulate cortical areas directly and effectively at depths up to 4 cm depending on the chosen parameters (Terao & Ugawa, 2002). It does this without causing pain, since the induced current does not have to pass through skin, where the nociceptors are located.

A major drawback of TMS is that the method induces a loud clicking sound and frequently induces somatosensory sensations. This can make subject blinding a challenge and requires careful planning of control conditions. Moreover, these sensory effects can make it difficult to disentangle the effects of the stimulation per se from the sensory induced activity.

Another drawback is that TMS is not able to directly stimulate deeper regions such as the hippocampus, or regions which are anatomically obstructed by other features of the brain. However, some recent research has suggested that it feasible to indirectly target such regions by stimulating regions that are connected to them as part of a network (Freedberg et al., 2019; Hermiller et al., 2019; J. X. Wang et al., 2014) (but also see (Hendrikse et al., 2020)).

3.4. Direct Electrical Stimulation

During direct electrical stimulation, an electrical current is applied directly to the brain through implanted electrodes. These electrodes can vary in their set-up and can therefore differ greatly in their range and effect. For example, stimulation between macro-channel electrodes has a much larger potential area of affect than stimulation originating from the much smaller microwires. Direct electrical stimulation has been integral in exploring the properties of a wide variety of brain areas, ranging from neocortical areas, to deeper sub-cortical areas (Cicmil & Krug, 2015; Davis et al., 1998; Lesser et al., 1986; Luders, 1987; Parker & Newsome, 1998; Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). Its biggest advantage is, that it is the most focal way of directly driving neuronal populations in human subjects and is currently the only established way to directly target subcortical areas such as the hippocampus. Additionally, since the stimulation is administered intracranially,

there is no risk of stimulating any peripheral neurons, ensuring that any observations are exclusively due to stimulation of the implanted region. This makes it an especially attractive method to probe the memory system due to the involvement of the hippocampus and the surrounding cortex (Mankin & Fried, 2020). While direct electrical stimulation has been used in many studies over the years to induce behavioural changes, the underlying neural mechanisms of direct electrical stimulation in humans has remained relatively underexplored.

Direct electrical stimulation is highly invasive. This means that it is difficult to implement and poses a high risk to the implantee. Therefore, its use in humans is only ethically acceptable in human patients, who are implanted with the electrodes for clinical reasons. This also means that the recorded data and the induced behaviour, runs the risk of not being representative of the general healthy population.

Besides its use in research, direct electrical stimulation has also established itself as a clinical tool. For example, it has been successfully used in the treatment of a variety of pathologies such as Parkinson's disease, epilepsy, dystonia, and depression (Bergman et al., 1990; Bronstein et al., 2011; Groiss et al., 2009; Hu & Stead, 2014; Scangos et al., 2021; Wu & Sharan, 2013).

4. Scope of the thesis

The following three chapters, based on experimental studies, will explore the role of the cortico-hippocampal network in the context of its relevance for the human ability for episodic memory as established by the sync-desync framework. Each chapter contains a study that aimed to establish causal links between previously established neural patterns and some form of behavioural measure, or as is the case for chapter 4, other established neural patterns. This is achieved by utilizing one or more of the above-described stimulation methods.

The first study, presented in chapter 2, intended to explore whether cortical entrainment produced by tACS can affect neural activity in the hippocampus in a way that is behaviourally relevant. This was done by adapting an established episodic memory paradigm that used sensory stimulation as a method of cortical entrainment (Clouter et al., 2017; Wang et al., 2018). The visual flicker was replaced by occipital tACS with the rationale that the originally observed effects should not depend on the method of entrainment. While tACS is known to be able to entrain cortical activity (as suggested by a plethora of tACS studies

measuring underlying single unit activity: Alekseichuk et al., 2019; Huang et al., 2017; Krause et al., 2019; Vieira et al., 2020), it is unknown how this entrainment of sub-threshold stimulation compares to the neural modulation produced by visual flicker.

The second study, presented in chapter 3, explored the wider cortico-hippocampal circuit by administering 1Hz rTMS to the left DLPFC during a list learning task over the course of two separate experiments. The left DLPFC is a neocortical area known to project to the hippocampus and has been implicated in episodic memory (Balconi, 2013). TMS had already previously been used to establish a causal relationship between the left DLPFC and episodic memory. High frequency rTMS (~20 Hz) was shown to reduce memory performance (Rossi et al., 2001; Sandrini et al., 2003). However, to cement the importance of the left DLPFC on memory performance, it would be interesting to attempt to boost memory performance instead. Consequently, 1 Hz rTMS was expected to improve memory performance, since 1 Hz and 20 Hz rTMS are assumed to have opposite effects on cortical excitability. The stimulation was complemented with concurrent EEG recordings to provide additional insight on the underlying neural mechanisms that may be relevant.

The third study, presented in Chapter 4, explored the effects of direct electrical stimulation throughout the human MTL, while recording single unit activity from the hippocampus and iEEG throughout the MTL. Its main goal was to characterize the electrophysiological response of the human hippocampus to single pulse electrical stimulation (SPES) and compare it to established responses in other brain areas and in animal models. Such characterization is vital for future studies seeking to stimulate the human MTL with the intention of modulating memory performance.

Chapter 2 : Investigating the Role of Phase-Synchrony During Encoding of Episodic Memories Using Electrical Stimulation

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Abstract

The multi-sensory nature of episodic memories indicates that communication between a multitude of brain areas is required for their effective creation and recollection. Previous studies have suggested that the effectiveness of memory processes depends on theta synchronization (4Hz) of sensory areas relevant to the memory. This study aimed to manipulate theta synchronization between different sensory areas in order to further test this hypothesis. We intend to entrain visual cortex with 4 Hz alternating current stimulation (tACS), while simultaneously entraining auditory cortex with 4 Hz amplitude-modulated sounds. By entraining these different sensory areas, which pertain to learned audio-visual memory associations, we expect to find that when theta is synchronized across the different sensory areas, the memory performance would be enhanced compared to when theta is not synchronized across the sensory areas. We found no evidence for such an effect in this study. It is unclear whether this is due to an inability of 4Hz tACS to entrain the visual cortex reliably, or whether sensory entrainment is not the underlying mechanism required for episodic memory

tACS, Theta Oscillations,Episodic Memory

1. Introduction

The creation and retrieval of episodic memories depends on communication between a multitude of areas throughout the brain. After information is first received and processed in sensory areas, it is eventually relayed to the hippocampus, a structure that has been implicated in episodic memory processes (Scoville & Milner, 1957). This communication has been suggested to be mediated by oscillatory firing patterns (Hanslmayr et al., 2016; Hanslmayr, Staudigl, et al., 2012; Parish et al., 2018). A prominent frequency range in the hippocampus is the theta rhythm (~4 Hz), which is assumed to be relevant to processes involving episodic memory (Griffiths, Parish, Roux, Michelmann, Van Der Plas, et al., 2019; Jacobs, 2014; B. C. Lega et al., 2012). Experiments in rodents have shown that certain parts of the theta phase modulate long-term potentiation, which is assumed to be the neural mechanism underlying memory encoding (Hasselmo, 2005).

A recent series of experiments from our lab aimed to show similar effects of theta-phase on memory encoding in humans (Clouter et al., 2017; D. Wang et al., 2018). In the first study, video clips accompanied by an arbitrary sound were presented. The participants were instructed to associate the presented videos with the accompanying sound. The videos and sounds were individually theta modulated. For the auditory stimuli, the volume was modulated. For visual stimuli, the luminance was modulated. The visual and auditory information was presented at different phase delays. The video clips could be presented in phase, or out of phase (phase delays of 90°, 180°, and 270°). We found that memory performance was significantly enhanced for clips where the sounds and videos were in phase compared to the out of phase conditions. In order to control for the possibility that only phase synchrony, independent of theta, drives the memory effect, two non-harmonic frequency bands were introduced as control conditions (1.7 Hz and 10.5 Hz), alongside another stimulation condition with a non-stationary waveform. The memory effect was not observed in any of the control conditions, suggesting that the effect depends on phase synchrony specifically in the theta band. The experiment was replicated in a subsequent study, where we recorded neural activity using electroencephalography during the experiment (EEG) (D. Wang et al., 2018). In this subsequent study we found that at a single-trial level, strength of entrainment could predict memory performance.

These studies together suggest there is an optimal theta-phase for memory. The underlying assumption is that the flickering stimuli entrain the respective sensory areas within the brain (Rager & Singer, 1998). Based on that assumption we hypothesize that this entrainment

ultimately affects how easy the items can be bound and processed in the context of memory. However, given the flickering nature of the stimuli used in these experiments, we cannot exclude the possibility that the observed memory effects are largely driven by inherent properties of our visual system. This mainly relates to findings suggesting that the visual system, but not the auditory system, discretely samples the environment in theta and alpha range frequencies (Landau & Fries, 2012; VanRullen et al., 2014) The implication is that by attempting entrainment with such heavily modulated stimuli, any memory effects might be mediated by purely perceptual effects. If entrainment is indeed the underlying mechanism that produces the observed effects, similar results should be observed when changing the mode of entrainment to a method that modulates the visual system more subtly and is less noticeable to the observer. A method for neural entrainment that has gained prominence in recent years is transcranial alternating current stimulation (tACS). This method is hypothesized to cause neural entrainment by biasing neural populations to fire at certain times, over others, without directly causing any action potentials (Antal & Paulus, 2013; Helfrich, Knepper, et al., 2014). This is unlike the flickering stimuli used in the previous studies, which lead to forced overt neural responses in the visual cortex.

The idea for the current study is to attempt entraining the visual system by using tACS over occipital areas while presenting un-modulated videos in unison with theta modulated auditory stimuli. The expectation is that if the previously discussed results are due to entrainment of the sensory modalities, the same effects should be observed, albeit with a smaller effect size since tACS would produce to a more subtle entrainment than a flickering stimulus.
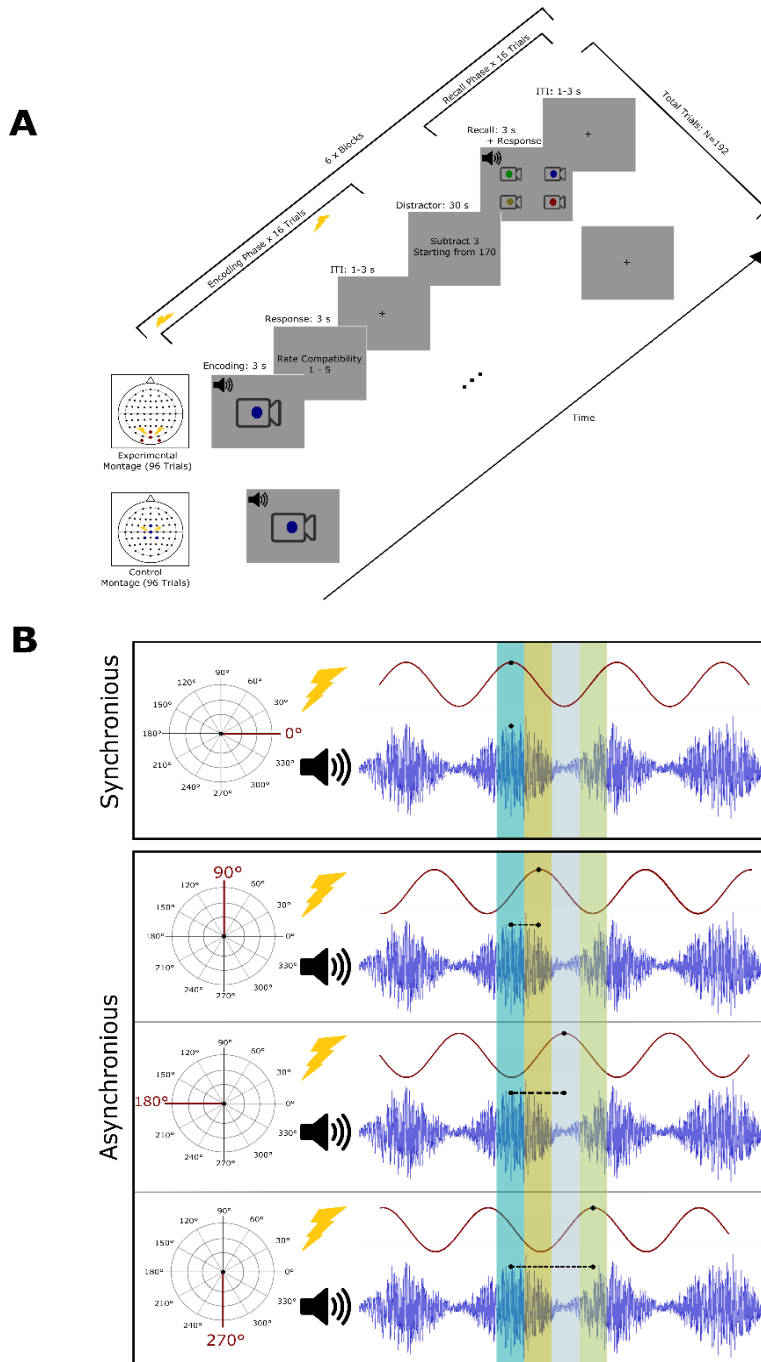
Fig 1-1 : A. Visual representation of the experimental procedure. The Experiment will be performed in two sessions, each with a different electrode montage. There will be a total of 192 trials spread over 12 blocks (6blocks per sessions) each containing 16 encoding and retrieval trials which are separated by a distractor task during which they have to countdown in steps of three from a random number. During the encoding phase of a block the participant will be instructed to judge how well a given auditory stimulus and visual stimulus fit together. For the retrieval phase participants will be instructed to match a cued sound to the correct video in a choice of four different videos. B. Illustration of the different conditions. Each condition depends on the phase relationship between the current (red) and the amplitude of the sound (blue). The conditions are assigned through the relative phase distance between the auditory and the electrical stimulation (illustrated by the dotted line). Colored sections represent the width of the bins determining what condition a given trial is assigned to.

2. Methods

2.1 Participants

In a Bayesian analysis framework it is legitimate to monitor the Bayes factor during data collection, since the Bayes factor is not biased in one direction with increasing sample size (unlike traditional frequentist analysis approaches based on p-values) (Berger & Wolpert, 1988; Biel & Friedrich, 2018; Rouder et al., 2012). Therefore, the number of tested participants was determined by monitoring the Bayes factor of the behavioral memory effect between conditions (with the following maximum and minimum: $30 =< N =< 120$). Subjects were tested until the Bayes factor (BF) either became at least 10 (in favor of the null hypothesis) or $< 1/10$ (in favor of the alternative hypothesis). A $BF > 10$ would indicate that the alternative hypothesis is at least 10 times more likely given the null hypothesis, while a $BF < 1/10$ would indicate the null hypothesis is 10 times more likely than the alternative. These BF values have been chosen based on common practices which are calibrated to produce results at least as stringent as an alpha of 0.02 in traditional frequentist analyses (Jeffreys, 1961).

The tested population was right-handed participants between the ages of 18-35 with normal hearing and normal vision or corrected-to-normal vision. All participants are screened in accordance to the tACS safety guidelines. They should have no history of any neuropsychiatric disorders or abnormalities, no active implants, and no recent use or previous dependency of any drugs. Participants have been recruited using the University of Birmingham Research Participation scheme at the University of Birmingham as well as flyers and posters distributed on the campus.

All participants were reimbursed for participation. All methods used are approved by the Birmingham University Ethics Committee

2.2 Stimulus material

This study used the same stimulus material as in Clouter and colleagues (Clouter et al., 2017). The auditory stimulus material is identical to the previously used material, meaning that the volume of the stimuli will be sinusoidally modulated at a 4 Hz frequency. This value was chosen in order to reduce the amount of differences with the studies this experiment tries to replicate. The peaks of the modulated signal oscillated between 0% and 100% of the volume. Moreover, the stimuli always start at 50% volume. The visual stimulus material was

left unmodulated. The sounds were randomly paired to a video for each session forming set clips. Every clip (N = 192 clips) is 3 s long.

Stimulus presentation occurred with the Psychophysics Toolbox extension implemented in MATLAB (Brainard & Vision, 1997; Kleiner et al., 2007; Pelli & Vision, 1997), on a 19" SynchMaster943B screen with a 75 Hz refresh rate at a 1280 x 1024 resolution connected to a computer equipped with a NVIDIA Quadro K600 636 MB Graphics card. The participants viewed this screen from a distance of approximately 70 cm. Auditory stimuli were presented through a set of ER3C headphones (Etymotic Research) as delivered via a UR22 USB Audiointerface (Steinberg).

Since the tACS stimulation occurs continuously, independent of the modulated auditory stimuli, trials have to be back-sorted (post-hoc) to determine phase alignment. Due to the highly timing dependent nature of the hypothesis, back-sorting was performed using a scalp electrode near the stimulation site to inform on the exact stimulation phase at a given point in time. The trials were binned for conditions where auditory flicker and tACS stimulation was: in-phase, 90° phase-shifted, 180° phase-shifted, or 270° phase-shifted (See Fig 1-1B). The bins were determined by centering the bin around the mean direction of each bin (0°, 90°, 180°, 270°) and sorted given a bin-size of $\pm45°$ around the centre (for trial numbers per condition, see *table 1*). The 0° bin label has been assigned to the bin at the positive peak of stimulation. This categorization is based on the findings in the tDCS literature, showing that anodal (positively charged) stimulation leads to increased excitability, while cathodal (negatively charged) stimulation leads to a decreased excitability (Brunoni et al., 2012; Nitsche et al., 2008; Nitsche & Paulus, 2000). Therefore, we assume that the excitable 0° phase is comparable to the 0° phase as resulting from exposure to a stimulus. For the auditory stimuli, all bins were calculated with a 10 ms phase-shift in order to account for conduction delays from hair cells to the auditory cortex (Corey & Hudspeth, 1979; King & Palmer, 1985). We also accounted for a 7 ms trigger delay and a 1 ms conduction delay resulting from the soundwaves travelling within the ear-tubes of the earphones.

Table 1-1: *Descriptives of trial-numbers as resulting from backsorting for each condition.*

Experimental		Control	
Mean	Standard Deviation	Mean	Standard Deviation
23.7027	4.479437	24.1982	3.865511
24.59459	4.888536	23.96396	4.201575
24.00901	4.691376	23.76577	3.995349
23.69369	4.03348	24.07207	4.170702

The conduction of electrical stimulation from the scalp to the visual cortex is assumed to be near instantaneous. This is based on the common assumption that the skin, skull, and brain tissue act as ohmic resistors, an assumption that is supported by intracranial recordings (Logothetis et al., 2007; Opitz et al., 2016). It is important to note that this assumption has recently been contested (see for example (Gomes et al., 2016)), since there is some minor capacitive (and possibly inductive) effects of neural tissue that are not noticeable in specific circumstances. However, the capacitive effects of neurons do not lead to phase delays exceeding 0.5° for external stimulation at 4Hz (as reported in (Opitz et al., 2016)). For the purposes of this study, delays of that magnitude are assumed to be negligible, since a 0.5° shift at 4 Hz would correspond to a delay of < 0.5 ms. This is not an uncommon practice, since fundamental neuroscientific models, most notably neuronal cable theories (Rall, 1995), make similar assumptions, and are therefore implicit in more complex analyses such as for example EEG/MEG source modelling methods (Hallez et al., 2007).

2.3 Stimulation

Stimulation was administered with a NeuroConn DC-STIMULATOR MC through four circular Ag/AgCl electrodes (12 mm diameter). These electrodes were held in place by Soterix HD 1A.2 electrodes filled with Signagel as a conductor. The electrodes were connected to the stimulator using the NeuroConn HDTarget Adaptor Box.

The centrally placed electrode was located at Oz, while the other three electrodes were placed radially at POZ, O9 and O10 (see Fig 1-2A). This HD-tACS arrangement was chosen due to its high focality compared to more traditional electrode montages (Helfrich, Schneider, et al., 2014; Saturnino et al., 2017). The current flow resulting from this montage was simulated using the SimNIBS 2.1.1 software package (Thielscher et al., 2015). This software allowed us to verify that the resulting current affects the visual cortex while having negligible effects on other areas (Fig 1-2B). The advantages of such a high focality are two-fold. First of all, the focality ensures that surrounding areas are not affected by stimulation to the same degree as the targeted area. Secondly, the high focality reduces the likelihood that a participant will experience phosphenes, since these are mostly related to currents reaching the retina through the scalp (Schutter & Hortensius, 2010; Schwiedrzik, 2009). This assertion was confirmed in three pilot sessions in which the subjects were stimulated for 20 minutes with the intended montages (control and experimental montage) with no ongoing task. No phosphenes were reported in any of the pilot sessions, nor during the final experiment, by any of the subjects.

The stimulation intensity was set to 1.5 mA (peak-to-baseline) at the central electrode. Stimulation at this current intensity is high enough to bias cortical firing patterns (Ali et al., 2013; Huang et al., 2017). This stimulation was ramped up and down for 10 s each at the beginning and end of each encoding block. Participants were stimulated for a total duration of 288 seconds (approximately 5 min) per block. All impedances were kept under 5 kΩ at all times to reduce any adverse effect stimulation might have on the skin. In order to reduce the skin sensation induced by the stimulation, EMLA cream was applied which has been previously used to reduce electrically induced sensations (Khatoun et al., 2018; McFadden et al., 2011).

Due to the relatively high intensity and low stimulation frequency used, we predicted that this would likely lead to some subjects experiencing somatosensory sensation. This would be problematic since recent research suggests that tACS induced entrainment could result from stimulation of nerves in the skin, rather than stimulation of the underlying cortex (Asamoah et al., 2019b). In order to control for this, a separate session was performed using a control montage. This montage was mirrored and centered around Cz in order to ensure that the recorded stimulation signal (RSS) resulting from the two montages is comparable. Thus, for this montage the return electrode has been placed at Cz while the surrounding electrodes was placed at CPZ, FC1, and FC2 respectively (see Fig 1-2A).
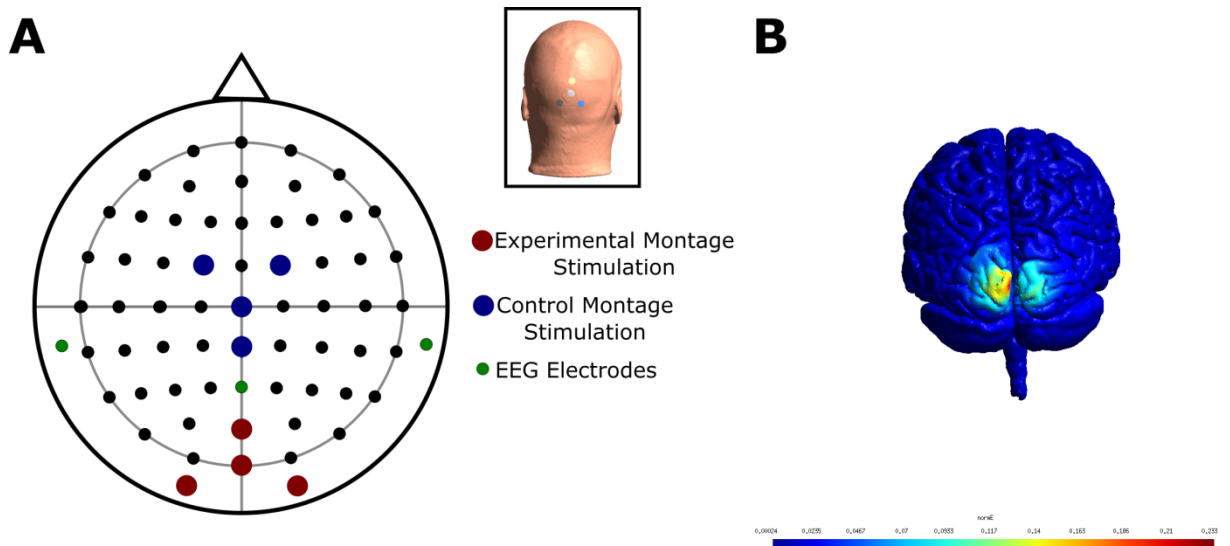
*Fig 1-2: **A.** Figure demonstrating the electrode montage. The coloured circular patches illustrate the location of the electrodes. The ground and reference of the RSS electrodes are each placed on the left and right mastoid respectively. **B.** Simulation of the normalized Electric field resulting from the montage in A. Note that the montage leads to quite a high focality.*

2.4 Recorded Stimulation Signal (RSS)

The recorded stimulation signal (RSS) was obtained using a Brainvision professional Brainamp MR plus amplifier at a sampling rate of 1000 Hz and with a scaling of 10 mV. The RSS was only recorded from one Ag/AgCl electrode (as used for standard EEG recordings) placed at location Pz for both montages. The reference was placed at the right mastoid, while the ground was placed at the left mastoid. Offline EEG was preprocessed with the Fieldtrip toolbox for MATLAB (Oostenveld et al., 2011). The data was band-pass filtered at 4 Hz, with a FIR filter with a band-with of 3-5 Hz. We did this, because the signals main purpose is to reliably extract the phase of tACS stimulation at every given trial. We limited ourselves to 4 Hz, because it is the frequency at which both stimuli are modulated. Any other frequencies in the RSS are probably caused by non-linearities. This signal is not relevant for determining the ongoing phase of stimulation. The RSS during the task was epoched to 2 s before and 5 s after onset of the clips. Subsequently, a Hilbert transformation was applied to the data in order to extract the phase angle at every point in time. This was done for both, the RSS signal and a sine-wave fitted to the envelope of the respective trial-specific auditory stimulus. These values were then subtracted from one another to obtain a phase difference value for each time-point. In order to avoid edge effects resulting from the Hilbert transforms, the median of the difference in phase angle was taken for the middle 1 sec period of the 3 second stimulus presentation (time-window of 2-3 s of each trial). The

median was taken to counter the slight oscillations resulting from the Hilbert transform, assuming that the phase difference stays constant throughout the time-window, as both stimuli were presented at exactly 4 Hz. This data was then be used to back-sort the trials into the respective conditions as described in section 2.2.

In order to ensure that the signal quality resulting from the RSS electrode would be sufficient for the planned back-sorting procedure, a pilot data-set was collected. For this recording, the subject underwent the described tACS stimulation with both montages (centered at Oz and Cz, respectively) and the described RSS electrode. The data was epoched around regularly administered (yet jittered) triggers. The conclusion from this pilot recording was that the RSS signal from both montages is suitable to allow for the planned back-sorting procedure (for an example see Fig 1-3]).
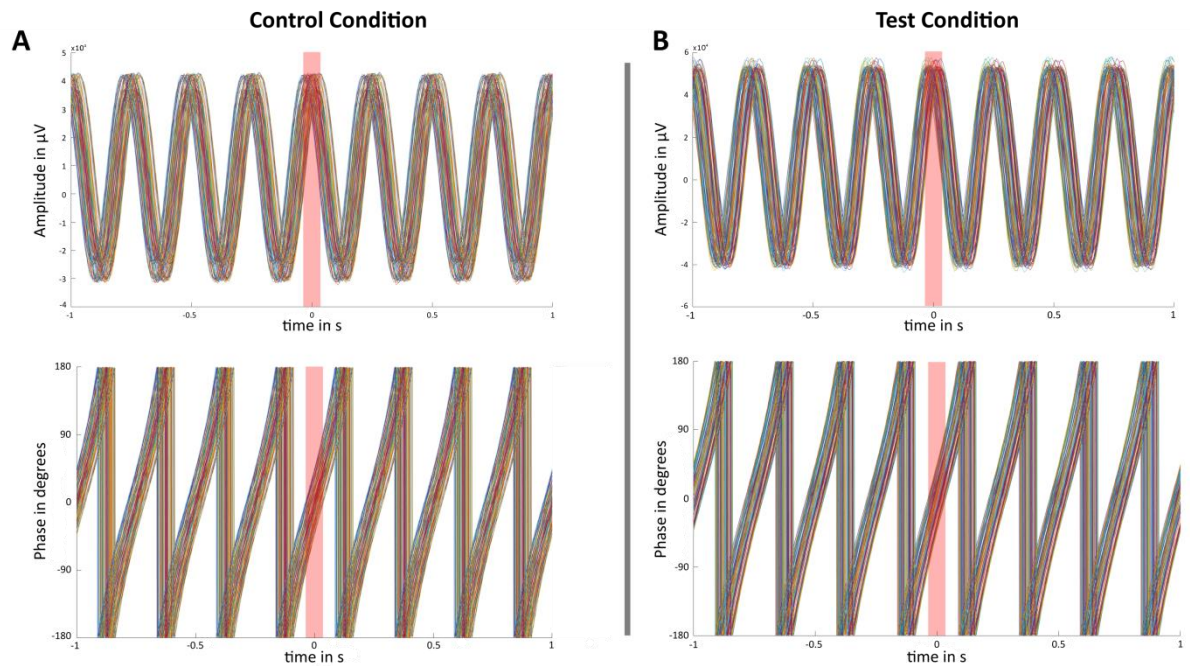
Fig 1-3: Figure demonstrating the RSS quality for the two different montages. This example only contains data from trials that were categorized of having phase angles between -45° and 45° (equivalent to the 0 phase condition in the actual experiment). The red bar indicates the time point 0 in all the figures. The upper figures always show the unfiltered raw signal while the lower figures demonstrate their corresponding phase-values **A)** Data collected with the control montage. **B)** Data from recordings with the experimental test montage. Note that the signal is so much stronger than native ongoing neural activity that barely any variance exists in the recorded signal amplitude. The stimulation artefact dominates the signal despite no filtering being applied.

2.5 Procedure

The experiment was administered in two separate sessions which were counterbalanced over the participants. One of the sessions was performed with the electrodes in the experimental montage (centered at Oz). In the control session, the electrodes were placed in the control montage (centered at Cz; see Fig's 1-1A and 1-2A). In order to reduce any skin sensations that might occur due to tACS stimulation, EMLA cream was applied to the central electrode where the current would be maximal. Following EMLA application, the stimulation electrodes were placed as specified in section 2.4. The participant would then be acquainted with the paradigm. For the encoding trial the instruction stated that the participant should judge how well each sound is suited to the given video in the context of a nature documentary, in order to ensure that the participant was paying attention to the experiment. The response was self-paced. The inter-stimulus interval (ISI) between each trial was able to take on any value between one and three seconds, with the exception of any multiples of 0.25 ± 0.05 s. This ensured that the ISI would never lead to two subsequent trials falling in the same condition.

Each session consisted of 6 blocks. Each block consisted of 16 trials. In each trial the 3 s clips (audio and video) were played and the participants were asked to create an association between the sound and the video. Following the encoding of all 16 trials, a distractor task was performed where the participant was instructed to continuously subtract 3 from a random number as fast as possible for 30 s. Following this, the participants were presented with a sound and 4 images of the clips. The participants then had to choose the correct video clip, i.e. the clip associated with the played sound. The three lures fulfill the following criteria. Firstly, the lure stimuli are stimuli that have been presented in the same stimulus block as the correct video stimulus. Secondly, the lure video stimuli have to have been presented in conjunction with a sound from the same instrumental category. These two measures ensure that the memory that is being tested for is truly episodic and cannot be solved based on familiarity signals. The selection in the retrieval phase was also self-paced. After the recall phase the participant could take a self-paced break. The procedure was then repeated for all blocks.

2.6 Data Analysis

As discussed in section 2.1, subjects were recruited to the experiment until the Bayes factor for the Bayesian paired sample t-test between the 0° and the 180° condition for the experimental montage exceeded 10, or fell below 1/10. Initial simulations showed that,

assuming the data would show half the effect size of the findings reported in the previous studies, the BF should fulfill the above requirement after about 40 participants. Once data-acquisition is halted, as per the stopping criteria discussed above, further data analysis was performed. Participants with low behavioral performance ($< 40\%$ correct; chance level: 25%) were excluded from further analysis. This relatively high threshold is chosen because it is important that the are participants actively engaged in the task and score high enough in general for any behavioral fluctuations to be visible, especially considering the stimulation method employed in this study. Moreover, any participants reporting phosphenes in the course of the experiment would be excluded from analysis.

To validate that tACS led to phase-dependent memory effects, two Bayesian implementations of the repeated measures ANOVA were applied to the data, one per session/montage. Subsequent Bayesian paired sample t-tests between all conditions would inform which conditions differ significantly from one another regarding their accuracy. These were corrected for multiple testing by fixing the prior probability that the null hypothesis holds across all comparisons to 0.5 (Westfall et al., 1997). Moreover, all tests were performed using a uninformative/objective Cauchy distribution as a prior, with r = 0.707 (Jeffreys, 1961; Rouder et al., 2009, 2012). All Bayesian analyses were performed using the R-based statistical software JASP (JASP, 2018; Wagenmakers et al., 2018). We also report the P-values for all the performed tests, as result from their analogous frequentist counterparts.

2.6.1 Exploratory Analysis: Subjective Sensations

While the EMLA cream numbs the skin and reduces the cutaneous sensation resulting from tACS, it does not eliminate this sensation completely in all subjects. For each session, every subject was asked whether they had any cutaneous sensations due to the tACS. This allowed us to partition the data according to cutaneous sensation, allowing us to test for an effect of sensation on behaviour. To this end, we performed an additional ANOVA with an added between-subject factor for 'reported sensation'.

2.6.2 Exploratory Analysis: Individual Sinusoidal Modulation

The above-described data analysis assumes that any entrainment resulting from tACS will be consistent across subjects. However, unlike for visual flicker, inter-subject variability could result in different phases of tACS producing the strongest excitatory (or inhibitory) effects. This will depend on many factors that will influence the eventual polarity, such as

the folding of the cortex. To further explore this issue in our analysis, we applied the 'MAX-OPP VS MIN-OPP' method, as described in Zoefel et al. (Zoefel et al., 2019). In short, the data is first aligned to a phase-bin with peak performance per subject, whereupon the phase-bin opposite of this peak is subtracted from the mean of the surrounding bins leading to a trough-to-zero-crossing difference value: d1. An equivalent operation is then performed by aligning the data to the bin with weakest trough performance and subtracting the opposite phase bin from the mean of the surrounding phase-bins, leading to a peak-to-zero-crossing value: d2. The two resulting values are subtracted from one another (d1-d2). If there is a sinusoidal modulation present, the distribution for d1 is positive, while d2 is negative, and the resulting difference is positive. Thus, if sinusoidal modulation of memory performance occurs, depending on the phase difference between the auditory stimuli and the tACS, then the resulting d1-d2 distribution should be positive. It is worth noting that the original findings of Clouter et al (Clouter et al., 2017) did not show a sinusoidal modulation *per se*, but a favored phase bin. As such we sought to explore the possibility that tACS might lead to a sinusoidal modulation with tACS. This analysis was not part of preregistration and is therefore exploratory.

3. Results

3.1 Main Results

As described in Methods, the difference in memory performance between the 0° and 180° phase condition was monitored as the dataset was collected. We found that the Bayes factor never reached a values of at least 10 for our experimental, nor alternative, hypotheses. We therefore collected the maximum preregistered number of subjects for this study (N=120). This Bayes factor difference eventually reached a value of $BF_{01} = 7.43$ in favor of the null hypothesis which is generally interpreted as moderate evidence that no difference exists between the two groups (p = 0.448) (see Fig 1-4). Of these, 38 subjects were excluded from further analysis since their behavioral performance did not meet the required criteria (average performance of > 40%), resulting in an N of 82. Thus, all subsequent analyses were only performed on the 82 subjects who conformed to this requirement. As expected, none of the participants reported any phosphenes.

The Bayesian repeated measure ANOVA testing for phase differences in the experimental condition, suggests that there is strong evidence for the null hypothesis ($BF_{01} = 40.97$; $BF_{10} = 0.024$). This concurs with the frequentist version of the analysis, which has a p-value that would not lead to a rejection of the null-hypothesis with an alpha of 0.05 ($F(3,243) = 0.464$; p = 0.708) (see Fig 1-5 for a plot of the memory performance per phase bin). Similarly, the corresponding Bayesian repeated measure ANOVA for the control condition also favors the null hypothesis ($BF_{01} = 1.49$; $BF_{10} = 0.67$), albeit with weaker evidence (BFs of < 3 are generally considered as anecdotal). This finding stands in contrast with the equivalent frequentist analysis, which would suggest rejecting the null hypothesis at an alpha = 0.05 ($F(3,243) = 2.939$, P = 0.034). The holm corrected post-hoc tests suggest a difference between the 0° and 90° condition (p = 0.033) and a borderline significant difference between 0° and 270° (p = 0.058), but no significant difference between 0° and 180° (p = 0.8). Given the Bayesian results and the tendency of p-values to converge towards zero given larger sample sizes, we refrain from further interpreting the results of the frequentist analysis.
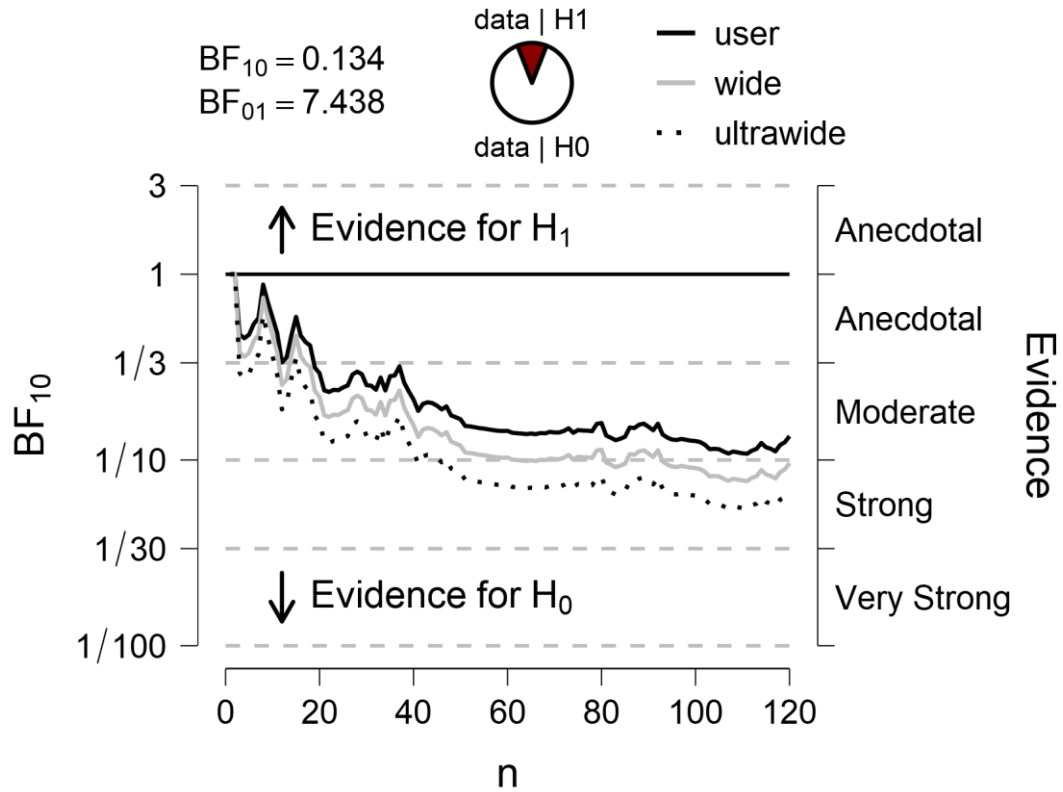
Fig 1-4*: Figure demonstrating the development of the Bayes Factor with every additionally added subject. The solid line indicates the analysis with the prior specified in the methods section. The other grey and dotted lines represent the same evolution with more conservative priors (assuming smaller effect sizes).*
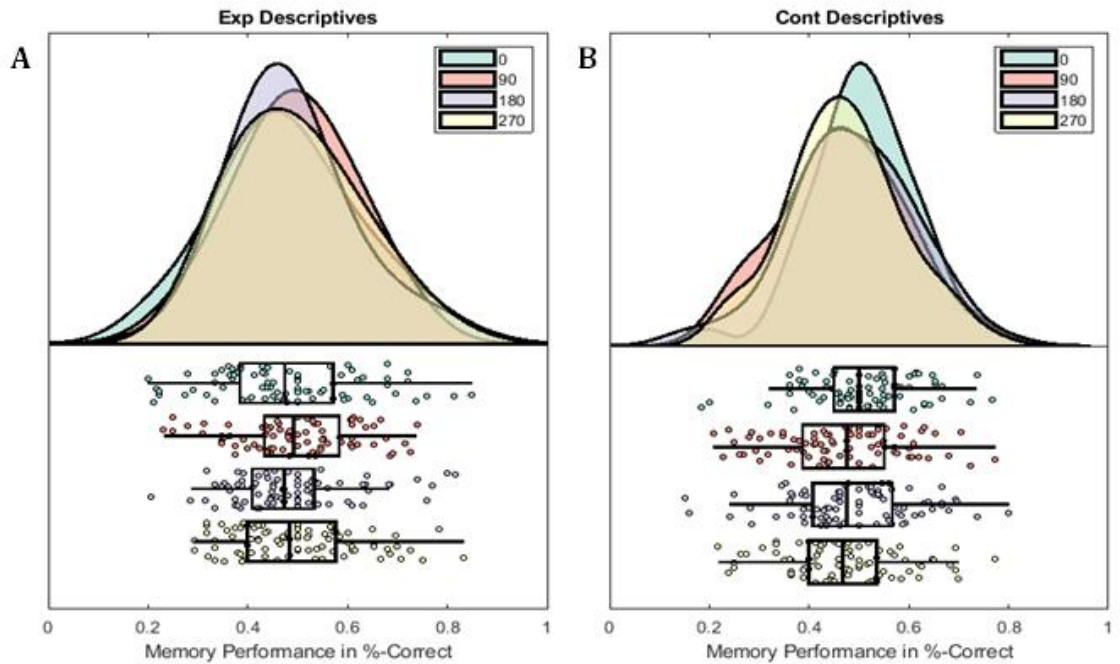
Fig 1-5*: Figure demonstrating the distribution of average memory performances for each subject per phase bin for the Experimental (**A**) and the Control Condition (**B**).*

3.2 Exploratory Analysis

The inclusion of self-reported cutaneous sensation as a between-subject variable in the model did not provide any evidence for an effect of sensation or an interaction between phase and sensation in either the experimental ($BF_{10}^{phase} = 0.018$, $BF_{10}^{Sensation} = 0.318$, $BF_{10}^{Phase*Sensation} = 0.004$; $p^{phase} = 0.679$, $p^{sensation} = 0.292$, $p^{phase*sensation} = 0.334$) nor the control condition ($BF_{10}^{phase} = 0.474$, $BF_{10}^{Sensation} = 0.138$, $BF_{10}^{Phase*Sensation} = 0.050$; $p^{phase} = 0.053$, $p^{sensation} = 0.987$, $p^{phase*sensation} = 0.278$))..

The 'MAX-OPP VS MIN-OPP' one-sample t-tests provided major evidence for the null-hypothesis, in that the distributions do not differ from 0 in a positive direction (Experimental Condition: $BF_{01} = 7.352$, $BF_{10} = 0.136$, $p = 0.634$; Control Condition: $BF_{01} = 3.602$, $BF_{10} = 0.278$, $p = 0.193$) (see Fig 1-6A). While visually exploring the data, it was noted that the distribution for the experimental condition appeared bi-modal. This could imply that only a subset of subjects respond to tACS. Additionally, this would violate the assumption of the performed t-test. This observation was confirmed with an adjusted 'Hartigan's dip test', which is optimized to detect bi-modal distributions (as described in (Kang & Noh, 2019)). This test concluded that the distribution of the experimental, but not the control condition was bimodal. The next step was to subtract the unimodal control condition, from the bimodal experimental condition. This was done in order to confirm whether there is a systematic difference between these two conditions, resulting from a subset of participants being successfully entrained by the tACS. If there is a systematic difference between the two conditions, this bimodal shape should be retained. This was not the case, leading to the conclusion that there was no evidence for sinusoidal modulation of memory performance depending on the phase-difference between auditory modulation and ongoing tACS (see Fig 1-6B).
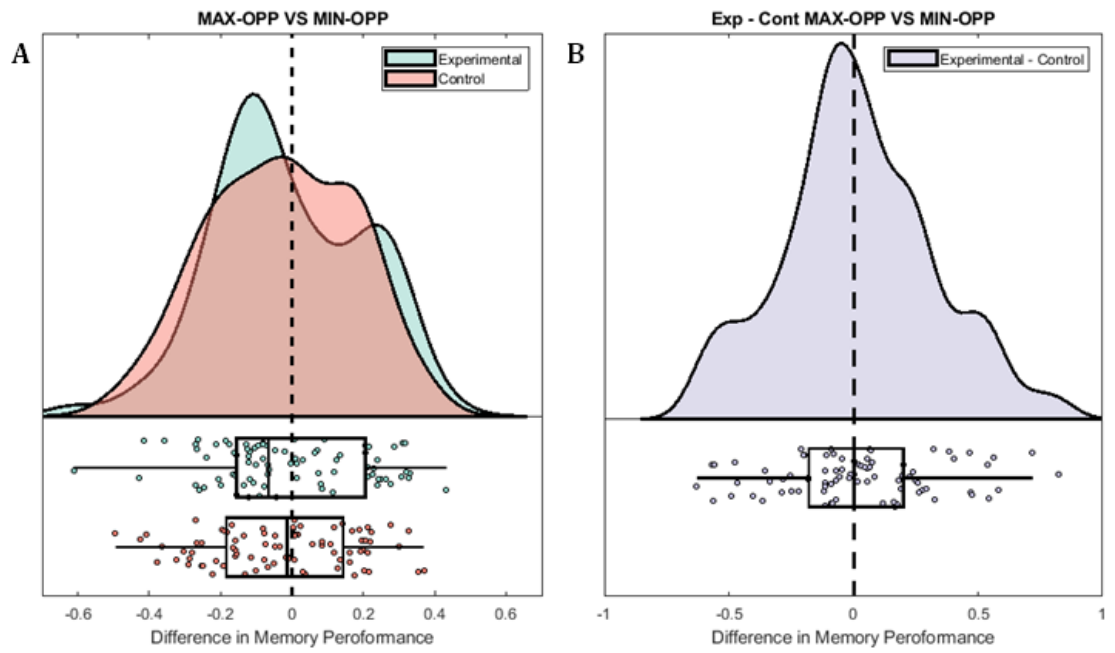
Fig 1-6: **A)** *Distributions resulting from the Max-OPP-Min-OPP analysis.* **B)** *Distribution of the difference between the experimental and control Max-OPP-Min-OPP*

4. Discussion

This study was unable to verify the findings of the previously described visual flicker studies (Clouter et al., 2017; D. Wang et al., 2018) using a different method of entrainment of the visual cortex. There could be multiple reasons for this inability to replicate these findings.

Firstly, it is possible that the results of the previous studies on which this study was based, were not inherent to entrainment effects in the brain but rather, due to the intrinsic properties of the presented stimulus material. Essentially this would mean that the original observed effect is not due to memory per se, but rather a perceptual effect. This argument is in line with studies showing direct interactions even between primary sensory cortices (Lakatos et al., 2007; Schroeder & Foxe, 2005; Stein & Stanford, 2008). It therefore appears possible that the strong rhythmic theta modulation of the stimuli itself impacted somehow on perception, which then had a knock-on effect on memory (i.e. items that are processed less efficiently in the first place, will be more difficult to retrieve later). Albeit it should be noted that in the original studies of Clouter et al. (Clouter et al., 2017) and Wang et al. (D. Wang et al., 2018) great care was taken to rule out an impact of such perceptual knock-on effects as much as possible.

Another possibility is that tACS does not succeed in entraining the visual cortex as we would have assumed. Much of the 'visual entrainment' tACS literature has focused on modulation of near-threshold level visual performances around the alpha band, since that is the endogenous frequency most dominant in the visual cortex (Helfrich, Schneider, et al., 2014; Kanai et al., 2008, 2010; Neuling et al., 2015; Zaehle et al., 2010). However, this study performed stimulation alongside natural stimuli (i.e. videos), alongside with stimulation at 4 Hz. Furthermore, we assumed that the tACS entrainment in the visual cortex would propagate downstream to higher level areas (i.e. hippocampus), where its signal is integrated with the auditory signal. It is quite possible that tACS is not able to entrain the brain enough to modulate the visual cortex sufficiently at the desired frequency for this propagation to occur, but rather influences only local activity in a very subtle way through its sub-threshold level modulation.

Furthermore, it is also conceivable that previously reported tACS effects might not result from actual neural entrainment. In order to verify that the underlying mechanisms for tACS effects are due to entrainment, research has been conducted that recorded EEG signal simultaneously with tACS (Helfrich, Schneider, et al., 2014; Neuling et al., 2015; Soekadar

et al., 2013; Voss et al., 2014). However, removing the tACS artefact from the EEG signal is not a trivial task that has arguably not yet been successfully accomplished (see (Neuling et al., 2017; Noury et al., 2016; Noury & Siegel, 2017, 2018) for an in-depth discussion of this issue). One proposed alternative mechanism is the so-called 'rebound' effect, under which tACS induces neural power-changes by compensation effects in individual endogenous frequency bands, following cortical inhibition resulting from the electrical current stimulation (Haberbosch et al., 2019; Perkel & Mulloney, 1974). If tACS does manipulate the brain through such mechanisms other than entrainment, this would explain our inability to find phase-dependent effects in this study

The scepticism about the mechanisms of tACS can even be taken a step further, by questioning the validity of tACS method in general. Recent studies concluded that the electric fields induced by tACS are simply too weak to cause any meaningful modulation of neural activity in general (Liu et al., 2018; Vöröslakos et al., 2018); but also see (Huang et al., 2017; Opitz et al., 2016, 2017). Under this view, most published tACS effects would be false positives, or result from alternative methods of entrainment such as phosphene and cutaneous sensation (Asamoah et al., 2019b; Schutter, 2016). The parameters chosen in this analysis would make it unlikely to observe any retinal effects, and cutaneous effects were addressed in our exploratory analysis that included sensory ratings.

Even if tACS can modulate brain activity, it is highly likely that the effect sizes for tACS, as with most research, are overestimated by the published literature due to publication bias. This increases the necessity of collecting large sample sizes (Button et al., 2013; Friston, 2013; Minarik et al., 2016). However, the trade-off of such increased sample sizes is an increased chance of false positive findings when using traditional frequentist analysis methods. With this fact in mind it is important to encourage the reporting of the Bayes Factor, since Bayesian analyses do not share this property of inflated significance with increased sample sizes (Biel & Friedrich, 2018; Dienes, 2011). We therefore believe that it is important that null-effects, such as the ones resulting from this study, keep being published. This enables more realistic estimates of the real effect sizes of stimulation methods, allowing for more accurate assessments of their limits. After all, non-invasive brain stimulation methods, such as tACS, have great potential as accessible research tools for the investigation of the underlying neural mechanisms of memory in humans and need to be understood more comprehensively.

Preregistration and data/materials availability

The Stage 1 manuscript was approved and formally registered on April 15, 2019, and may be downloaded from https://osf.io/qha3k, along with the comments raised during the reviewing process. All code that has been used to analyse the data, along with all the behavioral data and all notes made in the lab over the course of the experiment are available at https://osf.io/3ydph/. Legal copyright restrictions prevent public archiving of the movie material used for the experiment. These materials will be shared unconditionally on request to the corresponding author.

Acknowledgements

Chapter 3 : Stimulation of the left dorsolateral prefrontal cortex with slow rTMS enhances verbal memory formation

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Abstract

Encoding of episodic memories relies on stimulus-specific information processing and involves the left prefrontal cortex. We here present an incidental finding from a simultaneous EEG-TMS experiment as well as a replication of this unexpected effect. Our results reveal that stimulating the left dorsolateral prefrontal cortex (DLPFC) with slow repetitive transcranial magnetic stimulation (rTMS) leads to enhanced word memory performance. 40 healthy human participants engaged in a list learning paradigm. Half of the subjects (N=20) received 1 Hz rTMS to the left DLPFC while the other half (N=20) received 1 Hz rTMS to the vertex and served as a control group. Subjects receiving left DLPFC stimulation demonstrated enhanced memory performance compared to the control group. This effect was replicated in a within-subjects experiment where 24 participants received 1 Hz rTMS to the left DLPFC and vertex. In this second experiment, DLPFC stimulation also induced better memory performance compared to vertex stimulation. In addition to these behavioural effects, we found that 1 Hz rTMS to DLPFC induced stronger beta power modulation in posterior areas, a state which is known to be beneficial for memory encoding. Further analysis indicated that beta modulations did not have an oscillatory origin. Instead, the observed beta modulations were a result of a spectral tilt, suggesting inhibition of these parietal regions. These results show that applying 1 Hz rTMS to DLPFC, an area involved in episodic memory formation, improves memory performance via modulating neural activity in parietal regions.

Introduction

We are able to encode and store episodes that are rich in detail, filled with information and highly associative (Tulving, 1972). The first crucial step in forming episodic memories consists of processing the information at hand (Paller & Wagner, 2002). Before an event can be stored for later access it has to be represented (Hanslmayr et al., 2016). This involves posterior neocortical areas processing different sensory inputs under top-down control of prefrontal regions (Kirchhoff et al., 2000; Sommer et al., 1991). Being able to enhance this process via brain stimulation could prove invaluable not only for therapeutic interventions but also for gaining knowledge about how our brain accomplishes the complex task of forming episodic memories.

The left dorsolateral prefrontal cortex (DLPFC) has been demonstrated to play a role in memory formation (for a review, see (Balconi, 2013)). Stimulation at the DLPFC during encoding has been shown to reduce performance on verbal episodic memory tasks (Rossi et al., 2001; Sandrini et al., 2003). These reductions in performance have been mainly achieved with facilitative stimulation protocols (20 Hz stimulation). Thus, it seems that left DLPFC activity might have an inverse relationship to memory performance. Thereby, by inhibiting the left DLPFC, one would expect to see an increase in memory performance. Slow repetitive Transcranial Magnetic Stimulation (rTMS) has been shown to have an inhibitory effect on cortical areas (Casula et al., 2014; Chen et al., 1997; Maeda et al., 2000; Wassermann, 1998).

Monitoring the ongoing electrophysiological activity, with electroencephalography (EEG) can inform the mechanisms that lead to a given behavioural observation. We were particularly interested in monitoring the ongoing spectral profile, oscillations in the alpha-beta frequency band typically show a reduction in power during successful memory processing (see (Hanslmayr, Staudigl, et al., 2012) for a review), which might reflect more efficient stimulus processing [3].

We here report an incidental finding from the dataset of an existing study (Hanslmayr, Volberg, et al., 2012) in which the authors examined the role of the left DLPFC in voluntary forgetting. We re-analysed their rTMS-EEG dataset and found that 1 Hz rTMS applied to the left DLPFC during encoding of verbal material enhances memory performance. We further found that this rTMS-induced enhancement of memory performance co-occurred with stronger beta-power decreases, a state which is known to be beneficial for stimulus

processing (Klimesch et al., 2006). To ensure that the memory enhancing effects of rTMS are replicable, we conducted a second experiment which confirmed the memory enhancing effect of left DLPFC stimulation (experiment 2).

Results

Experiment 1: Behaviour

Participants were presented with two lists of ten words per encoding-retrieval run over the course of twelve runs. Following the six analysed lists, they were instructed to remember (i.e. keep in mind) the list just presented. After undertaking a short distractor task, participants were asked to recall all words from the two word lists just presented. The experimental group received 1 Hz rTMS to the left DLPFC during encoding of the second list and the control group received stimulation to the vertex (see Fig 2-1). It is important to note here, that the material analysed in this study only represents half of the completed trials by any given subject, as the original study also included lists that were to be forgotten as part of the original paradigm. Trials in these conditions are not further analysed in the context of this study.
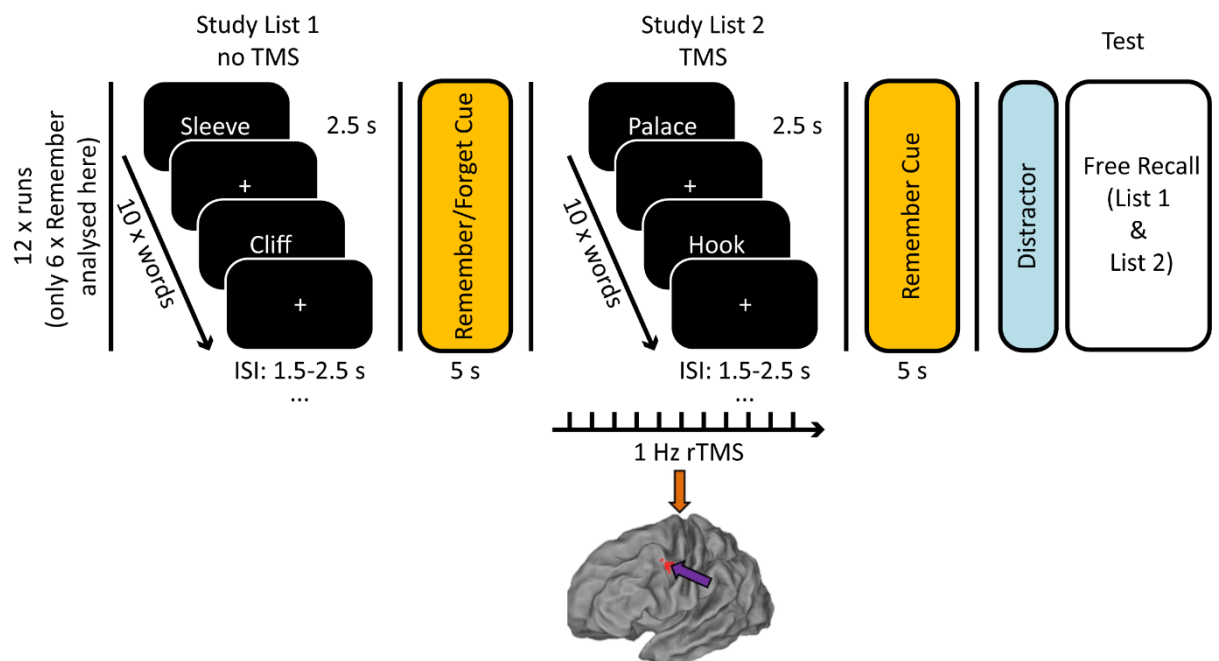
Fig 2-1. Experimental design. Arrows on brain model indicate stimulation site (DLPFC=purple, vertex=orange). Participants were asked to study two lists of 10 words over 12 runs. During encoding of list 2, 45 pulses of 1Hz rTMS were applied to the left DLPFC (MNI coordinates: -45, 6, 39) or vertex. Memory performance was assessed as percentage of correctly recalled words per list. The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.

To test the effect of rTMS on memory performance we conducted a 2 (List 1 vs List 2) x 2 (DLPFC vs vertex) mixed ANOVA. There was a significant positive effect of DLPFC stimulation on memory performance (main effect rTMS, $F(1,38)=5.096$, $p=0.03$, $\eta^2_p=0.118$) and a significant difference between memory for the first and second list (main effect list, $F(1,38)=17.242$, $p<0.001$, $\eta^2_p=0.312$). We also found a significant rTMS x LIST interaction ($F(1,38)=8.837$, $p=0.005$, $\eta^2_p=0.189$). Post-hoc independent samples t-tests revealed that the DLPFC group showed better memory performance compared to the vertex group for words presented during rTMS application (list 2, $t(38)=2.820$, $p=0.008$, Cohen's $d=0.892$ Fig 2-2D), but not for words presented before rTMS application (list 1, $t(38)=1.399$, $p=0.170$, Cohen's $d=0.443$, Fig 2-2B). Hence, the effects were specific to the application of rTMS to the left DLPFC.
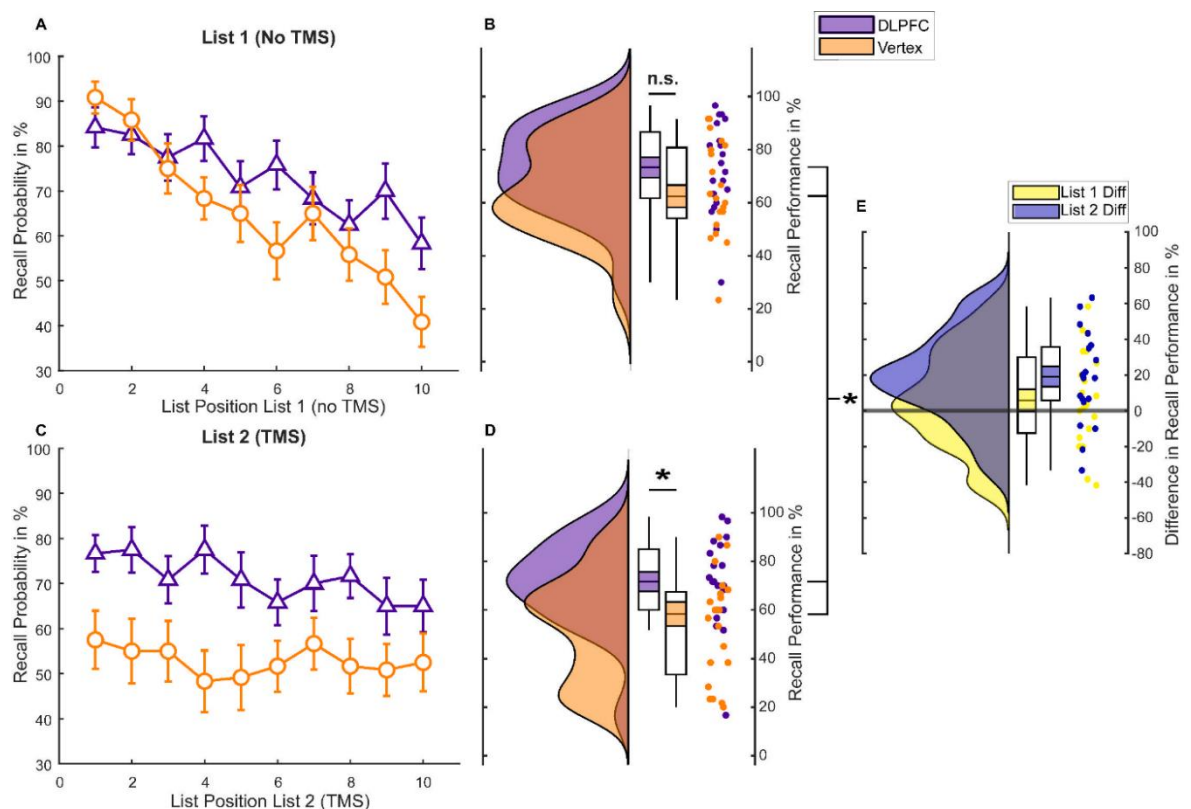
Fig 2-2. Behavioural memory performance in experiment 1. A) Serial position curve for List 1 words. Error bars depict standard errors of the mean. B) Raincloud plots of average memory performance for List 1 words across all blocks with paired boxplots (Allen et al., 2019). Coloured area within the box-plots indicate the standard error, while the circles depict individual data points. C) Serial position curve for List 2 words. Error bars depict standard errors of the mean. D) Memory performance for List 2 words. E) Difference in average memory performance between the DLPFC and vertex condition for each list (List 2 = Stimulation). The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.

In an exploratory follow-up ANOVA we investigated a possible effect of rTMS on serial position to assess whether left DLPFC stimulation affected the likelihood of recalling a word as a function of its list position (Murdock, 1962). Analysis of serial position curves revealed a significant LIST x POSITION x rTMS interaction ($F_{(9,342)}=2.435$, $p=0.011$, $\eta^2_p=0.06$). To unpack this 3-way ANOVA, we calculated two 2-way ANOVAs for each list separately. These ANOVAs showed a significant POSITION x rTMS interaction for list 1 ($F_{(9,342)}=2.703$, $p=0.005$, $\eta^2_p=0.066$), but no significant POSITION x rTMS interaction for list 2 ($F_{(9,342)}=0.893$, $p=0.532$, $\eta^2_p=0.023$, Fig 2-2C). The significant interaction in list 1 was due to enhanced recall rates for late position words in the DLPFC group compared to the vertex group (see Fig 2-2A). These results suggest that online rTMS to the left DLPFC equally increased memory performance in list 2 regardless of position, whereas for list 1 only late position words benefitted from stimulation.

Experiment 1: EEG

Post-stimulus beta power decreases have repeatedly been associated with successful memory formation [13,18,19]. Therefore, we first tested whether the DLPFC group would show stronger post-stimulus (0 to 1 s) beta power decreases (13-30 Hz) for words that were later remembered (hits) compared to the vertex group for list 2 trials. In order to test for a difference in this time and frequency window of interest the data were subjected to a cluster-based permutation test (Maris & Oostenveld, 2007). The results show significantly stronger beta power decreases (13-30 Hz) post-stimulus during DLPFC stimulation compared to vertex stimulation. This effect was evident over bilateral posterior sites post-stimulus ($p_{corr}<0.05$, Fig 2-3B; right post-stimulus topography). No effects were obtained for alpha (8-12Hz) or theta (4-7Hz) frequency bands in this time window. The time frequency plot at this negative electrode cluster, as well as the time course of beta power, is shown in Fig 2-3A and 2-3C (for the individual time frequency plots for the DLPFC and vertex condition see S1 Fig). Beta power showed a clear modulation due to rTMS with regards to word onset in the posterior electrode cluster. Specifically, stronger beta power pre-stimulus and lower beta power post-stimulus was observed during DLPFC stimulation compared to vertex stimulation.
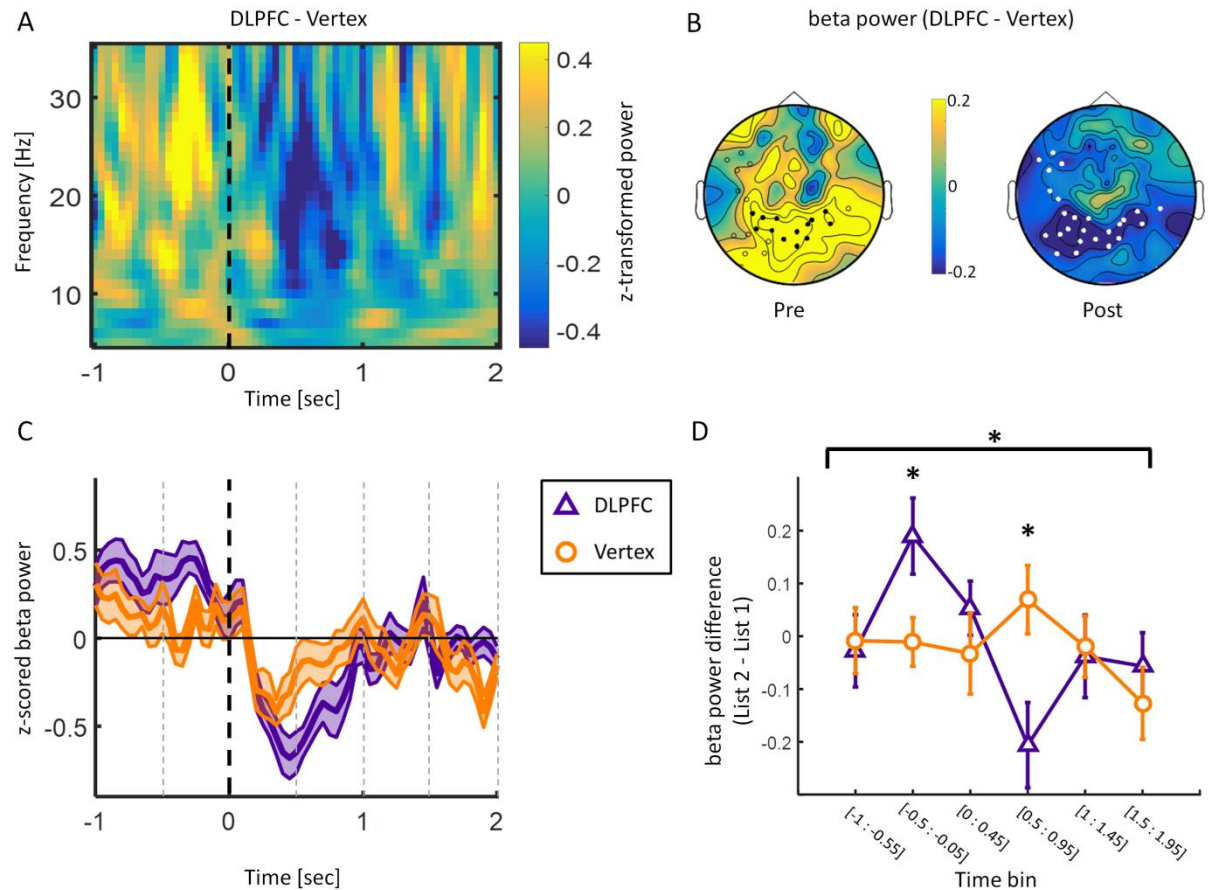
Fig 2-3. EEG results (only later remembered trials analysed). A) Time frequency plot for the difference between DLPFC and vertex during List 2 encoding averaged over electrode cluster demonstrating a significant negative difference (i.e. less power for DLPFC compared to vertex) between the DLPFC and vertex group in the beta frequency range post stimulus. Dashed line indicates word onset. B) Topographies depicting beta power (13-30 Hz) difference between DLPFC and vertex stimulation in time windows of interest (pre: -0.5 s to -0.05 s; post = 0 to 1 s). White circles depict significant negative electrode cluster post-stimulus. Black circles show electrodes within the negative cluster showing a positive difference pre-stimulus. C) Time course of beta power (13-30 Hz) averaged over the negative electrode cluster shown in B. Shaded area represents standard error of the mean. Black dashed line indicates word onset. Grey dashed lines depict time bins. D) Beta power difference (List 2 - List 1) over significant negative electrode cluster split by rTMS. Error bars show standard error of the mean. Data was split into six non-overlapping time bins: [-1s to -0.55s]; [-0.5s to -0.05s]; [0s to 0.45s]; [0.5s to 0.95s]; [1s to 1.45s]; [1.5s to 1.95s]. The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.

We further explored this beta power modulation to investigate whether it was specific to stimulation trials. Data from -1 s to 1.95 s relative to stimulus onset were split into six non-overlapping time bins (see Fig 2-3D) for List 1 and List 2 trials for the DLPFC and vertex group respectively. Data averaged over the significant negative electrode cluster were then subjected to a TIME (time bins) x LIST (List 1 vs List 2) x GROUP (DLPFC vs vertex) ANOVA which revealed a significant LIST x TIME x GROUP interaction ($F(5,190)=2.707$, $p=0.022$, $\eta^2_p=0.066$). Post-hoc independent samples t-tests revealed significant increases in beta power pre-stimulus (-0.5 s to-0.05 s: $t(32.347)=2.384$, $p=0.023$, Cohen's d= 0.754) and decreases in beta power post-stimulus (0.5 s to 0.95 s: $t(38)=-2.678$, $p=0.011$, Cohen's d=-0.847) in the DLPFC group compared to the vertex group (Fig 2-3D). These results indicate that 1 Hz rTMS at DLPFC modulated beta power predominantly in trials where the stimulation was applied.

Experiment 1: Spectral Tilt vs Oscillations

Recent research suggests that some broadband memory-related effects are driven by a change in spectral tilt (i.e. aperiodic components) rather than a change in narrow band oscillations (i.e. periodic components) (Burke et al., 2015). To investigate if the above reported effect of DLPFC stimulation on beta power is due to a change in oscillatory activity or a change in spectral tilt, we separated power-spectra into periodic and aperiodic components using the FOOOF toolbox (see Fig 2-4A for schematic representation of the components as labelled by FOOOF) (Donoghue et al., 2020). Moreover, we included components in the alpha band in this analysis, as the raw power spectra exhibited prominent alpha peaks (see Fig 2-4B).
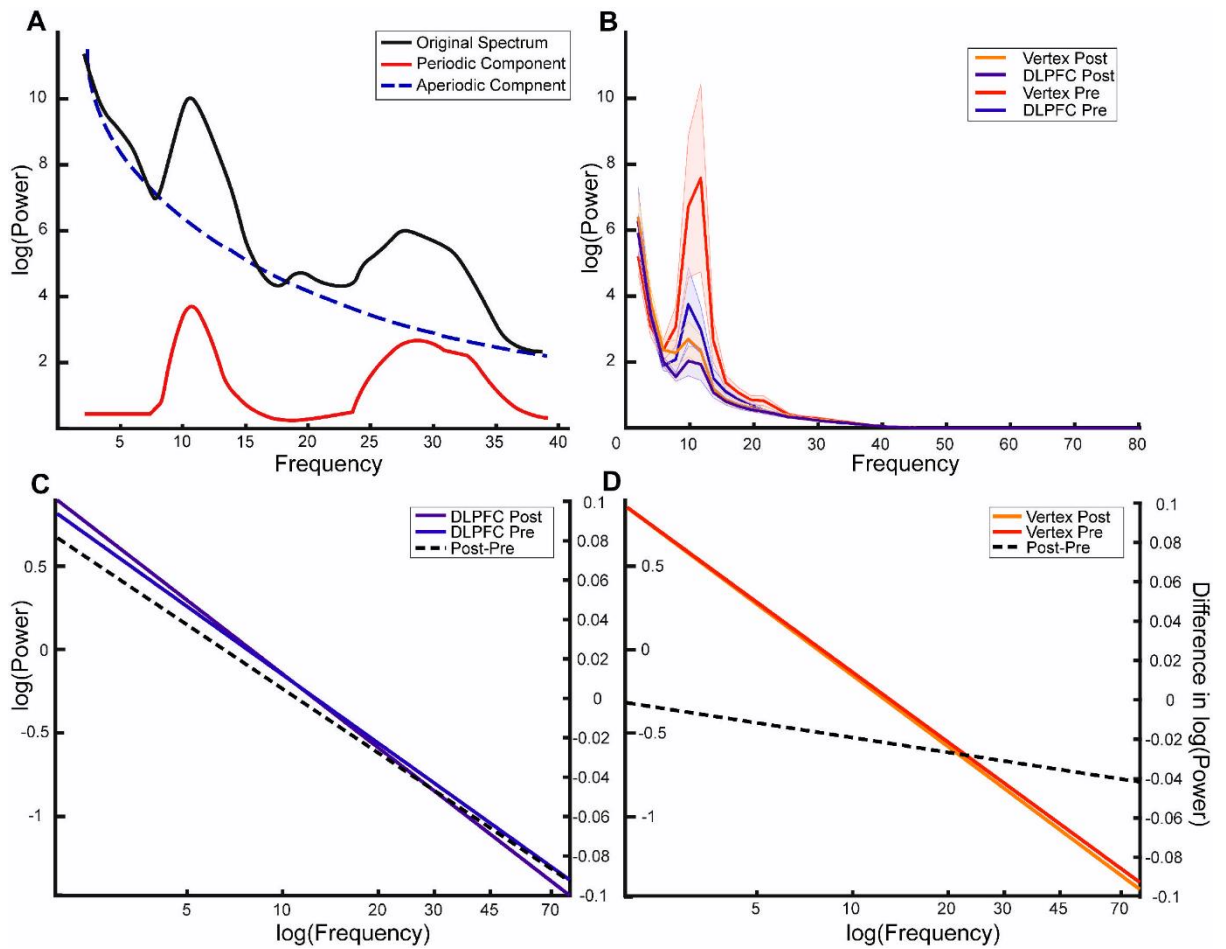
Fig 2-4. FOOOF analysis shows beta-effects are non-oscillatory in nature. *A) Schematic representation of the different components in a given power-spectrum. The black line represents a typical power-spectrum that is to be separated. The blue line is the corresponding log function following removal of the periodic peaks, thereby representing aperiodic properties of the signal. B) Power spectra separated by each condition. Shaded area indicates standard error. C)-D) Line plots of the mean aperiodic component before and after item presentation for the DLPFC and vertex condition, respectively. The right axis relates to the plotted post-pre difference (dotted line). The x-axis has been extended for illustrative purposes, to highlight the differences in slopes between the difference conditions. The actual fit was performed on data in the 1-40 Hz range. The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.*

We performed a 2 (pre vs post: TIME) x 2 (DLPFC vs vertex: STIMULATION) repeated-measurements ANOVA on the periodic and aperiodic components respectively, with TIME as a within subjects factor and STIMULATION as a between subjects factor. We observed a significant interaction effect for the aperiodic component, as reflected by the exponent and offset of the aperiodic component: Exponent: PREPOST x STIMULATION: $F_{(1,38)}=5.900$, $p=0.020$, $\eta^2_p=0.134$; Offset: PREPOST x STIMULATION $F_{(1,38)}=5.646$, $p=0.023$, $\eta^2_p=0.129$ (see Fig 2-4, for the distributions of the separate components see S2 Fig). No such interaction effect was observed for the ANOVA investigating the periodic/oscillatory activity in the beta frequency band (PREPOST x STIMULATION: $F_{(1,27)}=0.652$ $p=0.426$, $\eta^2_p=0.024$) or alpha frequency band (PREPOST x STIMULATION: $F_{(1,32)}=0.612$ $p=0.440$, $\eta^2_p=0.019$). For both these components only a TIME effect could be observed (beta: TIME: $F_{(1,27)}=012.267$ $p=0.002$, $\eta^2_p=0.312$) alpha: TIME: $F_{(1,32)}=26.471$ $p=0.001$, $\eta^2_p=0.453$). These results suggest that the interaction observed in the time-frequency representation was mainly driven by the aperiodic component, rather than narrow band oscillatory beta or alpha activity. In particular, the results suggest that DLPFC stimulation leads to a steeper aperiodic component where power decreases more quickly as frequency increases.

Experiment 2: Behavioural Replication

Experiment 1 revealed that 1Hz rTMS to the left DLPFC can increase memory performance for words that were presented during the stimulation compared to a control group. Enhancing long-term memory through rTMS would indeed be an important finding; especially with such a low frequency stimulation technique that does not require intracranial electrical stimulation or lengthy protocols. Given that our behavioural results were an incidental finding, we attempted an internal replication of the behavioural effect. To rule out any unspecific differences between the groups which might have contributed to the effects, we changed the study design to a within-subjects experiment. Furthermore, in this experiment the participants as well as the experimenter who interacted with them and scored their memory performance were naïve to the predicted effects of left DLPFC stimulation on memory. Other results of this study have already been reported (B. J. Stauch et al., 2020).

To test whether DLPFC stimulation leads to enhanced recall rates compared to vertex stimulation, we conducted a 2 (List 1 vs List 2) x 2 (DLPFC vs vertex) repeated-measurements ANOVA. We found a significant main effect for stimulation in the 2x2 rm-ANOVA, showing that DLPFC stimulation indeed led to higher memory performance compared to vertex stimulation (main effect rTMS, $F_{(1,22)}=6.778$, $p=0.016$, $\eta^2_p=0.236$). We

did not, however, observe a significant effect for list or a significant interaction (main effect List, $F(1,22)=2.943$, $p=0.100$, $\eta^2_p=0.118$; interaction Effect List X rTMS, $F(1,22)=0.009$, $p=0.926$, $\eta^2_p<0.01$). Post-hoc t-tests revealed a significant difference in recall performance between the DLPFC compared to the vertex condition for list 2 words, during the actual stimulation ($t(22) = 2.38$, $p = 0.026$, Cohen's d=0.496 ; see Fig 2-5D). This comparison was not statistically significant for list 1 words ($t(22) = 1.754$, $p = 0.093$, Cohen's d=0.366; see Fig 2-5B). This pattern suggests, that left DLPFC stimulation, once again led to enhanced memory performance compared to vertex stimulation. Analysis of the serial position curves (Fig 2-5A and 2-5C) revealed that recall performance across positions did not differ between the DLPFC and vertex condition in either of the two lists (rTMS x LIST x POSITION: $F(9,198)=1.061$, $p=0.394$, $\eta^2_p=0.046$; List 1: rTMS x POSITION $F(9,198)=1.612$, $p=0.114$, $\eta^2_p=0.068$; List 2: $F(9,198)=0.811$, $p=0.607$, $\eta^2_p=0.036$).

For most of the participants (N=18), the order in which words were recalled was also available. This allowed us to assess the amount of temporal clustering (Howard & Kahana, 2002) for list 1 and 2 words and to examine whether DLPFC stimulation affected the amount of contextual error. Such an effect would be predicted by theories implicating the DLPFC in organizing memory material into temporal clusters (Blumenfeld & Ranganath, 2007). A 2 (List 1 vs List 2) x 2 (DLPFC vs vertex) repeated measures ANOVA was conducted to determine whether temporal clustering is affected by stimulation. No significant main effects or interaction were observed (main effect for Stimulation: $F(1,17)=0.624$, $p=0.440$, $\eta^2_p=0.012$; main effect for List: $F(1,17)=0.017$, $p=0.899$, $\eta^2_p=0.003$; interaction List x Stimulation: $F(1,17)=0.452$, $p=0.511$, $\eta^2_p=0.007$). To ensure that we did not miss a potential effect of temporal clustering for list 2 items between the stimulation conditions, we performed a post hoc follow-up t-test on the List 2 only, which also failed to show a significant difference between stimulation conditions (List 2 DLPFC vs List 2 Vertex: $t(1,17)=-0.109$, 0.914). These results indicate that the memory enhancement effect of left DLPFC stimulation cannot be attributed to changes in temporal clustering of the words between or within lists. Rather, DLPFC stimulation seemed to have improved memory performance for each item independently.
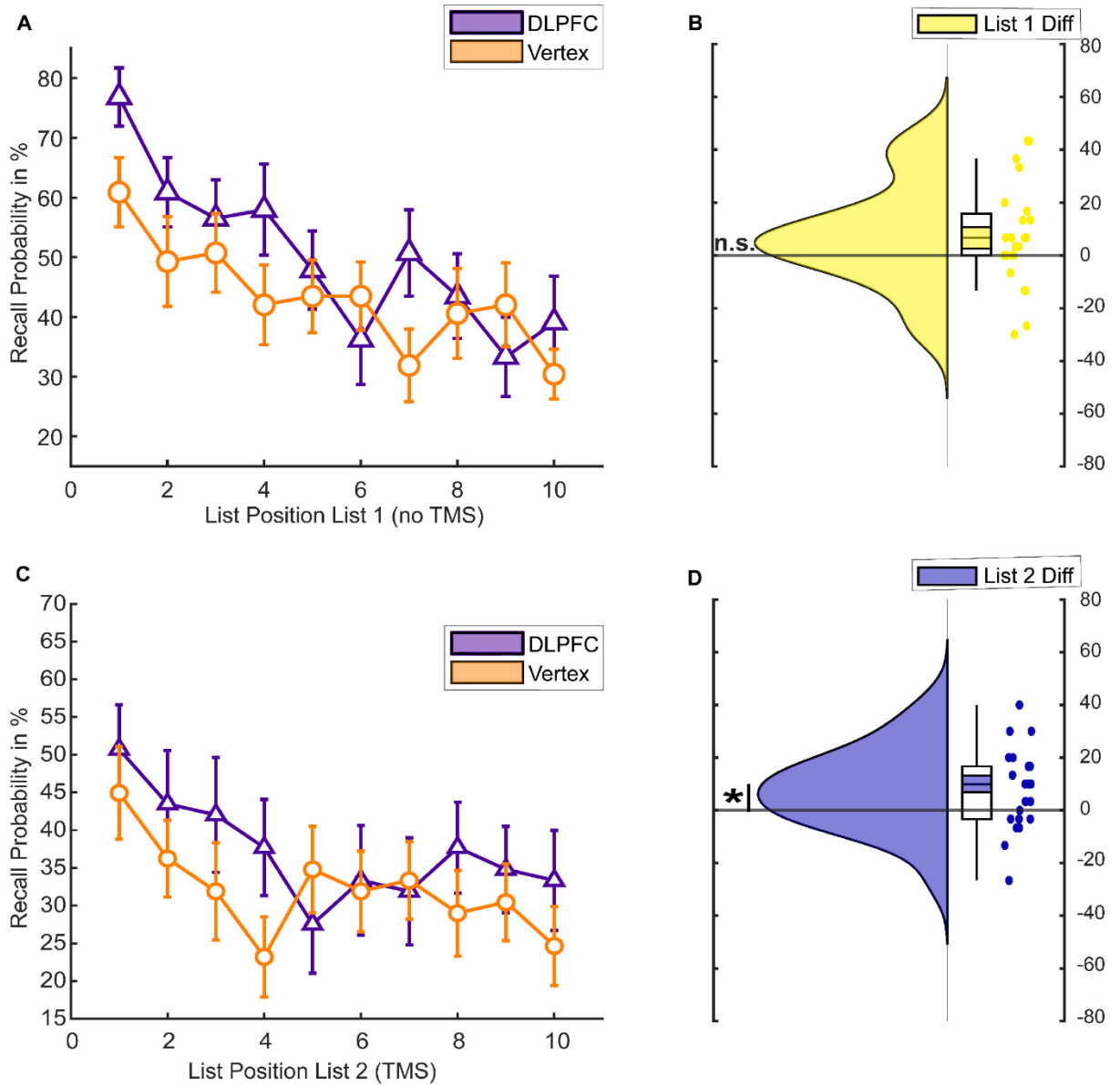
Fig 2-5. Behavioural memory performance in experiment 2. *A) Serial position curve for list 1 (N=23). B) Raincloud plots of memory performance for list 1 words (difference between DLPFC and vertex stimulation). Coloured area within the box-plots indicate the standard error, while the circles depict individual data points. C) Serial position curve for list 2. D) Raincloud plots of memory performance for list 2 words (difference between DLPFC and vertex stimulation). The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.*

Since experiment 1 and experiment 2 used virtually the same paradigm, we performed a continuously cumulative (weighted fixed-effect) meta-analysis over the two studies, in order to gain a more accurate estimate of the observed stimulation effect (Braver et al., 2014; Viechtbauer, 2010). We found that stimulation on the left DLPFC significantly boosts memory performance for both List 1 and List 2 words across the two studies (g = 0.32 [0.01, 0.63]; g = 0.40 [0.15, 0.65]) (see Fig 2-6).
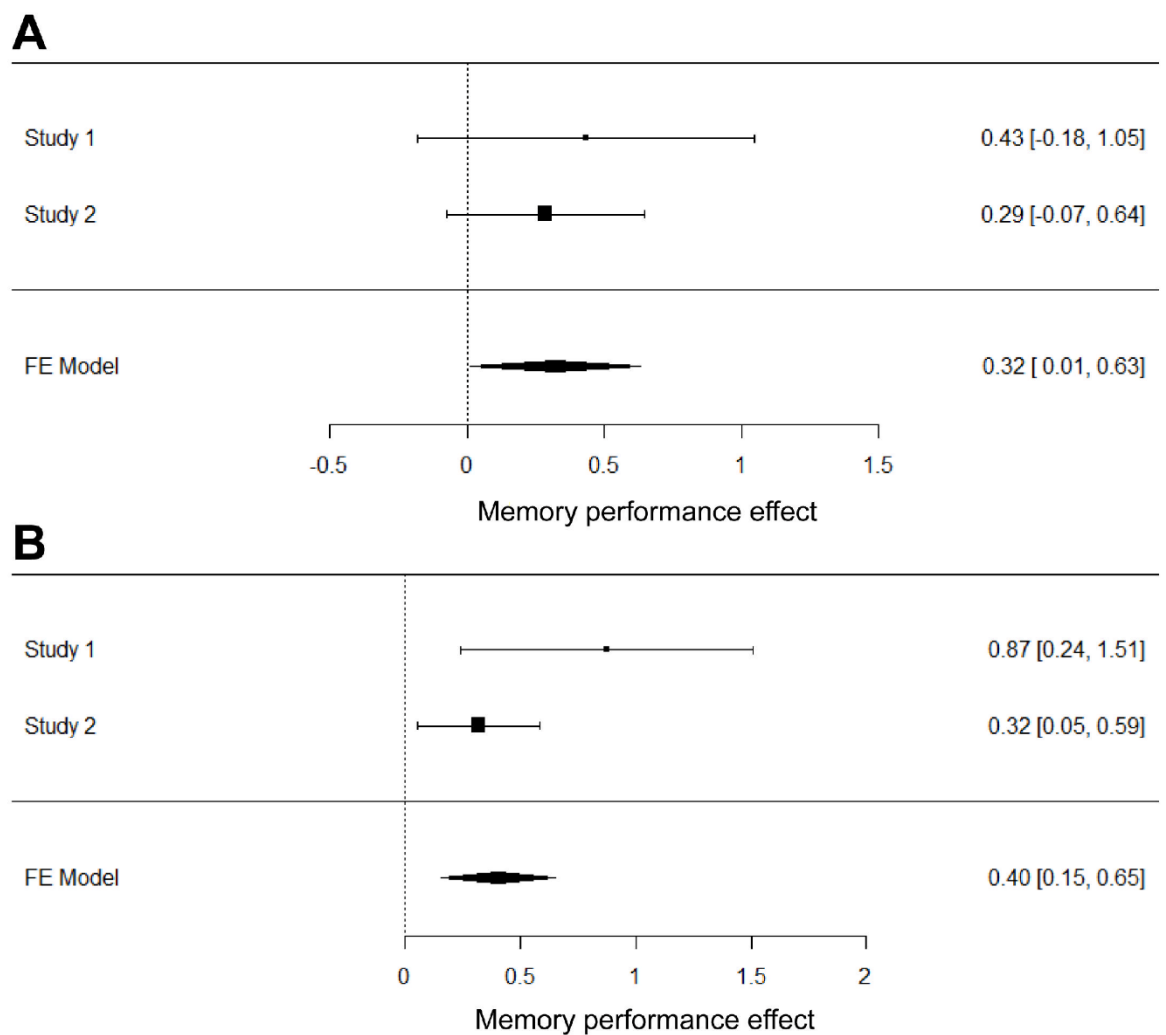
Fig 2-6. Meta-analysis of the behavioural results of the first and second experiment. *Forest plots of the meta-analytically combined DLPFC effect for List 1 (**A**) and List 2 (**B**) words. Error bars represent 95% confidence intervals, effect sizes were calculated as Hedge's g. The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.*

Discussion

We demonstrated in two experiments that 1 Hz rTMS delivered to the left DLPFC during episodic memory encoding boosts memory performance. Participants encoded two lists of words and received 1 Hz rTMS during word presentation. In a subsequent free recall test, participants recalled significantly more words from lists in which they received left DLPFC stimulation compared to vertex stimulation. The accompanying serial position and contextual clustering analyses suggest that left DLPFC stimulation enhances stimulus processing at a word-specific level without affecting associations between words. Simultaneously recorded EEG data for the first experiment indicated that 1Hz rTMS to the left DLPFC strengthened event-related power decreases in the beta frequency band in posterior areas. This was represented by higher beta power before word onset and lower beta power after word onset in the DLPFC group compared to the vertex group. Taken together our results show that slow rTMS can enhance memory performance, and that this memory enhancement effect was associated with increased stimulus induced beta power decreases, an established correlate of memory function (Hanslmayr, Staudigl, et al., 2012).

Power decreases in the alpha/beta frequency range is traditionally associated with stimulus processing in general (Klimesch, 2012). While power increases in these frequency bands have been linked to inhibition of irrelevant or potentially interfering information, event-related power decreases (i.e. disinhibition) have been observed over areas actively involved in stimulus processing (Jensen & Mazaheri, 2010; Pfurtscheller & Lopes da Silva, 1999; Waldhauser et al., 2012). This beta power reduction has previously been shown to be vital for successful encoding of verbal material (Hanslmayr et al., 2009, 2014; Hanslmayr, Volberg, et al., 2011). This makes sense conceptually, as areas in the MTL can only bind information that has been appropriately processed in down-stream neocortical areas (Moscovitch, 2008). Given its importance in information processing and representation, reduced activity in the alpha/beta frequency bands has been proposed to reflect active involvement of cortical areas during encoding of episodic memories (Hanslmayr et al., 2016; Hanslmayr, Staudigl, et al., 2012). Additionally, TMS has been shown to have network wide effects, which can extend throughout the brain (Hebscher & Voss, 2020; J. X. Wang et al., 2014). Consequently, it appears that the DLPFC stimulation, somehow encourages stimulus processing in parietal and occipital areas, as reflected in the decreased power in those areas. However, a slightly different interpretation could be made considering the result of the analysis separating the periodic and aperiodic components. The observed power changes

seem to result from an upwards (or clock-wise) rotation in the spectral tilt as observed by the increasing exponent and offset components, rather than a change in oscillatory components (see Fig 2-4). Previous research has suggested that the aperiodic component in electrophysiological signal may be the result of a neural ratio of excitation and inhibition in a local population of neurons (Miller et al., 2009). Within this framework, the observed rotation would be associated with increased inhibition (Gao et al., 2017). This would imply that the frontal stimulation has an inhibitory effect over the parietal cortex.

This interpretation would be consistent with the fact that we used a stimulation protocol (1 Hz rTMS) that is usually considered to have inhibitory effects on cortical excitability (Chen et al., 1997; Gerschlager et al., 2001). Such an interpretation would be consistent with fMRI studies showing that decreased activity in ventral parietal regions is usually positively correlated with memory encoding (Uncapher & Wagner, 2009). This interpretation would also be consistent with other studies reporting a reduction in memory performance when stimulating the left DLPFC with parameters considered to increase excitability (i.e. 20 Hz; (Rossi et al., 2001; Sandrini et al., 2003)). The behavioural effects observed in the two experiments described here therefore suggest an inhibitory relationship between the left DLPFC and verbal memory encoding. Further, the EEG results suggest that inhibition of the left DLPFC boosts event-related beta power decreases in the service of memory formation. This latter finding suggests that the DLPFC might actively limit the amount of stimulus processing in this memory paradigm. Inhibition of the DLPFC consequently leads to disinhibition in parietal down-stream areas. Such reductions in parietal beta power have previously been associated with an increased capacity of information coded into the neural signal (Griffiths, Mayhew, Mullinger, Jorge, Charest, et al., 2019). This increase in potentially coded information would then ultimately result in a better memory performance.

An important caveat of the above interpretation is that it rests on the assumption that online rTMS affects the brain in the same way as offline rTMS does. While rTMS is a method that has been around for decades, most of the mechanistic studies rely on offline effects, where stimulation is first applied and its effects on neural activity or task performance are measured afterwards. This is a consequence of the large artifact a TMS pulse induces in EEG and MRI measurements. Thus, it is conceivable that, while the offline 1Hz rTMS may have inhibitory aftereffects, these could result as type of rebound effect from the actual stimulation (and vice versa for the online 20 Hz stimulation employed in the other studies). There has also been a study that have called the inhibitory qualities of 1 Hz rTMS into question (Caparelli et al.,

2012). Moreover, the effects of TMS onto the wider network can differ quite drastically from the local effects (J. X. Wang et al., 2014). Thus, one should not discount the possibility that the parietal decreases might not be a result of modulating the DLPFC activity per se, but rather might result from influencing the memory network as a whole in which the DLPFC plays an important role.

Another possible interpretation, that disregards possible facilitative or inhibitory effects of rTMS, is that given our remote effects during left DLPFC stimulation, 1Hz rTMS may have influenced the functional connectivity between frontal and posterior regions (Ward et al., 2010). This enhanced connectivity would then lead to enhanced stimulus processing and improved memory performance as a result thereof. Indeed, a recent study has shown that 1 Hz rTMS can have opposite effects on different networks (Castrillon et al., 2020). Castrillon et al. found that while occipital stimulation led to signal propagation to down-stream areas, frontal stimulation disrupted network communication. Therefore, extrapolating this finding to the results presented in this paper, it is possible that the parietal beta power decrease is the result of a disrupted network communication, as opposed to local inhibition in the DLPFC per se.

Despite our robust behavioural results, care should be taken when interpreting behavioural rTMS effects. External effects arising from rTMS can influence behavioural measures even when an active control condition is used. DLPFC stimulation, for example, can lead to stronger muscle twitches and distraction than vertex stimulation (Meteyard & Holmes, 2018). This may be experienced as distracting and affect encoding performance accordingly. However, if this was the case, one would expect this to affect performance negatively rather than positively. Furthermore, several studies have found similar effects as those we report here using different stimulation techniques or stimulation in adjacent regions (Javadi & Walsh, 2012; Kirov et al., 2009; Zwissler et al., 2014). Additionally, Köhler and colleagues (Köhler et al., 2004) showed that when participants received 7Hz rTMS to the left inferior prefrontal cortex during a semantic encoding task (Köhler et al., 2004), their word memory performance was enhanced. Two control sites were additionally stimulated —the right inferior prefrontal cortex and a right parietal target. Only left prefrontal stimulation resulted in more high-confident hit rates. These findings strengthen our confidence that the results presented are not merely a by-product of unspecific side effects, such as muscle twitches.

Behaviourally the results in both experiments demonstrate a positive effect of left DLPFC stimulation on memory performance in general. However, the results of the two experiments

also differed slightly. Considering the first experiment, the memory effect was not only specific to the DLPFC stimulation condition compared to the vertex condition, but also significantly stronger for list 2 words (i.e. those words that were presented during rTMS) as indicated by the significant interaction between words list and stimulation condition. This finding was not replicated in the second experiment where there was no significant interaction between word list and stimulation condition. A possible reason might be carry over effects between lists. However, if this was the case, then the List by Stimulation interaction should also be absent in the first study. The only difference between the two experiments was that Experiment 1 had a between-subject design, while Experiment 2 had a within-subject design. Conceptually, there is no reason why the two designs would affect the difference between lists, as carry-over effects should still be present when a subject is only exposed to the DLPFC stimulation condition without an accompanying vertex stimulation condition. The results of the meta-analysis do support the possibility, that the significant interaction in the first study might be a false positive, because it suggests increases in memory performance for both lists across the two studies, thereby suggesting that rTMS during the second list might also enhance memory for previously encoded, but unstimulated items.

Another caveat inherent to the experiment is that due to the lack of a no stimulation condition for list 2, we are unable to completely exclude the possibility that Vertex stimulation reduces memory performance instead of DLPFC enhancing memory performance. A previous study using 1 Hz TMS and measuring fMRI BOLD signal concurrently showed that vertex stimulation does not affect the wider brain other than minor local changes, suggesting that vertex stimulation is a good control site (Jung et al., 2016).

Lastly, as we analyse data recorded in directed forgetting paradigms, it is unclear if our results generalize to other types of memory tasks. However, considering other work on DLPFC stimulation and episodic memory, the involvement of the DLPFC in episodic memory encoding in general seems to hold across tasks [6,7,8]. Future research could clarify this by stimulating the DLPFC with 1 Hz rTMS during more general episodic and relational memory tasks.

Conclusion

Our results indicate that 1 Hz rTMS applied to the left DLPFC during encoding of verbal material can enhance memory performance. This effect was linked to a well-known physiological correlate of memory formation: beta power decreases. Given the need for replication studies in general (Ioannidis, 2012) and for brain stimulation effects in particular (Veniero et al., 2017), we set out to replicate the initial incidental finding. In order to control for inter-individual differences (Hamada et al., 2013; López-Alonso et al., 2014; Wiethoff et al., 2014), we replicated our original result in a within-subjects investigation. The results of this second experiment replicated the memory enhancement effect resulting from 1 Hz left DLPFC stimulation. Therefore, online 1 Hz rTMS at left DLPFC appears to be an effective means of enhancing cognitive function in a memory task with potential applicability ranging from basic research to clinical intervention. Future studies should further explore how exactly 1Hz rTMS to the left DLPFC gives rise to more pronounced beta power decreases in posterior areas and enhanced memory as a result thereof.

Material and Methods

Experiment 1

Subjects

The data reported here was collected as part of a larger study (reported in (Hanslmayr, Volberg, et al., 2012) experiment 2). 48 healthy human participants were tested and subjects were randomly assigned to one of the two stimulation conditions. After artefact rejection and inspection of the EEG data, 40 participants remained in the sample, resulting in 20 participants per group (DLPFC group: mean age = 21.7, range 18-26, 8 males; vertex group: mean age = 22.3, range 18-27, 6 males). All participants were right handed, had normal or corrected-to-normal vision, reported no history of neurological disease or brain injury, and were screened for contraindications against rTMS (Wassermann, 1998). Written informed consent was acquired from each subject prior to the experiment. The study was approved by the ethics committee of the University of Konstanz (Project ID: "How the synchronized brain forms enduring memories") and conducted in accordance with the principles expressed in the Declaration of Helsinki.

Task and Stimulus Material

The stimulus material consisted of 240 nouns derived from the MRC Psycholinguistic Database (Coltheart, 1981). The material was translated into German and divided into 24 lists of 10 words. The lists were matched according to word frequency, number of letters, number of syllables, concreteness, and imageability (Hanslmayr, Volberg, et al., 2012). The presentation of the lists was counterbalanced across subjects. Each list was presented equally often across four conditions (Forget List 1, Forget List 2, Remember List 1, Remember List 2). The data was collected as part of a study that focussed on the causal involvement of the left DLPFC in voluntary forgetting (reported in (Hanslmayr, Volberg, et al., 2012), experiment 2). Participants performed 12 encoding-recall runs. In each run, particpants were presented with two lists of 10 words. After having studied the first 10 words, a cue was presented for 5 s, prompting participants to either forget the previously studied words or to continue remembering this list. The second list of 10 words was always followed by a remember cue. For this study, only the six remember runs, i.e. runs in which the first and second list had to be remembered, are included in the analysis. The words were presented in randomized order one at a time for 2.5 s, with a variable inter-stimulus interval of 1.5-2.5 s (during which a fixation cross was shown). After a short distractor task of 2 min (counting backwards in steps of 3 from a random number), participants were asked to freely recall as

many words from this run as possible in any order. Participants' reponses were recorded manually by the experimenter outside of the EEG room.

rTMS

During encoding of List 2, 45 pulses of 1Hz rTMS were applied at 90% resting motor threshold. One group of participants received rTMS to the left DLPFC, while the control group received rTMS to the vertex. The vertex was chosen as a control site, as it has been shown to not have any wide-ranging network effects for 1 Hz stimulation (Jung et al., 2016). The rTMS pulses and stimulus presentation were not synchronized by the experiment. Due to the nature the ISI being randomly chosen as a multiple of 0.25 seconds, there appeared to be a weak 4 Hz rhythm present (see S3 Fig). However, this bias did not systematically differ between stimulation conditions and therefore cannot explain the observed behavioral effects. rTMS was delivered using a Magstim Rapid2 stimulator with a figure-of-eight air filmed cooled coil (magstim; www.magstim.com). Prior to the main experiment, individual T1-weighted MRI scans were acquired with a 1.5T Philips scanner. In order to assure that the exact regions of interest were targeted, the stimulation was guided by a neuronavigation system (ANT-Visor; www.ant-neuro.com). Individual MRI scans were co-registered with the position of the rTMS coil and the precise targeting of the stimulation sites was monitored throughout the experiment. The coil was approximately angled 45° from the midline axis of the participant's head with the handle pointing backwards and laterally. The MNI coordinates for DLPFC stimulation were x=-45, y= 6, z=39 (Parish et al., 2018).

EEG recording and preprocessing

EEG was recorded throughout the task from 128 electrodes in an equidistant montage (ANT; www.ant-neuro.com). Participants were seated in a shielded room and data were recorded with a DC amplifier (ANT) at a sampling rate of 2048 Hz; data were offline re-referenced to average reference. Individual electrode positions were digitized at the beginning of the experiment (Xsensor, ANT). EEG data were preprocessed and analysed using Fieldtrip (Oostenveld et al., 2011). Due to excessive artifacts in the EEG during rTMS (Farzan et al., 2016), List 1 (no rTMS) and List 2 (during rTMS) trials were preprocessed separately. Preprocessing of rTMS-EEG data followed the guidelines and procedure outlined by Herring et al. (Herring et al., 2015), and described on the Fieldtrip tutorial website (https://www.fieldtriptoolbox.org/tutorial/tms-eeg/). EEG data were first cut into segments of -0.9s to 0.9s around the rTMS pulses. Data were visually inspected and data around the rTMS artifacts resulting from ringing and recharging of the stimulator were removed from

further analysis, as these can impact the performance of the subsequent pre-processing steps. The epoched data were subsequently subjected to an independent component analysis (runICA). This allowed the removal of rTMS related artefacts, eye-blink, eye movement and other remaining artefacts. Any missing data was interpolated with a cubic interpolation algorithm to avoid artificially induced artefacts in the data. The cleaned data epoched around word onset (-2s to 4s) were then downsampled to 500Hz. A low-pass filter (40 Hz cut-off) was applied and the data were visually inspected for remaining artefacts. Missing and rejected channels were interpolated (mastoids were removed resulting in 126 channels). For trials without rTMS (List 1), data were epoched -2s to 4s around the onset of the word, downsampled to 500 Hz, and low-pass filtered (40 Hz cut-off). After visually inspecting the data for artefacts, an ICA was applied in order to identify and remove ocular and muscle artefacts. The cleaned data were again visually inspected.

Data Analysis

Behavioural Analysis

In order to assess the effect of stimulation on recall performance, a mixed ANOVA with the within subjects factor LIST (List 1 and List 2) and the between subjects factor rTMS (DLPFC and vertex) was performed. We further tested whether DLPFC stimulation influenced the likelihood of recalling words as a function on a words' list position. To this end, serial position curves were calculated (Murdock, 1962). For every subject at every list position we coded whether a word was later recalled (1) or not (0). This was done for all six encoding-recall runs and subsequently averaged for every participant over the six runs. These data were then subjected to a 2 (DLPFC vs vertex) x 10 (position in list) x 2 (list 1 or list 2) ANOVA.

EEG Analysis

EEG data (-1.5s to 3 s) were subjected to a time-frequency decomposition (2 to 35 Hz in steps of 1 Hz) using Morlet wavelets (width 7) and z-transformed per trial across time for each subject, within each stimulation condition, to enable analysis of post- as well as pre-stimulus activity (Griffiths et al., 2016). Since we analysed the data in the context of an increased memory performance, which according to the sync/desync hypothesis should be characterized by cortical alpha/beta power decreases, only negative clusters were expected(Hanslmayr et al., 2016; Parish et al., 2018). Therefore, data from the DLPFC and vertex group were subjected to a one-tailed cluster based permutation test, averaged over

beta (13-30 Hz) and the post stimulus time window of interest (0 to 1 s). Alpha values were set to 0.05. All further analyses were conducted on the electrode sites identified as showing significant differences in beta between the two conditions.

To ensure that any observed effects were specific to stimulation trials, an additional analysis was performed comparing the List 1 and List 2 trials for the DLPFC and vertex groups respectively in a time-window from-1 s to 1.95 s relative to stimulus onset. This time-window was split into six non-overlapping time bins. The data was then analysed using a TIME (time bins) x LIST (List 1 vs List 2) x GROUP (DLPFC vs vertex) ANOVA accompanied by post-hoc independent samples t-tests (see S1 Text for a control analysis regarding potential trial imbalances).

The properties of observed power-changes were further investigated using the FOOOF toolbox (Donoghue et al., 2020). This method uses simultaneous fitting of the aperiodic spectrum component as well as spectral peaks. For this we analysed a 1-80 Hz band-pass filtered signal in the time-window of interest (resulting from the time frequency analysis) and an identically sized time-window before stimulus presentation. This time-window was chosen to minimize any effects the filtering process might have on the frequency spectrum. The model was subsequently fit using a frequency range of interest of 1-40 Hz to optimize fits for the low-frequency (alpha and beta) bands of interest. These components were then be analysed separately. We performed a 2 x 2 mixed repeated measure ANOVA (Pre vs Post (2) word presentation x DLPFC vs vertex (2) stimulation, for each component (the aperiodic exponent, the offset and the periodic peak power). Additionally, a control analysis was performed to ensure that there were no differences in model fits or residuals between the different FOOOF models that could alternatively explain any of the effects presented in this study (see S1 Table)

Experiment 2

The data of experiment 2 was part of a larger study that focussed on replicating the effect of rTMS on directed forgetting and is reported elsewhere (see(B. M. J. Stauch, 2017)).

Subjects

24 healthy human participants took part in this experiment (mean age = 19.04, range 18-28, 5 male). All participants were right handed, had normal or corrected-to-normal vision, reported no history of neurological disease or brain injury, and were screened against

contraindications against rTMS (Wassermann, 1998). Written informed consent was acquired from each subject prior to the experiment and participants were fully debriefed at the end. The protocol was approved by the ethics committee of the University of Birmingham (Project ID: ERN_14-0651) and conducted in accordance with the principles expressed in the Declaration of Helsinki.

Task and Stimulus Material

In this study, the participants as well as the experimenter interacting with the subjects were blind towards the hypotheses.

240 nouns were derived from the MRC Psycholinguistic Database (Coltheart, 1981) and divided into 24 Lists of 10 words. As in experiment 1, the lists were matched according to word frequency, number of letters, number of syllables, concreteness, and imageability (Hanslmayr, Volberg, et al., 2012). The presentation of the lists was counterbalanced across subjects so that each list was used equally often across eight conditions (DLPFC-Forget List 1, DLPFC-Forget List 2, DLPFC-Remember List 1, DLPFC-Remember List 2, vertex-Forget List 1, vertex - vertex List 2, vertex Remember List 1, vertex -Remember List 2). Participants performed 12 encoding-recall runs, split by stimulation condition. Whether the six DLPFC runs or the six vertex runs were conducted first was counterbalanced across subjects. The task was the same as in experiment 1. For this study, only the three remember runs per stimulation condition are included in the analysis. Participants' responses were recorded manually inside the testing room.

rTMS

The same stimulation parameters were used as in experiment 1. However, in this experiment, participants received both DLPFC and vertex stimulation in a blocked manner. The stimulation was delivered using a Magstim Rapid stimulator with a figure-of-eight coil (magstim; www.magstim.com). Prior to the main experiment, individual T1-weighted MRI scans were acquired using a 3T Philips Achieva MRI scanner. In order to assure precise stimulation, individual MRI scans were co-registered with the position of the rTMS coil and the stimulation was guided by a neuronavigation system (Brainsight; Rogue Resolutions; https://www.rogue-resolutions.com). The coil was held in place manually and the precision of the stimulation was monitored throughout the experiment. The same MNI coordinates as in experiment 1 were used.

Temporal Clustering

To investigate whether the observed memory effects could be explained due to contextual effects resulting from the stimulation, we calculated temporal clustering scores per participant for each respective list and stimulation condition (procedure is based on (Griffiths et al., 2016)). This procedure can be summarized with the formula:

$$\sum_{n=1}^{R} |ObservedDistance_{(n)} - ExpectedDistance|$$

Where the observed distance was defined as the absolute difference between the observed recall position and the position during encoding for each subsequently recalled item (R). For example if a subject recalls an item in the 3rd position and subsequently recalls an item in the 5th position the observed distance would be 2. The expected difference is the distance value that would be expected during optimal temporal clustering (Expected difference = 1; e.g., one would expect the 4th item to be recalled following the 3rd item yielding a difference of 1).

This yielded a temporal clustering value for each list and condition per participant (see S2 Table for values per condition). The items in list 1 were coded with the numbers 1-10, while items belonging to the second list were coded with numbers 11-20. These were then directly compared to each other using a 2x2 repeated measure ANOVA (List x Stimulation Condition).

Meta-Analysis

In order to combine the effect of stimulation over the two studies, a cumulative meta-analysis of the stimulation effect for the list 1 and list 2 items was performed using the R-package metafor (Viechtbauer, 2010). The analysis was performed by computing effect sizes (Hedge's g) for the individual relevant t-tests (independent and dependent for study 1 and 2 respectively), which were then used to run a weighted fixed-effect meta-analysis [26,63].

Acknowledgments

Supporting Information

S1 Fig: Time Frequency Representations for list 2 trials during encoding for the DLPFC and vertex stimulation condition, respectively. The plots contain the averaged activity from selected channels represented by red dots on the accompanying topography. Selected channels are characterized by a significant difference in beta power (i.e. less power in the DLPFC condition compared to the vertex condition). Word onset occurred at 0 s (indicated by dashed line). The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.
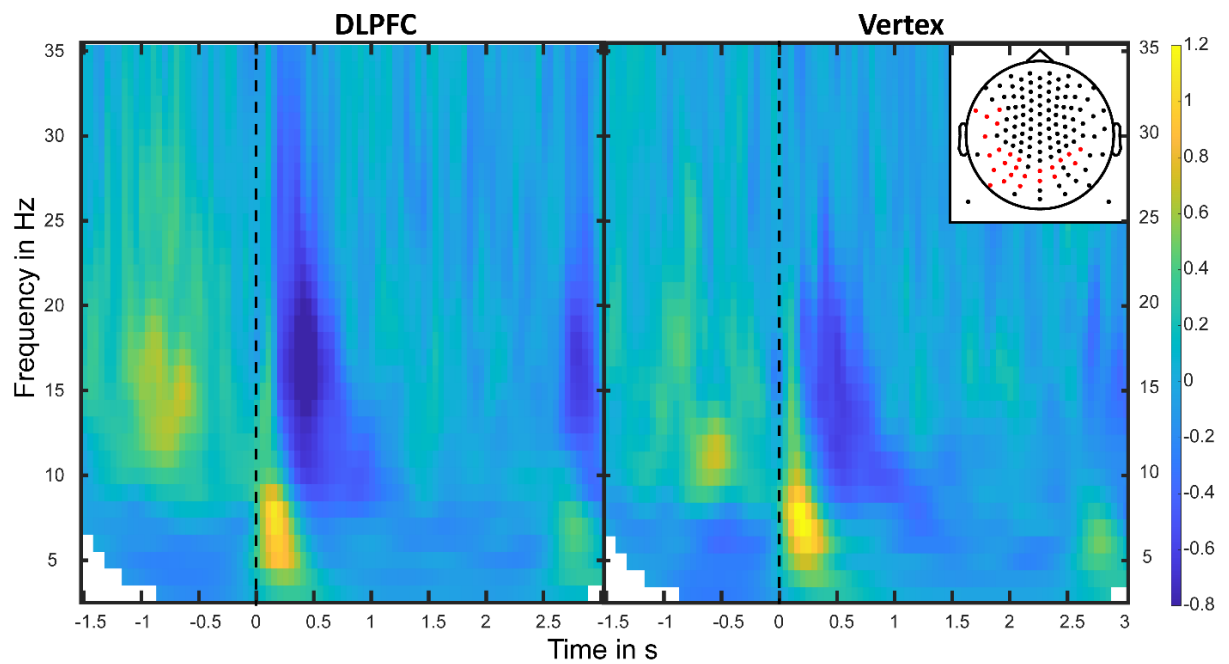
S2 Fig: Raincloud plots of the components resulting from the FOOOF analysis for the DLPFC condition (purple) and the vertex condition (Orange), for the pre and the post stimulus period, respectively. Each raincloud plot is paired with its respective boxplots. Coloured area within the box-plots indicate the standard error, while the circles depict individual data points for each participant respectively. The same subjects for the pre and post time-windows are connected by a line. The thick line illustrates the change in mean from pre to post. A) Raincloud plot of the alpha periodical component; B) Raincloud plots of the beta periodical component; C) Raincloud plots per stimulation condition for the offset of the aperiodical component at 0 Hz for pre and post stimulus period, respectively word onset time windows. Yellow line represents an identical aperiodical component with an increased offset. D) Raincloud plots per stimulation condition for the Exponent of the aperiodical component Hz post stimulus period, respectivelywindows. Yellow line represents an example for an identical component with a larger exponent. The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.

A Periodic Alpha Component

B Periodic Beta Components

C Aperiodic Component (Offset)

D Aperiodic Component (Exponent)
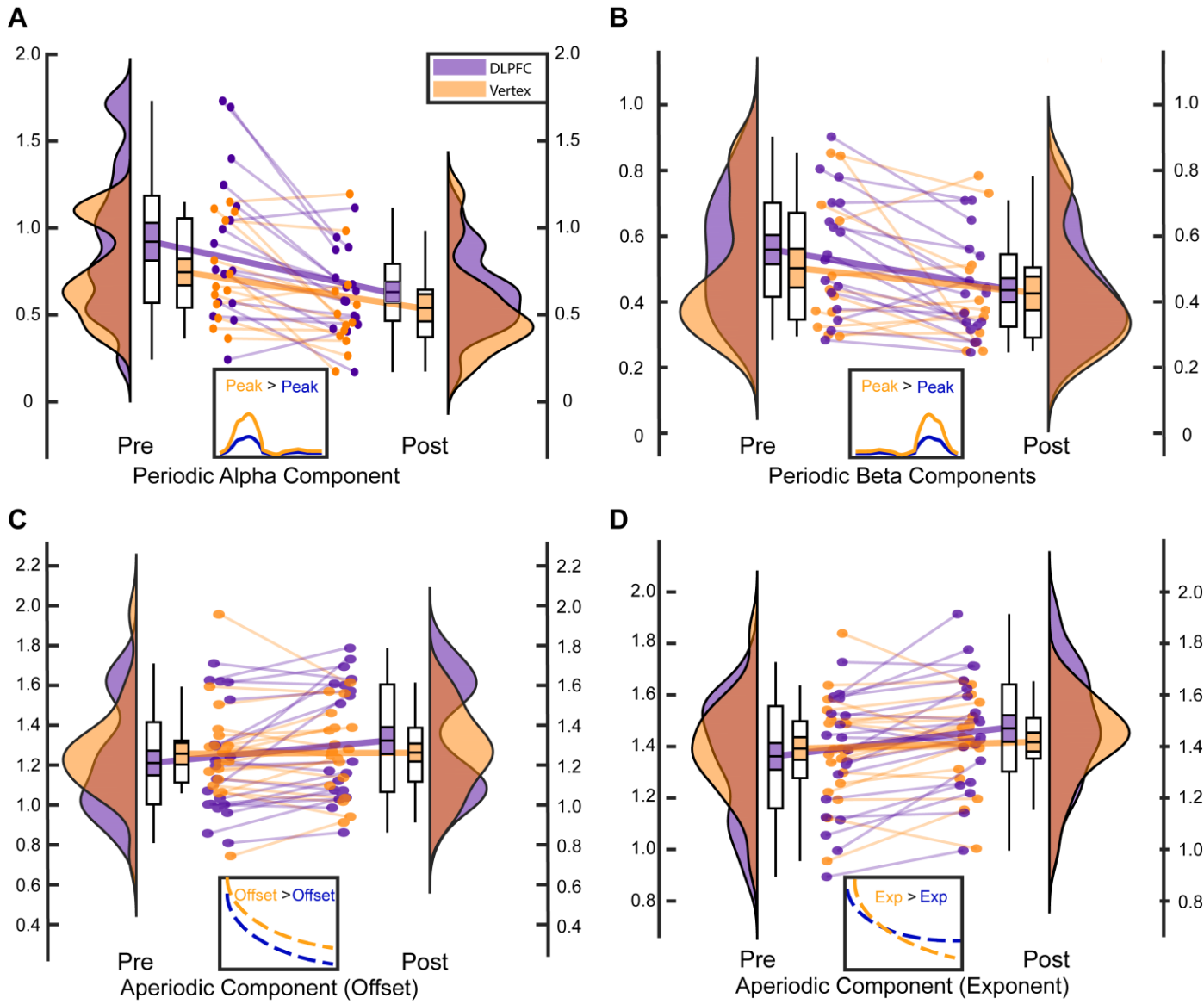
S3 Fig: A) Raincloud plot of time difference between the first occurrence of a TMS pulse post word presentation for every trial (N=2400; 1200 per condition). Coloured area within the box-plots indicate the standard error, while the circles depict individual data points for each participant respectively. A slight 4 Hz bias in timing is visible in both conditions based on how the ISI was implemented. With a perfectly random ISI a uniform distribution would be expected. However, a two-sample Kolmogorov-Smirnov test confirmed that these two distributions do not statistically differ from each other (k-s statistic: 0.0295; p = 0.6709). The data and scripts used to generate this figure can be found at https://osf.io/dyxjv/.

Shift in Pulse Timings per trial
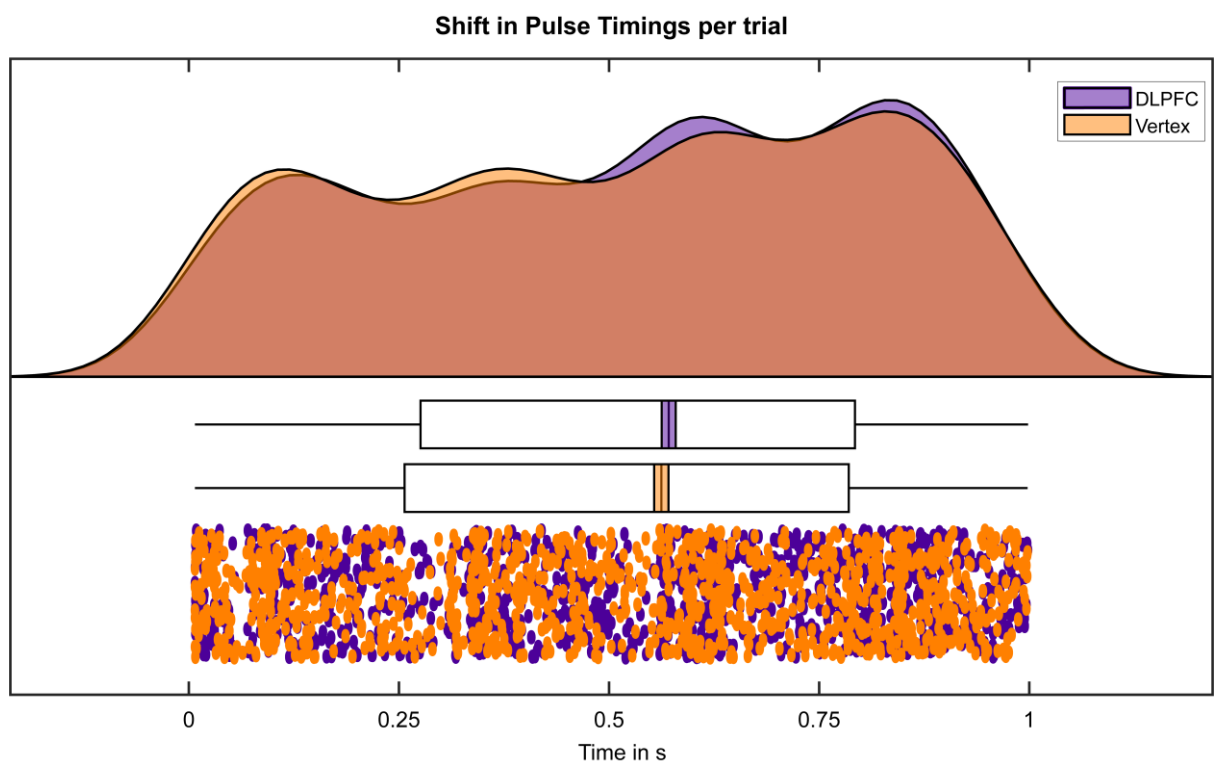
S1 Text: There was a considerable difference in the number of list 2 hits between the DLPFC and the vertex group because of the enhanced memory performance in the DLPFC group. (DLPFC: mean=23.1, SD=7.48; vertex: mean=17.25, SD=8.48). Power is not systematically biased by trial numbers, but we nevertheless tested whether this difference in trial numbers might have contributed to the observed effects. To this end, we randomly selected trials for each subject from the DLPFC group and matched these to the number of trials from subjects in the vertex group, ensuring that both groups have exactly the same trial numbers (mean: 17.25, SD: 8.48). As our main comparison of interest was the difference in beta power (13-30Hz) between the DLPFC and vertex group for list 2 trials, we conducted independent samples t-tests for data 0-1 s after word onset averaged over the negative electrode cluster identified earlier. This procedure was repeated 100 times, every time randomly selecting new subsets of trials for the DLPFC group. 100 t-tests on adjusted trial numbers revealed t values ranging from -3.9 to -2.377 (critical t for independent samples t-tests = 2.023; df=38). This analysis demonstrates that the difference in post-stimulus beta power decreases for list 2 words was not driven by differences in trial numbers.

S1 Table: To ensure that any observed effects of the FOOOF analysis are legitimate and not
a result due to differences in model fit we ran two 2 (within factor time: pre vs post)
x 2 (between factor stimulation, DLPFC vs Vertex) mixed ANOVAs as control
analyses. Since none of the factors showed a significant difference, the effects cannot
be attributed due to differences in model fits.

Mixed Anova of Model fit (R^2)

Within Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2
Time	0.002	1	0.002	3.706	0.062	0.05
Time * Stimulation	4.805e -5	1	4.805e -5	0.111	0.740	0.00
Residuals	0.016	38	4.310e -4			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2
Stimulation	1.540e -4	1	1.540e -4	0.489	0.489	0.005
Residuals	0.012	38	3.149e -4			

Note. Type III Sum of Squares

Mixed Anova of Residuals

Within Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2
Time	0.002	1	0.002	3.037	0.089	0.026
Time*stimulation	9.138e -5	1	9.138e -5	0.145	0.706	0.001
Residuals	0.024	38	6.316e -4			

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	
Stimulation	9.668e -4	1	9.668e -4	0.787	0.381	0.
Residuals	0.047	38	0.001			

Note. Type III Sum of Squares

S2 Table: Mean temporal clustering values per condition, with the accompanying standard deviation.

List	Stimulation	Mean	SD	N
L1	DLPFC	4.163	1.697	18
	Vertex	4.844	3.131	18
L2	DLPFC	4.381	2.142	18
	Vertex	4.484	2.261	18

Chapter 4 : Characterizing the Human Cortico-Hippocampal response to direct electrical stimulation

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Abstract

Direct electrical stimulation is a widely used tool in many areas within the field of neuroscience. It has repeatedly been used to investigate areas relevant to human episodic memory, such as the hippocampus without an understanding of what kind of responses such stimulation evokes. In this study five epilepsy patients under medical supervision, were implanted with multiple stereotactic depth electrodes terminating in the hippocampus that had the ability to record single neuron activity (SUA) along with iEEG measures at various depths in the implanted area. Characterization of the response suggests that direct electrical stimulation leads to an inhibitory local response that can travel far throughout the brain. The results of this study will inform the optimal choice of parameters for stimulation studies targeting the hippocampus in both, research, and clinical contexts, with the aim of improving memory function.

1. Introduction

The potential of direct electrical brain stimulation as a tool for studying the memory system has become apparent, ever since Penfield and Perot first reported that cortical stimulation within the temporal lobe of tested patients could trigger the vivid re-experience of distinct memories (Penfield & Perot, 1963). Subsequent research further established the medial temporal lobe (MTL), and particularly the hippocampus which plays a central role in integrating information from across the brain, as crucial for our ability to encode and recall episodic memories (Eichenbaum et al., 2007; Squire et al., 2004; Staresina & Davachi, 2009). This has made the area an obvious target for brain stimulation, in the context of researching the human memory system, as well as for clinical studies hoping to improve memory in pathological cases (Mankin & Fried, 2020; Suthana & Fried, 2014).

Direct electrical stimulation within the Hippocampus and its neighbouring areas, has been found to lead to a broad range of behavioural outcomes. While some studies reported memory improvements in stimulated patients (Fell et al., 2013; Hansen et al., 2018; Jun et al., 2019; Suthana et al., 2012), other studies found that direct stimulation decreases memory performance (Coleshill et al., 2004; Goyal et al., 2018; Jacobs et al., 2016; Lacruz et al., 2010). There are many possible reasons that could contribute to these divergent findings, ranging from differences in stimulation protocols, to different target selection procedures. However, this inability to pinpoint the exact mechanism is tied to the fact that, despite its wide use, our knowledge about the exact neurophysiological effects of direct stimulation in the human hippocampus is very scarce.

Stimulation responses can be characterized by their effects for different distances. Most information on the effects of direct electrical stimulation on populations of neurons in the direct vicinity of the stimulation electrodes comes from studies monitoring the sensory and motor cortical areas of anaesthetized animals (Butovas & Schwarz, 2003; Inghillerj et al., 1992; Logothetis et al., 2010). It has been found that on the level of a single neuron, the typical response to direct stimulation appears to be a short-lived increase in excitation, followed by sustained inhibition of varying lengths. The exact mechanism behind this pattern is still unknown. It has been hypothesized that this typical response arises architectural properties of connectivity between excitatory and inhibitory neurons throughout the brain (Logothetis et al., 2010).

The effects of direct electrical stimulation have been shown to not necessarily be limited to effects in the immediate vicinity of stimulation electrodes. Rather direct stimulation has the potential to affect regions much further than one would expect possible purely by the spread of the electrical current alone. For example thalamic stimulation has been found to cause the stereotypical excitation-inhibition response pattern in the primary visual cortex (Logothetis et al., 2010; Tehovnik et al., 2006; Tolias et al., 2005). This suggests that direct electrical stimulation can initiate a cascade of activity travelling throughout the brain's network. This should be taken into account when applying electrical stimulation. One especially interesting approach is a recent line of research stimulating the white matter instead of targeting the hippocampus directly when attempting to manipulate memory performance (Mankin et al., 2021; Mohan et al., 2020; Titiz et al., 2017). While showing promising initial results, the underlying mechanisms of white matter stimulation in humans have also remained largely unexplored.

Another useful measure for the characterization of neural responses to stimulation is by examining frequency spectrum of the local field potential (LFP) or more general intracranial electroencephalographical (iEEG) responses (Amengual et al., 2017; Reinhart et al., 2015; Thut et al., 2011). Information in the frequency spectrum can be divided into major components. The periodic component, which reflects oscillatory activity that carries information on how information is being coded, and the aperiodic component, which consists of broadband effects which follow Brownian-noise patterns (Donoghue et al., 2020, 2021). Different frequencies of the periodic component have been associated with many different functions in the brain (Buzsaki, 2006). The aperiodic component is frequently treated as noise but can actually still provide relevant information on underlying brain mechanisms. For example, the slope of aperiodic component has been linked to local excitation-inhibition balance (Gao et al., 2017), while the offset of the aperiodic component has been associated with ongoing firing rates (Manning et al., 2009).

The current study investigated the effects of systematic direct stimulation in the human hippocampus and wider MTL, to allow for a more targeted use of future instances of direct stimulation in humans. The stimulation was accompanied by recordings of intracranial electroencephalographic (iEEG) activity in the MTL and single unit activity (SUA) in the hippocampus. Stimulation occurred at various stimulation sites, enabling the characterization of the neural dynamics of direct stimulation within the hippocampus, it's surrounding white matter tracts, and within the temporal cortex.

Based on the animal literature outlined above we had several hypotheses. First of all, we hypothesized that direct electrical stimulation would lead to changes in local firing rate responses. Such a response would mostly likely manifest itself as the stereotypical excitation-inhibition response pattern demonstrated throughout different areas and species. This was based on the fact that this response pattern has been observed in different neocortical as well as subcortical stimulation sites in animals.

Second, we assumed that the stimulation response would propagate throughout the brain to distant connected areas. In particular, it was expected that stimulation in the hippocampus could cause responses in the neocortex and vice versa. This neocortical response should be larger for hippocampal stimulation than hippocampal response to neocortical stimulation. This difference was expected due to the role of the hippocampus as a hub where information is integrated from a multitude of connected areas. Driving such a hub regions should have a large impact on the downstream connected regions. In contrast to this, stimulation in the peripheral neocortical regions should have a much smaller impact, since it is only one of many areas giving input to the hippocamps. Furthermore, a lag of ~100-200 ms for hippocampal responses to neocortical stimulation and a ~200-300 ms lag is expected in the neocortex in response to hippocampal stimulation, based on a study looking at response-lags between these areas in an episodic memory task (Griffiths, et al., 2019).

Lastly, we hypothesized that stimulation in white matter would be able to induce neural responses that differed from the stereotypical excitation-inhibition pattern, since white matter does not contain interneurons.

2. Methods

2.1. Participants

The data was acquired from five patient (60% female; age: 35+-10.8; range: 23 to 53 y) under medical observation due to pharmacologically intractable epilepsy at the Queen Elizabeth Hospital Birmingham (QEHB) over the course of a total of nine sessions. Patients were implanted with 2-6 Behnke-Fried hybrid micro-macro electrodes (Ad-Tech Medical Instrument Corporation, Oak Creek, WI) per person terminating in the hippocampus for a period of 10-14 days to evaluate the possibility for a surgical resection as treatment (Engel et al., 2005). The location of the electrodes was based entirely on clinical requirements. Electrode locations were confirmed visually using pre- and post-op structural magnetic resonance imaging (MRI) scans (For an example of an electrode as registered by an MRI scan, see Fig 3-1 A). Written informed consent was obtained in accordance with the Declaration of Helsinki.

2.2. Data recording and pre-processing

2.2.1. iEEG

Each Behnke-Fried electrode consisted of eight macro-contacts and one microwire electrode bundle from which the iEEG signal was recorded (see Fig 3-1 C for a diagram). The microwire bundles were made up of 8 recording wires and a ninth reference wire. The microwire bundles recorded hippocampal SUA and local field potential (LFP) at a 32 000 Hz sampling rate through a 64-channel ATLAS Neurophysiology system (Neuralynx Inc.). The iEEG data acquired by the macro-contacts was recorded at a 1 024 Hz sampling rate. Most iEEG pre-processing steps were performed in MATLAB, using the fieldtrip toolbox, unless otherwise specified (Oostenveld et al., 2011).

After aligning the microwire iEEG/LFP data (MW) and the macro-contact iEEG data (MC), the MW data was down-sampled to 1000 Hz. Line noise was partly removed from the data using the Chronux toolbox (Bokil et al., 2010). All data was subsequently demeaned and cut into 6 second epochs (3 s pre-stimulation artifact 3 s post-stimulation artifact) and manually checked for artifacts resulting from noise or epileptic discharges. The period 20 ms before and 24 ms after stimulation onset was removed for all subsequent analyses based on simulations of the MW stimulation artifact showing that filter ringing persists for about 15 ms around the stimulation artifact. The trials were then sorted according to stimulation site as separate conditions. Each condition name is based on the lateral channel name (furthest

away from the cortex) at which stimulation was applied. The same steps were performed for the MC data, with the additional step of re-referencing all contacts per electrode to a channel located in white matter that had the least amount of measurable activity.

The conditions are split into local and distal conditions. Local refers to conditions where the recordings originate from the immediate vicinity of the source of stimulation (E.g. hippocampal MW activity during hippocampal stimulation). Distal stimulation on the other hand refers to recordings obtained from an area that is not within the same region of grey matter (E.g. hippocampal MW activity during stimulation in the neocortex).

For the calculation of event-related potentials (ERPs), iEEG activity was averaged per bundle. Activity from the bundles were subsequently averaged to create the grand-average ERPs. To make the ERPs of local and distal activity more comparable, the cumulative sum of the respective ERPs was calculated for the time-window running from stimulation onset to 1.2 s post stimulation.

The cumulative sum values were calculated over the ERP period. These values were normalized by dividing all values by the maximum cumulative sum value, creating an incrementally increasing value from 0 at time point 0 to 1 at time point 1.2. Thus, one could see the result as representing the percentage value of the completed ERP per time unit. These cumulative sum values from different ERPs can be compared to each other for every given time point. If a cumulative sum value is higher than another, this is an indication this ERP has progressed faster through its total response than another. If it is lower it is an indication that the ERP's response lagging behind in time. This allowed the comparison of time-courses of the ERPs for local and distal stimulation independent of polarity and precise pattern of the signal.

The frequency analysis was performed on the same level by using a multi-taper (specifically discrete prolate spheroidal sequences) fast Fourier transform with 1 Hz of spectral smoothing for frequencies ranging from 1 Hz to 30 Hz. The time window used was one second before and one second after the SPES pulse (pre: -1.022 - -0.022; post: 0.026:1.026). The resulting Frequency power-spectra were analysed further by separating the aperiodic and possible periodic components using the FOOOF toolbox (Donoghue et al., 2020).

2.2.2. SUA

SUA was extracted by performing spike detection and assisted spike sorting using the Waveclus toolbox (Quiroga et al., 2004). The same trial definition used for the MW and MC data was applied to the SUA data. The SUA data for each unit was also separated by stimulation site (for an example see Appendix 1). The data per stimulation site was then binned to correspond to a 1000 Hz sampling rate and convolved with a gaussian kernel yielding a Gaussian convolved (GC) firing rate for each condition (window size: 50 ms). The GC firing rate was normalized per unit by a z-transformation where each trial was subtracted with the average baseline firing rate over all trials for a given neuron and divided by the corresponding standard deviation derived over the baseline period of all trials for the normalized neuron.

Units were categorized as responsive or unresponsive to stimulation. A responsive unit was defined as a unit whose average GC firing rate to local hippocampal stimulation would exceed the 97.5[th] percentile or would fall below the 2.5[th] percentile of the average baseline activity after stimulation for at least 50 ms (see Fig 3-2A for an illustration). Responsive units were further analysed by subdividing the activity for each unit by the distance of stimulation. The estimated distance (d) between the unit and stimulation channel was defined was calculated as $d = \sqrt{(x2 - x1)^2 + (y2 - y1)^2 + (z2 - z1)^2}$, where x1, y1, and z1 are the respective anatomical coordinates as derived from the anatomical localization for the stimulation site while x2, y2, and z2 are the respective estimated coordinates of the microwire from which the unit was recorded. This estimation was based on extrapolation of insertion angle of the electrode and the length of the cut microwires.

2.3. Stimulation

Single pulse electrical stimulation (SPES) was applied repeatedly between a pair of neighbouring macro-channels. Each trial contains a 1 ms biphasic pulse (current strength: 8 mA, charge density: 96 μC/cm2/pulse). A pulse was applied 10-15 times per pair (see Fig 3-1B for an example of the stimulation artifact as recorded in MW). Stimulation always started at the most medial channel pair (i.e. in the hippocampus) and moved laterally along the electrode. Stimulation always started at the most anterior electrode and ended at the most posterior electrode (for an illustration see Fig 3-1C). Due to signal saturation resulting from electrical stimulation, MC activity at the stimulating channels is not interpretable. Only data

from channels adjacent to the active stimulation channels were used for local cortical activity (E.g., for the channel 7 condition only data from channel 8 was used).

2.4. Statistical Analysis

To compare the activity of the responsive and non-responsive neurons and to find differences in the cumulative sum of the ERPs, cluster-based permutations with 10 000 permutations were performed (Maris & Oostenveld, 2007). For the SUA activity the analysis was run as a two-tailed test with a cluster alpha of 0.05 on a time-window running from 0.1 s pre-stimulation to 1 s post-stimulation to be able to detect both increases and decreases in firing rate. The same analysis was performed for the cumulative sum, with the difference that the test was performed one-tailed as it was expected that the cumulative sum of local stimulation ERPs would always lead over the distal counterparts. Furthermore, only the post-stimulation time-window was tested from 0.026 to 1.026 seconds. The average difference in cumulative sum was calculated by averaging the time-difference within the resulting significant cluster.

For the Frequency analysis separate 2x2 (Stimulation: Local x Distal; Time: Pre x Post) Analyses of Variance (ANOVAs) were performed for the periodic and aperiodic components resulting from the FOOOF analysis. A Bonferroni corrected alpha was used for these ANOVAs.
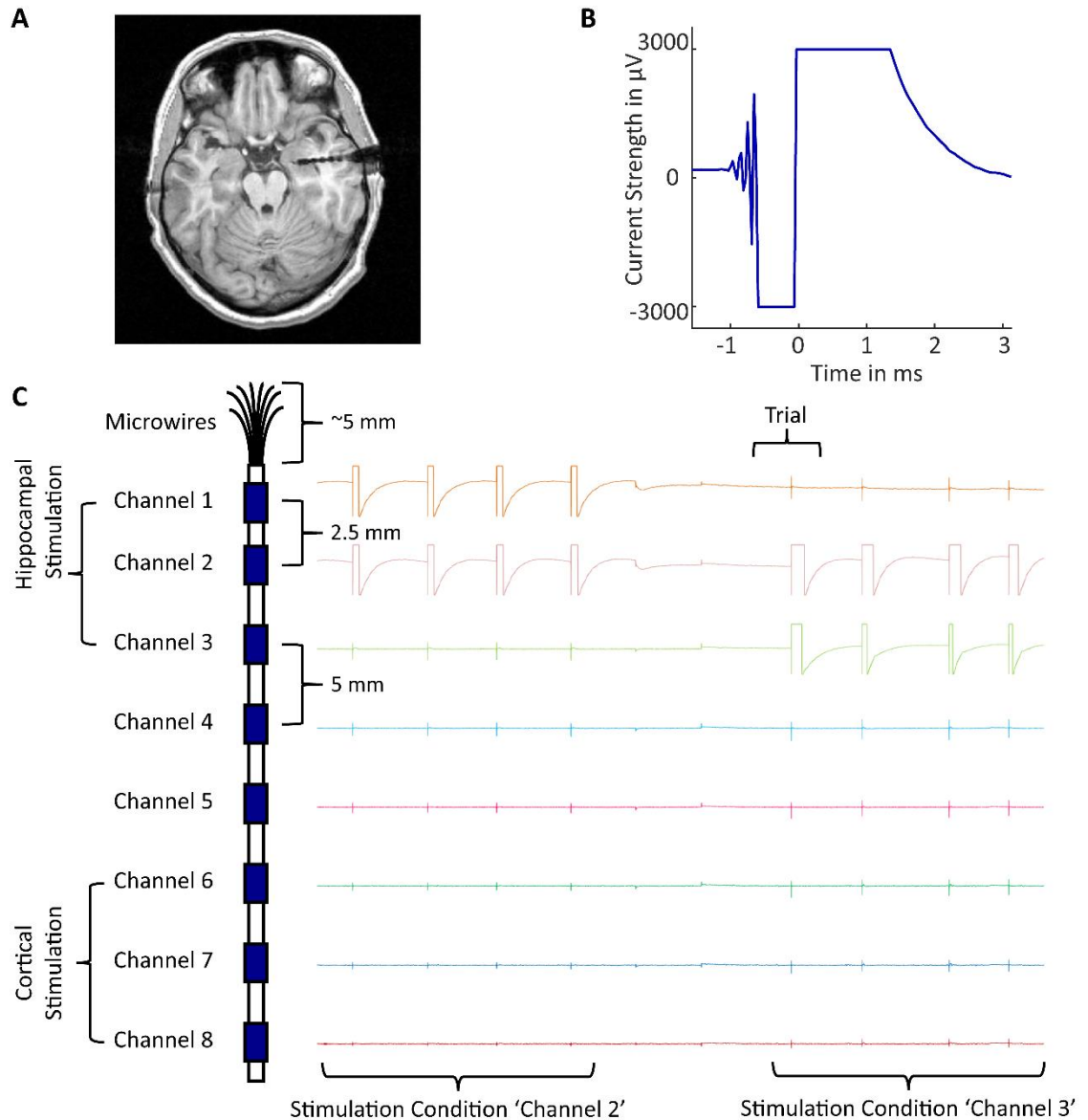
Fig 3-1: *Illustration of the stimulation set-up.* **A)** *Example horizontal section of structural post-op MRI scan. The inserted electrode is visible as a black line with each 'bead' being a macro channel on the electrode.* **B)** *Example stimulation artifact as recorded on a micro-wire. The square, bimodal shape is clearly visible with the signal returning to baseline already after 3 ms.* **C)** *Diagram illustrating the Behnke-Fried electrode along with example signal from two different conditions before trial alignment (pictured time-window ~90 seconds). The initial four stimulation pulses visible here were administered at the first and second channel, while the second set of pulses was administered between the second and third channel. Name for the condition is always derived from the outermost stimulated electrode of the pair.*

3. Results

A

Example SUA for a given Condition

B

Average Single Unit Response

39 Units (29%)

97 Units (71%)

Responsive Units
Unresponsive Units
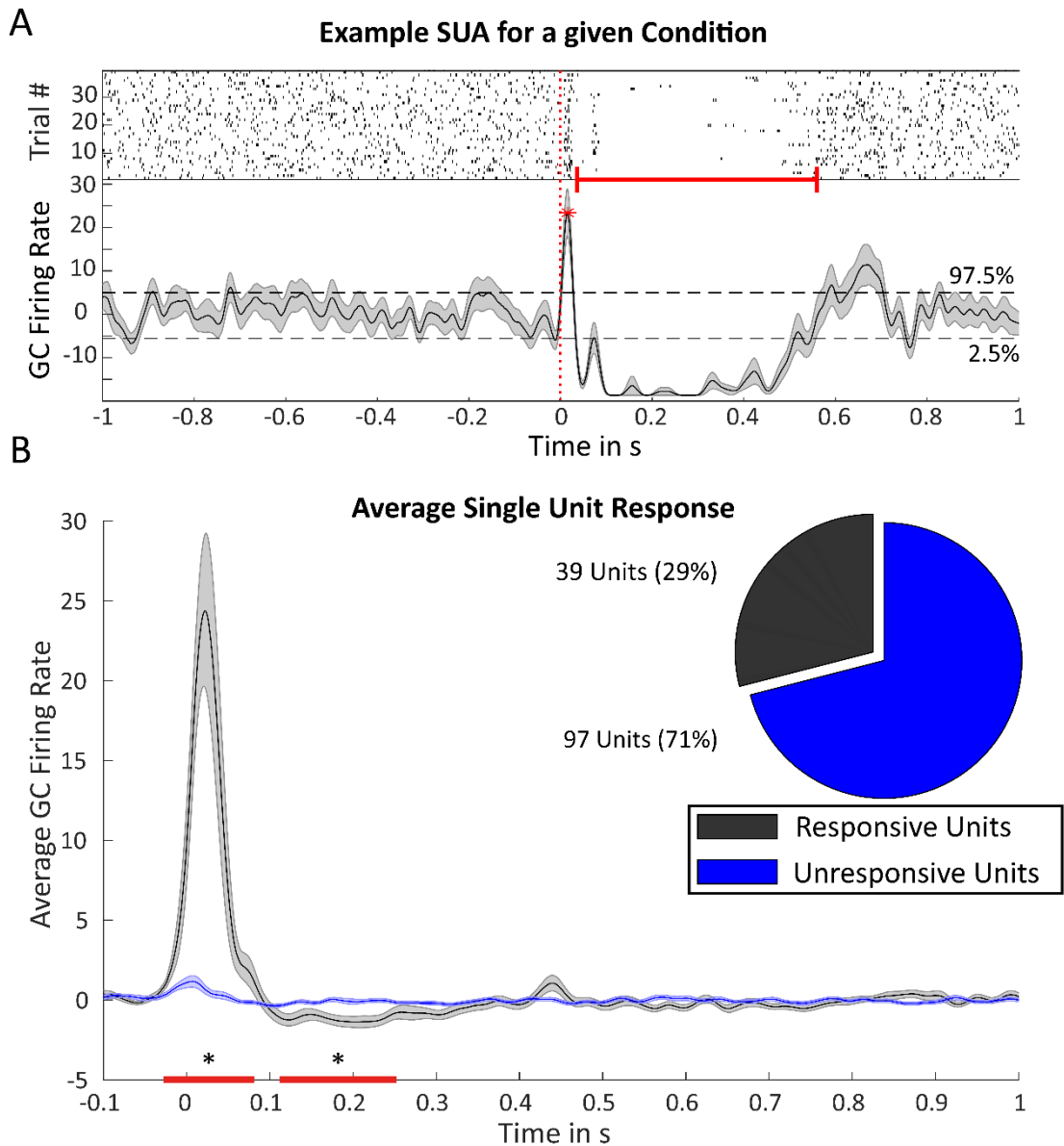
Fig 3-2: *Average SUA response to SPES. **A)** Illustration of the procedure used to calculate the GC firing rate per condition and the differentiation into responsive and unresponsive units. The vertical dotted red line indicates stimulation onset at time point 0. Top panel shows an example raster plot for a single unit during local a local stimulation condition. The bottom panel shows the corresponding GC firing rate. Horizontally dashed black lines indicate the boundary percentiles as determined in the pre-stimulation period used for classifying responsive units. Red star indicates an example of a peak following stimulation. The red horizontal bar indicates the length of the silent period. Shaded area indicates standard deviation. **B)** GC firing rate across all conditions averaged separately for responsive units (black) and unresponsive units (blue). Red horizontal bar marked with an asterisk (*) indicates clusters of activity with a significant difference between the two groups as detected by a cluster-based permutation test comparing the responsive and unresponsive units. Shaded areas indicate standard error of the mean. Pie chart illustrates the ratio of responsiveness of all detected units.*

3.1. SUA Response

Of all detected single units (N = 136), 29% showed a significant response to hippocampal stimulation (N= 39). As hypothesized, the typical average response pattern consisted of a marked increase in firing (cluster size: 110 ms, p = 0.0017), followed by a prolonged silent period (cluster size: 141 ms, p = 0.00049) (see Fig 3-2B).

Next, we tested whether this biphasic neuronal response is modulated by the distance of stimulation. Accordingly, we split conditions depending on the absolute distance between the approximate location of the recording microwire and the closest stimulated macro channel. For each condition the three following parameters were calculated: 1. The peak height, 2. the silent period length, 3. peak latency. Each of these three parameters was correlated against the calculated distance assigned to each condition after being normalized for each neuron (see Fig 3-3A). This analysis resulted in a significant negative correlation for peak height (r = -0.36, p => 0.0001) and silent duration (r = -0.28, p=> 0.0001) but not peak latency (r = 0.034, p = 0.3822). These results show that with increasing distance peak height gets smaller, and the silent period gets shorter. In contrast, peak latency appears not to vary linearly with stimulation distance.

To visualize these relationships in a different way, averaged GC firing rates were binned in 5 mm distance steps (see Fig 3-3B). These results confirm that the peak height and silent period length decrease with distance. In regard to peak latency, however, it appears that for distances exceeding 20 mm the peak in the responsive neurons is not more prominent than the peak in non-responsive neurons. (For a control analysis to verify whether the observed activity could result from direct propagation of the electric current conducted through the CSF as opposed to neuronal activity see Appendix 2).

In summary, analysis of the SUA response reveals that direct electrical simulation elicits a response pattern consisting of an initial excitation, followed by a period of inhibition. The intensity of both these responses is dependent on the distance to the stimulation site.
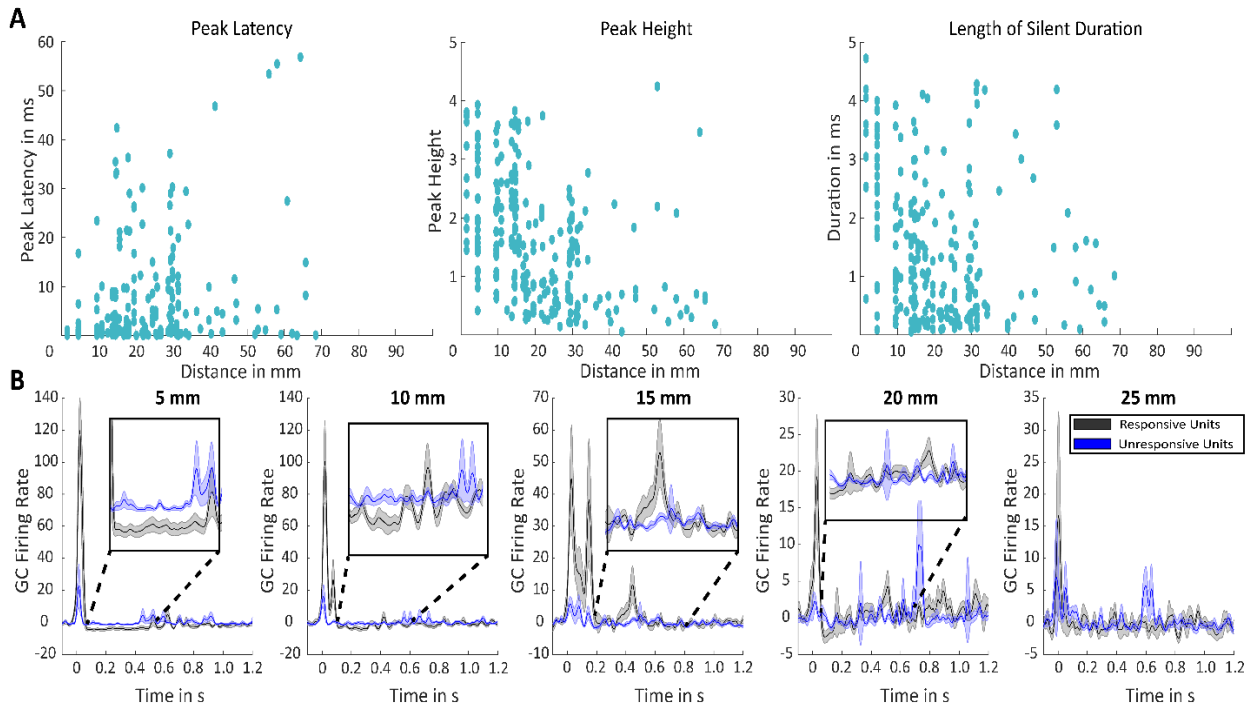
Fig 3-3: *SUA response as dependent on distance of stimulation site. **A)** Scatter plot of each parameter of interest respectively: peak latency, peak heigh, length of silent duration. Each dot represents the parameter as extracted from the average GC firing Rate for a condition at a given distance to the stimulation electrode. **B)** GC firing rates plotted per binned distance of the recording wire to the stimulation channel separated by the responsive and non-responsive neurons. Inset serves to highlight the parts of the post-stimulation response with a low amplitude. Shaded area indicates standard error of the mean.*

3.2. iEEG Response

The general LFP response to local stimulation is characterized by an initial negative deflection at ~100 ms, which is followed by a longer positive deflection at ~200 ms (Fig 3-4A). This pattern was consistently observed for local stimulation in both the neocortex as well as the hippocampal channels. For distal stimulation only a positive deflection could be observed, which was more pronounced in the cortical distal stimulation conditions compared to the hippocampal distal stimulation conditions (Fig 3-4B). This is likely a result of the nature of cortico-hippocampal connectivity. The pulse in the hippocampus targets a relatively larger population of neurons that will project to many areas in the neocortex. Neocortical stimulation instead drives a much smaller area of neurons in the hippocampus, since it is just one of many areas projecting to it.

To explore the properties of these ERP responses further, the cumulative sum of each condition was computed and averaged to establish whether there was systematic a lag between the responses in local vs the distal stimulation conditions (Fig 3-4C). A cluster-based permutation test comparing local vs distal cumulative sums of the responses revealed that the local ERP response would develop faster than the distal ERP response in both the hippocampus (p = 0.0098) and the neocortex (p = 0.0018) data. Maximum time difference for the hippocampal data and the neocortical data occurred at around the same time (Hippocampus: 406 ms; Neocortex: 395 ms post stimulation) with a peak difference of 148 and 136 respectively (average cumulative sum difference within the significant time-window: Hippocampus = 121ms; Neocortex = 80 ms). Thus, neocortical stimulation led to a response that was slightly more delayed in the hippocampus than the response in the neocortex in response to hippocampal stimulation.

For the frequency analysis the data was split into aperiodic and periodic components (for the log-transformed frequency spectra see Appendix 3). Due, to the lack of consistent of oscillatory peaks in the data, no reliable statistical comparison in that regard was possible. The aperiodic components were analysed using four 2 (Stimulation: pre x post) x 2 (Distance: local x distal) ANOVAs for the Offset and exponent of the MW and the MC data respectively (see Appendix 4 for the full output). There were no significant effects for the exponent in the MW or the MC data after Bonferroni correction of for the four tests. For the offset there was a significant effect of Stimulation and Distance in the hippocampal MW data (main effect for Stimulation: $F_{(1,14)}=10.181$, $p=0.007$, $\eta^2_p=0.160$; main effect for Distance: $F_{(1,14)}=8.964$, $p=0.010$, $\eta^2_p=0.157$; interaction Stimulation x Distance:

$F_{(1,14)}=3.863$, $p=0.070$, $\eta^2_p=0.047$) and a significant effect of stimulation for the neocortical MC data (main effect for Stimulation: $F_{(1,8)}=10.835$, $p=0.011$, $\eta^2_p=0.352$; main effect for Distance: $F_{(1,8)}=1.347$, $p=0.279$, $\eta^2_p=0.038$; interaction Stimulation x Distance: $F_{(1,8)}=4.306$, $p=0.072$, $\eta^2_p=0.044$). The absence of an effect of distance for the MC data makes sense, as the ERP data already revealed that the neocortex responds much more saliently to distal stimulation than the hippocampus. This means that distal stimulation in the neocortex leads to a change in offset post stimulation that is similar to the local stimulation as well.
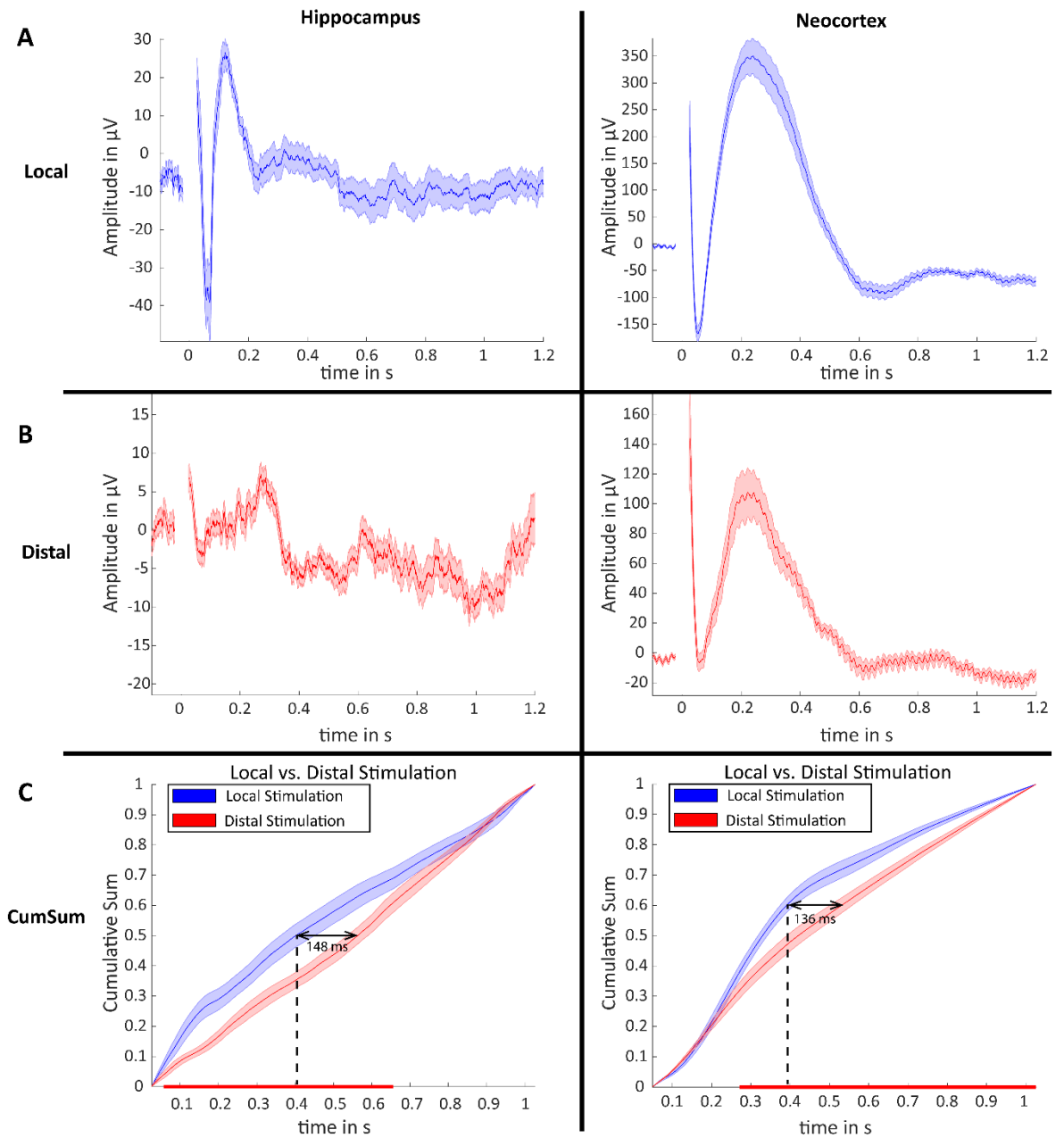
Fig 3-4: *iEEG responses to Local and Distal stimulation. Shaded area indicates standard error of the mean.* ***A)*** *Average ERP responses over all local stimulation conditions for the hippocampus (MW data) and the neocortex (MC data).* ***B)*** *Average ERP response over all distal stimulation conditions for the hippocampus (MW data) and the neocortex (MC data).* ***C)*** *Average cumulative sum of the ERP responses for each condition. Red horizontal line on the X-axis indicates cluster containing a significant difference between the two conditions. Dotted line indicates time stamp of the peak difference. Double-sided arrow indicates the value of the peak difference.*

3.3. White Matter Stimulation

One intriguing observation in the SUA data was that the distance dependent analysis revealed that the silent periods disappeared for stimulation at distances of around 15 mm from the bottom of the electrode onwards. Distances from approximately ~10 cm onwards tended to be located in white matter tracts. Such stimulation appeared to lead to a secondary burst of activity that appeared at a delay starting around 100 ms. To disentangle whether the response at these distances occurred due to stimulation in white matter or due to stimulation in other areas within the hippocampus that might be 10-15 mm away, the same analysis selecting single units in response to stimulation as before was used for white matter stimulation trials. The activity of the responsive units was compared to the activity of the non-responsive units in a time-window of -500 ms to 1200 ms relatively to stimulation onset with a cluster permutation test with the same parameters as used for the analyses above. This analysis yielded 28 units responding to white matter stimulation. The typical response seems indeed to be an increase in firing rate between ~100-200 ms. Importantly, no silent period was observed for this white matter stimulation which is in stark contrast to the pronounced silent period observed during local stimulation (see Fig 3-5).

In the corresponding white-matter ERP as measured in the hippocampus in the MW data, only two bundles showed any response (see Appendix 5) The frequency analysis on the white matter stimulation MW data likewise did not reveal any significant effects.
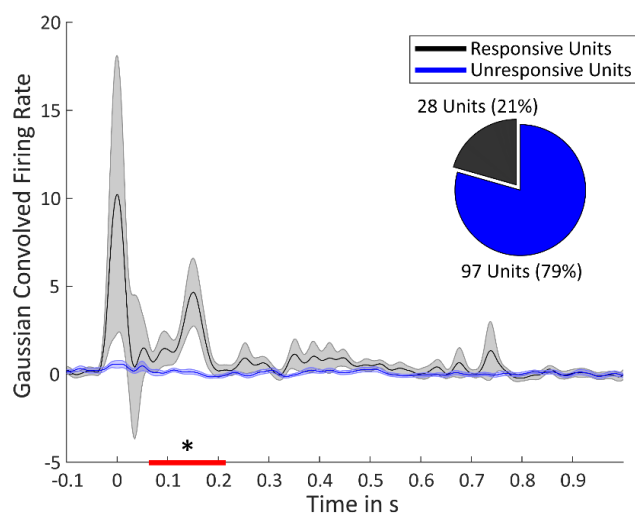
Fig 3-5: *GC firing rate response to stimulation at white matter channels Shaded area indicates standard error of the mean. Red Horizontal line indicates significant cluster between the responsive units to white matter stimulation vs. the unresponsive units. Ratio of responsive to unresponsive units is indicated with the pie chart.*

4. Discussion

The current study reports hippocampal and neocortical activity in response to stimulation throughout these areas. The main finding is that local stimulation in the human hippocampus generally seems to inhibit ongoing local activity after a brief period of extreme excitation.

This response can be observed in both, the SUA and LFP activity. The negative LFP deflections seem to line up with the initial neuronal excitation, while the positive LFP deflections occur in a similar time period as the following SUA silent period. The polarity of this LFP response matches the finding that negative deflections are a sign of excessive depolarization of neurons in an area, while positive deflections reflect hyperpolarization of the surrounding area (Buzsáki et al., 2016).

The excitation-inhibition response pattern is in line with what has been observed in the neocortex of non-human primates and rats in response to direct electrical stimulation (Butovas & Schwarz, 2003; Inghillerj et al., 1992; Logothetis et al., 2010). By using the data recorded at the cortical macro channels we were able to confirm that this stereotypical response also holds for stimulation in the human neocortex. Thus, such an excitation-inhibition response to stimulation appears to be universal across species and brain areas with varying neural architectures. The exact origin of the prolonged inhibitory silent period is still unknown.

One possibility is that the direct electrical stimulation initially mainly drives excitatory pyramidal neurons. This could be due to their large size compared to the smaller inhibitory interneurons and are thus more susceptible to voltage differences. This would then lead to the observed short firing increase in response to direct electrical stimulations. This burst in excitatory activity could then drive the inhibitory neurons in the network to start a compensatory response which inhibits all activity, overcorrecting for the initial excitation with a large period of inhibition.

An alternative possibility is that the inhibition is a result of the close interactions between excitatory pyramidal cells and surrounding inhibitory interneurons. The change in the local electric field would lead to excessive firing in all neurons. Here the firing of the more numerous pyramidal neurons is eventually drowned out by continuous firing of interneurons. The resulting interneuron activity would then lead to prolonged inhibition in the pyramidal neurons.

It is not possible to disentangle the two speculative scenarios from each other based purely on the findings of this study. Either mechanism would predict the increased peak-size and increased silent period length in response smaller distances/larger field strengths. They would also be compatible with the exploration of white matter stimulation, where stimulating in white matter can lead to excitatory responses in the brain without the corresponding silent period, since white matter only contains excitatory tracts and no inhibitory interneurons. Thus, the signal can travel unimpeded from the stimulation site into the hippocampus where it produces a more natural response, driving much less of the interneurons. The sparse reflection of activity in response to white matter stimulation in the LFP are likely because not all the stimulated white matter projects to the hippocampus. However, a large caveat here is the relatively weak response, which might be the real reason for the differences in firing observed here. Future research, targeting white matter stimulation more specifically should use connectivity measures (such as diffusion tensor imaging) to target white matter tracts in a more systematic way.

The above account on the underlying mechanism of the inhibitory response would further help explain why stimulation leads to an increased offset of the aperiodic component. Increased offsets (i.e. broadband power increases) are generally associated with increased spiking activity (Manning et al., 2009). It is much more likely to record SUA from excitatory pyramidal neurons, due to their larger size and numerosity in the hippocampus. Thus, the average GC firing rate in the SUA analysis is mostly driven by the excitatory pyramidal neuron response (Bezaire & Soltesz, 2013; Pelkey et al., 2017; Viskontas et al., 2007). LFP activity has been noted to be driven in large part by spiking of interneurons (Bazelot et al., 2010; Teleńczuk et al., 2017). Thus, the broadband increase in LFP activity would then be the result of increased interneuron activity. Surprisingly, we did not find a systematic effect of stimulation on the exponent of the aperiodic activity. Specifically, a steepening of the power spectrum would have been associated with increased inhibition in the context of synaptic excitation and inhibition balance (Gao et al., 2017). However, it is possible that the short excitation response would counteract the effectively counteract the contribution of the inhibition response over the time-window, keeping the excitation-inhibition balance constant and thereby explaining the lack of a steepening aperiodic slope.

Another interesting finding is that the inhibitory effect resulting from stimulation is retained across large distances; Stimulation in the hippocampus evoked a highly similar (albeit smaller) response pattern in the neocortex as it did for local stimulation. This is consistent

with findings such as Logothetis et al. (Logothetis et al., 2010), where thalamic stimulation produced inhibitory responses in occipital visual regions. As hypothesized the distal response in the hippocampus was much smaller than the neocortical distal response. This property of producing distal responses was leveraged in this study to obtain an estimate of how fast information can travel from the neocortex to the hippocampus and vice versa. The average delays observed in the cumulative sum analysis suggest a delay of ~100 ms, with peak delays in the ERPs becoming as large as 150 ms. These transduction delays correspond to cortical and hippocampal activity delays during memory encoding and are approximately twice as fast as the 200-300 ms delays between cortical activity and hippocampal activity observed naturally during memory retrieval (Griffiths, Parish, Roux, Michelmann, van der Plas, et al., 2019). This implies that the delays observed during encoding are likely purely due to the time it takes for the information in the neocortex to reach the hippocampus, while hippocampal activity does not travel instantly to the neocortex to be retrieved but rather requires additional processing steps in between the hippocampal activation and the eventual retrieval in the neocortex.

Overall, the results from this study will help with understanding the mechanisms of direct electrical stimulation in the human hippocampus. The characterization of the neuronal single unit and population activity helps inform parameter choices and can help with making narrower predictions on how direct stimulation will play out on behavioural performance.

Appendix
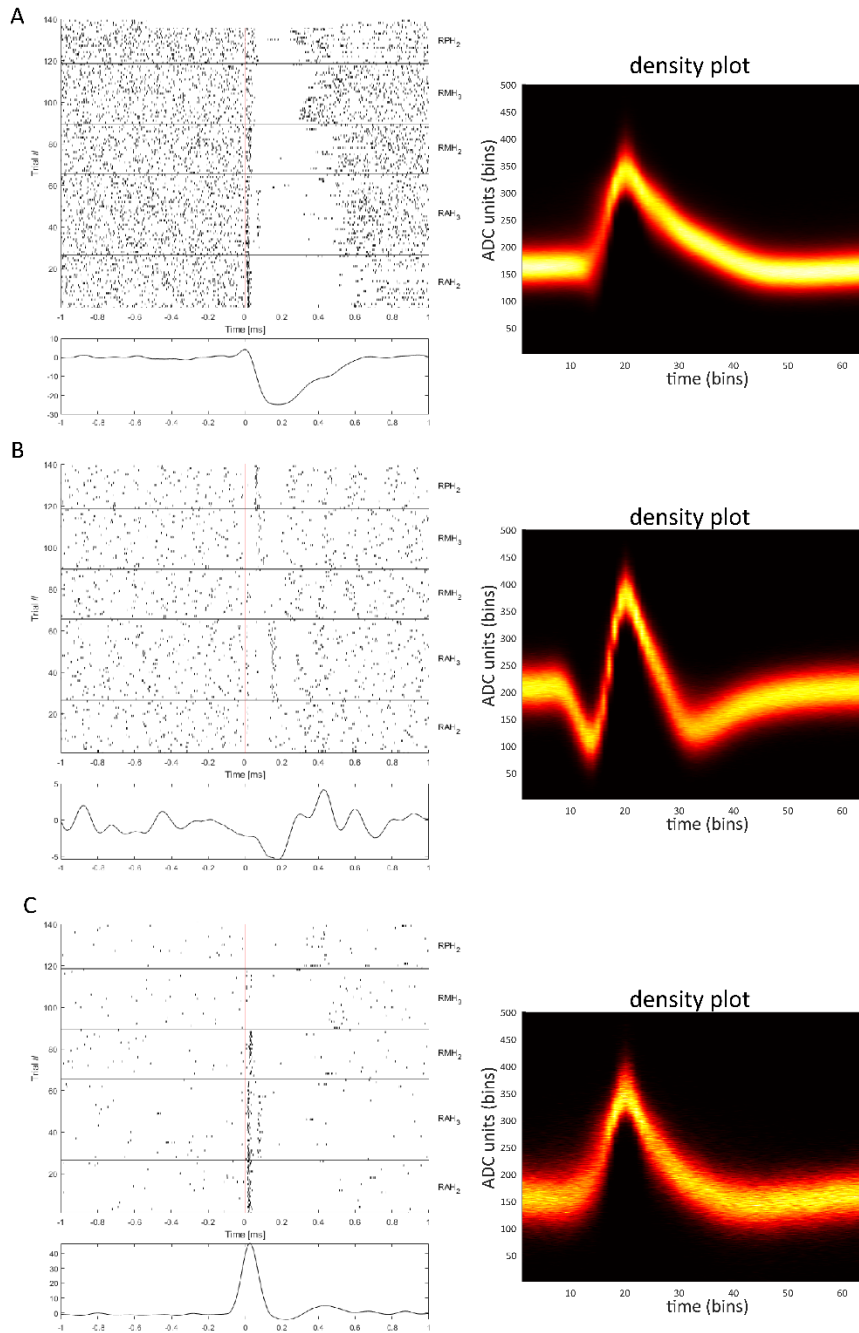
Appendix 1, Example Units: Examples of three different units exhibiting a significant response to Hippocampal stimulation. Top panels are the raster plots for every single trial separated by the different stimulation conditions (AH,MH,PH, referring to electrodes in the Anterior Hippocampus, Medial Hippocampus, and Posterior Hippocampus respectively). The red line indicates the time point at which the pulse was administered. The lower panel indicates the average GC firing rate over all conditions. The right column contains the density plot of the waveform for the respective unit.
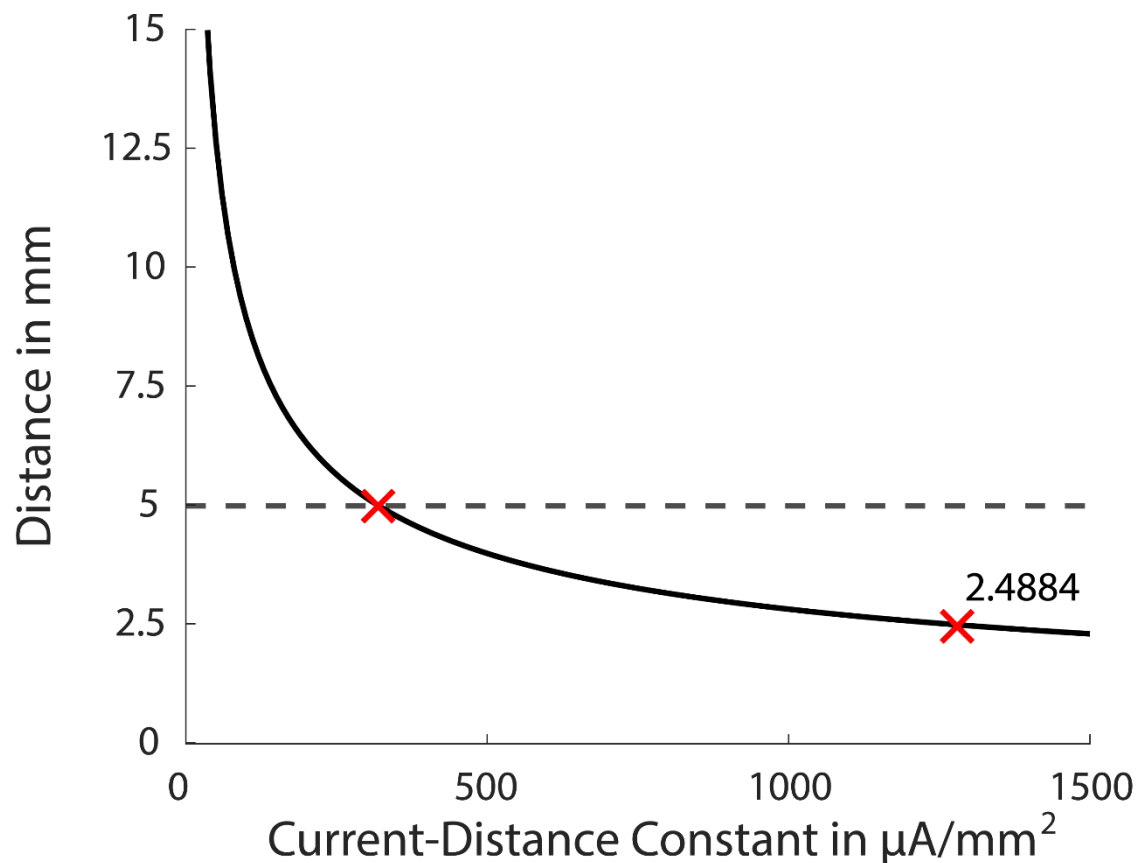
Appendix 2, Electric Spread: Diagram of the calculated current spread for the administered pulses plotted for each separate current-distance constant. The current distance constant indicates the capacity of neurons to conduct electrical current. This constant has been experimentally assed in Stoney et al. (1968). This figure was created to see how far off the calculations would have to be for the signal to not be neuronal in nature**.** The dotted line marks a 5 mm distance as that is the typical distance between the macro channels. The left-most red X highlights the value necessary for crossing the threshold for this distance with a Current-Distance Constant of ~400 μA/mm². The rightmost red X indicates the averaged current-distance constant determined for cortical neurons in primates. The calculated spread of current was calculated to be ~2.5 mm using the formula r = $\sqrt{\frac{I}{K}}$ (Stoney Jr et al., 1968; Tolias et al., 2005). For current spread to exceed a spread of 5 mm the original value would have to be wrong by approximately a factor of 3.
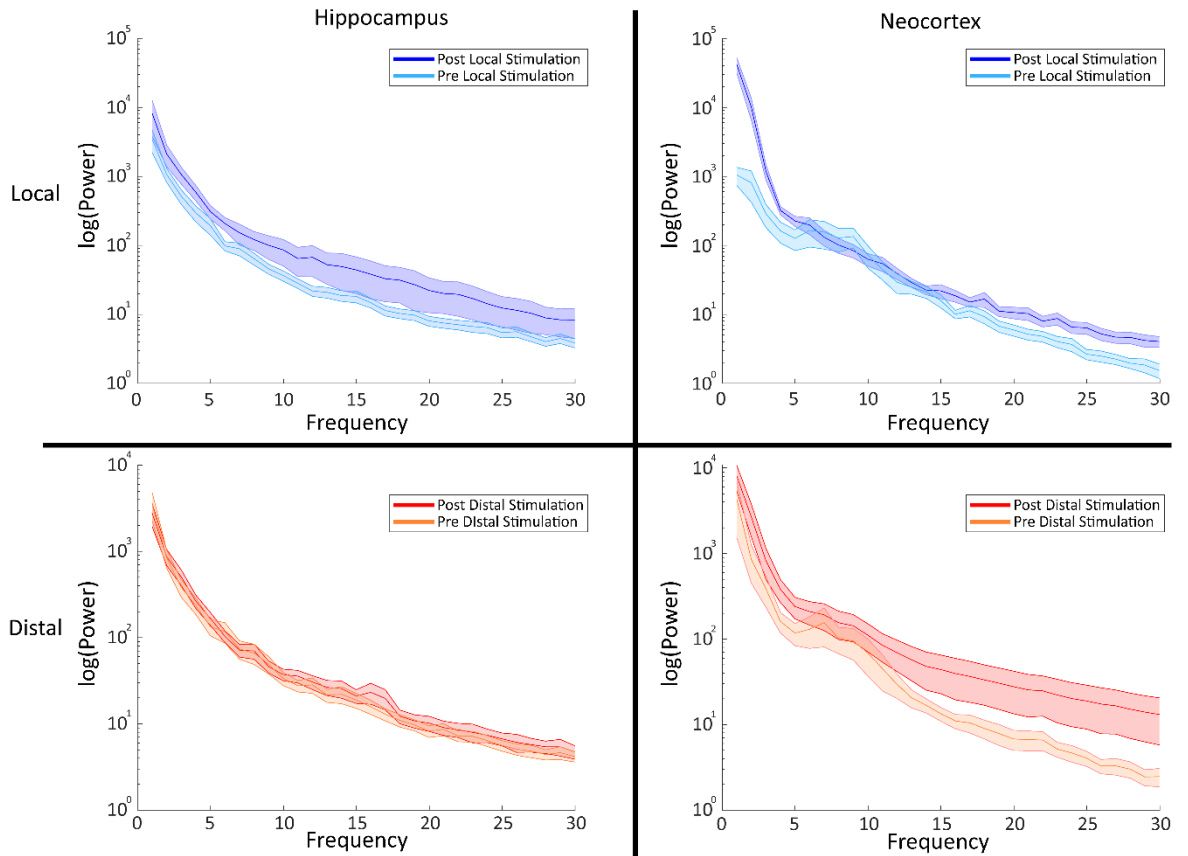
Appendix 3, Power-Spectra: Log-transformed frequency spectra contrasting pre- and post-stimulation for local and distal stimulation conditions in the Hippocampus (MW) and Neocortex (MC). Shaded area indicates the standard error of the mean.

Appendix 4: Full output of the 2x2 ANOVAs

Exponent MW

Cases	Sum of Squares	df	Mean Square	F	p	η²
Stimulation	0.044	1	0.044	0.978	0.34	0.024
Residuals	0.634	14	0.045			
Distance	0.22	1	0.22	7.021	0.019	0.121
Residuals	0.439	14	0.031			
Stimulation * Distance	0.017	1	0.017	0.504	0.49	0.009
Residuals	0.463	14	0.033			

Note. Type III Sum of Squares

Exponent MC

Cases	Sum of Squares	df	Mean Square	F	p	η²
Stimulation	0.459	1	0.459	1.835	0.213	0.084
Residuals	2	8	0.25			
Distance	0.471	1	0.471	2.228	0.174	0.086
Residuals	1.69	8	0.211			
Stimulation * Distance	0.242	1	0.242	3.109	0.116	0.044
Residuals	0.623	8	0.078			

Note. Type III Sum of Squares

Offset Micro

Cases	Sum of Squares	df	Mean Square	F	p	η²
Stimulation	0.522	1	0.522	10.181	0.007	0.16
Residuals	0.718	14	0.051			
Distance	0.513	1	0.513	8.964	0.01	0.157
Residuals	0.801	14	0.057			
Stimulation ✳ Distance	0.153	1	0.153	3.863	0.07	0.047
Residuals	0.556	14	0.04			

Note. Type III Sum of Squares

Offset Macro

Cases	Sum of Squares	df	Mean Square	F	p	η²
Stimulation	3.559	1	3.559	10.835	0.011	0.352
Residuals	2.628	8	0.328			
Distance	0.383	1	0.383	1.347	0.279	0.038
Residuals	2.273	8	0.284			
Stimulation ✳ Distance	0.441	1	0.441	4.306	0.072	0.044
Residuals	0.82	8	0.103			

Note. Type III Sum of Squares
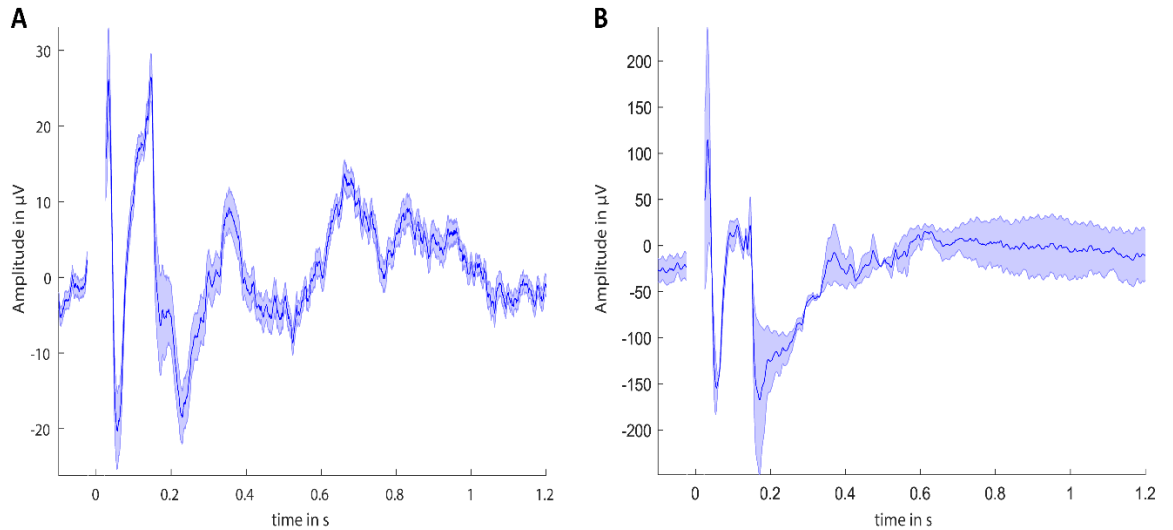
Appendix 5, White-matter ERP: ERP time-courses of white-matter stimulation **A)** Grand Average ERP time-course of all Microwires **B)** Grand Average ERP time-course of only those microwires that show a response to the white matter stimulation. Shaded area indicates the standard error of the mean.

Chapter 5 : General Discussion

The studies, as outlined in the previous chapters of this doctoral thesis, have each probed the cortico-hippocampal network in different ways. The following chapters will summarize the main findings of each study and discuss their results in relation to the sync-desync framework as well as each other. Furthermore, this chapter will provide suggestions for future research based on the studies of this thesis for academic as well as clinical research applications.

1. Main Findings

1.1. Study 1 – 4 Hz Occipital tACS

Study 1 (chapter 2) was unable to affect memory performance by coupling 4 Hz tACS to 4 Hz auditory sensory stimulation. This is surprising given that this paradigm has been successful in modulating memory performance when occipital entrainment was performed using sensory stimulation in previous studies (Clouter et al., 2017; D. Wang et al., 2018). According to the sync-desync framework the manner of entrainment should not really play a role in affecting behaviour.

The study design does not allow to disentangle the reasons why stimulation is unsuccessful in having an effect on memory performance. One possible explanation could be that tACS is unsuccessful in entraining the visual cortex, despite the choice of stimulation parameters and montages. This would be quite surprising given that other tACS experiments have managed to modulate activity in the visual cortex with similar parameters in the past (Helfrich, Schneider, et al., 2014; Ruhnau et al., 2016). However, the stimulated frequency in such studies was around the alpha band (7-12 Hz) which is closer to the dominant endogenous frequency in the visual cortex and therefor easier to entrain.

Another possibility is that the original findings from Clouter et al. (2017) were driven by another mechanism than entrainment effects propagating to the hippocampus. For example, it has not been definitely settled yet whether sensory stimulation causes entrainment of neurons, network resonance, or modulates neurons in a altogether different fashion (Haegens & Golumbic, 2018; Helfrich et al., 2019). A combination of findings such as, that 4 Hz flicker is perceived as brighter and has higher phase locking values than other flickering frequencies (Bertrand et al., 2018), direct connections between sensory cortices (Lakatos et al., 2007; Schroeder & Foxe, 2005; Stein & Stanford, 2008) and the relevance of 4 Hz

oscillations in attentional sampling might contribute to the originally observed effects (Helfrich et al., 2018; Landau et al., 2015; Lowet et al., 2016; Spyropoulos et al., 2018).

Lastly, it is possible that the produced entrainment by tACS is too weak to be transmitted to down-stream areas, as the sub-threshold activity produced by tACS is much less salient than the sensory stimulation which drives neurons directly. This would be in line with a recent visual flicker study, showing that frequency tagging at imperceptible frequencies induces local gamma phase-locking that is visible in the occipital cortex but not strong enough to affect downstream areas (Duecker et al., 2021).

Regardless of the exact mechanism it appears that tACS is not a suitable entrainment method for indirectly targeting the hippocampus through sensory cortices.

1.2. Study 2 – 1 Hz rTMS of the left DLPFC

In study 2 (chapter 3), 1 Hz rTMS applied to the left DLPFC during encoding was beneficial for memory performance during list learning tasks. The electrophysiological data further corroborated this by showing that the 1 Hz rTMS affects neocortical desynchronization in the parietal cortex at the beta band frequency.

The relationship of beta-desynchronization and episodic memory performance is consistent with the sync-desync framework (Hanslmayr et al., 2016; Hanslmayr, Staudigl, et al., 2012). According to the results of this rTMS study, the observed desynchronization of broadband alpha/beta power is not truly oscillatory. Rather the desynchronization seems to be driven by an upwards rotation of the aperiodic component. More specifically, the stimulation increases the slope (aka spectral tilt), which is associated with an increase in inhibition (Gao et al., 2017). This account is distinct from other research that suggests naturally occurring neocortical alpha/beta power decreases are not based on changes in spectral tilt (Fellner et al., 2019). These finding are not necessarily at odds with each other. It is possible that the artificial broadband alpha-beta power decreases, induced by rTMS of the left DLPFC, affect the oscillatory responses in the network as well.

1.3. Study 3 – SPES stimulation in the hippocampus

The main finding of study 3 (chapter 4) is that local direct electrical stimulation follows a distinct canonical response pattern. The pattern consists of an initial short-lasting excitatory response, followed by a long-lasting inhibitory response. This response has been observed before in cortical areas of diverse animal models (Butovas & Schwarz, 2003; Inghillerj et

al., 1992; Logothetis et al., 2010). This implies that the observed response pattern is a general property cortical and sub-cortical areas. Moreover, the same response pattern was observed for local stimulation in the neocortex. This further corroborates the idea that the response pattern is intrinsic to the basic architecture of cortical areas.

Basic signal transduction delays were estimated based on the difference in normalized average cumulative sum values calculated from event-related potentials in the hippocampus and cortex. This analysis revealed that the peak difference between local and distal stimulation for both directions was about ~140 ms. Such a delay is consistent with findings of delays during encoding, of another study as performed by Griffiths et al. (2019). This study estimated its transduction delays based on the lag in onset of oscillatory activity as predicted by the sync-desync framework. It measured the delay between alpha/beta desynchronization increases in the neocortex and gamma synchronization increases in the hippocampus during encoding (100-200 ms) and vice versa during retrieval (200-300 ms). Comparing their data to our data, suggests that during retrieval the signal from the hippocampus takes a longer time to reach the neocortex than predicted purely by connectivity. Thus, the hippocampus seems to require additional processing before it is able to signal the cortex to replay a given memory. Whether this is due to the signal ramping up within the hippocampus, or whether the information is relayed somewhere else first remains to be seen.

2. TMS & SPES

The observed canonical response pattern, first described above, is not just limited to direct electrical stimulation studies using Single Pulse Electrical Stimulation (SPES). This response pattern has also been reported in TMS studies monitoring single unit activity (Day et al., 1989; Li et al., 2017; Mueller et al., 2014; Romero et al., 2019). This is ultimately not very surprising from a mechanistic perspective. Both methods ultimately induce a very strong, but focal electric field in the brain. The manner this field is induced, be it directly or through an induced magnetic field, should matter very little to response of the stimulated neurons. Indeed studies directly comparing these methods report similar findings for the two methods (V. Di Lazzaro et al., 1998; Inghillerj et al., 1992). Despite this, it appears that studies using TMS and direct electrical stimulation seldom inform each other.

The parameter-space of TMS and direct electrical stimulation studies is generally vastly underexplored. There is a need for further studies establishing the mechanistic underpinnings

of electrical stimulation of any kind. For example, while study 3 finds behavioural effects using 1 Hz rTMS, the mechanisms underlying these results are only poorly understood. It is still unknown what exactly 1 Hz TMS does and why it is commonly assumed to be inhibitory. Based on the responses in this study 4, one might speculate that 1 Hz TMS causes repeated inhibition since the silent period extends for most of the second post-pulse. Thus, the time-window is dominated by the inhibitory silent period compared to the very short excitatory firing period. As stimulation is applied at higher frequencies, more excitatory responses occur in the inhibitory period, which could explain excitatory responses for ~20 Hz stimulation. Stimulation intensity likely also play a large role in these effects, as the silent period becomes shorter at lower intensities. Moreover, at certain intensities the excitation might be retained without a silent period altogether.

Such speculation has only limited use. In the end these speculations need to be tested experimentally, to either confirm the hypotheses derived from them or reveal alternative methods of action. The only way to confirm such hypotheses is to perform systematic direct electrical stimulation, or TMS, studies with concurrent neurophysiological recordings using multiple pulses at different frequencies and different intensities.

3. Connectivity

The studies performed as part of this thesis highlight the importance of taking connectivity between different brain regions into consideration when applying neural stimulation methods such as TMS and SPES. Stimulation of the neocortex did not produce hippocampal responses as consistently as local stimulation did to the hippocampus. However, consistent targeting of the hippocampus from the neocortex is possible, based on connectivity-informed TMS studies (Hebscher & Voss, 2020; Wang et al., 2014). These studies defined a target region (in this case the hippocampus) as a seed region and determined hypothetical neocortical target areas based on functional connectivity. The functional connectivity was established using task-specific fMRI activations as a guide. A similar analysis for direct electrical stimulation studies could allow for more specific predictions.

Instead of functional connectivity analyses, one could employ anatomical connectivity measures, such as diffusion tensor imaging (DTI) to aid study designs and hypothesis formations. For example, traditional modelling measures only take into account the local electric spread within an area. However, as both study 3 (TMS) and study 4 (direction electrical stimulation) have shown the potential of such stimulation methods to manipulate

activity throughout whole networks indirectly. By knowing which areas are connected directly models of local electric field spreads could be updated to include effects in more distant but connected areas.

This could be especially helpful in the context of white matter stimulation during episodic memory tasks. Such experiments have recently been suggested as a viable alternative to targeting grey matter directly in the context of memory studies (Mankin et al., 2021; Mohan et al., 2020; Stephani & Koubeissi, 2015; Titiz et al., 2017). Preliminary data from study 4 suggests that white matter stimulation might be able to produce responses that are exclusively excitatory and may therefor aid memory performance without producing the same inhibitory response that local stimulation produces, since no inhibitory neurons are targeted directly. By using anatomical connectivity measures, the relevant fibre bundles projecting to the hippocampus could be targeted directly to investigate the feasibility of this approach more closely.

4. Clinical Applications

In theory, any method with the potential to manipulate behaviours or neural patterns also has potential clinical applications. This also holds true to the stimulation methods employed in this thesis (Alexander et al., 2019; Iaccarino et al., 2016; Sankar et al., 2015; Voigt et al., 2019). There are several findings within this series of studies that have the potential to be of clinical relevance. rTMS has previously been used to treat the symptoms of cognitive decline in patients at risk for Alzheimer's disease due to mild cognitive impairment. A review of several rTMS studies in the context of memory enhancement, to combat cognitive decline, has stated that the evidence is currently inconclusive (Birba et al., 2017). The parameters used in study 3, where the left DLPFC was targeted using 1 Hz rTMS, could be useful to update and optimize these procedures and may help to alleviate the symptoms of cognitive decline in the future.

Furthermore, findings from study 4, are useful for the pursuit of understanding electrical stimulation methods more intimately. This will allow for better predictions when targeting neuropathological issues with the hippocampus and cortico-hippocampal communication, such as Alzheimer's disease or other forms of dementia. One could for example try to leverage the excitatory part of the observed canonical pattern resulting from direct electrical stimulation to encourage firing within specific theta-phases by utilizing closed-loop deep brain stimulation designs (akin to Ezzyat et al., 2018 and Scangos et al., 2021) to encourage

theta-gamma coupling in the hippocampus, which is known to be associated with improvements in memory performance (Griffiths, et al., 2019; J. Lisman, 2005; Tort et al., 2009). Stimulation sites throughout the network might further be useful to improve communication between the different areas. The fact that the stimulation is reduced with distance is also of clinical interest, since the responses to further stimulation appeared to cease having an inhibitory component. The difference in relative amplitude might therefor be the key to understanding why a given stimulation paradigm will be excitatory or inhibitory.

5. Conclusions

Many methods used by neuroscientists allow us to open a window into the brain and observe neural activity. This thesis aimed to step through this window and actively manipulate the brain to understand the episodic memory system better. It causally explores the relationship between the hippocampus and neocortical areas with a variety of stimulation methods over multiple studies. The studies have found that: 1. Occipital tACS is not suitable to indirectly entrain activity in the hippocampus. 2. 1 Hz TMS is causally linked to memory performance increases and activity changes in the parietal cortex. 3. SPES in the human hippocampus causes a distinct response pattern that consists on average of a short excitatory and a prolonged inhibitory response, which not only affects the immediate area of stimulation but can propagate throughout the brain. These studies have contributed to the understanding of the cortico-hippocampal network and will help inform future stimulation studies, in the hope of eventually significantly improving memory in those with cognitive decline or other memory disorders.

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