MODULATING EPISODIC MEMORY FORMATION USING NON-INVASIVE BRAIN STIMULATION

by

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ABSTRACT

Oscillatory activity in the beta frequency range accompanies the formation of long-term memories. Beta power decreases have frequently been shown to correlate with memory formation. However, the causal relationship between beta desynchronization and episodic memory encoding remains unclear. This thesis investigates the causal role beta oscillations play in memory formation and explores ways in which non-invasive brain stimulation can be used to test these causal mechanisms. More specifically, this thesis investigates whether increasing beta power impairs memory formation and whether decreasing beta power improves memory. We used two different non-invasive brain stimulation techniques: tACS was used to increase beta power and impair memory formation, while rTMS was used as a means of decreasing beta power and enhancing memory performance. Chapters 2 and 3 indicate that transient beta tACS does not modulate beta oscillations and does not impair memory formation, while slow rTMS effectively enhanced memory formation by modulating beta power in remote areas, in Chapter 4. This thesis emphasises that negative results are not only important, but necessary to advance our understanding of how non-invasive brain stimulation can help us unravel the causal role that beta oscillatory activity plays in the formation of episodic memories.

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PUBLICATIONS AND CONTRIBUTION

The work presented in this thesis contains material that has been published or is being prepared for publication. Published papers and articles in preparation have been adjusted to form a coherent thesis. Data for Chapters 2 and 3 were collected, analysed, interpreted, and written up by myself. Co-authors had supportive or advisory roles or assisted with data collection. Figure 4 was made with the generous assistance of Rodika Sokoliuk. Data for Chapter 4 were analysed, interpreted, and written up by myself. Data for experiment 2, Chapter 4, were also collected by me. Co-authors assisted with data collection or had advisory roles.

Published articles

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Articles in preparation

Braun, V., Stauch, B. J., Hanslmayr, S. (2018). *Slow rTMS to the left DLPFC enhances verbal memory formation.* Manuscript in preparation.

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tACS	transcranial alternating current stimulation
rTMS	rhythmic transcranial magnetic stimulation
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
BOLD	blood oxygenation level dependent
TMS	transcranial magnetic stimulation
tES	transcranial electrical stimulation
tDCS	transcranial direct current stimulation
EEG	electroencephalography
DLPFC	dorsolateral prefrontal cortex
ROC	receiver operating characteristic
MEP	motor evoked potential
M1	primary motor cortex
FDI	first dorsal interosseous
ICA	independent component analysis
BA	Brodmann area

LIST OF APPENDICES

CHAPTER 1: EPISODIC MEMORY FORMATION AND NON-INVASIVE BRAIN STIMULATION – THEORETICAL BACKGROUND AND OVERVIEW

This thesis investigated whether two different non-invasive brain stimulation techniques may be used in novel ways to study the relationship between beta oscillations and episodic memory formation. In this chapter research into episodic memory formation will be reviewed, the oscillatory correlates of successful episodic memory formation outlined, and the importance of desynchronized activity in the beta frequency range for memory encoding presented. As correlational studies cannot infer a causal relationship between oscillatory activity and memory formation, the two non-invasive brain stimulation techniques utilized in this thesis will be introduced—rhythmic transcranial magnetic stimulation (rTMS) and transcranial alternating current stimulation (tACS). The chapter concludes by giving an overview of the research presented in this thesis.

Modulating Episodic Memory Formation using Non-Invasive Brain Stimulation

Episodic memory refers to the remarkable ability to remember and re-experience past events. Although an event may only have been experienced once, the details can be brought back easily and the episode can be remembered in detail (Tulving, 2002). How does the brain achieve this complex task?

Successful formation of episodic memories relies heavily on stimulus-specific information processing during memory encoding (Paller & Wagner, 2002). An event can only be stored effectively for later access if the information has been represented and processed sufficiently (Hanslmayr, Staresina, & Bowman, 2016; Paller & Wagner, 2002). Therefore it has been proposed that brain processes present during encoding of items that will subsequently be remembered are crucial for episodic memory formation (see for example Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998). Increasing evidence suggests that oscillatory activity in the beta frequency band (13-30Hz) is related to successful memory encoding (Hanslmayr, Staudigl, & Fellner, 2012). Beta power decreases over areas associated with task-related processing have frequently been shown to correlate with memory formation (Hanslmayr, Volberg, et al., 2011) and alpha/beta desynchronization has been suggested to reflect effective information processing (Hanslmayr, Staudigl, et al., 2012; Klimesch, 2012). However, the direct contribution of beta desynchronization in memory processes cannot be inferred from correlational studies alone. Whether these oscillatory patterns are causally involved in, or are a by-product of, memory formation remains unclear.

Non-invasive brain stimulation may be an effective way to address this issue. By affecting oscillatory activity in a predictable manner, transcranial brain stimulation may be used to shed light on the relationship between beta power decreases and episodic memory formation (Hanslmayr, Matuschek, & Fellner, 2014). This thesis seeks to identify ways in which non-invasive brain stimulation may be used to study the formation of episodic memories.

Research reported in this thesis set out to investigate how the electrophysiological underpinnings of episodic memory formation may be studied using non-invasive brain stimulation techniques. In doing so, this thesis investigates two key questions: What role do beta oscillations play in memory formation (i.e. causally) and indirectly therefore, can brain stimulation be used practically to test these causal mechanisms? The first part of this thesis (Chapters 2 and 3) investigates whether transient transcranial alternating current stimulation (tACS) applied in the beta frequency range can entrain beta oscillations and may therefore be a useful tool in investigations into the relationship between beta desynchronization and memory processes. In Chapter 2, two experiments will be reported in which we studied the effects of transient beta tACS on episodic memory formation. This chapter sought to examine whether tACS may be used as a suitable alternative or addition to rTMS. Chapter 3 further explored whether the stimulation parameters used in Chapter 2 would in general be effective in entraining beta oscillations. The latter part of this thesis (Chapter 4) demonstrates that slow rhythmic transcranial magnetic stimulation (rTMS) may be used to modulate memory formation by affecting beta power in remote areas.

The state of the field is such that we do not know the details of the causal relationship between beta oscillatory activity and episodic memory and how this

relationship may be studied using non-invasive brain stimulation. That is, whether increasing beta power impairs memory formation and whether decreasing beta power improves memory. To examine this, we used two different non-invasive brain stimulation techniques. tACS was used as a means to increase beta power and impair memory formation, while rTMS was used as a means of decreasing beta power thereby enhancing memory performance. This thesis therefore also examines whether these stimulation techniques can be used to influence underlying oscillatory activity in such a way to modulate episodic memory formation.

1. Episodic Memory

Memory is the fundamental ability underlying the storage, organization, recovery, and use of information. We rely on memory when learning facts and acquiring new skills (Sherry & Schacter, 1987). It forms the basis of crucial processes including the remembering of personal experiences, the learning of motor skills or the recognition of objects (Haberlandt, 1999). Long-term memory has traditionally been divided into different subsystems separating non-verbal procedural memories from verbal memories (Schacter & Tulving, 1994). Non-verbal or implicit memory operates without conscious awareness or intention. It incorporates our ability to undertake motor tasks and includes conditioned reactions (Squire, 2004). Explicit or verbal memory can further be divided into two different systems. While semantic memory refers to the knowledge of learned facts, episodic memory consists of memories for specific events and experiences (Tulving, 1972).

Episodic memory refers to the remarkable ability to mentally travel backwards in time to reconstruct a past event and re-experience this episode (Tulving, 2002). Episodic memories are associative and replete with detail. Episodic memory contains information about a specific event that occurred in a certain place,

and time, and centres around the person themselves (Tulving, 1984). Hence, memory traces containing this information have to be formed so that the information can be accessed when needed – this process refers to episodic memory encoding or formation (Tulving, 1984). In order to enable effective storage of an event, it has to be processed and represented sufficiently (Paller & Wagner, 2002). This is accomplished by neocortical areas processing different sensory and semantic aspects of an event (Hanslmayr et al., 2016). This important step can determine how likely it is that the episode will be remembered. The "depth" of encoding determines the probability that information will be subsequently recalled (Craik & Lockhart, 1972). And so, processes that take place during encoding contribute to the formation of episodic memories. Exactly how this complex task of forming episodic memories is accomplished is an ongoing field of research.

1.1 Episodic Memory Formation

Episodic memory relies on the effective formation of detailed memory traces (Tulving, 1984). This requires that the content of the event is processed and represented to a sufficient degree (Paller & Wagner, 2002). Hence, successful episodic memory formation relies on stimulus-specific processing in the encoding stage (Hanslmayr et al., 2016). Several brain areas have been found to be involved in these processes. While encoding of non-verbal material has mostly been linked with activity in right frontal regions (Brewer et al., 1998; Kelley et al., 1998), verbal episodic memory formation has been associated with left frontal activation (Kim, 2011). In a comprehensive meta-analysis, Kim (2011) determined brain areas associated with memory formation. By analysing data from 74 published fMRI studies the author found that especially the left inferior frontal gyrus (IFG), a brain

area involved in semantic processing of verbal material (Otten, Henson, & Rugg, 2001), contributes to the successful formation of verbal memories. Hence, brain areas involved in the processing of stimulus-specific information are also tightly associated with forming episodic memories for these stimuli.

1.1.1 Beta Power Decreases and Episodic Memory Formation. Episodic memory formation of verbal material has been linked to left prefrontal activation (Kim, 2011). Oscillatory activity in similar regions has also been found to correlate with successful memory formation (Hanslmayr, Volberg, et al., 2011). Brain oscillations represent periodic changes in the local field potential and are assumed to play a crucial role in shaping synaptic plasticity by establishing synchronous firing patterns (Hanslmayr et al., 2016; Hanslmayr, Staudigl, et al., 2012). Therefore, they are key to successful memory encoding and play an important part in memory reactivation (Fell & Axmacher, 2011).

Concerning episodic memory, most research has focused on synchronisation and its role in memory formation. Power increases in the theta (~4-7Hz) and gamma (>40Hz) bands, in particular, have been associated with memory function (Düzel, Penny, & Burgess, 2010; Hanslmayr, Staudigl, et al., 2012; Nyhus & Curran, 2010). Nyhus and Curran (2010) proposed that theta and gamma synchronization supports encoding and retrieval of episodic memories by promoting communication between cortical and hippocampal regions. According to their framework gamma oscillations act as a binding mechanism in the cortex as well as between the cortex and the hippocampus, while theta oscillations order the memory representations temporally and may exert top-down control. Apart from synchronised activity, power decreases reflecting local desynchronization (Pfurtscheller & Lopes da Silva, 1999) have also

been found to play a crucial role in episodic memory processes (Klimesch, Doppelmayr, & Hanslmayr, 2006). Desynchronized activity in the alpha (8-12Hz) and beta (13- 30Hz) bands especially have been shown to correlate with episodic memory performance (Hanslmayr, Staudigl, et al., 2012). Several studies have shown that power decreases in the alpha/beta frequency range are not only rapidly reactivated during memory retrieval (Waldhauser, Braun, & Hanslmayr, 2016) but also predict successful memory encoding (Hanslmayr, Spitzer, & Bäuml, 2009). Beta oscillations in particular have been implicated in episodic memory formation (Griffiths, Mazaheri, Debener, & Hanslmayr, 2016; Scholz, Schneider, & Rose, 2017). Beta desynchronization has been observed in regions associated with task performance (Meeuwissen, Takashima, Fernández, & Jensen, 2011) and correlates with BOLD activity in stimulus-processing areas during successful memory formation (Hanslmayr, Volberg, et al., 2011). Hanslmayr and colleagues (2011) localized beta power decreases during successful verbal memory encoding to the left inferior frontal gyrus (IFG), a region which has been linked to semantic processing and successful semantic memory encoding in numerous studies (Kim, 2011).

Episodic memory formation relies on the representation of stimulus-specific information (Paller & Wagner, 2002). It has been suggested that desynchronized activity is particularly important for stimulus processing and memory formation (Hanslmayr et al., 2016). By desynchronizing local neural assemblies, beta power decreases are assumed to enhance the memory system's information coding capacity (Brittain & Brown, 2014; Hanslmayr, Staudigl, et al., 2012). Hanslmayr and colleagues (2012) examined the relationship between information richness, synchrony, and neural firing rate by simulating firing rates of neural populations under different levels of synchrony. Applying Shannon's Entropy as a measure of

information richness (Shannon & Weaver, 1949), the authors could demonstrate that the more a local neural assembly is desynchronized the more information is encoded in the spiking pattern. Hence, cortical areas involved in stimulus processing may code stimuli more efficiently and may be able to represent information in more detail during periods of low synchrony (Hanslmayr et al., 2016). Therefore, beta power decreases, reflecting cortical areas actively processing information, may be key for the successful formation of episodic memories (Klimesch et al., 2006).

The above review highlights the importance of desynchronized oscillatory activity for memory processes. The formation of long-lasting episodic memories relies on events to be represented with sufficient detail and information to be processed in its entirety (Paller & Wagner, 2002). Beta power decreases have been linked to neural firing and have also been shown to occur over task relevant areas (Hanslmayr, Volberg, et al., 2011; Hanslmayr, Staudigl, et al., 2012). Hence, desynchronized oscillatory activity in the beta frequency band is thought to represent stimulus-specific information processing and may therefore contribute to the formation of highly specific memory traces (Hanslmayr et al., 2016).

1.2 Conclusion

Event-related beta desynchronization occurs over areas actively involved in stimulus processing and correlates with memory performance (Hanslmayr, Volberg, et al., 2011). However, the direct contribution of beta power decreases to the memory formation process remains underspecified. Non-invasive brain stimulation techniques could be used to relate memory formation to beta desynchronization more directly.

2. Non-Invasive Brain Stimulation

Beta power decreases have been proposed to contribute to the formation of memory traces by enabling cortical areas to represent stimuli more efficiently (Hanslmayr, Staudigl, et al., 2012). These oscillatory correlates of memory formation have been identified using the so-called *subsequent memory paradigm* (Brewer et al., 1998; Paller, McCarthy, & Wood, 1988; Paller et al., 1987). This technique allows researchers to dissociate brain regions and activity patterns that may be involved in forming episodic memories from unrelated neural activity. Activity during encoding trials of items that will later be remembered is contrasted with encoding activity for items that will be forgotten. Any activity patterns that differ between these two conditions is thought to reflect processes involved in successful memory formation. While important insights have been gained from these analyses, it cannot be inferred whether this activity is crucial for memory formation or whether it is merely an epiphenomenal by-product of other activity. Non-invasive brain stimulation methods may provide a way to manipulate brain function and therefore to test the causal impact of beta oscillations on memory formation (Thut, Miniussi, & Gross, 2012).

Non-invasive brain stimulation is a term that refers to a variety of different techniques. They share the common feature of safely stimulating cortical regions, thereby interfering with brain function from the surface of the scalp, without the need for invasive manipulation (Thut et al., 2017). The overall aim when applying non-invasive stimulation techniques is to change brain activity in a specific way and measure the outcome of this change. As a result, these techniques enable researchers to draw causal conclusions about the relationship between neural function and

cognition (Taylor, Walsh, & Eimer, 2008). Non-invasive brain stimulation methods can crudely be divided into magnetic and electrical stimulation techniques.

2.1 Transcranial Magnetic Stimulation

One of the most well-established and frequently used non-invasive brain stimulation techniques is transcranial magnetic stimulation (TMS) (Walsh & Cowey, 2000). Barker and colleagues were among the first to describe the use of TMS for human cortical stimulation (Barker, Jalinous, & Freeston, 1985). Since then, TMS has been used extensively in a variety of studies investigating human cortical and cognitive function; indeed, it has even been considered for therapeutic intervention in a variety of disorders (for a review see Wassermann & Lisanby, 2001). TMS can be applied without thorough preparation of the human scalp. The stimulation is delivered by passing electrical currents through the TMS coil, thereby inducing strong magnetic fields that can penetrate the skull and induce electrical currents in cortical regions of the brain. These electrical currents modulate underlying neural activity by depolarizing membrane potentials and eliciting action potentials (Walsh & Cowey, 2000). Hence, TMS influences neural firing directly and is strong enough to interfere with ongoing brain activity (Allen, Pasley, Duong, & Freeman, 2007).

To study the relationship between brain oscillations and cognitive function, TMS can also be applied rhythmically. The application of several TMS pulses at a certain frequency has been proposed to modulate ongoing oscillatory activity (Thut, Schyns, & Gross, 2011). Rhythmic TMS (rTMS) can be used to entrain brain oscillations in order to investigate the causal relevance of oscillatory activity in a given region for behavioural outcomes (Thut, Veniero, et al., 2011). Furthermore, TMS can be used not only to modulate cortical function by entrainment of brain

oscillations, it can also be applied in ways that enhance or inhibit cortical areas in general, and it is a useful tool to measure cortical excitability (Kobayashi & Pascual-Leone, 2003). TMS can further be used to investigate network functions (Bortoletto, Veniero, Thut, & Miniussi, 2015). It has been shown that TMS pulses can not only influence activity in the stimulated regions, but also affect anatomically or functionally connected remote areas (Min et al., 2016; Pascual-Leone, Walsh, & Rothwell, 2000). For example, by applying rTMS to an area that has known functional connections with the hippocampus, Wang and colleagues (2014) were not only able to strengthen the connectivity between these regions, but to boost memory performance as a function of this enhanced connectivity. The authors applied 20 min. of 20Hz rTMS (2s stimulation, 28s no stimulation) to the left lateral parietal cortex over five days. This resulted in enhanced functional connectivity between the stimulated region and the hippocampus as well as enhanced associative memory performance compared to sham stimulation. Hence, rTMS has the potential to enhance memory performance and may be used to induce remote effects that contribute towards changes in behaviour (Pascual-Leone et al., 2000).

TMS has been demonstrated to be a useful technique to study the brain-behaviour relationship. However, as with any technique, TMS has its limitations. TMS and rTMS in particular have given rise to concerns over their safety which must be considered by experimenters prior to their utilization (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). For example, rTMS at certain frequencies can only be applied for limited periods of time and should not be used at higher frequencies (i.e. ~>20Hz). Stimulation at higher frequencies, in particular, has been reported to cause pain arising from peripheral muscle and nerve stimulation, and can lead to distracting muscle twitches when applied to certain areas (Rossi et al., 2009; Tik et

al., 2017). These side effects, together with the sounds that are produced by the stimulator, provides potential sources of confounds and present a challenge to researchers when constructing control conditions – blinding participants to conditions is difficult. Newly developed non-invasive brain stimulation techniques have been proposed which may overcome these issues (Herrmann, Rach, Neuling, & Strüber, 2013). For example one alternative to rTMS involves alternating electrical current stimulation.

2.2 Transcranial Alternating Current Stimulation

Stimulating the brain using electricity is not a novel idea (see for example Merton, Hill, Morton, & Marsden, 1982). However, it has recently regained popularity and is now considered to be an established way to safely stimulate the brain (Nitsche et al., 2008). Transcranial electrical stimulation (tES) is a term summarising a variety of techniques. tES refers to techniques in which weak electrical currents are passed between at least two electrodes attached to the scalp. The application of direct current (tDCS) has been shown to affect the membrane potential of underlying cortical tissue. Depending on the polarity of the current, tDCS may increase (anodal tDCS) or decrease (cathodal tDCS) the likelihood of neuronal firing and therefore affects cortical excitability (Nitsche & Paulus, 2000). Transcranial alternating current stimulation (tACS) has emerged as a new tool that can be used to investigate the causal role that brain oscillations play in certain cognitive processes (Herrmann et al., 2013).

By alternating the current between two electrodes at certain frequencies, tACS is thought to entrain brain oscillations (Herrmann et al., 2013). tACS has been shown to modulate the amplitude (Helfrich, Schneider, et al., 2014) and frequency of

ongoing neural activity (Vosskuhl, Huster, & Herrmann, 2015), affect synchronization between brain regions (Helfrich, Knepper, et al., 2014; Stonkus, Braun, Kerlin, Volberg, & Hanslmayr, 2016), and modulate behaviour accordingly (Antal & Herrmann, 2016). As tACS does not produce distracting sounds or cause painful muscle or nerve stimulation, finding suitable control conditions is considered easier than for rTMS experiments (Herrmann et al., 2013). Moreover, stimulation with higher frequencies is also possible, making tACS a potentially useful stimulation technique for experimental research (Antal & Paulus, 2013). Since neural firing has been shown to synchronize with externally applied rhythmic electrical stimulation (Ozen et al., 2010), tACS is not only a relatively experimenter-friendly technique, but presents a promising method for studying the relationship between oscillatory activity and cognitive function (Herrmann, Strüber, Helfrich, & Engel, 2015). However, recent studies have criticised the effectiveness of tACS in entraining brain oscillations (see for example Lafon et al., 2017), making it important to further understand when and how this method can be a used in cognitive research.

2.3 Conclusion

tACS and rTMS are useful techniques for non-invasively stimulating cortical areas, modulating behaviour, and may ultimately contribute to our understanding of the relationship between oscillatory activity and cognitive function. Although the oscillatory correlates of memory formation are well known it remains for future research to go beyond correlative evidence if the field is to learn more about the relationship between beta power decreases and episodic memory. tACS and rTMS

are useful, promising techniques which may provide more information about this relationship.

3. Overview of the Thesis

Increasing evidence emerges that oscillatory activity accompanies successful memory encoding and represents stimulus processing (Hanslmayr et al., 2016). Power decreases, in the beta frequency band in particular, have been linked to successful encoding of verbal material (Griffiths et al., 2016; Hanslmayr, Volberg, et al., 2011; Hanslmayr et al., 2009; Hanslmayr, Staudigl, et al., 2012). However, whether these power decreases are causally involved in the memory formation process remains elusive. Non-invasive brain stimulation could help to overcome this issue. rTMS as well as tACS have emerged as techniques capable of entraining brain oscillations and changing behavioural outcomes accordingly (Herrmann et al., 2015; Thut, Schyns, et al., 2011).

Modulating brain oscillations in a controlled way and measuring changes in behaviour would be an important step when aiming to understand how oscillatory activity is related to episodic memory formation. A recent rTMS study addressed this issue (Hanslmayr et al., 2014). Hanslmayr and colleagues applied rTMS to the left inferior frontal gyrus (IFG) of participants while they were engaged in a list-learning paradigm. During each encoding-retrieval run, participants were presented with a list of 20 words. 18 pulses of rTMS were delivered 500ms after word-onset to the left IFG at three different frequencies (beta, alpha, and theta). After a short distractor, participants were asked to freely recall any item they could remember from this run. Only stimulation at beta had an effect on memory performance. The findings suggest that beta desynchronization in the left IFG is indeed crucial for encoding of verbal material. Artificially synchronizing (i.e. entraining) the left IFG with beta during memory encoding – and hence preventing desynchronized activity in this frequency

band – led to decreased memory performance compared to all other conditions. These results strongly suggest a causal relationship between beta oscillations in the prefrontal cortex and verbal memory encoding, and support the notion that decreased oscillatory activity is more than a mere by-product of memory formation. However, the details of this relationship, causal or otherwise, remain unclear.

Hanslmayr and colleagues demonstrated in a list-learning paradigm that higher beta power in the left IFG during verbal memory encoding is deleterious for subsequent remembering. Although participants were instructed to utilize certain encoding strategies (i.e. deep vs. shallow encoding) the nature of the task itself casts doubt on whether participants used only these strategies. The free recall paradigm deployed in their study consisted of several encoding-retrieval runs. Participants would have been aware of the nature of the task after the first run since it involved recalling previously viewed items and may have employed other strategies than those expressed by the experimenter. A more sensitive measure of memory strength, such as recognition paradigms, may be used instead in order to investigate whether the results obtained by Hanslmayr and colleagues (2014) can be obtained when encoding strategies are controlled for more stringently (Lockhart & Craik, 1990).

Furthermore, it remains unclear whether the interfering effects of rTMS are specific to the beta frequency band. Hanslmayr and colleagues stimulated with beta as well as two control frequencies (10.7Hz, 6.8Hz). Though supported by electrophysiological studies linking beta power to memory performance, it remains unclear whether higher stimulation frequencies might have similar, or even stronger, effects on memory performance. The specificity of beta stimulation with rTMS is therefore unknown.

Hanslmayr and colleagues haven shown that beta power increases are detrimental to episodic memory formation (Hanslmayr et al., 2014). Although this might support the notion that beta power decreases are necessary for memory encoding, more research is needed to support this claim. Therefore, it remains for further studies to provide more evidence linking beta desynchronization and episodic memory formation directly.

The present thesis seeks to address this. To do so it will explore whether different ways of applying non-invasive brain stimulation can be used to evaluate the link between beta oscillatory activity and long-term memory formation. Chapters 2 and 3 investigated whether transient tACS could be used to study the causal relationship between beta power and memory formation. By delivering event-related transient tACS in Chapter 2, we attempted a conceptual replication of the effects reported in Hanslmayr, et al. (2014) and sought to identify whether tACS is a suitable alternative to rTMS. The studies reported in Chapter 2 were designed to investigate whether inducing beta oscillations in the IFG using tACS specifically impairs memory performance in a recognition paradigm. The specific effects of beta stimulation were explored by using two higher control frequencies in addition to the same frequencies used by Hanslmayr and colleagues. Since tACS is an exciting and relatively new technique, we aimed to investigate whether tACS would be a useful tool for cognitive research when applied for short durations. During successful memory formation, beta power decreases occur within milliseconds of stimulus presentation and may last for 1-1.5s (Hanslmayr, Volberg, et al., 2011). To be able to interfere with this process only, we applied beta tACS for brief periods during stimulus presentation.

Oscillatory activity associated with cognitive tasks shows highly dynamic behaviour, and although these dynamics can be studied under constant stimulation (as has been mostly done previously), we investigated whether tACS can be used to modulate cognitive function (in Chapter 2) and motor cortex excitability (in Chapter 3) when applied over similar time scales using different stimulation parameters. In Chapter 2 we investigated the effect of different electrode sizes and stimulation intensities, whereas in Chapter 3 we explored whether different electrode montages would have an impact on transient beta tACS's ability to entrain brain oscillations. Findings from Chapters 2 and 3 indicate that transient tACS delivered in the beta frequency range might not be an effective means of studying the link between dynamic oscillatory processes and episodic memory formation. In Chapter 2, 2s of beta tACS did not modulate episodic memory formation. Likewise in Chapter 3, 10s of beta tACS did not have an effect on MEP size.

Chapter 4 concerns itself with whether there may be a means by which lower beta power could be induced using non-invasive brain stimulation. In a simultaneous EEG-TMS experiment, we found that slow rTMS induces not only beta power decreases, but also a stimulus-specific modulation of beta power which is beneficial for memory encoding. More specifically, we showed in two experiments that 1Hz rTMS applied to the left DLPFC during encoding of verbal material enhances memory performance.

Taken together, this thesis explores the means by which various kinds of brain stimulation may be used to study the relationship between beta oscillations and memory formation. It concludes that negative results are not only important, but necessary in order to advance our understanding of how transcranial brain

stimulation can help us unravel the electrophysiological underpinnings of episodic memory formation.

CHAPTER 2: TRANSIENT BETA TACS DOES NOT MODULATE EPISODIC MEMORY FORMATION

During cognitive tasks, brain oscillations show a highly dynamic behaviour. For instance beta oscillations decrease in power within a couple of milliseconds during memory processing. If tACS should be useful for addressing causal questions about these dynamics it must influence brain oscillatory behaviour in a similar time range. In a series of experiments we investigated whether event-related, transient tACS in the beta frequency range can be used to modulate the formation of episodic memories. The current chapter sought to replicate and extend findings from a recently published rTMS study. 72 healthy human participants engaged in an incidental encoding task of verbal and non-verbal material while receiving tACS to the left and right inferior frontal gyrus (IFG) at 6.8Hz, 10.7Hz, 18.5Hz, 30Hz, 48Hz, and sham stimulation, for 2s during stimulus presentation. Our findings are consistent with the notion that event-related, transient tACS in the beta frequency range cannot be used to modulate episodic memory formation.

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1. Introduction

Brain oscillations represent rhythmic fluctuations in the local field potential and play a crucial role in establishing synchronous firing patterns (Fries, 2005). Especially oscillations in the beta frequency range (~13-30Hz) have been linked to a variety of cognitive and sensorimotor processes (Brittain & Brown, 2014; Hanslmayr, Staudigl, et al., 2012; Kuhlman, 1978; Pfurtscheller, 1992; Pfurtscheller, Neuper, Andrew, & Edlinger, 1997). Beta power decreases, for example, have been shown to predict successful memory encoding (Hanslmayr et al., 2009). Desynchronized activity in the beta band is negatively correlated with BOLD activity (Hanslmayr, Volberg, et al., 2011) and occurs in areas associated with task-related processing (Meeuwissen et al., 2011). Despite the numerous associations between episodic memory and beta oscillations, the causal relationship between them remains unclear.

Transcranial alternating current stimulation (tACS), an increasingly popular non-invasive human brain stimulation technique (Herrmann et al., 2013), has been proposed to enable exploration of the causal links between brain oscillatory activity and cognitive processes. Recent findings suggest that tACS entrains brain oscillations in a frequency specific way (Helfrich, Schneider, et al., 2014; Witkowski et al., 2015). This modulation of underlying oscillatory activity can affect behaviour (Jaušovec & Jaušovec, 2014; Jaušovec, Jaušovec, & Pahor, 2014; Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012; van Driel, Sligte, Linders, Elport, & Cohen, 2015), interacts with underlying oscillatory activity (Brittain, Probert-Smith, Aziz, & Brown, 2013; Feurra et al., 2013; Neuling, Rach, & Herrmann, 2013; Schmidt,

Iyengar, Foulser, Boyle, & Fröhlich, 2014; Zaehle, Rach, & Herrmann, 2010), and elicits frequency specific neuronal spiking (Ali, Sellers, & Fröhlich, 2013).

tACS could be an efficacious and powerful method in cognitive research, if it can be used to modulate brain oscillations in a time-critical way (Ruhnau, Keitel, Lithari, Weisz, & Neuling, 2016; Stonkus et al., 2016). During cognitive tasks brain oscillations exhibit dynamic behaviour and are modulated in the range of seconds. Indeed, brain activity associated with memory processes may occur for 1s to 1.5s after stimulus onset (Otten & Rugg, 2001a; Paller et al., 1987). Moreover, beta power, which would seem to play a key role, desynchronizes during episodic memory encoding within milliseconds of stimulus presentation (Hanslmayr, Volberg, et al., 2011). Although Ali and colleagues (2013) successfully showed that tACS may be used to entrain brain oscillations within the order of seconds in computational models and ferrets, most studies that have demonstrated effects of tACS on behaviour in humans have applied tACS during cognitive tasks in a more sustained way. This has resulted in stimulation durations of up to 20min (Helfrich, Schneider, et al., 2014; Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Neuling et al., 2013; Polanía et al., 2012; van Driel et al., 2015; Zaehle et al., 2010), making it difficult to interpret the specifics of the relationship between cognitive function and oscillatory activity. In order to demonstrate that tACS is indeed a useful tool for modulating, and thereby investigating, the oscillatory basis of dynamic cognitive processes, tACS should be administered for brief periods during specific phases of cognitive tasks in event-related, randomized designs.

1.1 Aim of this Chapter

In the present chapter we sought to investigate the effectiveness of event-related transient beta tACS. In two experiments we explored whether tACS in the beta frequency range is effective in modulating episodic memory formation.

Using rhythmic transcranial magnetic stimulation (rTMS), Hanslmayr and colleagues (Hanslmayr et al., 2014) explored the role of beta oscillations in the left IFG during memory encoding. By artificially synchronizing the left IFG via rTMS in the beta frequency range, memory formation for words was impaired at beta but not at other frequencies. These findings provide a first causal link between beta power decreases and episodic memory. However, due to safety considerations (Rossi et al., 2009; Wassermann, 1998) rTMS stimulation could not be applied at higher frequencies, and hence the effects of rTMS stimulation at higher frequencies was not investigated. Therefore in the present chapter, we sought to replicate and extend these findings, and examine in greater depth whether tACS may be a used in addition to rTMS. Hanslmayr and colleagues (2014) used a free-recall task; in order to extend their findings while ensuring that encoding processes were controlled across subjects, we used an incidental encoding task incorporated in a recognition paradigm. Participants were aware that their ability to recall stimuli would be tested in the free-recall paradigm used by Hanslmayr et al. (2014), hence the incidental encoding task reported in this chapter allowed for better control of encoding strategies and may be considered a more sensitive measure of memory strength (Hanslmayr & Staudigl, 2014). The effects of beta tACS administered to the IFG on encoding of verbal and non-verbal material were investigated over two experiments. Several studies report material-specific lateralization during episodic memory

encoding with left frontal involvement during encoding of verbal material and right frontal activation for non-verbal material (Floel, 2004; Kelley et al., 1998; Kim, 2011). In two experiments we applied tACS at five different frequencies (6.8Hz, 10.7Hz, 18.5Hz, 30Hz, 48Hz) to the left and right IFG in an event-related design. The only differences between experiments 1 and 2 were electrode size and stimulation intensity, enabling comparisons of the relative contributions of these parameters to outcome. In both experiments participants were engaged in an incidental encoding task of verbal and non-verbal material and tACS was applied with stimulus onset for 2s. In each experiment the stimulation frequency and the stimulation site were selected randomly on a trial-by-trial basis. Given the preponderance of studies linking beta power decreases to successful memory formation, we hypothesized that beta (18.5Hz) tACS should only affect memory performance for words when administered to the left IFG (as has been shown by Hanslmayr et al. using rTMS) while right IFG stimulation should result in decreased memory performance for non-verbal material only.

2. Material and Methods

2.1 Participants

Participants were screened for contraindications against transcranial alternating current stimulation prior to the experiment (Poreisz, Boros, Antal, & Paulus, 2007). 36 subjects participated in experiment 1 (24 female; mean age: 20.03 +/- 2.38 years) and 36 in experiment 2 (24 female, mean age: 20.97 +/- 2.22 years). All participants were right handed, had normal or corrected-to-normal vision and reported no history of neurological disease or brain injury. Informed consent was acquired from each subject prior to the experiment. All were naive to the hypotheses

of the study and were fully debriefed at the end of the experiment. The study was approved by the ethics committee of the University of Birmingham.

2.2 Stimulus Material

Word stimuli consisted of 270 nouns derived from the MRC Psycholinguistic Database, Version 2.00 (Coltheart, 1981) and were presented in black. These were divided into 18 lists of 15 words and were matched for word frequency, word length, number of letters, number of syllables, concreteness, and imaginability. Face stimuli consisted of 270 faces drawn from several face databases. The faces were emotionally neutral and were presented in black and white on a black background. These were divided into 18 lists of 15 stimuli and were matched for gender, hair colour, and approximate age. Stimuli were presented in a randomized order, and counterbalanced across subjects. 360 stimuli (180 words, 180 faces) were presented during encoding and retrieval, serving as old items in the retrieval period, 180 stimuli (90 words, 90 faces) were presented during retrieval only, serving as new items (Figure 1).

2.3 Experimental Setup and Procedure

Participants were seated approximately 80cm from a 19 inch LCD monitor (resolution: 1280 X 1024 pixels, 60Hz frame rate). Stimuli were presented on a grey background on the centre of the screen using the Psychophysics Toolbox extension for Matlab (Brainard, 1997). Before the start of the main experiment participants were familiarized with tACS and desensitized to the stimulation intensity in order to avoid adverse reactions.

2.3.1 Encoding. During encoding, participants had to perform a pleasantness rating of a presented stimulus on a 4-point rating scale (very pleasant – very unpleasant). Answers were given manually by pressing one of four buttons on a computer keyboard using the middle and index finger of both hands; whether the left or right hand corresponded to the *pleasant* or *unpleasant* category was counterbalanced across subjects (Figure 1A). Starting with stimulus onset, tACS was administered to the left and right IFG at different frequencies throughout the 2s stimulus presentation. In order to replicate and extend the findings from Hanslmayr et al. (Hanslmayr et al., 2014), tACS was applied at 18.5Hz. Furthermore, the two control frequencies used in Hanslmayr et al. (Hanslmayr et al., 2014) (6.8Hz, 10.7Hz) plus two higher frequencies (30Hz, 48Hz) as well as sham stimulation were chosen as controls, resulting in 15 trials per condition. The sequence of the stimulation conditions was counterbalanced across subjects and pseudo randomized so that the same frequency and the same stimulation site did not occur in more than four consecutive trials.

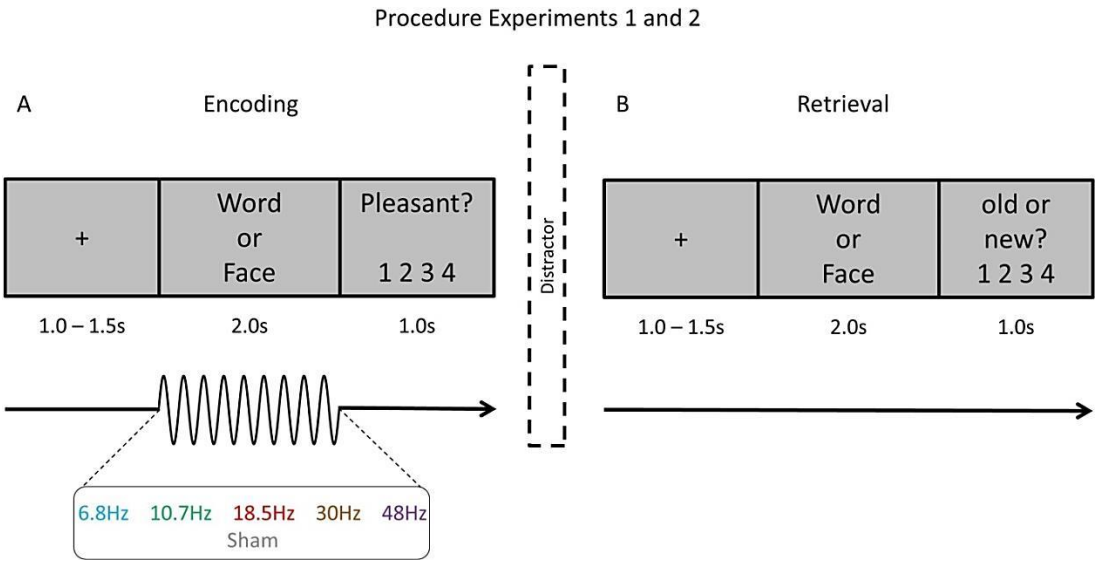

Figure 1. Experimental design Chapter 2. 360 stimuli (180 words, 180 faces) were presented during the encoding block (A). Participants had to rate the pleasantness of a stimulus on a 4-point rating scale (very pleasant – very unpleasant). During the 2s stimulus presentation, tACS was administered to the left and right IFG at 6.8Hz, 10.7Hz, 18.5Hz, 30Hz, 48Hz, as well as sham stimulation. The material was counterbalanced across subjects so that every stimulus was paired with every stimulation condition equally often throughout the experiment. During the retrieval block (B) the 360 stimuli presented during encoding as well as 180 new items (90 words, 90 faces) were shown. Subjects were asked to rate their confidence of an item being old or new on a 4-point rating scale (very sure old - very sure new).

2.3.2 Retrieval. Following the encoding section, two distractor tasks were used to ensure that participants did not rehearse the study material. First, participants were required to count aloud backwards in steps of seven from a 3-digit number for 1min, after which time they were asked to rate the intensity of the stimulation induced sensations and phosphenes for every stimulation condition separately. Phosphene and intensity ratings collapsed over both experiments can be found in

Appendix C. These tasks were followed by the recognition phase. Here, the 360 items presented during encoding, along with 180 new items were presented in a randomized sequence. Subjects were asked to rate how confident they were that an item was old or new on a 4-point rating scale ranging from *very sure old* to *very sure new* (Figure 1B). Answers were given manually by pressing one of four buttons on a computer keyboard using the middle and index finger of both hands; whether the left or right hand corresponded to *old* or *new* items was counterbalanced across subjects.

2.3.3 Transcranial Alternating Current Stimulation. In order to investigate the effects of electrode size while keeping the current density underneath the electrodes, and possible skin sensations, comparable, experiments 1 and 2 only differed with respect to electrode size and stimulation intensity. In experiment 1, the stimulation was applied via four donut-shaped rubber electrodes with a diameter of 5cm (14 cm^2, NeuroConn, Ilmenau, Germany) at an intensity of 1mA (2mA peak to peak). In experiment 2, the stimulation was applied using round rubber electrodes with a diameter of 3.7cm (10.75 cm^2, NeuroConn, Ilmenau, Germany) at an intensity of 0.8mA (1.6mA peak to peak). The resulting estimated current density in the skin underneath the electrodes was in both experiments of approximately 0.07mA/cm^2. Transcranial alternating current stimulation was delivered via a 4 channel DC Stimulator MC (NeuroConn, www.neuroconn.de). In both experiments, the stimulation electrodes were placed at EEG electrode positions FP1, C5, FP2, C6 (Figure 2). These positions were selected using a neuro-targeting software (Soterix Medical Inc, New York, USA) which uses a finite-element model of a template adult brain to model the current distribution in the brain. Stimulation sites were chosen to result in the highest target field intensity in the left inferior frontal gyrus (Figure 2A).

In order to keep the sensations equal between stimulation conditions, the placement for the right IFG stimulation was derived by mirroring the montage for the left IFG stimulation onto the right hemisphere (Figure 2B). Impedances were kept below 5kOhm using Ten20 conductive paste (Weaver and Company, Aurora/Colorado). In both experiments, tACS was applied at 6.8Hz, 10.7Hz, 18.5Hz, 30Hz, and 48Hz for 2s at stimulus onset during encoding (see Figure 1). Additionally, sham stimulation was applied. During sham stimulation, the current was ramped up and down at the beginning and at the end of the 2s stimulation period for around 300ms in all of the five stimulation frequencies.

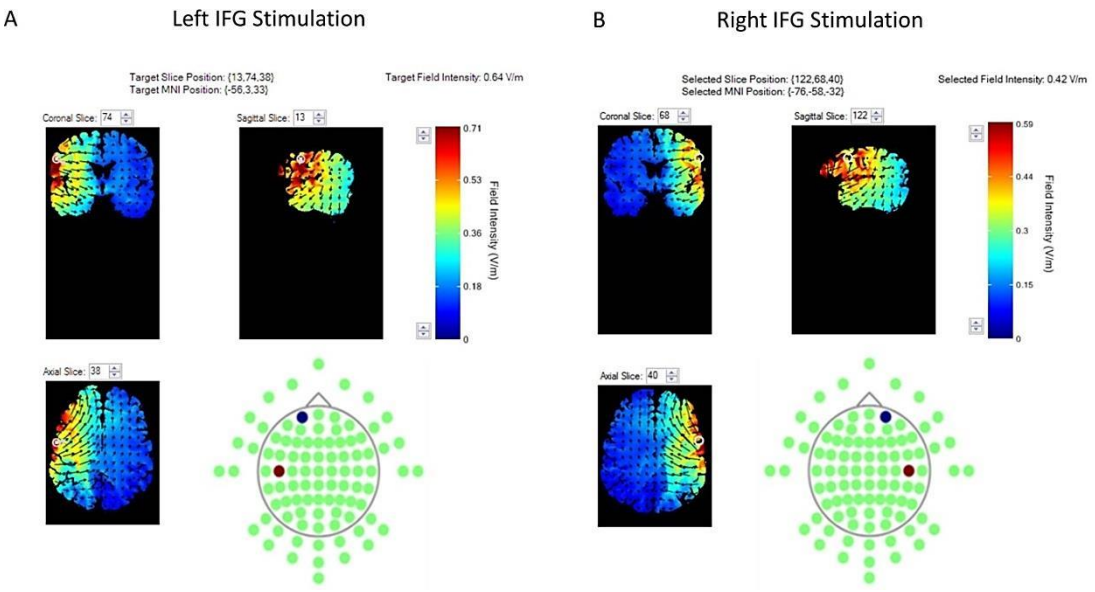

Figure 2. Stimulation electrode configurations for the left inferior frontal gyrus (A) and right inferior frontal gyrus (B). Optimal electrode placement for the left IFG (BA 9) was mirrored onto the right hemisphere. Current field intensity is shown using a finite-element model, provided by Soterix Medical Inc. The field intensities are shown for a stimulation of 2mA, whereas in the present experiments stimulation intensities of 1mA and 0.8mA were used.

2.4 Data Analysis

Correctly identified old stimuli (*hits*) were classified using a receiver operating characteristic (ROC) procedure. In order to control for individual response biases, every subject's neutral response criterion was determined indicating which buttons a participant used for an old response and thus providing a bias free measure of memory strength (Hanslmayr et al., 2009). This was accomplished by plotting the diagonal between a hit rate of 1 and false alarm rate of 1 in addition to each subject's ROC curve. If the false alarm rate of a given button was lower than the crossing point of the diagonal and the ROC curve, old items associated with this button were classed as hits. Likewise if the false alarm rate of a response was higher than the crossing point, old items associated with this response were classed as misses.

The effects of tACS on memory performance were investigated for verbal and non-verbal material separately using ANOVAs with the within-subjects factors *Stimulation Site, Stimulation Frequency,* and with the between-subjects factor *Experiment.* Bayesian analyses were also conducted in order to further investigate the amount of evidence for the null and alternative hypotheses (Rouder, Speckman, Sun, Morey, & Iverson, 2009; Verhagen & Wagenmakers, 2014).

3. Results

3.1 Memory Performance

As the stimulation was only administered during encoding, false alarm rates were the same across stimulation conditions. Nevertheless it is important to assess whether participants could in general discriminate between old and new items. General recognition accuracy (d') for sham stimulation demonstrated good memory performance in the verbal and non-verbal task (see Table 1). No difference between the experiments ($F(1,70) = 0.427$, $p = 0.515$) and no interaction between stimulus material and experiment ($F(1,70) = 0.787$, $p = 0.378$) could be found. In both experiments, words were remembered better than faces: $F(1,70) = 181.773$, $p < 0.001$.

Table 1
Recognition accuracy (d') for sham stimulation (collapsed over left and right stimulation) split by stimulus material and experiment

	Words	Faces
Experiment 1	2. 6221 (0.19457)	1.2582 (0.09565)
Experiment 2	2.8312 (0.17148)	1.2751 (0.08259)

Note. Standard errors appear in parentheses below d' values.

A 3-way ANOVA revealed no interaction between the stimulation frequency, stimulation site, and experiment for verbal material, $F(5,350) = 0.987$, $p = 0.426$. Hence, data of both experiments were merged into one dataset (Figure 3A). No interaction between stimulation frequency and stimulation site could be observed,

$F(5,350) = 1.7$, $p = 0.134$. We specifically expected a difference between left 18.5Hz stimulation and left sham stimulation (Hanslmayr et al., 2014). However, the t-test indicated no significant difference between these two conditions; $t(71) = 0.204$, $p = 0.839$.

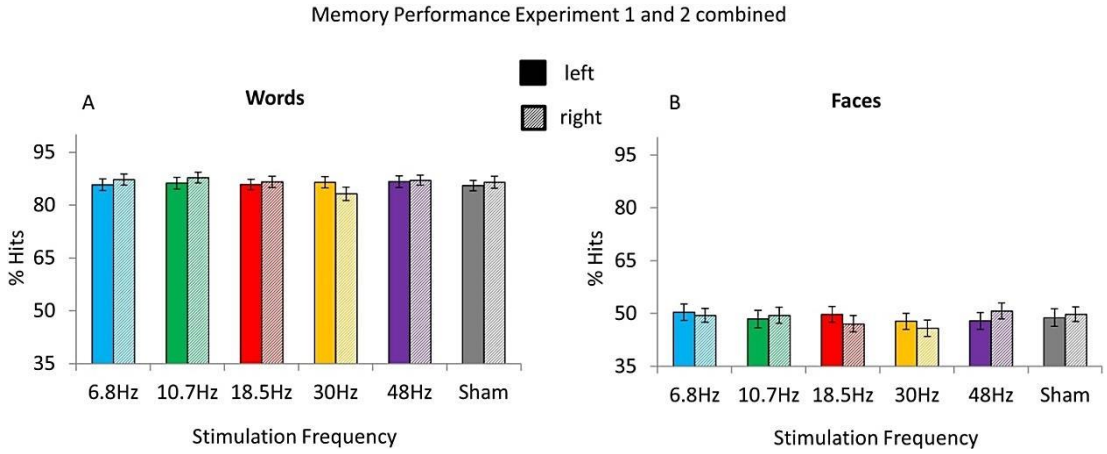

Figure 3. Memory performance for words (A) and faces (B) split by stimulation condition and stimulation site (data of experiments 1 and 2 combined). Bayesian t-tests indicate no difference in memory performance between left beta stimulation and left sham stimulation for words (A) and between right beta stimulation and right sham stimulation for faces (B). Error bars show standard errors of the mean.

A 3-way ANOVA for non-verbal material revealed no interaction between stimulation frequency, stimulation site, and experiment $F(5,350) = 0.992$, $p = 0.423$. Therefore, data of both experiments were also combined (Figure 3B). No interaction between stimulation frequency and stimulation site could be found, $F(5,350) = 1.11$; $p = 0.355$. There was no difference between right 18.5Hz stimulation and right sham stimulation; $t(71) = -1.377$, $p = 0.173$.

3.2 Bayesian Statistics

In contrast to Hanslmayr et al. (Hanslmayr et al., 2014), we did not find an effect of left beta stimulation on memory performance for verbal material. Likewise, we did not find effects of right beta tACS on memory performance for non-verbal material. However, traditional null-hypothesis testing cannot confirm the absence of an effect. Therefore Bayesian analyses were conducted (JASP Team (2016). JASP (Version 0.8.0.0)[Computer software]) (Rouder et al., 2009).

We specifically expected left 18.5Hz tACS to decrease memory performance for words while right 18.5Hz stimulation should have resulted in decreased memory performance for faces. To quantify evidence for equivalence between conditions, we computed a one-sided JSZ Bayes Factor comparing left 18.5Hz and sham stimulation with default prior scales (r = 0.707) for verbal material. This comparison revealed substantial evidence for the Null, BF_{01} = 8.98, demonstrating that the data were 8.98 times more likely under the null than under the alternative hypothesis. For non-verbal material, the one-sided JSZ Bayes Factor comparing right 18.5Hz and sham stimulation with default prior scales (**r** = 0.707) revealed anecdotal evidence for the Null, BF_{01} = 1.72, demonstrating that the data were 1.72 times more likely under the null than under the alternative hypothesis.

In showing evidence that left beta tACS did not have an effect on memory performance for words, our results conflict with the earlier demonstration by Hanslmayr and colleagues (2014) of a significant difference in memory performance for verbal material between left beta rTMS and sham stimulation. To provide a more direct test as to whether our findings failed to replicate this study, we also computed a Replication Bayes factor (Verhagen & Wagenmakers, 2014) that was calibrated to

quantify whether the present results are more congruent with no difference or with a difference comparable to that observed by Hanslmayr et al. (Hanslmayr et al., 2014). This comparison also revealed strong evidence in favour of the Null, BF_{01} = 11.89, suggesting that the present experiment has failed to replicate that earlier finding.

4. Discussion

In this chapter, we examined whether event-related, randomized tACS can be used to modulate beta oscillations during episodic memory formation. We specifically expected 18.5Hz tACS to decrease memory performance only for words when administered to the left IFG while right 18.5Hz stimulation should have resulted in decreased memory performance for non-verbal material only. Although similar protocols using rTMS were able to show that left beta stimulation impairs encoding of verbal material (Hanslmayr et al., 2014), the present study failed to show such an effect. Beta tACS did not modulate the formation of episodic memories when applied in a temporally sensitive, event-related, randomized manner. This could be partially due to the lower number of trials per condition in these experiments compared to the rTMS study. However, a considerably higher number of participants was tested in order to account for this. Additionally, Bayesian analyses revealed evidence for the null effect. Therefore, these results suggest that tACS in the beta frequency is not a suitable alternative to rTMS. As tACS affects neurons in a more subtle fashion than TMS (Nitsche et al., 2008), tACS might not be strong enough to interfere with underlying oscillatory activity in such a short period of time (Strüber, Rach, Neuling, & Herrmann, 2015).

Desynchronized oscillatory activity reflects active involvement of cortical areas during stimulus processing (Hanslmayr et al., 2016) and there is an abundance of studies linking desynchronization in the beta frequency range and episodic memory encoding. Especially semantic processing of verbal material is linked to activity in the left IFG which correlates with desynchronized activity in the beta frequency range and predicts the successful encoding of long-term memories (e.g. Hanslmayr, Volberg, et al., 2011; Hanslmayr, Staudigl, et al., 2012). Decreased beta power for successfully remembered items has even been reported when EEG was recorded outside the laboratory (Griffiths et al., 2016). Although a causal link between these processes has been demonstrated using rTMS (Hanslmayr et al., 2014), in the two studies presented here tACS did not affect memory performance. In experiment 1 stimulation electrodes with an unconventional shape were chosen. However, changing the electrodes and thus potentially increasing focality (while keeping the current density comparable) from experiment 1 to experiment 2 did not impact on memory performance. It remains therefore an open question whether beta power decreases in the prefrontal cortex play a causal role in episodic memory formation or whether they are a mere by-product of the process. The experiments presented in this chapter did not provide a clear answer to this question and, despite convincing correlational evidence presented earlier, it may be that beta desynchronization is not involved in the formation of episodic memories.

4.1 Conclusion

Stimulating the prefrontal cortex for 2s with beta tACS did not modulate episodic memory formation. However, from the present data we cannot infer with certainty whether beta power is not associated with memory formation or whether

tACS did not entrain brain oscillations in that area and is therefore not suitable for unravelling the causal relationship between transient beta oscillatory activity and cognitive function.

Chapter 3 will address this issue by further investigating the usefulness of tACS for cognitive research. There, a more direct means of quantifying the effectiveness of transient beta tACS in beta oscillation entrainment will be presented.

CHAPTER 3: TRANSIENT BETA TACS DOES NOT MODULATE MOTOR CORTEX EXCITABILITY

The current chapter addresses the question of whether 10s of beta tACS is sufficient to entrain brain oscillations in the primary motor cortex (M1). Beta phase over sensorimotor areas correlates with the size of motor evoked potentials and tACS over motor areas has been shown to modulate MEP amplitude. In order to examine whether transient beta tACS has the potential to entrain beta oscillations, we conducted a simultaneous tACS-TMS experiment. By administering tACS to M1 at the individual motor beta frequency for eight subjects, we investigated the relationship between the size of TMS induced MEPs and tACS phase. Investigating the effects of tACS on MEP size allowed us to quantify the effectiveness of transient beta tACS more directly than in Chapter 2. However, as in Chapter 2, we did not find any influence of beta tACS on behavioural outcomes. Our results revealed that MEP size was not modulated by tACS phase, indicating that our stimulation protocol did not entrain beta oscillations in M1.

This research was published in:

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1. Introduction

Beta oscillations are tightly linked to motor function (Pfurtscheller et al., 1997) with power and phase of beta oscillations influencing MEP size (Keil et al., 2014; Schulz, Ubelacker, Keil, Müller, & Weisz, 2014). The phase of beta oscillations over fronto-central areas, for example, correlates with the amplitude of motor evoked potentials (Keil et al., 2014). Furthermore, tACS at beta has been used to entrain beta oscillations in the motor cortex and influence MEP size accordingly (Feurra et al., 2011). In the experiment reported this chapter we aimed to investigate whether 10s of tACS tuned to the individual motor beta frequency can lead to a modulation of the amplitude of TMS evoked MEP by the tACS phase.

In Chapter 2 we reported a failure to show an effect of transient beta tACS on the formation of episodic memories. In the present study we explored the effectiveness of transient beta tACS in a simultaneous tACS-TMS experiment. Beta oscillations have been associated not only with different cognitive functions but with sensorimotor processing as well (Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013). Moreover, voluntary movement has been linked to specific modulation of oscillatory activity in the beta frequency band (Jurkiewicz, Gaetz, Bostan, & Cheyne, 2006; Pfurtscheller & Berghold, 1989; Salmelin, Hämäläinen, Kajola, & Hari, 1995). During preparation and execution of movements beta power decreases over sensorimotor regions, whereas beta power increases above baseline level following movement completion (Jurkiewicz et al., 2006; Pfurtscheller et al., 1997). Beta desynchronization during movement execution, as well as beta rebounds, have been localized to the contralateral hand regions of the motor cortex (Jurkiewicz et al., 2006). It has been further demonstrated that power and phase of beta oscillations

over the motor cortex influences the amplitude of transcranial magnetic stimulation (TMS) evoked potentials (MEPs) (Keil et al., 2014; Schulz et al., 2014).

Given this relationship between beta oscillations and motor function, several simultaneous tACS-TMS studies have investigated the causal relationship between beta power and corticospinal excitability (Feurra et al., 2011, 2013), with recent studies investigating whether the phase of 20Hz tACS can be used to modulate MEP amplitude (Guerra et al., 2016; Nakazono, Ogata, Kuroda, & Tobimatsu, 2016; Raco, Bauer, Tharsan, & Gharabaghi, 2016). However, in these studies tACS was applied for prolonged periods of time. Raco and colleagues (Raco et al., 2016) for instance applied 20Hz tACS for 200s and found a phase-dependent modulation for the last three MEPs only indicating that shorter stimulation protocols might not be successful in entraining brain oscillations in the motor cortex.

The ability to modify beta oscillations within a short period of time in an event-related, randomized manner is crucial when quantifying the effectiveness of beta tACS and ultimately its usefulness for modulating dynamic cognitive processes. With tACS being an exciting and relatively new technique, it is important to investigate not only when it works but also the specifics of when it doesn't. Therefore, different stimulation parameters were used to reveal the ideal stimulation set-up for transient tACS. The effects of different electrode sizes on episodic memory formation have already been investigated in Chapter 2. Additionally, the specific effects of beta tACS were investigated using four control frequencies and sham stimulation. This chapter further explored the usefulness of tACS for cognitive research and sought to identify whether different electrode montages would lead to more effective modulation of beta oscillations during transient beta tACS.

1.1 Aims of this Chapter

As the above review suggests, the present chapter had two distinct aims. Since episodic memory performance is a rather indirect means of determining the effectiveness of brain stimulation, it explored the effect of transient beta tACS on MEP size. This, more direct way of quantifying the effectiveness of brain stimulation (Barker et al., 1985; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001; Nitsche et al., 2008; Pascual-Leone et al., 1998) allowed us to explore whether traditional montages with one electrode placed directly over the target area are more effective than montages in which both stimulation electrodes are positioned adjacent to the target area (as in the previous chapter). Second, the stimulation duration used in the present experiment was increased to 10s which, in contrast to Chapter 2, allowed us to investigate whether slightly longer (though nonetheless relatively short) stimulation durations influence motor cortex excitability. In Chapter 2, transient beta tACS did not modulate memory performance. However, the reason behind this null finding remained unclear. Therefore this chapter investigated whether beta tACS can entrain beta oscillations when applied for 10s. By measuring the effect of tACS phase on MEP size, we were able to quantify stimulation success more directly and aimed at addressing the question whether transient beta tACS can entrain beta oscillations.

In the present experiment, two modifications were also made to the stimulation procedure: Although the same electrode size was chosen for this experiment as in experiment 2 (Chapter 2), lower stimulation intensities were used in order to reduce possible side effects, such as phosphenes, that were reported frequently by participants in the previous study. The procedure was also modified to

optimize tACS parameters by stimulating at the participants' individual beta frequency rather than using a standard frequency (e.g. 20Hz).

2. Material and Methods

2.1 Participants

Eight participants completed the experiment (all male; mean age: 29.38 +- 4.93 years). Participants were screened for contraindications against tACS and TMS prior to the experiment (Poreisz et al., 2007; Wassermann, 1998). All participants were right handed, had normal or corrected to-normal vision, and reported no history of neurological disease or brain injury. Informed consent was acquired from each subject prior to the experiment. The study was approved by the ethics committee of the University of Birmingham.

2.2 Experimental Setup and Procedure

Due to safety considerations, the experiment was split into two sessions consisting of the same experimental procedure. The break between the sessions was controlled so that both sessions took place at two consecutive days at the same time of the day.

2.2.1 Determination of Each Participant's Motor Beta. Before the start of each session, the participants' individual motor beta frequency was determined using a finger tapping task. After a rest period of 2min, participants were asked to tap with the fingers of their right hand prompted by corresponding numbers on the screen for 2min. During this task, EEG was recorded using Ag-AgCl scalp electrodes (NeuroConn, Ilmenau, Germany) at 1000Hz sampling rate over C3, C4, Pz and Cz, referenced to the right mastoid. The EEG recordings were off-line re-referenced

against Pz. The data from the tapping and rest condition were split into 4s segments, subjected to a multitaper frequency transformation using Hanning tapers, and then subtracted from each other. As beta power decreases more over contralateral electrodes during the execution of movement as compared to rest (Pfurtscheller et al., 1997), the individual motor beta frequency was determined as the frequency in the beta range (13Hz-30Hz) that showed the strongest power decrease in C3 compared to C4.

2.2.2 Transcranial Magnetic Simulation. Transcranial magnetic stimulation (TMS) was delivered with a Magstim Rapid stimulator via a 70mm double coil (magstim; www.magstim.com) to the left motor cortex at 110% motor threshold (identified without active tACS, but over the tACS electrode). The stimulation site (M1) was defined as the position on the scalp which elicited the strongest MEP response: The coil was angled at 45° from the midline axis of the participant's head with the handle pointing backwards. MEPs were recorded from different points at the scalp in order to obtain the position that elicited the strongest response. Motor thresholds were estimated using a modified binary search (Tyrrell & Owens, 1988) with amplitude changes of 100 μV peak-to-peak or more being considered an MEP. In every session 420 TMS pulses were delivered randomly every 2.5s – 4.5s (at an average inter stimulus interval of 3.5s) (Keil et al., 2014) throughout the experiment. The TMS pulses were triggered using an in-house Matlab script that controlled the TMS via a USB Data Acquisition Device (Measurement Computing).

2.2.3 Transcranial Alternating Current Stimulation. tACS was delivered via a 4 channel DC Stimulator MC (NeuroConn, www.neuroconn.de). The stimulation was applied using round rubber electrodes with a diameter of 3.7cm

(10.75 cm^2, NeuroConn, Ilmenau, Germany) at an intensity of 0.7mA (1.4mA peak to peak), resulting in an estimated current density in the skin underneath the electrodes of 0.065 mA/cm^2. Two electrode montages were used in order to compare the efficiency of montages with one electrode positioned directly over the target area (Feurra et al., 2011, 2013) with montages in which the target area is located between the stimulation electrodes (for an example of the latter, see previous chapter). Three tACS electrodes were used, placed at M1 and EEG electrode positions Pz and Fp1, resulting in two electrode montages. For montage 1 current was being passed between M1 and Pz (Feurra et al., 2011, 2013), whereas for montage 2, current was being passed between Fp1 and Pz. This setup allowed us to use the same reference electrode, Pz, in both stimulation conditions. In this way a randomized stimulation protocol was achievable with only three stimulation electrodes. The montage was chosen randomly on a trial-by-trial basis with the restriction of the same montage not occurring in more than four consecutive trials. Impedances were kept below 5kOhm using Ten20 conductive paste (Weaver and Company, Aurora/Colorado).

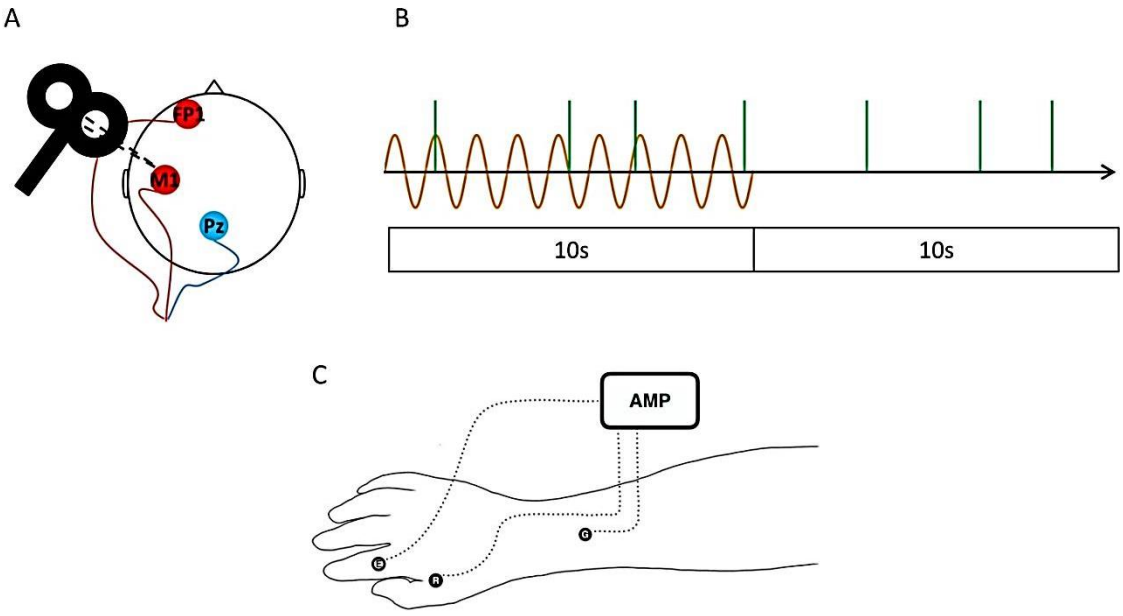

Figure 4. tACS-TMS procedure for Chapter 3. Two different tACS montages were used: M1-Pz and FP1-Pz (A). TMS pulses (depicted in green) were delivered throughout the trial every 2.5s-4.5s to the left motor cortex over the tACS electrode placed at M1. tACS was applied at the individual motor beta frequency (depicted in orange) for 10s followed by a 10s period without tACS (B). MEPs were measured from the first dorsal interosseous (FDI) muscle of the right hand (C). Each session consisted of 70 trials.

2.2.4 tACS-TMS Procedure. During the experiment, participants were seated comfortably in front of a computer screen. No task was involved. Subjects were instructed to keep their hands as relaxed as possible, while looking at a fixation cross in the centre of the screen. Single pulse TMS was delivered throughout the experiment over the tACS electrode placed at M1 (Figure 4), while participants received tACS at their individual motor beta frequency. tACS was applied for 10s, followed by a 10s period without stimulation. The electrode montage with which the stimulation was delivered (i.e. FP1-Pz or M1-Pz), was pseudorandomised such that the same montage was never repeated more than four times. Motor evoked potentials

were measured from the first dorsal interosseous (FDI) muscle of the right hand using Ag-AgCl EEG electrodes (BrainAmp MR plus, Brainvision). Every 17-18 trials, participants were given a short break and the TMS coil was cooled down, resulting in four tACS-TMS blocks per session. The tACS artefact was recorded from one Ag-AgCl EEG electrode placed at Cz, referenced to the right mastoid.

2.3 Data Analysis

Data were analysed using FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011), the CircStat toolbox (Berens, 2009), and in-house MATLAB scripts. As the tACS stimulator was mains operated while the amplifier used to record the MEPs was battery operated, the different power supplies (different current draws) between these two systems resulted in high levels of noise in the MEP data. Hence, the peak-to-peak amplitudes of the motor evoked potentials were not easily accessible. Therefore, MEP data (-0.15s to 0.15s around the TMS pulse) were subjected to a time-frequency composition (20-1000Hz, steps of 5Hz) using Morlet wavelets (width 7) and baseline corrected (baseline window: -0.15s to -0.05s). MEP amplitude was defined as the peak of the mean signal change between 20Hz and 50Hz, 0-50ms following the TMS pulse. In order to adjust for noise introduced by the break periods and possible changes in position of the TMS coil, MEP amplitudes in every block were z-transformed, ensuring that data from every block were comparable. To extract phase angles of tACS, EEG data recorded from electrode Cz were Hilbert transformed. Due to the TMS artefact distorting the phase estimates, phase angles were extracted 5ms prior to the TMS pulse (Keil et al., 2014). In order to test for phase entrainment effects, MEP amplitudes of every single trial were correlated with the tACS phase 5ms prior to the TMS pulse. These circular to linear correlations

between the normalised MEP amplitudes and tACS phase were calculated as implemented in the circular statistics toolbox (Berens, 2009). Additionally, the data were binned into four different tACS phase bins centred around 0° (*peak)*, 90° (*falling flank*), 180° (*trough*), 270° (*rising flank*) (Raco et al., 2016), and normalised MEP amplitudes at those tACS phase bins were subjected to a repeated measures ANOVA. Average number of samples per phase bin: Trough: 96.25 samples (SE=3.55), Peak: 98.375 samples (SE= 4.93), Rising Flank: 85.625 samples (SE=3.13), Falling Flank: 87.5 samples (SE=4.23).

3. Results

3.1 MEP Modulation

Normalised single trial MEP amplitude by tACS phase collapsed across both montages is shown in Figure 5B. Circular to linear correlations revealed no correlation between MEP amplitude and tACS phase; overall: ρ_{cl} = 0.0249, p=0.4021; Montage 1: ρ_{cl} = 0.0167, p=0.8141 (Figure 6A); Montage 2: ρ_{cl} = 0.0442, p=0.2394 (Figure 6B).

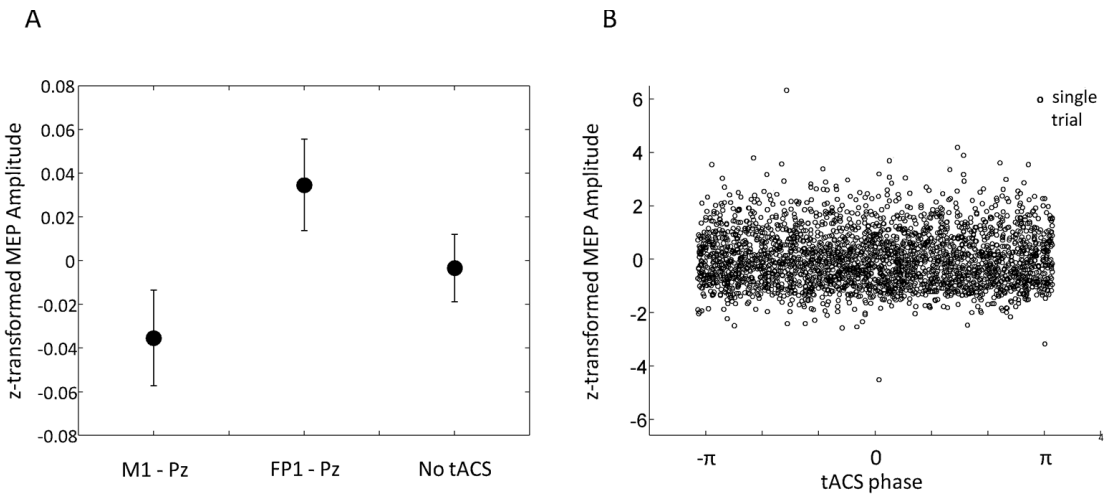

Figure 5. (A) Normalised mean MEP amplitude split by tACS condition. Error bars show standard errors of the mean. (B) Single trial MEP size by tACS phase.

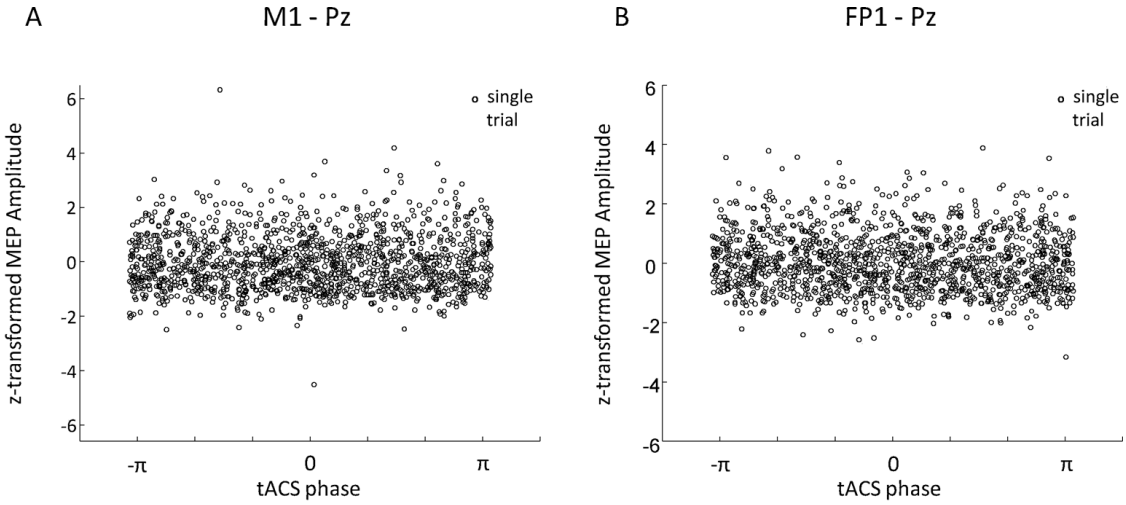

Figure 6. Single trial normalised MEP amplitude by tACS phase. (A) tACS electrodes at M1 and Pz. No significant correlation between MEP amplitude and tACS phase could be found, $\rho_{cl} = 0.0167$, $p = 0.8141$ (B) tACS electrodes at FP1 and Pz. No significant correlation between MEP amplitude and tACS phase could be found, $\rho_{cl} = 0.0442$, $p = 0.2394$.

A 3-way ANOVA with the factors *Session, Montage* and *Phase bin* showed no main effect of the tACS phase (Figure 7); $F(3,21) = 0.223$, $p = 0.880$. No interaction between the phase bins and tACS montage could be found either, $F(3,21) = 0.730$, $p = 0.546$, however, there was a trend towards a main effect for tACS montage with higher MEP amplitudes at M2 (FP1-Pz) than M1 (M1-Pz); $F(1,7) = 5.338$, $p = 0.054$. Averaging over the four phase bins for montage 1 and 2 separately reveals that overall, there was no significant difference in MEP size between tACS trials in either of the montages and no-tACS trials (Figure 5A); Montage 1 (M1-Pz): $t(7) = -0.949$, $p = 0.374$; Montage 2 (FP1-Pz): $t(7) = 1.121$, $p = 0.299$.

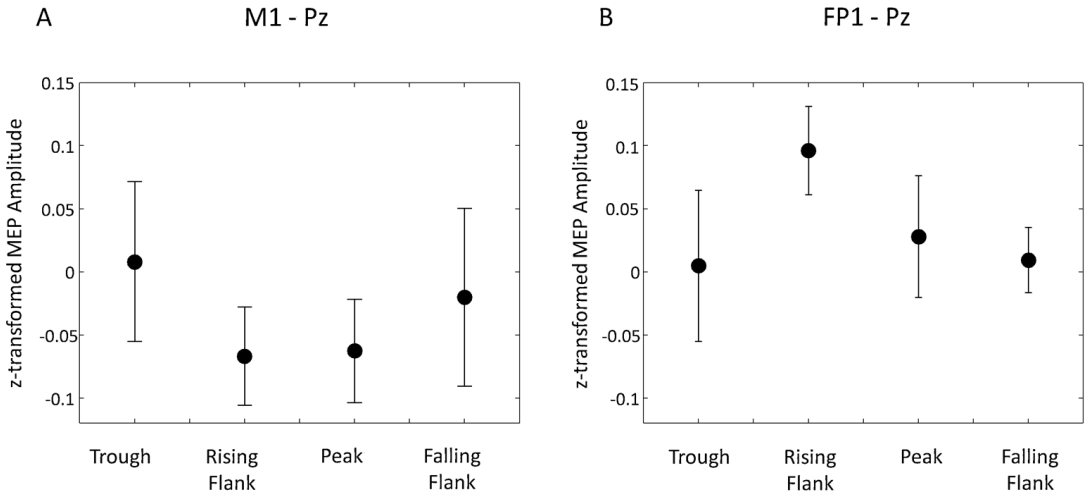

Figure 7. Mean normalised MEP amplitude split by 4 different tACS phase bins: 180° (trough), 270° (rising flank), 0° (peak), 90° (falling flank). (A) tACS Montage 1: M1-Pz. (B) tACS Montage 2: FP1-Pz. Error bars show standard errors of the mean.

3.2 Bayesian Statistics

We expected MEP amplitude to be modulated by the tACS phase. A JZS Bayes factor ANOVA (Rouder, Morey, Speckman, & Province, 2012) with default

prior scales revealed strong evidence for the null compared to the main effects model *Phase bin,* $BF_{01} = 20.246$.

3.3 Validation of MEP Measurement

Due to noise in the MEP data produced by the tACS stimulator, amplitudes of the motor evoked potentials were not easily accessible. Hardware noise of the stimulator was strong enough to be picked up by the electrodes at the hand, making peak-to-peak measurements impossible. Using the time-frequency composition of the MEP data together with baseline corrections allowed us to estimate the size of the MEPs. This method was validated using 40 trials per subject that were recorded without the stimulator being switched on. For every participant the peak-to-peak amplitudes correlated highly with the amplitude measurements obtained from the time-frequency analysis (p-values < 0.001). This indicates that we indeed arrived at good estimates of MEP size with our method.

3.4 Beta Frequencies and Resting Motor Thresholds

Participants' individual motor beta frequency and resting motor threshold was determined before every session. The average frequency was 18.66Hz (range 14.5Hz to 24.75Hz); average resting motor threshold was 62.31 (range 51 to 71%).

4. Discussion

The experiment presented in this chapter sought to examine if corticospinal excitability can be modulated via entrainment of beta oscillations in the primary motor cortex using tACS. By applying tACS to M1 at the individual motor beta frequency, we investigated the relationship between TMS induced MEPs and tACS phase. As in Chapter 2, and as previous studies indicate (Raco et al., 2016), we did not find a clear entrainment effect; MEP size was not modulated by tACS phase. We believe that this is due to the rather short tACS stimulation period (10s) used. Studies that reported phase effects of beta tACS on MEP size used longer stimulation durations (Guerra et al., 2016; Nakazono et al., 2016; Raco et al., 2016), whereas MEP size was not phasically modulated when applying 30s of slow oscillatory tDCS (Bergmann et al., 2009). Although other studies investigating motor cortex excitability using tDCS had sample sizes similar to this study (Bergmann et al., 2009; Furubayashi et al., 2008; Jeffery, Norton, Roy, & Gorassini, 2007), we cannot rule out that a higher number of participants may have increased the probability of finding a phase effect of beta tACS on MEP amplitude. Future studies should therefore consider testing more subjects in order to replicate these findings with greater sample sizes.

During cognitive tasks brain oscillations show a highly dynamic behaviour, particularly those in the beta frequency range (13-30Hz). For instance beta oscillations decrease in power within a couple of milliseconds during memory processing (e.g. Hanslmayr, Volberg, et al., 2011) or movement execution (e.g. Jurkiewicz et al., 2006). Such dynamic processes can be studied under constant stimulation (e.g. throughout a cognitive task) in order to reveal state-dependent

effects. However, to answer causal questions about specific time-sensitive oscillatory processes, our findings would need to show that tACS is capable of consistently and robustly modulating oscillatory behaviour over similar time periods. For tACS to be a suitable technique for such manipulations in future cognitive paradigms, we would therefore have expected strong effects in this experiment. However, we did not find that event-related, randomized, transient beta tACS modulates motor cortex excitability. This further supports our findings from Chapter 2. Taken together, our findings suggest that transient tACS in the beta frequency range may not be suited for explorations of the causal relationships between transient oscillatory brain activity and cognitive processes.

This failure to find an effect of beta tACS on cognition or cortical excitability—and the finding that such statistically positive effects are unlikely—reveals that the effectiveness of tACS is a complex issue. On the one hand, tACS applied over minutes appears to be effective in modulating behaviour and brain oscillations (Brittain et al., 2013; Helfrich, Schneider, et al., 2014; Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Neuling et al., 2013; Polanía et al., 2012; Raco et al., 2016; Zaehle et al., 2010). Indeed, if tACS is used to synchronize and desynchronize distant brain regions, even relatively short stimulation durations (1s-1.8s) in other frequencies seem to be successful (Stonkus et al., 2016). Yet, the findings from Chapter 2 and 3 indicate that tACS applied in the range of seconds in order to modulate brain oscillations in one brain area is not effective (Strüber et al., 2015; Vossen, Gross, & Thut, 2015). Hence, though tACS may be used to stimulate brain areas when applied for long durations and to influence the synchrony between

distant brain regions given brief durations, our findings suggest that it does not influence oscillatory function in one brain regions over such short durations.

Before utilizing beta tACS as a means of investigating the causal relationship between oscillatory brain activity and cognitive processes, several issues regarding the use of beta tACS protocols need to be addressed, such as current distribution in the brain, optimal electrode placement, recommended stimulation intensities, recommended stimulation durations etc. Though a growing body of modelling studies addresses these issues (Dmochowski, Datta, Bikson, Su, & Parra, 2011; Mehta et al., 2015; Miranda, Lomarev, & Hallett, 2006; Opitz, Paulus, Will, Antunes, & Thielscher, 2015; Saturnino, Antunes, & Thielscher, 2015), the respective models must be validated extensively by experimental data before it will be possible to apply tACS more effectively in cognitive research (Datta, Truong, Minhas, Parra, & Bikson, 2012). Event-related transient beta tACS could then be a useful and promising method. Yet as long as these problems remain unsolved, tACS may remain ineffective in unravelling the causal relationship between transient beta oscillatory activity and cognitive function.

4.1 Conclusion

In Chapter 2, transient beta tACS failed to modulate episodic memory formation. Likewise, in this chapter, 10s of beta tACS did not result in a phasic modulation of MEP amplitude. Taken together, the results from Chapters 2 and 3 therefore indicate that transient tACS in the beta frequency range might not be an effective means of studying the causal relationship between transient beta oscillations and memory formation.

Beta tACS proved unsuccessful in modulating beta oscillations and may therefore be unsuitable for investigations into how beta oscillations contribute to the formation of episodic memories. One possible explanation for this technological shortcoming may arise from the fact that the electrical fields induced by tACS may be too weak to interfere with underlying beta oscillatory activity (Lafon et al., 2017).

In order to explore an alternative means of testing the causal link between beta oscillations and episodic memory encoding, we tested the efficacy of rTMS as a means of modulating memory formation in Chapter 4. TMS modulates neural activity more directly (Walsh & Cowey, 2000) and has been shown to influence beta oscillations (Brignani, Manganotti, Rossini, & Miniussi, 2008; Fuggetta, Pavone, Fiaschi, & Manganotti, 2008; Paus, Sipila, & Strafella, 2001). Chapter 4 explores, in two experiments, whether slow rTMS may be used to modulate beta oscillations and affect memory formation accordingly.

CHAPTER 4: SLOW RTMS TO THE LEFT DLPFC ENHANCES VERBAL MEMORY FORMATION

This chapter presents an incidental finding from a simultaneous EEG-TMS experiment as well as a replication of this unexpected effect. 40 healthy human participants engaged in a list learning paradigm. Half of the subjects (N=20) received 1Hz rTMS to the left DLPFC while the other half (N=20) received 1Hz 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 double-blind within-subjects design. 24 participants received 1Hz rTMS to the left DLPFC and Vertex. As in the first experiment, DLPFC stimulation led to better memory performance compared to Vertex stimulation. In addition to these behavioural effects, we found electrophysiological evidence that 1Hz rTMS induces a state which is known to be beneficial for memory encoding. EEG data from the first experiment shows that the DLPFC group demonstrated stronger beta power modulation than the Vertex group in posterior areas. These results demonstrate that 1Hz rTMS applied to an area which is known to be involved in episodic memory formation leads to stronger memory performance and elicits electrophysiological correlates of more efficient stimulus processing.

This research is being prepared for publication:

Braun, V., Stauch, B. J., Hanslmayr, S. (2018). *Slow rTMS to the left DLPFC enhances verbal memory formation.* Manuscript in preparation.

1. Introduction

Beta power decreases have been associated with successful memory performance (Hanslmayr, Staudigl, et al., 2012). Consistent with this, artificially increasing beta power using rTMS can impair memory formation (Hanslmayr et al., 2014). In Chapters 2 and 3 beta tACS proved unsuccessful in entraining beta oscillations and hence did not modulate episodic memory encoding. Therefore in this chapter we focused on rTMS as an established method to modulate memory processes (Hanslmayr et al., 2014; Wang et al., 2014). Two experiments presented in this chapter demonstrate that slow rTMS has the potential to enhance verbal memory performance and modulate beta power.

We are able to encode and store episodes that are rich in detail and filled with information (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 must be represented (Hanslmayr et al., 2016). This involves posterior neocortical areas processing different sensory inputs guided by prefrontal regions (Kirchhoff, Wagner, Maril, & Stern, 2000; Paller & Wagner, 2002; Sommer, Schweinberger, & Matt, 1991). Optimizing this process could prove invaluable, not only for therapeutic interventions, but also for gaining knowledge about how the brain accomplishes the complex task of forming episodic memories.

Brain stimulation may be used to enhance long-term memory formation and contribute towards investigating how episodic memories are formed. Applying intracranial stimulation (Ezzyat et al., 2017) or rhythmic transcranial magnetic stimulation (rTMS) (Wang et al., 2014) to areas involved in memory formation can

lead to enhanced memory performance. However, past research using these methods has either been restricted to a specific cohort (i.e. epilepsy patients (Ezzyat et al., 2017)) or has involved high-frequency, repetitive offline stimulation over multiple days (Wang et al., 2014). Attempts to enhance memory formation using shorter non-invasive stimulation protocols have led to mixed results. Some experiments have shown that applying tDCS to the left DLPFC during episodic memory encoding, for example, leads to enhanced memory performance (Javadi & Walsh, 2012; Zwissler et al., 2014), while others have failed to demonstrate an effect (de Lara, Knechtges, Paulus, & Antal, 2017). The ability to enhance memory performance using non-invasive brain stimulation methods and to investigate the mechanisms that lead to these effects could advance our understanding of memory processes (Floel & Cohen, 2007).

In the present study we report an online slow rTMS protocol that boosts long-term memory formation. In contrast to the protocols reviewed above, in which stimulation was applied for prolonged periods, 1Hz rTMS stimulation was applied during stimulus encoding for periods of 45s. Nonetheless it influenced memory formation. Simultaneously recorded EEG data enabled us to explore the mechanisms underlying these rapid changes and provided further support for the view that beta desynchronization plays a role in episodic memory formation (Hanslmayr et al., 2014).

1.1 Aim of this Chapter

We here present an incidental finding from a study by Hanslmayr and colleagues (Hanslmayr, Volberg, et al., 2012) in which the authors examined the role of the left dorsolateral prefrontal cortex (DLPFC) in voluntary forgetting. In the

current study we re-analysed their TMS-EEG dataset (experiment 1). To foreshadow our results, we found that 1Hz rTMS applied to the left DLPFC during encoding of verbal material enhances memory performance. Event-related desynchronization in the beta frequency band (13-30Hz) has robustly been associated with successful episodic memory formation (Hanslmayr, Staudigl, et al., 2012). Hence, we also explored whether enhancement of memory performance elicited by rTMS corresponded with greater beta power decreases. In order to ensure that our effects are replicable, we conducted an internal within-subjects replication of the behavioural effect (experiment 2).

2. Material and Methods

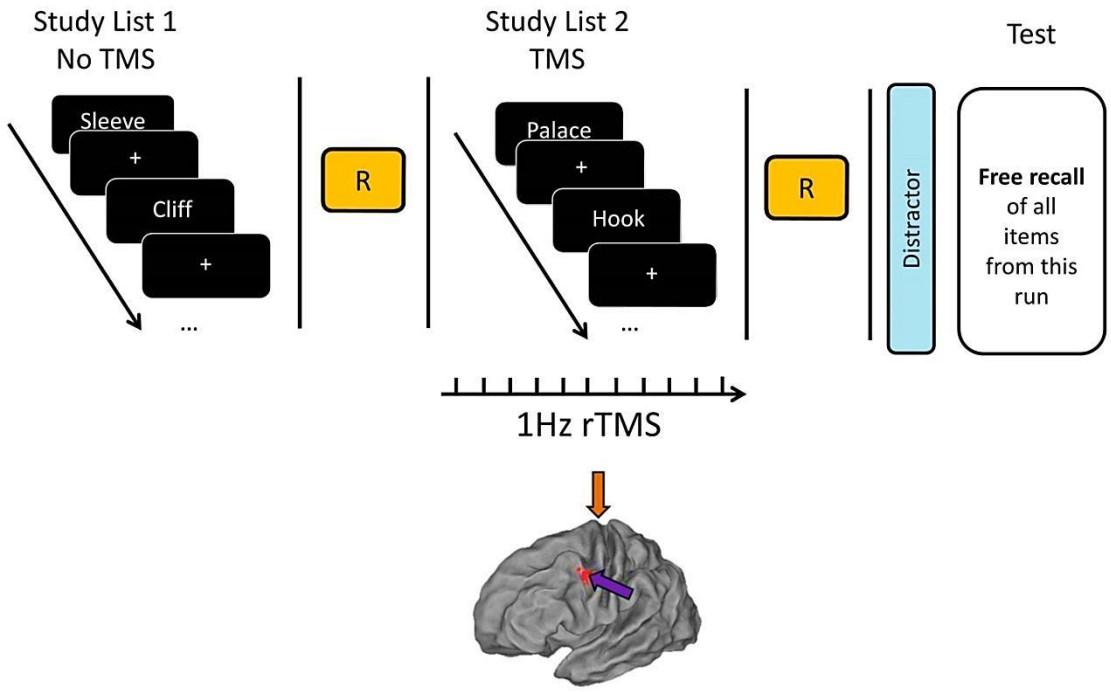

Figure 8. Experimental design Chapter 4. Arrows indicate stimulation site (DLPFC=purple, Vertex=orange). Participants were asked to study two lists of 10 words. During encoding of list 2, 45 pulses of 1Hz rTMS were applied to the left DLPFC (MNI coordinates: -45, 6, 39) or Vertex. Words were presented in randomized order one at a time for 2.5s, with a variable inter-stimulus interval of 1.5-2.5s (fixation cross). After a short distractor task, participants were asked to recall as many items from this run as possible. Memory performance was assessed as percentage of correctly recalled items per list.

2.1 Experiment 1

2.1.1 Participants

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 TMS (Wassermann, 1998). Informed consent was acquired from each subject prior to the experiment. The study was approved by the ethics committee of the University of Konstanz.

2.1.2 Experimental Setup and Procedure

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 containing 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 and conditions (forget list 1, forget list 2, remember list 1, remember list 2). The data was collected as part of a study that focused on the causal involvement of the left DLPFC in voluntary forgetting (reported in Hanslmayr et al., 2012, experiment 2). Participants performed 12 encoding-recall runs. In each run, participants were presented with two lists of 10 words. After having studied the first 10 words, a cue was presented for 5s prompting participants to either forget the previously studied items 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, 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 2.5s, with a variable inter-stimulus interval of 1.5-2.5s (fixation cross). After a short distractor task, participants were asked to freely recall as many items from this run as possible in any order (Figure 8). Participants' responses were recorded manually by the experimenter outside of the EEG room.

2.1.2.1 Transcranial Magnetic Stimulation. 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. There was no relationship between the timing of the TMS pulses and the stimulus presentation. TMS 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 high resolution images 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 TMS 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 (Hanslmayr et al., 2012).

2.1.2.2 EEG Recording and Preproccessing. 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 2048Hz; 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 TMS (Farzan et al., 2016), list 1 (no TMS) and list 2 (during TMS) trials were preprocessed separately. Preprocessing of EEG-TMS data followed the guidelines and procedure outlined by Herring et al. (Herring, Thut, Jensen, & Bergmann, 2015) adapted to our dataset. EEG data were first cut into segments of -0.9s to 0.9s around the TMS pulse. Data were visually inspected and data around the TMS pulse were removed from further analysis. The epoched data were subjected to an independent component analysis (runICA). This allowed the removal of TMS related artefacts, eye-blinks, eye movements and other remaining artefacts. TMS artefacts were detected by inspecting ICA components time-locked to the TMS pulse. This way, TMS evoked muscle and decay artefacts could be identified and removed. The cleaned data were epoched around word onset (-2s to 4s) and data around the TMS pulse containing remaining artefacts were replaced using cubic interpolation. Subsequently, the data were downsampled to 500Hz, a low-pass filter of 40Hz was applied and the data were again visually inspected for remaining artefacts. Missing channels were interpolated (mastoids were removed resulting in 126 channels). For trials without TMS (list 1), data were epoched -2s to 4s around the onset of the word, downsampled to 500Hz, and low-pass filtered at 40Hz. After visually inspecting the data for artefacts, an ICA was applied in order to identify ocular and muscle artefacts. The cleaned data were again visually inspected.

2.1.3 Data Analysis

2.1.3.1 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 *TMS* (DLPFC and Vertex) was performed. We further tested whether DLPFC stimulation influenced the likelihood of recalling items as a function on an item's list position. To this end, serial position curves were calculated (Murdock, 1962). For every subject at every list position we coded whether an item 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.

2.1.3.2 EEG Analysis. EEG data (-1.5s to 3s) were subjected to a time-frequency decomposition (2 to 35 Hz in steps of 1Hz) using Morlet wavelets (width 7) and z-transformed in order to enable analysis of post- as well as pre-stimulus activity (Griffiths et al., 2016). As only negative clusters in the beta frequency range were expected, data from the DLPFC and Vertex group were subjected to a one-tailed cluster based permutation test, averaged over beta (13-30Hz) and the post stimulus time window of interest (0 to 1s). 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 visualize and identify sources of this beta power modulation, Dynamic Imaging of Coherent Sources beamforming analyses were conducted (Gross et al., 2001). Individual electrode positions as well as individual t1-weighted MRI scans were available. For each individual, filters were calculated using activity in the post

stimulus (0.25s to 0.75s) and pre stimulus (-0.55s to -0.05s) time window. As we were interested in the modulation of beta power within these time windows, activity pre stimulus served as the baseline period. Cross-spectral density and source power were estimated using frequency analysis with multitapers as implemented in Fieldtrip (Oostenveld et al., 2011) for a frequency range of 19-26Hz (identified visually as the common frequency range of the strongest effects pre and post stimulus). This was done separately for the DLPFC and Vertex group. Source localization results were visualized using Caret (http://brainvis.wustl.edu).

2.2 Experiment 2

2.2.1 Participants

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 TMS (Wassermann, 1998). 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. The data was collected as part of a larger study that focused on replicating the effect of TMS on directed forgetting and is reported elsewhere (see Stauch, 2017).

2.2.2 Experimental Setup and Procedure

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 forget 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 (see Figure 8). 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.

2.2.2.1 Transcranial Magnetic Stimulation. 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 high resolution images 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 TMS 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.

2.2.3 Data Analysis

In this second experiment we specifically hypothesized that DLPFC stimulation would lead to enhanced recall rate compared to Vertex stimulation for list 2 items. Therefore a one-side paired t-test was conducted in order to assess whether the effect from experiment 1 was replicated.

3. Results

3.1 Experiment 1

3.1.1 Behaviour

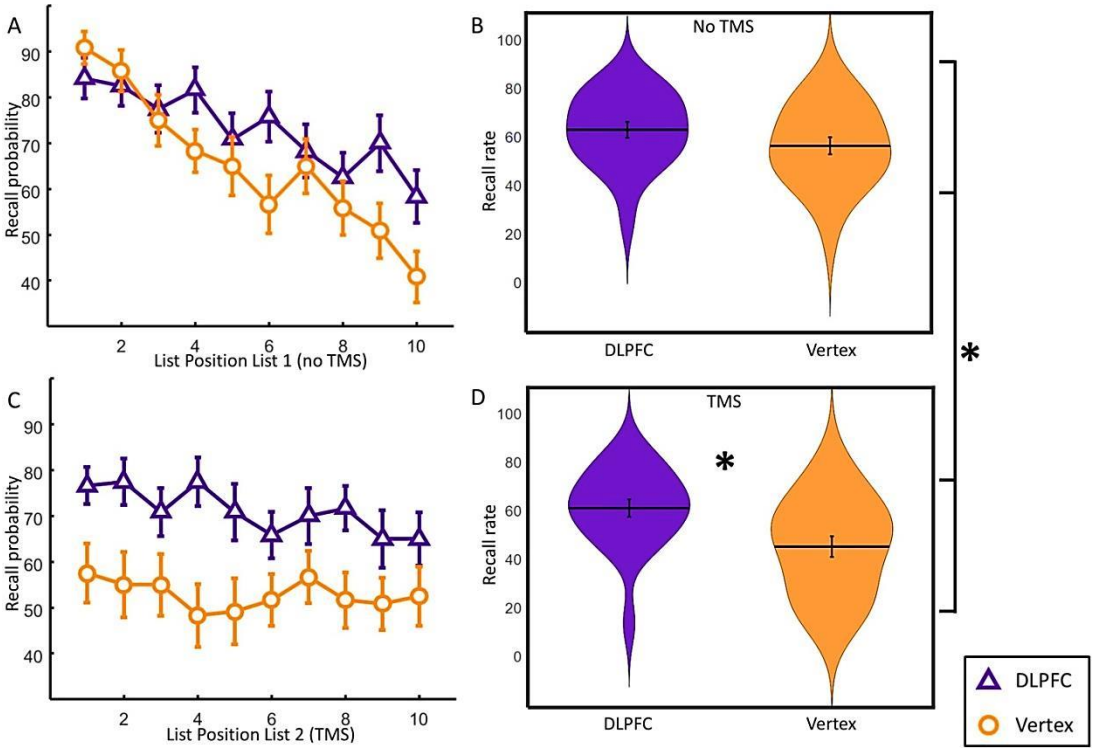

Figure 9. Memory performance experiment 1, Chapter 4. A. Serial position curve for list 1 items. Error bars depict standard errors of the mean. B. Violin plots of memory performance for list 1 items (Hoffmann, 2015). Black line indicates the mean recall rate. Error bars depict standard error of the mean. C. Serial position curve for list 2 items. Error bars depict standard errors of the mean. D. Memory performance for list 2 items. Black line indicates the mean recall rate. Error bars show standard error of the mean.

In order to test the effect of TMS on memory performance we conducted a 2 (list 1 vs list 2) x 2 (DLPFC vs Vertex) mixed ANOVA. There was a significant difference between the groups (main effect *TMS*, $F(1,38) = 5.018$, $p = 0.031$) and a

significant main effect for the factor *List* ($F(1,38) = 15.728$, $p < 0.001$). We also found a significant *TMS* x *List* interaction ($F(1,38) = 9.130$, $p = 0.004$). Post-hoc independent samples t-tests revealed that the DLPFC group showed better memory performance than the Vertex group only for words presented during TMS application (list 2, $t(38) = 2.820$, $p = 0.008$, Figure 9D). This was not the case for words presented before TMS was applied (list 1, $t(38) = 1.365$, $p = 0.18$, Figure 9B). Hence, the effects were specific to the application of rTMS to the left DLPFC.

In an exploratory follow-up ANOVA we investigated the effect of serial position in order to assess whether left DLPFC stimulation affected the likelihood of recalling an item as a function of its list position (Murdock, 1962). Analysis of serial position curves revealed a significant *List* x *Position* x *TMS* interaction ($F(9,342) = 2.354$, $p = 0.014$). There was only a significant interaction between list position and TMS ($F(9,342) = 2.725$, $p = 0.004$) when TMS was not applied (list 1), which is due to enhanced recall rates for later items in the DLPFC group compared to the Vertex group (see Figure 9A). This was not the case in list 2 when TMS was applied (*Position* x *TMS*: $F(9,342) = 0.865$, $p = 0.557$, Figure 9C). Hence, online rTMS to the left DLPFC equally increased memory performance regardless of item position in list 2, whereas there was a slight benefit for later items in the preceding list 1 in the DLPFC group.

3.1.2 EEG

Post-stimulus beta power decreases have repeatedly been associated with successful memory formation (Hanslmayr, Staudigl, et al., 2012). Therefore, we first tested whether the DLPFC group would show stronger beta power decreases (13-30Hz) post-stimulus (0 to 1s) for items that were later remembered (hits) compared

to the Vertex group for list 2 trials. In order to test whether there is a difference in this time and frequency window of interest and over which areas a beta power decrease would occur, the data were subjected to a one-tailed cluster based permutation test (Maris & Oostenveld, 2007). We found a significant negative difference between the DLPFC and Vertex group at posterior sites in the beta frequency range (13-30Hz) post stimulus ($p_{\text{one-sided}} = 0.016$) (depicted in Figure 10B; right topography). No effects could be found for alpha (8-12Hz) or theta (4-7Hz) frequency bands in this time window ($p_{\text{two-tailed}} > 0.05$). The time frequency plot at this ROI as well as the time course of beta power is shown in figure 10A and 10C. Beta power shows a clear modulation with regards to word onset in this posterior electrode cluster with stronger beta power pre-stimulus and lower beta power post-stimulus. We therefore further explored this beta power modulation in order to investigate whether it was specific to stimulation trials. Data from -1s to 1.95s were split into six non-overlapping time bins (see Figure 10D) 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 *TMS* (DLPFC vs Vertex) ANOVA. There was a significant *List* x *Time* x *TMS* interaction ($F(5,190) = 2.676$, $p = 0.023$). In order to investigate the specific effects of stimulation, the difference between list 2 (TMS) and list 1 (no TMS) trials was subjected to post-hoc independent samples t-tests (Figure 10D). This analysis further revealed significant increases in beta power pre-stimulus (-0.5s to-0.05s: $t(32.293) = 2.350$, $p = 0.025$) and decreases in beta power post-stimulus (0.5s to 0.95s: $t(38) = -2.662$, $p = 0.011$) in the DLPFC group compared to the Vertex group. These results indicate that slow rTMS at DLPFC modulated beta power predominantly in trials where the stimulation was applied. Source estimates

visualising the strongest cluster showing this beta power modulation for DLPFC and Vertex for list 2 trials are depicted in figure 11. No statistical analyses were conducted on the source data, to avoid issues arising from different noise biases between the two groups. The strongest beta power modulation is visible for the DLPFC group at parietal and occipital sites including left and right BA 7 and 19 as well as right BA 39.

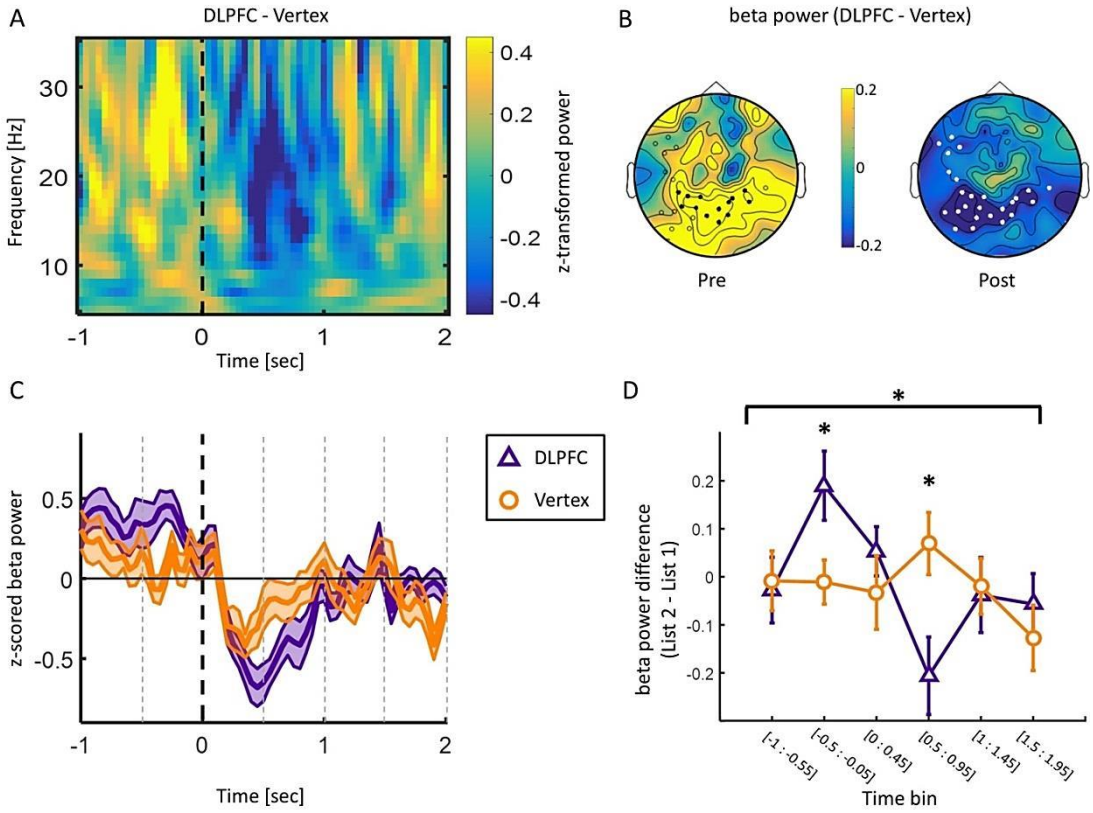

Figure 10. EEG results Chapter 4 (only later remembered trials analysed). A. Time frequency plot for the difference between DLPFC and Vertex during list 2 encoding averaged over electrode cluster demonstrating a significant negative difference between the DLPFC and Vertex group in the beta frequency range post stimulus (ROI). Dashed line indicates stimulus onset. B. Topographies depicting beta power (13-30Hz) difference between DLPFC and Vertex in time windows of interest (pre: -0.5s to -0.05s; post = 0 to 1s). White circles depict significant negative electrode cluster post-stimulus (ROI). Black circles show electrodes within the negative cluster showing a positive difference pre-stimulus. C. Time course of beta power (13-30Hz) averaged over negative electrode cluster (ROI). Shaded area represents standard error of the mean. Black dashed line indicates stimulus onset. Grey dashed lines depict time bins. D. Beta power difference (list 2 - list 1) over significant negative electrode cluster (ROI) split by TMS. 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].

There was a considerable difference in the number of list 2 hits between the DLPFC and the Vertex group after artefact rejection and due to enhanced memory performance in the DLPFC group. (DLPFC: mean=23.1, SD=7.48; Vertex: mean=17.25, SD=8.48). Although, unlike phase based measures (Vinck, van Wingerden, Womelsdorf, Fries, & Pennartz, 2010), power is not systematically biased by trial numbers, we tested nevertheless whether this difference could have accounted for our effects. We therefore randomly selected trials for each subject from the DLPFC group and matched these to the number of trials from subjects from the Vertex group, so that overall both groups would have the same number of trials (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 0-1s after stimulus 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 revealed that the difference in post-stimulus beta power decreases for list 2 items was not biased due to the difference in trial numbers.

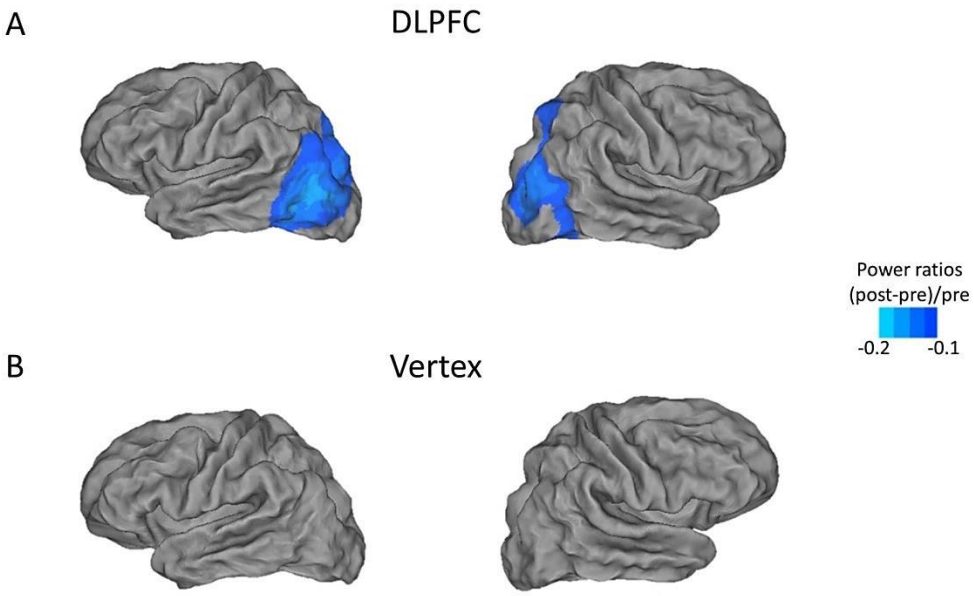

Figure 11. Baseline corrected source estimates for EEG power differences (19-26Hz; pre=-0.55s to -0.05s; post=0.25s to 0.75s). A. DLPFC B. Vertex. Strongest negative differences are depicted.

3.2 Experiment 2

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 in patients or lengthy stimulation protocols. Given that our behavioural results were an incidental finding, we attempted an internal replication of the behavioural effect. In order to control for non-specific differences between the groups that might have contributed to the

effects we changed the design to a within subjects study. Furthermore, in the present study 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 performance.

As hypothesized, a significant difference in recall performance between the DLPFC compared to the Vertex condition emerged for list 2 words (i.e. during the actual stimulation; $t(23) = 1.767$, $p_{one\text{-}sided} = 0.045$). Left DLPFC stimulation led to enhanced memory performance compared to Vertex stimulation. Analysis of the serial position curves (Figure 12A) revealed that recall probability did not differ between the DLPFC and Vertex condition in either of the two lists (*TMS* x *List* x *Position*: $F(9,198) = 1.061$, $p = 0.394$; list 1: *TMS* x *Position* $F(9,198) = 1.612$, $p = 0.114$; list 2: $F(9,198) = 0.811$, $p = 0.607$).

For most of the participants (N=19), the order in which items were recalled was also available. This allowed us to assess the amount of temporal clustering (Howard & Kahana, 2002) for list 2 items (procedure is explained in depth in Griffiths et al., 2016) and to examine whether DLPFC stimulation affected the amount of contextual clustering. Such an effect would be predicted by theories implicating the DLPFC in organizing memory material into temporal clusters (Blumenfeld & Ranganath, 2007). A two-tailed dependent samples t-test was conducted to compare temporal clustering between DLPFC and Vertex trials. There was no difference in temporal clustering between the DLPFC and Vertex condition (list 2: $t(18) = -0.0231$; $p = 0.82$) indicating that the memory enhancement effect of left DLPFC stimulation cannot be attributed to an increased temporal clustering of items.

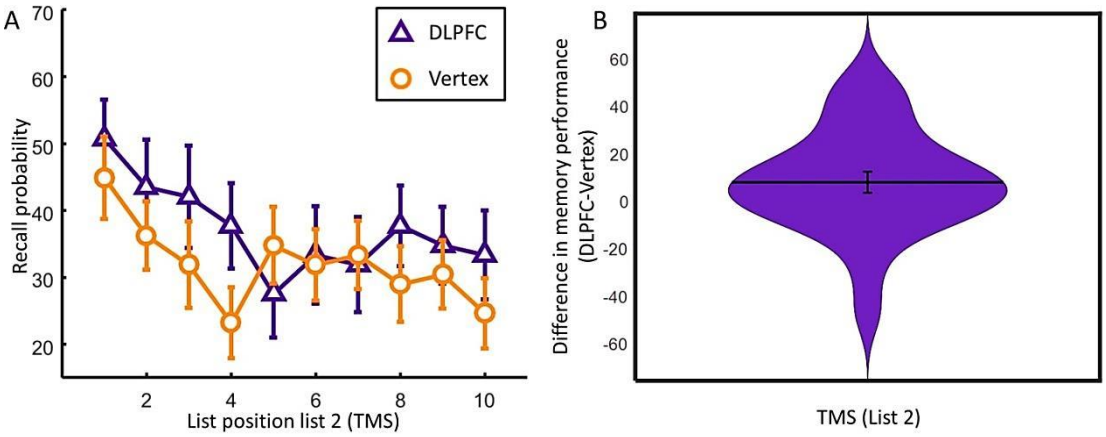

Figure 12. Memory performance experiment 2, Chapter 4. A. Serial position curve for list 2 (N=23). B. Memory performance for list 2 items (difference between DLPFC and Vertex stimulation). Black line depicts the mean difference. Error bar shows standard error of the mean.

4. Discussion

We demonstrated in two experiments that 1Hz rTMS delivered to the left DLPFC during episodic memory encoding boosts memory performance. Participants encoded two lists of words and received 1Hz rTMS during item presentation. In a subsequent free recall test, participants recalled significantly more items from lists in which they received left DLPFC stimulation compared to Vertex stimulation. Simultaneously recorded EEG data for the first experiment indicated that 1Hz rTMS to the left DLPFC strengthened event-related desynchronization 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. This effect was specific to items that were presented in list 2, i.e. during 1Hz rTMS. 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 desynchronization, an established correlate of memory function (Hanslmayr, Staudigl, et al., 2012).

Our results show that stimulating an area involved in episodic memory encoding results in item-specific memory enhancement. Memory performance was increased when participants received 1Hz rTMS to the left DLPFC compared to Vertex stimulation. This effect was specific to items that were presented during stimulation. Memory performance for lists in which stimulation was not applied did not differ between the conditions, indicating online effects of DLPFC stimulation on item encoding. Furthermore, left DLPFC stimulation did not affect recall probability of items differently depending on their list position. Analyses of serial position curves indicated that DLPFC stimulation enhanced memory encoding for list items equally regardless of when they were presented to participants. Likewise contextual clustering analyses in experiment 2 indicated that left DLPFC stimulation did not lead to stronger temporal clustering. For the first experiment a *Position* by *Stimulation* interaction was obtained for list 1, indicating that later items were recalled better before DLPFC stimulation started. However, this effect was not replicated in the second experiment. Therefore, the behavioural effects suggest that 1Hz rTMS to the left DLPFC enhances memory performance specifically for items that were presented during stimulation, but without affecting any particular position in the list. This absence of a serial position effect, together with the absence of an effect on temporal clustering, further suggests that left DLPFC stimulation enhances stimulus processing at an item-specific level whilst not affecting associations between items.

Successful encoding of verbal material relies on event-related power decreases in the beta frequency band (Hanslmayr, Volberg, et al., 2011; Hanslmayr et al., 2014, 2009). Furthermore, desynchronized activity in the alpha/beta frequency range is traditionally associated with stimulus processing in general (Klimesch, 2012). While event-related synchronization in these frequency bands has been linked to inhibition of irrelevant or potentially interfering information, event-related desynchronization (i.e. disinhibition) has been observed over areas actively involved in stimulus processing (Jensen & Mazaheri, 2010; Pfurtscheller & Lopes da Silva, 1999; Waldhauser, Johansson, & Hanslmayr, 2012). Alpha/beta power has been shown to be higher over areas storing to-be-inhibited information, whereas alpha/beta power is lower over areas actively involved in the representation of sensory information (Jokisch & Jensen, 2007; Waldhauser, Braun, & Hanslmayr, 2016). Episodic memory formation relies on effective stimulus processing during encoding. Only if the content of the presented information is represented properly in neocortical areas, can medial temporal lobe regions such as the hippocampus effectively bind the information together to form strong, associative, long-lasting memories (Hanslmayr et al., 2016). Given its importance in information processing and representation, desynchronized 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). In the present study, 1Hz rTMS to the left DLPFC was accompanied by stronger event-related beta desynchronization in parietal and occipital regions. This effect was specific to trials in which stimulation was applied and corresponded to enhanced memory performance for these items. Behavioural results indicated that left DLPFC stimulation affected item-specific encoding processes. This was corroborated by our

electrophysiological findings. We therefore conclude that the stronger posterior beta power deceases observed in experiment 1 reflect enhanced item-specific processing at the perceptual and/or conceptual level, and that his enhanced processing led to increased memory performance.

Event-related alpha/beta desynchronization has been linked to successful memory formation (Klimesch et al., 2006). Event-related power modulations are typically obtained by contrasting post-stimulus with pre-stimulus activity (Pfurtscheller & Lopes da Silva, 1999), which makes it difficult to determine whether higher pre-stimulus activity or lower post-stimulus activity was responsible for successful memory encoding. Evidence suggests that both processes are involved in episodic memory formation. For instance, recent studies have shown that higher pre-stimulus alpha/beta activity is related to successful memory formation (Fell et al., 2011; Salari & Rose, 2016; Schneider & Rose, 2016; Scholz et al., 2017). Using brain-computer-interface techniques, Salari and colleagues (2016) showed that items presented when beta power was high were more likely to be remembered. Furthermore, stronger post-stimulus beta power decreases have been linked to memory encoding in experiments in which pre- and post-stimulus activity are not contrasted (Griffiths et al., 2016).

Klimesch and colleagues (2006) proposed that it is the difference between pre and post-stimulus power that is important for cognitive performance. To this end, stimulation protocols which either increase pre-stimulus power, or decrease post stimulus power are effective means to increase performance (Klimesch, Sauseng, & Gerloff, 2003). The present results suggest slow rTMS delivered to the left DLPFC boosts both of these processes and thus increases the reactivity of event-related beta

power. This enhanced dynamical range of beta power was associated with increased memory performance. Hence slow rTMS over DLPFC is a means to drive pre and post-stimulus beta power in a way that optimizes memory encoding.

Slow rTMS (~1 Hz) is often regarded as an inhibitory stimulation protocol (Chen et al., 1997). Studies investigating motor evoked potentials have frequently demonstrated that slow rTMS leads to decreased cortico-spinal excitability (Chen et al., 1997; Gerschlager, Siebner, & Rothwell, 2001). Surprisingly, we found enhanced memory performance using such an arguably inhibitory rTMS protocol. However, the purportedly inhibitory effect of 1Hz rTMS has been called into question (Caparelli et al., 2012). Slow rTMS has been shown to enhance cognitive performance especially when it is applied to frontal areas (Ward et al., 2010) and increases blood flow in stimulated regions (Knoch et al., 2006; Li et al., 2004). For example, Ward and colleagues (2010) demonstrated that subjects showed increased performance in a reaction time task after receiving 1Hz rTMS to the dorsal premotor cortex. Furthermore, they found enhanced connectivity between the stimulated region and remote brain areas. These outcomes led them to conclude that increased connectivity could be the mechanisms by which 1Hz rTMS enhances cognitive function. In the present study we found that 1Hz left DLPFC stimulation can lead to desynchronized activity in posterior areas—a process which is reflective of active processing (Klimesch, 2012). Given our remote effects during left DLPFC stimulation, 1Hz rTMS may have increased functional connectivity between frontal and posterior regions (Tik et al., 2017), resulting in enhanced stimulus processing and improved memory performance.

Despite our robust behavioural results care should be taken when interpreting TMS effects. Extraneous effects arising from TMS itself can often influence behavioural measures even when an active control condition is used. DLPFC stimulation, for example, can lead to stronger sensations than Vertex stimulation. Facial muscles are more likely to be stimulated as well, leading to stronger muscle twitches in the DLPFC condition. This may be experienced as distracting and affect encoding performance accordingly. However, several studies have found similar effects as those we report here using different stimulation techniques. For example, stimulating left prefrontal areas using tDCS can enhance memory formation (Javadi & Walsh, 2012; Kirov, Weiss, Siebner, Born, & Marshall, 2009; Zwissler et al., 2014). Furthermore, Köhler and colleagues (2004) showed that stimulating the left prefrontal cortex using 7Hz rTMS results in effects similar to our own findings. Participants received 7Hz rTMS to the left inferior prefrontal cortex during a semantic encoding task (Köhler, Paus, Buckner, & Milner, 2004). Two control sites were additionally stimulated —the right inferior prefrontal cortex and a left parietal target. Only left prefrontal stimulation resulted in more high-confident hit rates. These findings are consistent with our own, and suggest that the results presented here are not merely a by-product of unspecific side effects.

4.1 Conclusion

Our results indicate that 1Hz 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 growing demand for replication studies in general (Ioannidis, 2012) and brain stimulation effects in particular (Veniero, Benwell, Ahrens, & Thut,

2017), we set out to replicate the initial incidental finding. In order to control for inter-individual differences (see for example Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014; Wiethoff, Hamada, & Rothwell, 2014), we replicated the original result in a within-subjects investigation. The findings of the second experiment reported in this chapter replicated the memory enhancement effect for items presented during 1Hz left DLPFC stimulation.

Therefore, online 1Hz rTMS of the left DLPFC appears to be an effective means of enhancing cognitive function in a classic memory task with potential applicability ranging from basic research to clinical intervention. It remains for future research to discover how 1Hz rTMS to the left DLPFC gives rise to more pronounced beta power decreases in posterior areas and enhanced memory as a result thereof.

CHAPTER 5: GENERAL DISCUSSION - SUMMARY OF FINDINGS AND FUTURE DIRECTIONS

This chapter outlines the main findings of this thesis and discusses these with respect to the broader literature. This thesis examined ways in which the formation of episodic memories can be linked causally to beta oscillatory activity with transient tACS and slow rTMS. Findings presented in Chapters 2 and 3 indicate that tACS delivered at the beta frequency might not be an effective tool for cognitive research, and especially for the investigation of short-lived oscillatory activity. In addition to these results, this chapter reviews published tACS research that casts doubt on whether tACS may be used to entrain brain oscillations in general. It will propose that 1Hz rTMS is a more effective technology for examining the relationship between beta oscillations and memory performance. The uses and effectiveness of 1Hz rTMS as a means of improving memory will be discussed. Possible mechanisms underpinning the electrophysiological influence of 1Hz rTMS, and recommendations for future directions will be proposed. Limitations of this thesis are elucidated throughout. As unexpected findings, as well as null results, are common in brain stimulation research, the need to quantify stimulation effectiveness by measuring stimulation outcomes on a behavioural and electrophysiological level will be outlined.

The experiments reported in this thesis investigated how electrophysiological underpinnings of episodic memory formation may be studied using non-invasive brain stimulation. This thesis explored the role beta oscillations play in memory formation and how brain stimulation may be used to test the causality of this relationship. In doing so, this thesis has evaluated the efficacy of transient beta tACS and slow rTMS as means of investigating the relationship between beta oscillations and long-term episodic memory formation. Desynchronized oscillatory activity, especially in the beta frequency band, has been shown to accompany successful episodic memory formation (Hanslmayr, Staudigl, et al., 2012; Salari & Rose, 2016) and is thought to reflect active processing of information (Hanslmayr et al., 2016). Hence, the ability to modulate beta oscillations non-invasively would prove invaluable in the attempt by researchers to unravel the causal relationship between beta power decreases and episodic memory formation.

In Chapter 2 we reported two experiments in which we studied the effects of transient tACS on episodic memory formation. We aimed to answer the question as to whether tACS could prove a suitable alternative or addition to rTMS when studying the relationship between short-lived oscillatory activity and episodic memory function. Participants were engaged in an incidental encoding task of verbal and non-verbal material. During stimulus presentation, subjects received tACS at five different frequencies and sham stimulation to the left or right IFG for 2s in an event-related, pseudo-randomized manner. Memory performance was assessed in a subsequent recognition test. In order to examine the effects of electrode size, the two experiments presented in Chapter 2 differed only with regards to electrode size and stimulation intensity. Taken together, the experiments presented in Chapter 2 demonstrated that beta tACS does not modulate episodic memory formation.

Chapter 3 further explored whether the stimulation parameters (i.e. stimulation duration, electrode montage, electrode size) used in Chapter 2 would in general be effective in entraining beta oscillations using transient beta tACS. In order to obtain a more direct measurement of stimulation success, we decided to assess the modulation of TMS evoked MEPs. In a simultaneous tACS-TMS experiment, participants received 10s trains of tACS at their motor beta frequency while single pulse TMS was delivered to the hand motor cortex. It has been shown that MEP size is modulated by the phase of beta oscillations over motor areas (Keil et al., 2014). To investigate whether beta tACS entrained beta oscillations in the motor cortex, we assessed whether MEP amplitude was modulated as a function of tACS phase. Furthermore, we investigated the influence of different tACS montages on entrainment success. As in Chapter 2, there were no effects of tACS on measured outcomes. 10s of beta tACS was not sufficient to modulate MEP size in Chapter 3. So, Chapters 2 and 3 indicated that irrespective of electrode size or stimulation intensity (experiments 1 and 2, Chapter 2), or whether oscillations in the IFG (Chapter 2) or motor cortex (Chapter 3) were the target, beta tACS failed to modulate beta oscillations.

As tACS proved unsuccessful in modulating beta oscillations, we turned to rTMS in Chapter 4 in order to investigate an incidental finding from a simultaneous EEG-TMS experiment. Participants were engaged in a list learning paradigm. During every encoding-retrieval run, subjects were presented with two lists of words. During encoding of the second list one group of participants received 1Hz rTMS to the left DLPFC whereas the control group received 1Hz rTMS to the Vertex. Participants who received left DLPFC stimulation exhibited enhanced memory performance for words presented during stimulation relative to the control group. This effect was

linked to more pronounced event-related beta desynchronization in posterior areas during left DLPFC stimulation, indicative of enhanced item-specific stimulus processing (Klimesch, 2012). These behavioural effects were confirmed in a within-subjects replication.

Non-invasive brain stimulation methods are valuable techniques when investigating the relationship between brain processes and cognitive function (Thut et al., 2017). Compelling evidence is now emerging that brain stimulation methods are capable of entraining or influencing brain oscillations without the need for invasive methods. This thesis has focused on two techniques in particular: rTMS and tACS. rTMS has been shown elsewhere to entrain brain oscillations in underlying cortical areas (Thut, Veniero, et al., 2011). Additionally, it has the potential to not only influence cortical activity in the stimulated areas, but to also affect remote regions along with entire networks (Wang et al., 2014), making it a powerful technique for studying the relationship between brain function and behaviour (Bortoletto et al., 2015). Recently, the application of alternating currents has been introduced as a novel way to examine the relationship between brain oscillations and behaviour (Herrmann et al., 2013). tACS, while relatively new, has been shown to influence oscillatory activity (Helfrich, Schneider, et al., 2014) and modulate behaviour accordingly (Vosskuhl et al., 2015). Importantly, stimulation with tACS can be set to higher frequencies than is possible with rTMS without eliciting harmful effects (Antal & Paulus, 2013). As a result, tACS would be a useful and practical technique if it were shown to be effective.

1. The Effects of Transient Beta tACS on Episodic Memory Formation and Motor Cortex Excitability

Transient oscillatory activity has been associated with a variety of cognitive outcomes (Başar, Başar-Eroğlu, Karakaş, & Schürmann, 1999). Desynchronized activity over sensory areas is thought to reflect active processing of stimuli and correlates with successful memory formation (Klimesch et al., 2006). As episodic memory formation relies on the encoding of stimuli (Tulving, 1984) studying brain processes associated with stimulus processing is a crucial aspect of episodic memory research (see for example Paller et al., 1987). Beta power decreases linked to the successful formation of memories have been observed up to 1s/1.5s after stimulus onset (Griffiths et al., 2016; Hanslmayr, Volberg, et al., 2011). Studying the causal relationship between this transient oscillatory process, in this particular time window, and memory performance requires modulation of these processes in a temporally sensitive manner (Stonkus et al., 2016).

In a series of experiments in Chapters 2 and 3 we explored whether tACS in the beta frequency range, applied in the range of seconds, is an effective means of entraining brain oscillations and thereby influencing behavioural outcomes. In Chapter 2 we showed that 2s of beta tACS during presentation of a stimulus is not sufficient to modulate memory performance. We failed to replicate findings obtained from an rTMS study (Hanslmayr et al. 2014), casting doubt on the effectiveness of transient beta tACS for cognitive research. Similarly in Chapter 3, 10s of beta tACS did not modulate MEP amplitude, further supporting the notion that transient beta tACS might not be strong enough to influence or entrain ongoing beta oscillatory activity.

1.1 Failure to Replicate rTMS Effects Using tACS

In Chapter 2 we sought to conceptually replicate findings reported by Hanslmayr and colleagues (2014). In the original study, stimulating the left IFG during verbal memory encoding with beta rTMS impaired memory performance. Using tACS we were unable to obtain similar results. That is, beta tACS delivered for 2s to the prefrontal cortex did not modulate episodic memory formation. However, rTMS and tACS differ greatly in a number of important parameters.

tACS induces weaker electric fields than TMS, applies less focal stimulation, and is thought to modulate rather than induce neural activity (Priori, Hallett, & Rothwell, 2009). Hence, tACS may not have been sufficiently strong to interfere with underlying neural activity and entrain prefrontal beta oscillations with the parameters used and over the short time period at which it was applied in Chapter 2. Measured electrical field strengths in tACS studies using conventional electrodes and stimulation intensities range from 0.16 V/m (Lafon et al., 2017) to 0.5 V/m (Opitz et al., 2016) whereas TMS has been shown to elicit field strengths of over 100V/m (Reithler, Peters, & Sack, 2011). The sizeable differences between field strengths elicited by TMS and tACS may account for our failure to replicate the results of the original study. Future research should take these into account when seeking to replicate rTMS findings using tACS. Apart from the difference between the field strengths induced by each stimulation technique, TMS stimulation is also more focal than tACS. TMS has been reported to stimulate approximately areas of $5cm^2$ of cortex (Thielscher & Kammer, 2004), whereas tACS, as deployed in this thesis, elicits a much broader electrical field (see Figure 2). Moreover, and in contrast to the tACS experiments reported in Chapters 2 and 3, Hanslmayr and colleagues (2014)

guided their stimulation using neuronavigation techniques. MRI scans from every participant were obtained and target regions identified for each subject individually. The TMS coil was placed such that the target area could be stimulated effectively, and the position of the coil was monitored throughout the experiment in order to assure precise stimulation. However in Chapter 2, placement of the stimulation electrodes was determined using commercially available software that modelled current distribution based on one adult male brain only (Soterix Medical Inc, New York, USA). Given these differences between the techniques, more efforts should be made to improve the precision of tACS.

Advances have been made to increase focality of tES. Multi electrode arrays have been reported to lead to more focal stimulation (Dmochowski et al., 2011; Sadleir, Vannorsdall, Schretlen, & Gordon, 2012). Furthermore, the development of *temporal interference stimulation* may provide another way to stimulate cortical areas more precisely (Grossman et al., 2017). For example, Grossman and colleagues stimulated mice with two high frequency fields simultaneously. The fields used greatly exceeded the level necessary for normal neural firing (i.e. >= 1kHz) but their frequencies differed only marginally. This protocol evoked neural firing at rates approximating the difference between each stimulation frequency. Furthermore, their technique made it possible to stimulate areas without affecting overlaying cortical neurons, leading to more precise stimulation, making tACS all the more effective (Dmochowski & Bikson, 2017). Recent studies have also shown that individual brain anatomy can greatly affect current distribution (Opitz et al., 2015). Therefore adjusting electrode placement, electrode shape, and other parameters according to individual MRI scans increases the specificity and efficacy of tACS protocols

(Cancelli, Cottone, Di Giorgio, Carducci, & Tecchio, 2015; Datta et al., 2009; Saturnino et al., 2015).

Although Chapter 2 failed to replicate findings that had previously been obtained with rTMS, differences between the techniques might account for this outcome: tACS induces weaker electric fields and less focal stimulation than TMS. In spite of efforts to increase the efficacy of tACS stimulation by individualizing stimulation parameters (etc.), the questions remain as to whether beta tACS, when applied in the range of seconds, is effective at modulating underlying oscillatory activity.

1.2 Stimulation Duration – a Factor to Consider for tACS Studies

During a variety of cognitive tasks, brain oscillations display highly dynamic activity with power changes occurring in the range of seconds on average (Başar et al., 1999). When trying to uncover the relationship between these transient processes and behaviour, brain stimulation methods must first be effective in modulating underlying activity over similar durations. However, findings from experiments presented in this thesis cast doubt on whether tACS in the beta frequency range may be successful in doing so.

Our failure to find effects of tACS on behaviour contradicts previous findings. tACS applied for minutes has been shown to modulate a variety of cognitive processes (see for example Jaušovec et al., 2014; van Driel et al., 2015). Such results have been accompanied by convincing electrophysiological (e.g. Ali et al., 2013; Ozen et al., 2010) and modelling evidence (e.g. Ali et al., 2013). tACS has also been shown to successfully modulate performance on a visual perception task when applied for shorter periods to synchronize and desynchronize distant brain

regions (Stonkus et al., 2016). Data from animal studies and slice preparations further suggest that the brief stimulation durations used in Chapter 2 and 3 ought to have been successful in entraining oscillations (Ali et al., 2013). However, research has also shown that when using tACS to entrain brain oscillations in a given region, shorter stimulation durations have nonetheless failed to modulate behaviour (e.g. Strüber et al., 2015; Vossen et al., 2015). Furthermore, when applying tACS for 1s, electrophysiological findings obtained with 20min of stimulation could not be replicated (Strüber et al., 2015). For example, stimulating participants at their individual alpha frequency for 20min resulted in enhanced alpha power after stimulation (Neuling et al., 2013). Yet, applying tACS at short intermittent intervals of 1s at the participant's individual alpha peak frequency in a similar paradigm did not yield any such effects (Strüber et al., 2015). tACS did not enhance alpha power when applied for shorter durations, nor did it lead to greater phase locking, suggesting that it had failed to entrain alpha oscillations. In line with this, simultaneous tACS-TMS studies have revealed that although tACS may entrain beta oscillations in the motor cortex (Guerra et al., 2016; Nakazono et al., 2016), and modulate MEP size as a function of tACS phase, such effects are likely to occur only after the stimulation has been applied for several minutes (Raco et al., 2016).

Such findings demonstrate that stimulation duration may play a key role in the effectiveness of tACS, and give reason to doubt on its effectiveness as a technique that can be used to examine the relationship between transient oscillatory activity and behaviour.

1.3 tACS and Entrainment: the Emergence of Null Findings

tACS could be a powerful tool to explore the relationship between brain oscillations and cognitive functions (Herrmann et al., 2013). Despite numerous findings which support the notion that tACS can be used to entrain brain oscillations, others call the idea into question (Kleinert, Szymanski, & Müller, 2017; Krause & Cohen Kadosh, 2014; Lafon et al., 2017; Reato, Rahman, Bikson, & Parra, 2013; Veniero et al., 2017; Veniero, Vossen, Gross, & Thut, 2015; Vossen et al., 2015). Indeed mixed results in human studies are matched by similarly ambiguous findings in slice preparations and animal models. Reato and colleagues (2013) for example argued that tACS effects may be more complicated than is often implied in work with humans. Although they showed that tACS entrains oscillatory activity, it also induces unexpected non-linear effects depending on the underlying network (Reato et al., 2013, p 4). Recent work has also explored whether tACS is effective as a means of entraining oscillations in human subjects. Due to excessive stimulation artefacts, measuring entrainment during brain stimulation is challenging (Noury, Hipp, & Siegel, 2016). Therefore increased EEG power after the stimulation has ended is normally assumed to represent entrainment (e.g. Marshall, Helgadóttir, Mölle, & Born, 2006; Neuling et al., 2013). However, Vossen and colleagues have proposed that increased alpha power typically observed after prolonged alpha tACS might not reflect alpha entrainment (Vossen et al., 2015). Rather, the authors conclude that aftereffects of tACS on EEG power are more likely to be indicative of plastic changes that build up over time. Vossen and colleagues (2015) applied trains of 8s or 3s alpha tACS in an intermittent fashion to the occipital cortex of healthy human participants while recording EEG data. The authors observed increased alpha power only after tACS had been applied for 8s. However, these aftereffects did not

exhibit the properties typically associated with an entrainment account (Thut, Schyns, et al., 2011). For example, whether or not the tACS trains were in or out of phase did not affect EEG aftereffects. Likewise, these aftereffects were not specific to stimulation frequency and phase locking in the time period immediately after the stimulation was not observed. These results indicate that entrainment, if present, did not outlast the stimulation and cast doubt on the ability of tACS to entrain brain oscillations in general.

As described earlier, tACS induces relatively weak electrical fields in the brain. Recently the issue as to whether the weak field intensities induced by tACS are strong enough to interfere with an active network has been called into question (Lafon et al., 2017; Opitz et al., 2016). For example, Lafon and colleagues (2017) collected intracranial recordings in humans during tACS, thus providing unique insights into the mechanisms behind the technique. The authors stimulated epilepsy patients with 0.75Hz and 1Hz tACS during non-REM sleep while recording neural activity from implanted electrodes. Entrainment of slow wave activity was determined by measuring spindle and gamma activity as a function of tACS stimulation. Though previous research has shown that slow tACS during non-REM sleep may be used to entrain slow wave activity (Marshall et al., 2006), tACS in this study neither entrained sleep spindles, modulated the relationship between spindle and gamma activity, nor induced slow waves after stimulation during sleep, indicating that tACS failed to entrain slow oscillations. More importantly the authors reported that stimulating with intensities even greater than those typically used in tACS studies led to field intensities below what would be needed to result in entrainment (Lafon et al., 2017). These findings are consistent with the idea that tACS might not be effective in modulating neural oscillations.

Recent studies have cast doubt on whether tACS effects are the result of neural entrainment. Although a growing body of studies report null findings (e.g. Brignani, Ruzzoli, Mauri, & Miniussi, 2013) and internal failed replications (Veniero et al., 2017), others continue to report effects on behaviour and neural activity (Kasten & Herrmann, 2017; Johannes Vosskuhl, Huster, & Herrmann, 2016). It is therefore necessary to further examine these findings.

1.4 The Effectiveness of Transient Beta tACS

Evidence regarding the effectiveness of tACS is mixed. Although in general tACS is often reported to be an effective means of influencing membrane potentials (e.g. Ozen et al., 2010), the effects of alternating currents on network function are thought to be variable and potentially unpredictable (Reato et al., 2013). Moreover, recent studies suggest that utilizing tACS can result in negative or mixed behavioural findings (see e.g. Veniero et al., 2017).

Future research ought therefore to investigate the link between tACS and brain oscillations. More work is needed to understand the mechanisms which underpin its oscillatory effects, aim to understand whether and how tACS can be a useful tool for cognitive research, and thereby inform researchers on the parameters which are effective in inducing the desired oscillatory outcomes. Optimal electrode montages (Datta et al., 2009; Dmochowski et al., 2011), intensities most effective for stimulation, and the ideal shape of electrodes (Cancelli et al., 2015), and timing for stimulation must be understood first, before transient tACS may be utilized as a technique. Though an increasing number of sophisticated computational and animal/in vitro models have been developed, future research must confirm whether these data are applicable to human subjects. The findings presented in this thesis

indicate that transient tACS in the beta frequency range is not an effective tool for cognitive research, at least not with the stimulation protocols used here.

2. The Effects of Slow rTMS on Episodic Memory Formation

Beta power decreases have been linked with successful memory performance (Hanslmayr, Staudigl, et al., 2012). Similarly, artificial increases in beta power (evoked by rTMS) can hinder memory formation (Hanslmayr et al., 2014). However, non-invasive brain stimulation may be used to do more than merely impair episodic memory encoding. The two experiments presented in Chapter 4 demonstrated that rTMS can also be used to enhance verbal memory formation.

Humans are able to recall episodes experienced many years prior to recall (Tulving, 2002). However, episodic memory is limited (Paller & Wagner, 2002). Several research groups have set out to explore whether different types of brain stimulation can be used to enhance long-term memory formation. Whether through the use of electrical currents induced via electrodes implanted in the brain of epileptic patients (Ezzyat et al., 2017) or the application of non-invasive methods such as rTMS (Wang et al., 2014) and tDCS (Javadi & Walsh, 2012; Zwissler et al., 2014), brain stimulation may not only advance out understanding of memory function (Floel & Cohen, 2007) but might contribute to therapeutic interventions. Indeed, Wang and colleagues (2004) have shown that rTMS has the potential not only to enhance memory, but that it may lead to remote effects that contribute to behavioural changes (see also Pascual-Leone et al., 2000).

As with these studies cited here, in Chapter 4 we also demonstrated that rTMS influences remote regions and induces a state known for its beneficial effects on stimulus processing (Klimesch et al., 2006).

2.1 1Hz rTMS to the Left DLPFC Enhances Stimulus Processing

A first causal link between beta oscillations and memory performance was provided by Hanslmayr and colleagues (2014). Artificially synchronizing the left prefrontal cortex with beta rTMS during stimulus presentation decreased memory performance. In Chapter 4 we showed that beta power can be modulated by applying slow rTMS to the left DLPFC.

Successful formation of episodic memories is linked to event-related power decreases in the beta frequency band (Hanslmayr, Volberg, et al., 2011). It has further been proposed that memory formation may be more successful when cortical areas are deactivated before the presentation of the to-be-remembered items (Klimesch et al., 2006). Increased alpha/beta power is thought to reflect cortical deactivation (i.e. inhibition) (Jensen & Mazaheri, 2010; Klimesch, 2012) whereas desynchronized activity has been linked to neural firing and active stimulus processing (Hanslmayr et al., 2016; Pfurtscheller & Lopes da Silva, 1999). This is particularly true for the beta frequency band, in fact the pattern has been observed in a plethora of studies in which higher pre-stimulus beta power (Schneider & Rose, 2016) and post-stimulus beta desynchronization (Hanslmayr, Volberg, et al., 2011) have correlated with successful episodic memory formation. In Chapter 4 we showed that these processes can be enhanced via non-invasive brain stimulation. Administering 1Hz rTMS to the left DLPFC during episodic memory encoding enhanced pre-stimulus beta power and decreased post-stimulus beta power in posterior regions. Moreover, these effects

were specific to trials in which rTMS was applied and corresponded with enhancements in memory performance.

Left frontal areas, including the target region stimulated in Chapter 4 (left DLPFC), have been shown to be involved in successful encoding of verbal material (Wagner et al., 1998), especially when semantic processing is of importance (Kim, 2011; Otten et al., 2001; Otten & Rugg, 2001b). As a result, the left prefrontal cortex has been the target of brain stimulation studies which have sought to understand the details of its relationship with memory function (e.g. Kirov et al., 2009; Köhler, Paus, Buckner, & Milner, 2004b; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2001). In Chapter 4, 1Hz rTMS applied to the left DLPFC during verbal memory encoding led to enhanced memory performance. Moreover, left DLPFC stimulation was linked with modulation of beta power in posterior regions, resulting in superior stimulus processing (Klimesch, 2012). It has also been shown that the interplay between frontal and posterior regions is especially important for processing and organizing material in working memory (Corbetta & Shulman, 2002; Naghavi & Nyberg, 2005; Smith, Jonides, & Koeppe, 1996; Wagner et al., 1998), which could be crucial for memory formation (Blumenfeld & Ranganath, 2006; Fletcher, Shallice, & Dolan, 1998). However, in the experiments reported here, DLPFC stimulation enhanced stimulus processing without affecting associations between items. DLPFC stimulation did not affect the amount of contextual clustering or enhanced memory performance for items at particular positions in the list. Rather, temporal clustering analysis and analyses of serial position curves revealed that 1Hz left DLPFC stimulation increased stimulus processing at an item-specific level.

Therefore item-specific stimulus processing in posterior areas, guided by prefrontal regions could be a crucial mechanism by which verbal memories are encoded. In Chapter 4, we were able to show that this process may be boosted by stimulation of the left DLPFC with 1Hz rTMS.

2.2 Future Directions

Chapter 4 showed that 1Hz rTMS—a stimulation protocol thought to inhibit underlying cortical excitability (Chen et al., 1997)—improves memory performance. Indeed, left DLPFC stimulation gave rise to a state that is thought to be beneficial for stimulus processing (Klimesch, 2012). Moreover, these effects were elicited online during stimulation. This has implications not only for future research but also for possible clinical interventions.

Slow rTMS has traditionally been understood to reduce cortical excitability (Chen et al., 1997). When stimulating the motor cortex, slow rTMS applied for 15min. decreases the amplitude of motor evoked potentials. However, evidence is now emerging which links 1Hz rTMS to increased blood flow (Knoch et al., 2006; Li et al., 2004), better behavioural performance, and enhanced connectivity between target and remote areas (Ward et al., 2010). Such finding cast doubt on the purely inhibitory role that this stimulation protocol has been reported to play. Moreover, animal work has revealed that slow frequency rTMS actually increases spontaneous neural firing immediately after the TMS pulse (Allen et al., 2007). In Chapter 4 1Hz rTMS was applied during verbal memory encoding for 45s per run. Behavioural as well as EEG analyses revealed that 1Hz rTMS increased item specific stimulus processing and thus enhanced memory encoding online. We can only speculate as to whether our stimulation protocol enhanced or inhibited the targeted region. However,

studies that have reported inhibitory effects for slow rTMS have usually applied stimulation for prolonged periods (see for example Chen et al., 1997; Gerschlager et al., 2001). Whether online effects of slow rTMS differ from the effects that follow extensive stimulation remains an open question.

1Hz rTMS to the left DLPFC robustly enhanced memory formation and modulated posterior beta power. However, it remains unclear whether these effects are specific to the stimulation frequency or the stimulation site used in Chapter 4. Other studies have reported similar behavioural and electrophysiological effects with different stimulation techniques (Javadi & Walsh, 2012) and different rTMS frequencies (Klimesch et al., 2003; Köhler et al., 2004). For example, Köhler and colleagues (2004) demonstrated increased verbal memory performance after stimulating the left inferior prefrontal cortex with 7Hz rTMS during memory encoding. Additionally, Klimesch and colleagues (2003) found that stimulating the frontal or parietal cortex at the participant's individual alpha frequency modulated posterior alpha power in a similar way to that reported in our study (Klimesch et al., 2003). Given findings such as these it is important to test how specific the effects obtained in Chapter 4 are. Explorations of different stimulation frequencies and stimulation sites may contribute to a more complete understanding of the mechanisms behind such effects.

Alpha/beta oscillations have not only been implicated in memory formation, but in a variety of other cognitive functions (i.e. attention, perception, working memory, etc.) (Engel & Fries, 2010; Hanslmayr, Gross, Klimesch, & Shapiro, 2011; Klimesch, 1999, 2012; Klimesch et al., 2003; Sauseng et al., 2005, 2009; Womelsdorf & Fries, 2007). Alpha/beta power has been shown to be elevated over

cortical areas responsible for storing to-be-inhibited, irrelevant, and potentially interfering information (Jensen & Mazaheri, 2010; Waldhauser et al., 2012). In contrast, alpha/beta power is decreased over areas that are actively involved in the representation of sensory information (Waldhauser et al., 2016). Future research might therefore wish to investigate whether a similar rTMS protocol as that used in Chapter 4 is also effective in modulating cognitive performance in general (see for example Klimesch et al., 2003). In particular the ability to target remote areas, and to increase their processing strength online, deserves further investigation. Various clinical populations display deficient task-related modulations of alpha/beta power (Kustermann, Rockstroh, Kienle, Miller, & Popov, 2016; Meconi et al., 2016). Patients suffering from schizophrenia, for example, show less lateralization of alpha power when asked to attend to stimuli in a visual hemifield paradigm compared to healthy controls (Kustermann et al., 2016). Our research suggests that 1Hz rTMS may be an effective means of influencing and enhancing brain functions. As such it has the potential for application in clinical interventions, in particular with respect to these clinical populations.

3. The Importance of Measuring Stimulation Success

The studies reported in this thesis set out to investigate ways in which the electrophysiological underpinnings of episodic memory formation may be investigated using non-invasive brain stimulation. From Chapter 2 we learned that transient beta tACS does not modulate memory performance, while Chapter 4 revealed unexpected effects of slow rTMS on episodic memory formation. However, the mechanisms by which long-term memory formation was, or was not modulated are not evident from behavioural effects alone. And so, this thesis also attests to the

importance of measuring neural activity during stimulation (Reithler et al., 2011; Siebner et al., 2009; Taylor et al., 2008; Thut et al., 2017). Without such measures it is not possible to quantify whether a brain stimulation protocol has modulated underlying neural activity let alone whether it has done so in the expected way.

Measuring stimulation outcomes not only on a behavioural, but also on an electrophysiological level is vital in order to understand how stimulation protocols influence behavioural outcomes. In Chapter 2 brain activity during stimulation was not recorded. Therefore we were unable to conclude whether beta oscillations in the left IFG are not involved in verbal episodic memory formation, or whether our transient tACS protocol simply failed to modulate beta oscillations in the prefrontal cortex. Only by testing whether transient beta tACS, in general, leads to beta oscillatory entrainment and by using more objectively quantifiable stimulation outcomes (i.e. MEP amplitude) in Chapter 3, we were able to conclude that transient beta tACS is an ineffective means of modulating beta oscillations and therefore episodic memory formation. In Chapter 4 1Hz rTMS to the left DLPFC during encoding of verbal material enhanced memory performance. Surprisingly, we found enhanced memory performance using this, arguably, inhibitory rTMS protocol. However, the mechanisms responsible for this effect could not be revealed from the behavioural effects alone. Simultaneously recorded EEG data allowed us to investigate the electrophysiological effects associated with this behavioural outcome. While we could not unravel the effects in their entirety, the EEG data provided us with important insights concerning this effect. 1Hz rTMS to the left DLPFC resulted in modulation of beta power in posterior areas reflecting item specific stimulus processing (Hanslmayr et al., 2016). Beta power was significantly lower after word onset and significantly higher immediately before word onset in the DLPFC group

compared with the control group. These findings highlight the mechanisms through which slow rTMS can boost memory, inferences which would not have been possible without having first analysed the effects of rTMS on neural activity during the task.

Brain stimulation experiments set out to understand how a neural process contributes to certain behavioural outcomes. In this respect they are thought to complement correlational findings from imaging studies (Herrmann et al., 2015). However, if target behaviours are not modulated in the predicted way (or are not modulated at all) drawing conclusions about the role of oscillatory underpinnings of these behaviours proves difficult. This issue is especially apparent when the success of a stimulation protocol is measured solely in terms of the modulation of the behaviour in question. Although brain stimulation studies are thought to provide causal links between brain processes and behaviour, making inferences about such links proves challenging when manipulations lead to null results or contradictory findings on the behavioural level: It is unclear whether the stimulation protocol failed to modulate neural activity in the predicted way or whether the neural process was not causally related to the behavioural outcome.

There are a growing number of null findings and demands for replication studies, especially regarding brain stimulation effects (Lafon et al., 2017; Veniero et al., 2017). Therefore investigating why and when brain stimulation techniques do not yield positive behavioural outcomes is increasingly important. In cognitive paradigms various factors can contribute to null findings, making it difficult to assess whether the stimulation has been successful. By stimulating the primary motor or visual cortex the outcomes of brain stimulation may be measured more objectively,

independent of cognitive processes. This can be done by measuring motor evoked potentials (Feurra et al., 2013), physiological tremor (Mehta et al., 2015) or other peripheral effects like phosphenes (Romei, Rihs, Brodbeck, & Thut, 2008). Though measuring the outcomes of stimulation applied to the primary motor cortex, for example, is relatively straightforward, evaluating the effects of stimulation applied to other brain areas is more difficult. Recording neural activity using fMRI, MEG or EEG during or directly after stimulation may provide a useful starting point when seeking to understand how transcranial brain stimulation could be used to study cognitive processes (Siebner et al., 2009; Thut et al., 2017). Although analysing data recorded during stimulation presents a challenge (Farzan et al., 2016; Noury et al., 2016) and naturally is more demanding of researchers, overcoming these issues is essential to advancement. Although methods are currently being developed that remove stimulation artefacts from EEG recordings, other measures might be used to quantify the success of a stimulation technique. These could include the analysis of data after the stimulation has ended (see for example Hanslmayr et al., 2014; Stonkus et al., 2016; Veniero et al., 2015) or neural activity known to be associated with the neural process in question. Lafon and colleagues (2017), for example, used neural activity usually coupled with their oscillatory process of interest in order to assess whether their stimulation protocol entrained brain oscillations. The authors sought to entrain slow oscillations in participants during non-REM sleep while recording neural activity from intracranial electrodes. Lafon and colleagues opted to measure activity coupled with slow waves (i.e. sleep spindles and gamma activity) to assess whether their stimulation protocol had been a success. They did so with this measure, rather than analysing slow oscillatory activity directly, since although activity coupled to slow waves would also have been affected by the stimulation,

unlike slow oscillatory activity itself, sleep spindles and gamma activity would not be contaminated by it. With their unique dataset Lafon and colleagues revealed that tACS did not entrain slow waves during sleep and indeed might not even be strong enough to interfere with the functioning of active networks during sleep. Having measured stimulation success (or lack of success) more directly, the authors found evidence that the technical shortcomings of previous research may have led them to false conclusions.

Previous research has shown that slow tACS during sleep may entrain slow wave activity and lead to enhanced declarative memory performance (Marshall et al., 2006). Although Lafon and colleagues (2017) failed to demonstrate entrainment of slow wave activity, the authors were unable to relate their findings to memory performance—memory performance was not assessed in their research. In this respect, the authors had tested the efficacy of tACS on only one outcome. It is not possible therefore to use their research to conclude that tACS does not influence behaviour. A combination of behavioural and electrophysiological findings is crucial if experiments are to explore the effects of non-invasive brain stimulation on underlying neural activity and behaviour, and so to shed light on the reasons as to why tACS works in some paradigms and yet it fails to do so in others.

Quantifying whether a stimulation protocol has successfully modulated underlying activity is a crucial step in unravelling the correlational relationship between brain activity and behaviour. This is especially true for researchers faced with unexpected effects. The present thesis demonstrates that it is necessary to understand whether and how a given stimulation technique interacts with neural activity in order to evaluate the link between this and its behavioural outcomes.

Chapter 3 supported our conclusion that transient beta tACS is not an effective means of entraining oscillatory activity. So the stimulation protocol used in Chapter 2 was most likely not successful in modulating beta oscillations in the IFG. What's more, the neurophysiological mechanisms behind the unexpected behavioural finding reported in Chapter 4 could only be investigated because EEG data was recorded during rTMS. Hence, by examining the boundary conditions in terms of which parameters work and acquiring measures of oscillatory function directly, research may identify the techniques and protocols that are effective. Only when these are known can brain stimulation be effective as an experimental tool, and useful to researchers who wish to explore the contributions that certain brain activity makes to cognition.

4. Conclusion

Beta power decreases accompany successful formation of episodic memories (Hanslmayr, Volberg, et al., 2011). However, more evidence is needed to show that beta desynchronization, while undoubtedly associated with episodic memory formation, is *causally* involved in this process. If effective, non-invasive brain stimulation would enable research into this relationship (Thut et al., 2017). Throughout this thesis, I have presented experiments which sought to examine the efficacy with which different non-invasive brain stimulation techniques modulate beta oscillations, with the aim to manipulate episodic memory formation. Two stimulation techniques were evaluated and the effects of novel stimulation protocols were tested. In doing so, we sought to discover the involvement of beta power decreases in memory formation. Event-related transient beta tACS proved ineffective in modulating short-lived beta oscillations in the prefrontal cortex. In contrast, an

online slow rTMS protocol brought about pronounced beta power modulation and robustly enhanced memory performance.

Taken together, the research presented in this thesis highlights the importance of null and unforeseen findings, along with novel uses of existing techniques. Advancing our understanding of transcranial brain stimulation may help us unravel the causal role that oscillatory activity, such as beta power decreases, play in the formation of episodic memories.

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Appendix A

Chapter 2: Memory Performance Experiment 1

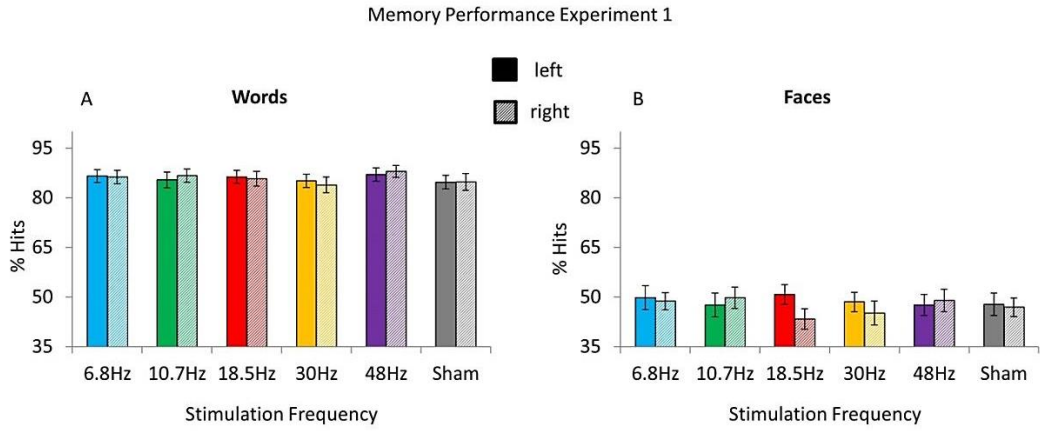

Figure A. Memory performance for words (A) and faces (B) split by stimulation condition and stimulation site for experiment 1 is shown.

No interaction between stimulation frequency and stimulation site could be found for words, $F(5,175) = 0.226$, $p = 0.951$. There was no difference between left 18.5Hz stimulation and left sham stimulation, $t(35) = 0.859$, $p = 0.396$.

No interaction between stimulation frequency and stimulation site could be found for faces, $F(5,175) = 1.618$, $p = 0.157$. There was no difference between right 18.5Hz stimulation and right sham stimulation, $t(35) = -1.287$, $p = 0.207$.

Appendix B

Chapter 2: Memory Performance Experiment 2

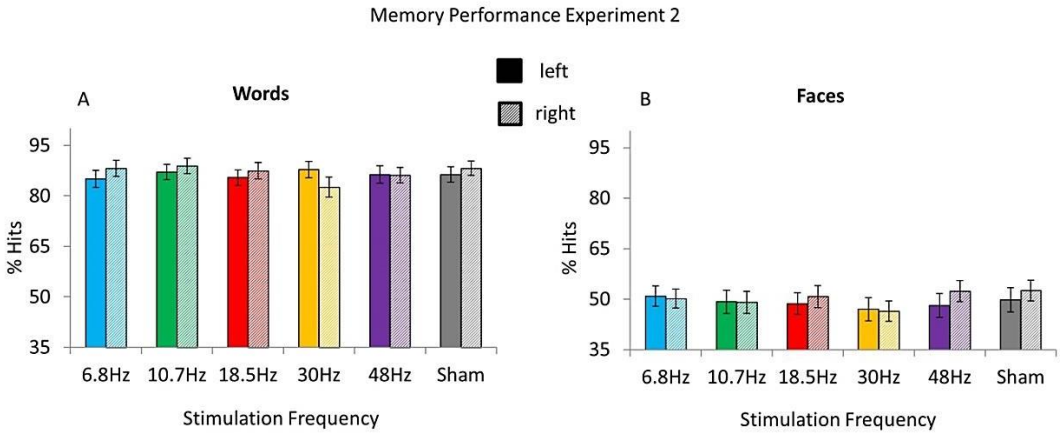

Figure B. Memory performance for words (A) and faces (B) split by stimulation condition and stimulation site for experiment 2 is shown.

Although a significant interaction between stimulation frequency and stimulation site could be found for words, $F(5,175) = 2.558$, $p = 0.029$, there was no significant difference between left 18.5Hz stimulation and left sham stimulation, $t(35) = -0.354$, $p = 0.726$.

No interaction between stimulation frequency and stimulation site could be observed for faces, $F(5,175) = 0.526$, $p = 0.756$. No difference between right 18.5Hz stimulation and right sham stimulation could be found, $t(35) = -0.657$, $p = 0.515$.

Appendix C

Chapter 2: Intensity and Phosphene Ratings

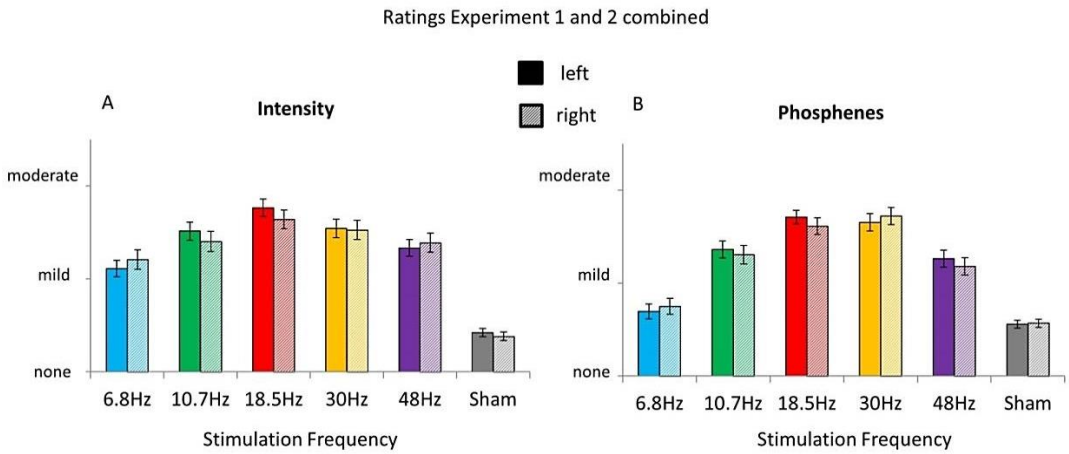

Figure C. Ratings of the intensity of the stimulation (A) and the strength of the stimulation induced phosphenes (B) collapsed over both experiments. Participants rated the sensations on a 6-point rating scale (none – unbearable; none = 1; mild = 2; moderate = 3).

The mean ratings for the stimulation conditions are shown. Subjects were asked to rate the intensity of the stimulation induced sensations and phosphenes for every stimulation condition separately on a 6-point rating scale (none – unbearable). Friedman ANOVAs were carried out to test for difference between the stimulation conditions. Neither the ratings for stimulation intensity nor strength of perceived phosphenes differed between left and right stimulation. However, there were significant differences between the stimulation frequencies for both, the intensity as well as the phosphene strength ratings.

Appendix D

Chapter 3: Hardware Noise in MEP Data

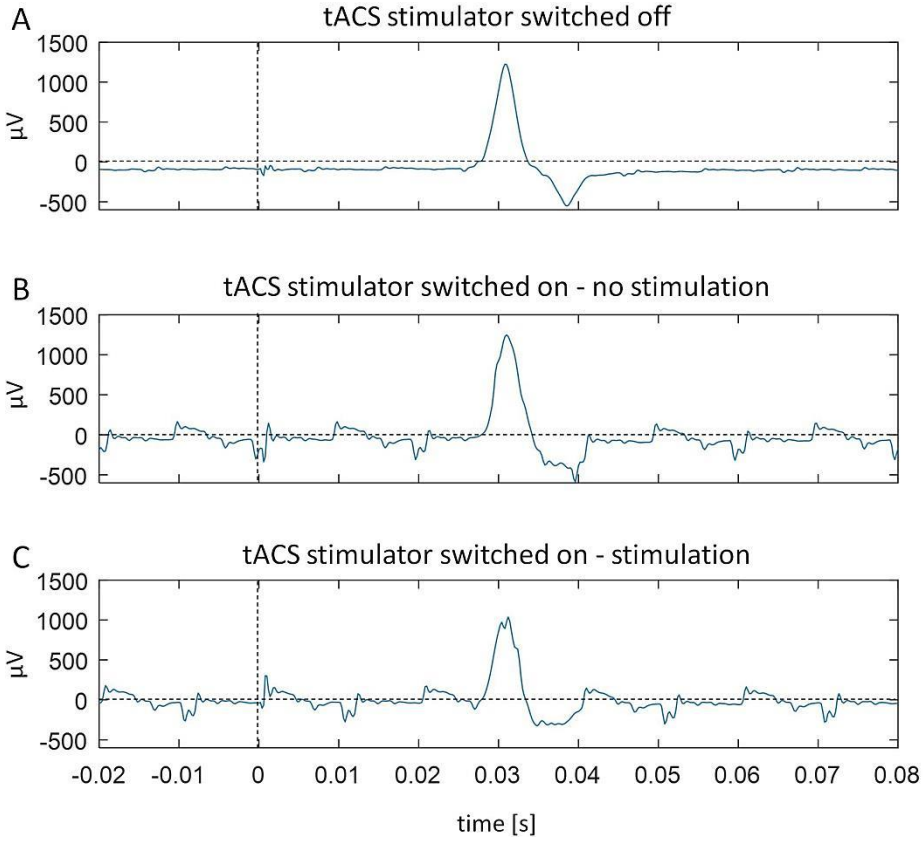

Figure D. MEP recordings of a single subject. 3 single trials are depicted. A. MEP recording with the tACS stimulator switched off. B. MEP recording with the stimulator switched on but during a no-tACS trial. C. MEP recording during tACS

Appendix E

Chapter 3: tACS Artifacts

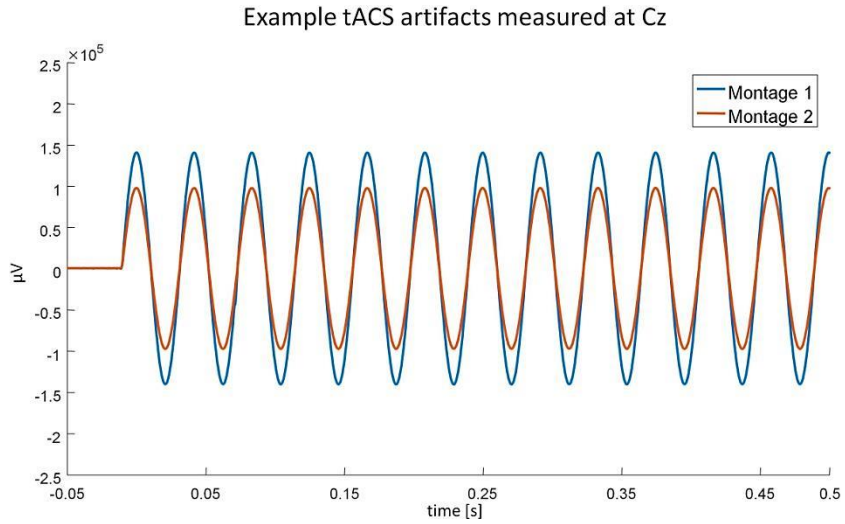

Figure E. Single trial example of tACS artifacts measured at Cz for Montage 1 and 2. There was no phase shift between the artifacts

Appendix F

Chapter 3: MEP Amplitude Before z-Transformation

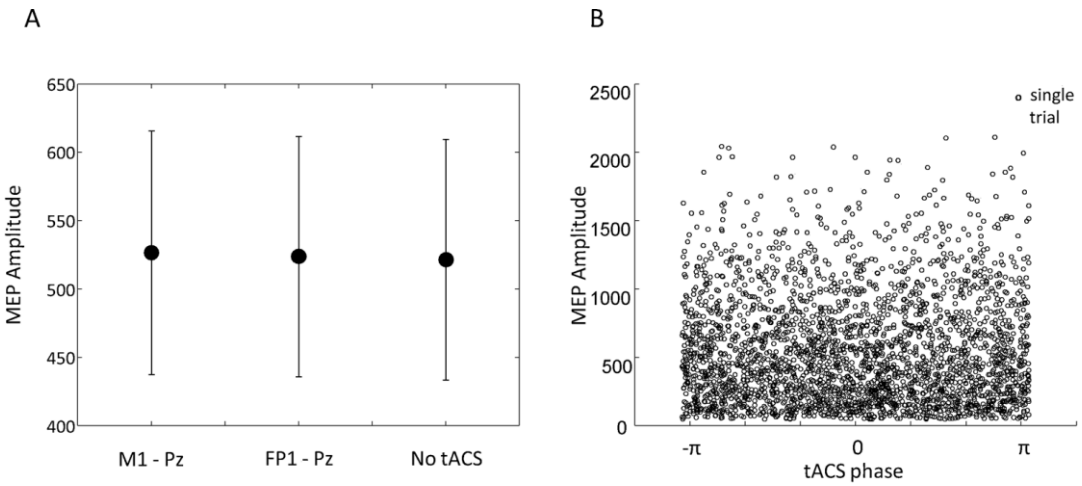

Figure F. (A) Mean MEP amplitude split by tACS condition. No difference between the conditions could be found. Error bars show standard errors of the mean. (B) Single trial MEP size by tACS phase. No correlation between MEP size and tACS phase could be found, ρcl = 0.0304, p = 0.2574

Appendix G

Chapter 3: MEP Amplitude Before z-Transformation Split by Montage

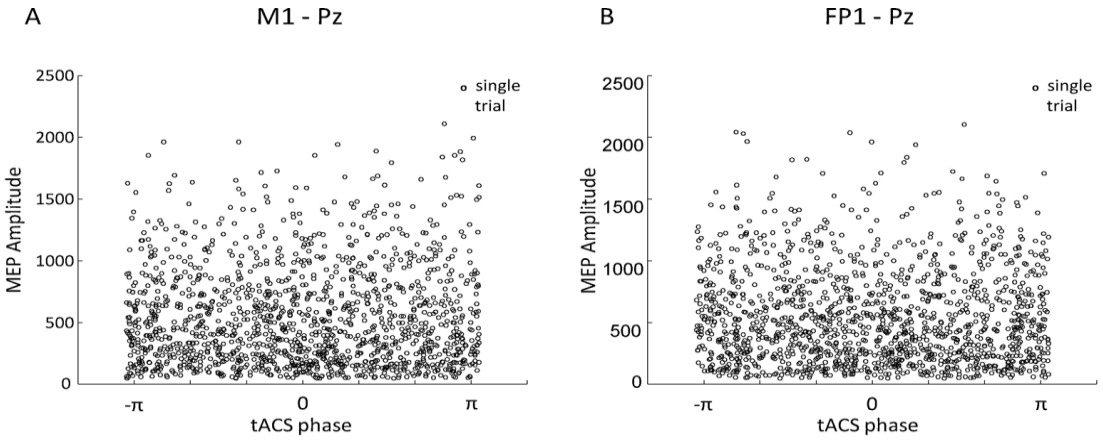

Figure G. Single trial MEP amplitude by tACS phase. (A) tACS electrodes at M1 and Pz. No significant correlation between MEP amplitude and tACS phase could be found, ρcl = 0.0202, p= 0.7395. (B) tACS electrodes at FP1 and Pz. No significant correlation between MEP amplitude and tACS phase could be found, ρcl = 0.0487, p = 0.1763.

Appendix H

Chapter 3: MEP Amplitude Before z-Transformation – Phase Bins

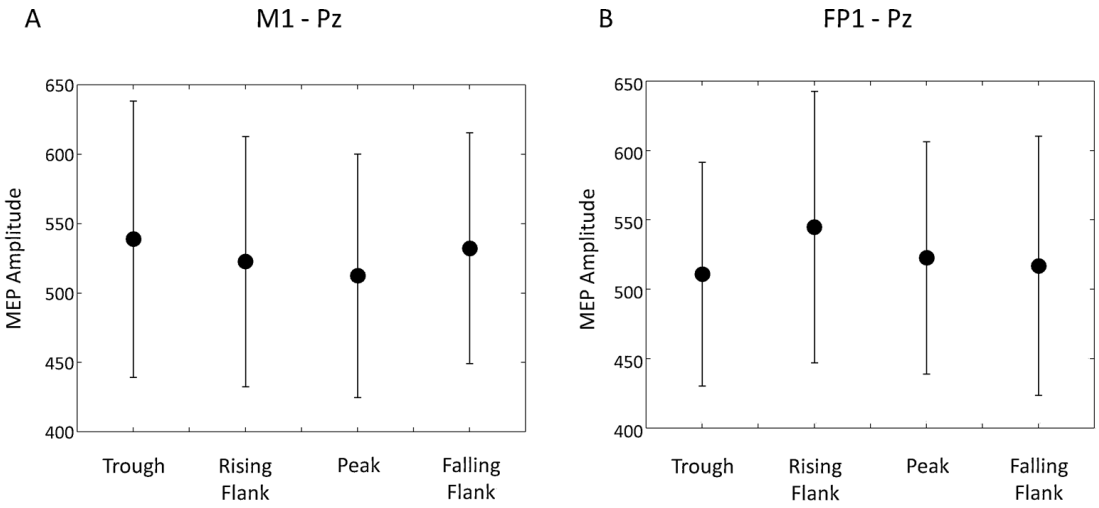

Figure H. Mean MEP amplitude split by 4 different tACS phase bins: 180° (trough), 270° (rising flank), 0° (peak), 90° (falling flank). (A) tACS Montage 1: M1-Pz. (B) tACS Montage 2: FP1-Pz. Error bars show standard errors of the mean. A 3-way ANOVA with the factors *Session*, *Montage* and *Phase bin* showed neither a main effect for the tACS phase, $F(3,21)= 0.423$, $p=0.739$, nor an interaction between electrode montage and phase, $F(3,21)= 0.698$, $p=0.564$. There was a main effect of *Session,* $F(1,7)= 6.649$, $p=0.037$.

Appendix I

Chapter 4: Memory Performance Experiment 2

Table I
Memory Performance Chapter 4, Experiment 2 split by stimulation condition and list

	DLPFC	Vertex
list 1 – no TMS	51.11 (3.96)	43.89 (4.58)
list 2 –TMS	39.58 (4.66)	31.67 (3.42)

Note. Standard error of the mean is depicted in parentheses.