Brain oscillatory correlates in working memory and attentional control processes

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Abstract

Human working memory and selective attention processes in need of top-down cognitive control rely on interactions within local neural populations and between distant brain areas in a fronto-parietal neural network. Brain oscillatory dynamics drawing on slow oscillatory activity in the theta frequency range are associated with (1) information exchange between global and local networks needed for the integration of top-down controlled mental templates and bottom-up visual processing, through transient phase-synchronization with fast gamma activity, (2) the prefrontal top-down control of remote brain areas, where frontal-midline theta phase may provide cyclic windows of opportunity in which task-active posterior areas can access prefrontal resources, or are denied access and (3) the coordination of excitable periods within the fronto-parietal network, through long-range theta coherence. In this thesis, four research projects are presented. In a newly developed visual search task, we demonstrated that in conditions where participants kept a single targets' properties in mind for visual search, cross-frequency synchronization between theta and gamma phase transiently increased in right posterior cortex, but not in conditions where one out of multiple mental templates was successfully matched. Thereby, we extend previous work proposing transient theta-gamma phase synchronization as a neural correlate of matching incoming sensory information with top-down controlled mental templates, and we provide novel evidence for limitations in memory matching during multiple template search. Second, we probed the causal relevance of more sustained fronto-parietal interaction, during voluntary resource allocation in visuospatial working memory. We found frontal-midline theta phase dependent effects of TMS over right, but not left, parietal cortex on working memory performance, when prioritizing contralateral visuospatial information during working memory maintenance. TMS selectively disrupted task accuracy when delivered during the more excitatory frontal-midline theta phase (i.e. the trough). Based on this pilot data, we recommend effect size estimates and implications for follow-up studies. Third, we conducted a pre-registered study using multi-site theta tACS for synchronizing or desynchronizing a left fronto-parietal network, but could not reproduce a beneficial or detrimental effect on verbal working memory performance in an easy letter recognition task. Our results indicate that a beneficial effect of synchronous fronto-parietal theta tACS can only be observed in a working memory task of high difficulty. In order to make our contribution to increasing reproducibility and robustness in transcranial brain stimulation research, we next investigated the usefulness of Bayes Factor analyses over conventional tests to differentiate between cases where a particular application of TBS had no effect or whether results were merely inconclusive. In a series of simulated TBS experiments with differing sample size and effect size, we show that Bayes factors tests may be highly useful for demonstrating conclusive evidence for non-effects and outline how they can be used in practice.

Contents

List of abbreviations

BF	Bayes factor
CFS	Cross-frequency phase synchonization
EEG	Electroencephalography
fMRI	functional Magnetic Resonance Imaging
H0	null hypothesis
H1	alternative hypothesis
MEG	Magnetoencephalography
PAC	phase-amplitude coupling
PET	Positron Emission Tomography
tACS	Transcranial Alternating Current Stimulation
TBS	Transcranial Brain Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
WM	Working Memory
FM-theta	frontal-midline theta

Chapter 1

General introduction and current work

The research projects presented in this thesis focused on investigating human theta-band activity and theta-to-gamma cross-frequency coupling in fronto-parietal brain networks during working memory and attentional operations and their interplay. The first section of the General Introduction briefly describes theories of working memory and attention. The second section introduces existing evidence indicating that both of these rely on mechanisms of top-down control within fronto-parietal brain networks. The third section reviews studies on brain oscillatory activity in humans, non-human primates and rodents for demonstrating why and how brain oscillatory dynamics have been investigated to examine these mechanisms, and which insights these studies have brought about. In separate sub-sections, this third section thereby summarizes the current evidence which has associated (a) local theta and gamma activity, (b) fronto-parietal theta coherence, (c) local cross-frequency interaction, and (d) fronto-parietal cross-frequency interaction, with the top-down integration and coordination of distributed neural networks involved during tasks requiring attentional and working memory control processes. The fourth section briefly summarizes the evidence which is immediately relevant for the current work. The General Introduction concludes with a presentation of the aims of the current work and the derived research questions for the four projects which are presented in this thesis.

1.1 Working memory and attention

To thrive in a complex environment, we need to select currently relevant pieces of information or ignore irrelevant ones. In addition, we have to remember and process relevant information in the absence of sensory input in order to solve cognitively challenging tasks. Such selective attention and working memory processes, as well as interactions among them, are vital to many situations of our everyday life. They have been studied intensely in cognitive psychology as well as cognitive neuroscience over the last decades (for recent reviews, see e.g. Christophel et al., 2017; Moore & Zirnsak, 2017; Nee & D'Esposito, 2018; van Moorselaar & Slagter, 2020).

Working Memory is understood as a limited-capacity system for retaining information and performing mental operations on the stored information which is classically thought to be comprised of multiple components or to be realized through different states of activation depending on the allocation of attention (D'Esposito & Postle, 2015). Prominent models assume that working memory consists of an attentional-control system for central executive processes which exert top-down control over subsidiary systems for the short-term storage of verbal and visuospatial information which are connected with long-term memory and interact through an episodic buffer (Baddeley, 2000; Baddeley

et al., 2011; Baddeley & Hitch, 1974). Others propose that the sensory store and central executive systems interact with working memory information which comes from a currently activated memory component within long-term memory, more specifically, from the subset of activated memory in the focus of attention (Cowan, 1999, 2001), or a region of direct access from which the focus of attention will select information (Oberauer, 2009). Thus, the allocation of selective attention has been proposed to play a central role in working memory processing.

Likewise, selective attention is thought to comprise representation of sensory information and its executive control. While visual perception can be guided by bottom-up, stimulus-driven processes like salience, it is often rather influenced by top-down, goal-directed processes, like selective attention, to select relevant and ignore non-relevant visual input (Kastner & Ungerleider, 2000). Current theories of visual attention hold that a representation of an attentional template is kept in working memory, and leads to a bias in the competition for neuronal resources in favour of visual stimuli that match with this attentional template (Bundesen, 1990; Bundesen et al., 2005; Desimone & Duncan, 1995; Duncan & Humphreys, 1989). Thus, attentional selection in visual perception is assumed to be influenced by top-down expectancies about incoming sensory information.

In classical task paradigms such as during visual search for a target among distractors or during working memory maintenance of cued visual-spatial information, both attentional and working memory processes are assumed to be involved. Generally, it is assumed that attentional and working memory mechanisms may interact or even overlap and this view is well supported by behavioural evidence and by evidence that similar neural networks are recruited, especially involving prefrontal cortex (e.g. Awh & Jonides, 2001; Awh et al., 2006; Bahmani et al., 2019; Olivers, 2008; Soto et al., 2007; Theeuwes et al., 2009)

1.2 Brain mechanisms of top-down processing

Attentional and working memory operations in need of top-down cognitive control have been consistently associated with an increased brain activation within a distributed cognitive control network (Cole & Schneider, 2007; Dosenbach et al., 2008; Harding et al., 2015). They especially involve dorsolateral prefrontal cortex and parietal, as results from human functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies and from recordings in non-human primates suggest (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000; Naghavi & Nyberg, 2005; Rottschy et al., 2012).

Importantly, working memory and attention were also found to share common neural mechanisms. Prefrontal brain regions are known to impact lower visual cortex for the top-down control of visual perception from working memory (Gazzaley & Nobre, 2012; Soto et al., 2008). This kind of top-down modulation of sensory cortices can be well investigated by analysis of oscillatory brain activity. Neuronal populations are thought to be formed by and to communicate through frequency-specific rhythmic oscillations, where their communication is either facilitated through aligned rhythms and therefore

aligned excitability windows, or inhibited when rhythms are out-of-phase (Engel et al., 2001; Fries, 2005, 2015; Womelsdorf et al., 2007). Thus, interaction within local populations or between distant brain areas, such as between prefrontal regions and lower visual cortex, is likely represented by neuronal coherence. Converging evidence suggests that rhythmic brain activity provides the functional basis for top-down cognitive control and that oscillatory dynamics reflect key mechanisms whereby the prefrontal cortex coordinates long-range brain networks (Helfrich & Knight, 2016).

1.3 Brain oscillatory correlates of working memory and attention

Such synchronous neuronal activity can be either studied directly by invasive recordings of rhythmical oscillations of the field potential; or studied indirectly through scalp magneto- or electroencephalography (MEG or EEG), which records neural activity composed of the sum activity of synchronous excitatory and inhibitory postsynaptic potentials from large groups of neurons which are synchronously active. Over the last decades, studies recording brain oscillatory activity in humans, non-human primates and rodents have associated all kinds of cognitive processes with event-related changes in oscillatory brain patterns involving various (delta, theta, alpha, beta and gamma) frequency bands (Jensen et al., 2019). And more recently, a growing number of studies used transcranial brain stimulation (TBS) techniques such as transcranial magnetic stimulation (TMS) (Thut & Miniussi, 2009) and transcranial electric stimulation, especially alternating current stimulation (tACS) (Riddle & Frohlich, 2021; Vosskuhl et al., 2018) for non-invasively investigating the causal role of neural oscillations in cognition (Veniero et al., 2019). Rhythmic sensory stimulation or neurofeedback have been another tool for modulating oscillations (Herrmann et al., 2016).

A brain oscillatory mechanism consistently associated with the top-down integration and coordination of distributed neural networks involved during tasks requiring attentional and working memory control processes, is slow frequency oscillatory activity in the theta (4-8 Hz) band (Cavanagh & Frank, 2014; Karakaş, 2020; Sauseng et al., 2010; Sauseng & Klimesch, 2008). The central role of slow frequency oscillatory activity for integrating distributed neural networks is compatible with the general observation that cortico-cortical interactions may occur on different scales and that the size of the neural network(s) involved will determine the frequency range of their dynamics (Von Stein & Sarnthein, 2000). Theory and evidence strongly suggest that long-range networks, such as involved in top-down processes, draw on low frequencies in the theta (4-8 Hz) and alpha (8-12 Hz) range, whereas more local small-range networks for task-specific operations draw on high frequency dynamics in the gamma band (>30 Hz), and that cross-frequency interaction is required for functional integration between these local and global networks (Canolty & Knight, 2010; Fell & Axmacher, 2011; Fries, 2005; Lisman & Jensen, 2013; Palva & Palva, 2018; Sauseng & Klimesch, 2008; Siegel et al., 2012; Von Stein & Sarnthein, 2000).

1.3.1 Local theta and gamma activity

During tasks requiring cognitive resource allocation, such as during the maintenance and manipulation of information in working memory or sustained attention, theta band activity over frontal midline electrodes has been reported to increase in amplitude with increasing cognitive demands (Eschmann et al., 2018; Gevins et al., 1997; Jensen & Tesche, 2002; Sauseng et al., 2007). This so-called frontal-midline theta activity was found to be generated in human medial prefrontal as well as anterior cingulate cortices and has been consistently associated with a need for cognitive control (Cavanagh & Frank, 2014; Hsieh & Ranganath, 2014; Mitchell et al., 2008). There seems to be a causal link between prefrontal theta activity and working memory performance under high task demands. This has been both demonstrated for prioritizing representations in working memory as demonstrated using a combination of repetitive TMS and fMRI (Riddle et al., 2020) and shown for working memory updating or set shifting as shown following frontal theta neurofeedback training (Enriquez-Geppert et al., 2014). An increase of local theta activity during working memory operations has also sometimes been reported for posterior brain areas (Gulbinaite et al., 2014; Moran et al., 2010; Osipova et al., 2006).

Modulation of local fast oscillatory brain activity in the gamma band has also been shown in connection to working memory and attention. Gamma band activity over frontal and posterior sensory and non-sensory brain areas is thought to reflect processes related to object representations, attentional selection and active maintenance or manipulation of information (Haegens et al., 2010; Jensen et al., 2007; Tallon-Baudry et al., 1998). Increased processing demands have been associated with an amplitude increase of local gamma oscillatory activity (Roux & Uhlhaas, 2014). Such local gamma oscillatory activity in task-relevant brain regions was found to increase with working memory load (Howard et al., 2003; Palva et al., 2011; van van Vugt et al., 2010) and to be predictive of individual working memory capacity (Honkanen et al., 2015; Palva et al., 2010; Roux et al., 2012) or individual attentional capacity (Rouhinen et al., 2013).

1.3.2 Fronto-parietal theta coherence

In addition to such local activity, large-scale distributed networks drawing on theta oscillations have been associated with working memory. Long-range within-frequency phase synchronization should enable efficient information transfer between brain regions during excitable periods and can be measured as coherence between distant sensors or sources (Fell & Axmacher, 2011; Sauseng & Klimesch, 2008). Activity in the theta band was found to exhibit phase consistency between midline frontal and lateral frontal, motor and sensory sites during cognitive control processes (Cavanagh & Frank, 2014). Theta phase synchronization between human frontal and parietal areas has repeatedly been found during tasks involving visuospatial (Sarnthein et al., 1998; Sauseng et al., 2005) or verbal working memory (Polanía et al., 2012) and task switching (Cooper et al., 2015; Sauseng et al., 2006) and evidence from intracranial recordings in the macaque brain corroborated these observations (Phillips et al., 2014). Fronto-parietal phase synchro-

nization has been shown to increase with increasing working memory load and to be predictive of individual working memory capacity (Palva et al., 2010). A reduction of fronto-parietal theta coherence during working memory manipulation was observed in patients with schizophrenia along with lower working memory performance (Berger et al., 2016; Griesmayr et al., 2014).

Studies using tACS even provided a causal link of fronto-parietal theta coherence and working memory performance, by applying tACS oscillating at theta frequency for either synchronizing or de-synchronizing fronto-parietal theta coherence and demonstrating a modulation of working memory performance depending on whether synchronous or asynchronous theta tACS was delivered (Alekseichuk et al., 2017; Polanía et al., 2012; Röhner et al., 2018; Tseng et al., 2018; Violante et al., 2017). This 'synchronization- desynchronization' effect was first shown in a seminal study by Polanía et al. (2012), who reported that in-phase tACS over a fronto-parietal theta-network led to faster response times whereas anti-phase tACS led to slower response times in a verbal working memory task compared to placebo stimulation.

1.3.3 Local cross-frequency interactions

While long-range slow-frequency phase synchronization may support information transfer within a network, a key mechanism for integrating neuronal processing which is distributed into different neuronal assemblies operating in individual frequency bands might be phase-based cross-frequency interactions. For example, phase coupling between theta and gamma band activity would be a suitable mechanism for the temporal coordination of multi-item working memory. Prominent computational models proposed that maintaining items in capacity-limited working memory may be realized through activity in neuronal subsets coding for individual items that need sequential activation: Some proposals suggested that this temporal coordination could be achieved by activating the respective local subsets at different phase angles at a global slow-frequency oscillation, whereby individual memory items may be coded though gamma waves nested into a theta cycle (Jensen & Lisman, 1998; Lisman & Idiart, 1995; Lisman & Jensen, 2013). Alternative proposals assumed that these individual memory items may be coded though theta-coupled gamma bursts (Herman et al., 2013; van Vugt et al., 2014). Existing empirical studies on theta-gamma coupling during multi-item working memory (Axmacher et al., 2010; Kamiński et al., 2011; Sauseng et al., 2009; Vosskuhl et al., 2018; Wolinski et al., 2018) may be interpreted as evidence for both of the proposed models, as we discussed in previous work (Sauseng et al., 2019), but still convincingly demonstrate an association of cross-frequency interactions between theta and gamma activity with multi-item working memory coordination. Different forms of such phase-based cross-frequency interactions have been of interest (see e.g. Jensen & Colgin, 2007; Witte et al., 2008), but cross-frequency phase synchronization and phase-amplitude coupling are most commonly investigated and found to be related to attentional and working memory processes.

An increase in cross-frequency phase synchronization (CFS) indicates that slower and faster oscillatory neural activity are both aligned in phase, and may enable consistent

spike-time relationships between neuronal assemblies oscillating in different frequencies (see e.g. Palva & Palva, 2018; Sauseng et al., 2010; Sauseng & Klimesch, 2008). Studies focussing on CFS in the context of working memory and attention are rather sparse. However, CFS between slow oscillatory activity in the theta to alpha range and fast oscillatory activity has been reported during visual working memory maintenance (Chaieb et al., 2015; Palva et al., 2005; Siebenhühner et al., 2016), and its strength correlated with individual working memory capacity (Palva et al., 2005; Siebenhühner et al., 2016). Similarly, CFS between alpha and gamma band activity was shown to be associated with attention and predicted individual limits of attentional capacity (Rouhinen et al., 2020). There is also evidence that a rather transient synchronization between theta and gamma phase in posterior parietal brain areas is associated with tasks requiring the integration of top-down controlled mental templates with bottom-up visual processing (Holz et al., 2010; Sauseng et al., 2008). This has led to the proposal that, concerning the activation of mental templates from working memory and their comparison with sensory input, cross-frequency phase synchronization between theta and gamma band oscillations can be regarded as a candidate neural mechanism underlying this process (Sauseng et al., 2015; Sauseng et al., 2010).

Phase-amplitude coupling (PAC), where the amplitude of fast oscillatory activity is modulated by slow-frequency phase, is thought to integrate activity across different spatial and temporal scales, whereby slow oscillations produce cyclic excitability windows that influence local cortical activity (see e.g. Canolty & Knight, 2010; Jensen et al., 2014). Slow oscillatory activity in the theta range has been demonstrated to entrain neuronal spiking and fast oscillatory activity (Canolty et al., 2006; Fell & Axmacher, 2011; O'Keefe & Recce, 1993; Sirota et al., 2008).These were more likely to occur during the phase of maximal excitability (i.e. near the trough phase) than during the other phases of slow frequency oscillations in the theta or alpha range (Haegens et al., 2011; Siegel et al., 2009; Womelsdorf et al., 2010). During attentional and working memory processes in humans, PAC has been reported, where bursts of fast oscillatory activity are clustered into specific phases of theta, or sometimes alpha band activity (Axmacher et al., 2010; Daume et al., 2017; Demiralp et al., 2007; Sauseng et al., 2008; Sauseng et al., 2009; Schack et al., 2002). For example, coupling of gamma phase to the trough phase of theta oscillations was found to increase contralateral to the visual hemifield relevant for working memory maintenance, showed a load-dependent increase and predicted individual working memory capacity (Sauseng et al., 2009).

1.3.4 Fronto-parietal cross-frequency interaction

Such a neuronal phase coding mechanism where fast oscillatory is coupled to specific phases of the slow oscillation has not only been found locally, but also between distant sites. Studies in rodents demonstrated that prefrontal and hippocampal theta oscillations entrain local neuronal firing and gamma oscillations in prefrontal and tegmental neurons, which were shown to become phase locked to theta oscillations during working memory (Fujisawa & Buzsaki, 2011; Sirota et al., 2008). In the human EEG, the phase of

slow oscillatory frontomedial activity has been found to be synchronized with distributed fast oscillatory activity (Griesmayr et al., 2010). It was proposed that long-range brain networks can be efficiently coupled or decoupled through a mechanism where fast oscillatory activity in posterior areas is nested into the excitatory or the inhibitory phase of slow oscillatory frontomedial activity, which has been found in younger adults, but not in older adults during a demanding working memory task (Pinal et al., 2015). In line with this, in a previous study we found that right temporo-parietal gamma band activity was nested into frontal-midline theta waves, depending on the level of cognitive control required in a working memory task (Berger et al., 2019). Specifically, posterior gamma activity was aligned towards the peak phase of frontal-midline theta under low load conditions, but under high load conditions it was aligned to the trough phase of frontal-midline theta waves. Demonstrating the direct causal relevance of this mechanism, working memory performance in the most difficult task condition was disrupted when TMS delivered over the right temporo-parietal cortex was applied while frontal-midline theta was at its excitatory phase (i.e. near the trough) and thus at the phase to which temporo-parietal gamma activity was coupled (Berger et al., 2019). This suggests that frontal-midline theta phase represents a gating mechanism for the allocation of cognitive control which controls the communication between frontal and parietal cortex, allowing task-relevant posterior cortical areas to access frontal cognitive resources depending on task demands.

1.4 Interim summary: key aspects for the current work

In sum, previous work demonstrates that slow frequency oscillatory activity plays a central role for connecting distributed neural networks involved in working memory and attentional operations, and that cross-frequency interaction is required for functional integration between local and global neural networks. The discussed evidence which is immediately relevant for the current work can be summarized as:

- Fronto-parietal theta coherence could provide coordinated excitable periods enabling efficient information transfer within the working memory theta network (Cavanagh & Frank, 2014; Fell & Axmacher, 2011; Sauseng & Klimesch, 2008). It may be even directly related to working memory performance, as proposed by a seminal study by Polanía et al. (2012) who applied phase-dependent tACS to modulate a fronto-parietal theta network and showed that anti-phase tACS led to slower and in-phase tACS to faster response times in a verbal working memory task.
- Local cross-frequency phase synchronization between theta and gamma activity has been associated with tasks requiring the integration of top-down controlled mental templates with bottom-up visual processing (Holz et al., 2010; Sauseng et al., 2008), such that a transient increase of theta-gamma CFS in posterior parietal cortex is proposed as a neural correlate of memory matching (Sauseng et al., 2015; Sauseng et al., 2010). It may integrate neuronal processing which is distributed into neuronal assemblies and across frequency bands by enabling a transient spike-

time consistency between the oscillating neuronal populations of a global fronto-parietal theta network and a local network operating in the gamma frequency range (Palva & Palva, 2018; Sauseng et al., 2010; Sauseng & Klimesch, 2008).

- Fronto-parietal phase-amplitude coupling where bursts of posterior gamma activity cluster into different phases of the frontal-midline theta cycle depending on task difficulty has been found to be a behaviourally relevant mechanism for successful visual working memory performance (Berger et al., 2019). During working memory maintenance, frontal midline theta phase may provide cyclic windows of opportunity in which task-relevant posterior areas can access prefrontal resources, whereas during non-preferred phases, this access to prefrontal resources is denied (Berger et al., 2019; Pinal et al., 2015).

1.5 Aims of the current work

Building on this previous work, the aim of the current work was to investigate brain oscillatory signatures supporting information transfer within and between global and local neural networks which are involved in human working memory and attentional processes. This was achieved by comparing how previously established oscillatory correlates generalize under different conditions and in different task paradigms, by probing their causal relevance for behaviour and by trying to reproduce established effects. To this end, we used a variety of methodological approaches including the acquisition of EEG data, or the modulation of endogenous brain activity using a combination of TMS and EEG or using frequency-specific tACS, or the analysis of simulated data.

In **Project I**, we asked how the previously proposed oscillatory correlate of memory matching in visual search (Sauseng et al., 2015; Sauseng et al., 2010) is affected by the number of mental templates that could be matched to incoming visual input. If the proposed transient theta-gamma CFS in posterior parietal is indeed associated with integrating top-down controlled mental templates from working memory with bottom-up visual processing, then it should differ between conditions where a single or multiple mental templates could be matched with visual input, reflecting limitations due visual search for multiple templates. We investigated this in an EEG study where participants completed a visual search task with complex abstract stimuli, where they had to hold in mind a single or of multiple targets' visual properties.

For **Project II**, we were interested in whether the clustering of neural activity at task-active parietal brain areas into specific frontal-midline theta phase segments (Berger et al., 2019) can also be affected by other factors than task difficulty. We asked whether such a mechanism is influenced by the voluntary allocation of cognitive resources in visuospatial working memory, specifically, by the amount of priority given to respective information. In a pilot study, we combined EEG and TMS to investigate the extent to which parietal TMS disrupted task performance depending on when it was delivered with respect to the frontal-midline theta phase and on whether it was delivered to the contralateral

task-active (i.e. involved in prioritizing information) or ipsilateral task-inactive (i.e. non-prioritizing) hemisphere.

In **Project III**, we aimed to reproduce a 'synchronization- desynchronization' effect on response times using fronto-parietal theta tACS. In this pre-registered study, we carefully reproduced the behavioural and tACS protocols from the seminal study by Polanía et al. (2012). In order to control for potential confounds due to electrode montage and electric field strength between in-phase and anti-phase tACS conditions, we used an additional in-phase condition that enables a more focal stimulation of frontal and parietal cortex, as suggested by electrophysiological modelling (Saturnino et al., 2017). This allowed us to also investigate whether it will have at least as much of a facilitatory effect as the classical in-phase stimulation condition.

In **Project IV**, we aimed to demonstrate how non-significant findings from TBS studies can inform future research, using a data simulation approach. This is important because the use of appropriate statistical tools which enable insights about which TBS intensity, frequency or montage is effective or ineffective, may increase the reproducibility of TBS effects (for a more detailed introduction, the reader is kindly referred to Chapter 5). In a series of simulates TBS experiments, we compared conventional significance testing to Bayes factor tests, which allow evaluating evidence both for the research hypothesis and for the null hypothesis (e.g. Dienes, 2011; Kruschke, 2011; Rouder et al., 2009) and may therefore be highly useful for the TBS community.

Chapter 2

Project I: Theta-gamma CFS during memory matching in visual search

This chapter comprises the research article that has been published in NeuroImage in 2021, entitled "EEG cross-frequency phase synchronization as an index of memory matching in visual search" (Biel et al., 2021).

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Contributions:

Anna Lena Biel: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, Project administration;

Tamas Minarik: Conceptualization, Writing – Review & Editing;

Paul Sauseng: Conceptualization, Methodology, Validation, Resources, Writing – Review & Editing, Supervision, Funding acquisition.

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EEG cross-frequency phase synchronization as an index of memory matching in visual search

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ABSTRACT

Visual perception is influenced by our expectancies about incoming sensory information. It is assumed that mental templates of expected sensory input are created and compared to actual input, which can be matching or not. When such mental templates are held in working memory, cross-frequency phase synchronization (CFS) between theta and gamma band activity has been proposed to serve matching processes between prediction and sensation. We investigated how this is affected by the number of activated templates that could be matched by comparing conditions where participants had to keep either one or multiple templates in mind for successful visual search. We found a transient CFS between EEG theta and gamma activity in an early time window around 150 ms after search display presentation, in right hemispheric parietal cortex. Our results suggest that for single template conditions, stronger transient theta-gamma CFS at posterior sites contralateral to target presentation can be observed than for multiple templates. This can be interpreted as evidence to the idea of sequential attentional templates. But mainly, it is understood in line with previous theoretical accounts strongly arguing for transient synchronization between posterior theta and gamma phase as a neural correlate of matching incoming sensory information with contents from working memory and as evidence for limitations in memory matching during multiple template search.

1. Introduction

Working memory and selective attention interact in many situations of our everyday life, influencing how we perceive the world. Image yourself looking for your car keys that you must have left somewhere in the kitchen. During your search, you will scan a rich visual environment for something that matches the representation of keys that you have in mind. Such situations are commonly described as visual search. Brought to a cognitive psychology laboratory, participants in a visual search paradigm are usually asked to search for a target object among a number of distractor objects presented on a computer screen. Current theories of attention hold that when we are searching for a target, then keeping a template representation of the target in working memory – a so called attentional template – leads to a bias in the competition for neuronal resources in favor of template-matching stimuli (Bundesen, 1990; Bundesen et al., 2005; Desimone and Duncan, 1995; Duncan and Humphreys, 1989). Insight into the neural mechanisms underlying the activation of such mental templates and their comparison with sensory input comes from studies in healthy humans (Gayet et al., 2017; Soto et al., 2007; Spaak et al., 2016) patients with frontal lesions (Soto et al., 2006; Yago et al., 2004), lesion studies in primates (Everling et al., 2006; Lba and Sawaguchi, 2003; Rossi et al., 2007), as well as from formal theoretical models (Friston, 2005) . Thereof, especially prefrontal brain regions are known to be involved in visual search and the top-down control of visual perception from working memory by impacting on lower visual cortex (for review, see Soto et al., 2008).

Interactions between higher and lower brain areas, as assumed to be involved in visual search, can be well investigated by analysis of oscillatory brain activity. Interaction within or between brain areas is implemented by synchronous neural activity, as reflected by rhythmical oscillations of the field potential which can be recorded using scalp electroencephalography (EEG). Oscillatory EEG activity is commonly reported to play a functional role for perceptual and cognitive processes (Buzsáki and Draguhn, 2004; Fell and Axmacher, 2011; Fries, 2005). Two brain areas are assumed to be functionally coupled when their activity is more synchronous than what would be expected from random fluctuations. It has been suggested that the complexity of the neural network(s) involved will determine the frequency range of the dynamics in a given interaction (Buschman and Miller, 2007; Fell and Axmacher, 2011; Fries, 2005), such that long-range interactions during top-down processes draw on lower frequencies in the theta band (~6 Hz)

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and alpha band (~10 Hz), whereas higher frequency, such as gamma band (>30 Hz), interactions characterize more local, small-network interactions.

Long-range interregional synchronization between human prefrontal and parietal areas has repeatedly been found for oscillatory brain activity in the theta or alpha frequency range, for example during highly demanding working memory tasks (e.g. Sarnthein et al., 1998; Sauseng et al., 2005; von Stein et al., 2000). Synchronous gamma band activity has been linked to bottom-up processes such as feature-binding and awareness (for review, see Engel and Singer, 2001), however, it also been associated with processing demands related to object representations, directed attention and active maintenance or manipulation of information (e.g. Axmacher et al., 2006; Friese et al., 2013; Jensen et al., 2007). Thereby, the common underlying mechanism is a need for comparison of sensory input with memory content as proposed by Herrmann et al. (2004), who suggest a central role of gamma-band responses in matching memory contents with sensory input. However, it has been argued that this model would well account for the matching with long-term memory information but less well for the matching with mental templates kept in working memory (Holz et al., 2010; Sauseng et al., 2015) so that in addition, a long-range fronto-parietal network drawing on theta band oscillations is expected to be involved.

A neural mechanism for this involvement may be phase synchronization between theta and gamma band activity, as proposed in a framework that could well account for the activation of mental templates from working memory, controlled by frontal resources and replayed into higher visual areas drawing on a theta network, and their comparison with sensory input, wherefore synchronization with gamma band phase is suggested (Sauseng et al., 2010, 2015). Theta band activity has been shown to generally have a strong influence on local cortical activity both in the human and animal brain, namely by entraining neuronal spiking and fast oscillatory activity, such as gamma band activity (Canolty et al., 2006; Fell and Axmacher, 2011; O'Keefe and Recce, 1993; Sirota et al., 2008). From studies using EEG in humans, perceptual and working memory processes have been associated with theta-gamma frequency interaction (Berger et al., 2019; Demiralp et al., 2007; Griesmayr et al., 2010; Sauseng et al., 2008, 2009; Schack et al., 2002). Such cross-frequency coupling is commonly taken as an indicator of an exchange of information between global and local neuronal networks (see Sauseng and Klimesch, 2008). Especially phase synchronization could integrate neuronal processing which is distributed into neuronal assemblies and across frequency bands by enabling consistent spike-time relationships between the oscillating neuronal populations; and cross-frequency phase-synchronized input to pyramidal layer 5 cells may facilitate neuronal bursting of these cells (Palva and Palva, 2018). So, concerning the activation of mental templates from working memory and their comparison with sensory input, cross-frequency phase synchronization between theta and gamma band oscillations can be regarded as a candidate neural mechanism underlying this process (Sauseng et al., 2010, 2015).

In the current study, we asked whether the number of activated mental templates that could be matched with sensory input does influence memory matching in visual search, as presumably reflected by a transient cross-frequency interaction between theta and gamma frequencies. Whether it is possible to look for multiple objects at the same time is a question of active debate and ongoing research. Some studies corroborate a serial bottleneck that requires alternating between items (Olivers et al., 2011; Ort et al., 2017), whereas others rather support a parallel model assuming less efficient, but parallel processing of each item (Beck et al., 2012; Hollingworth and Beck, 2016; Ort et al., 2019) or assume hybrid models (e.g. Bays and Husain, 2008). In a range of different paradigms, clear multiple target costs have been found both on the behavioral and the EEG level, indicating that multiple-target search seems to be limited in capacity, however, evaluating the exact processing stage at which serial or parallel processing limitations occur, has proven difficult or led to sometimes mixed results (for review, see Ort and Olivers, 2020). The aim of the current study was to investigate the stage of memory matching, by measuring theta-gamma phase synchronization as a proposed neural correlate.

Indeed, there is evidence in support of the involvement of a transient theta to gamma phase synchronization in posterior parietal brain areas in integrating top-down controlled mental templates with bottom-up visual processing (Holz et al., 2010; Sauseng et al., 2008). In cases where our expectancies and the actual visual input match, a higher transient phase synchronization than in case of a non-match has been found between posterior theta and gamma oscillations. For example, in a delayed-match-to-sample working memory paradigm, Holz et al. (2010) found stronger right-hemispheric posterior EEG theta to gamma phase synchronization for congruent in comparison to incongruent trials 150–200 ms post probe presentation. Additionally, the authors reported a resetting of theta phase shortly before this, leading them to propose that a posterior phase resetting of theta band oscillations could enable the transient cross-frequency synchronization with high frequency activity in the gamma band range found shortly after. Unexpectedly, stronger theta-high gamma phase synchronization for non-match than match was seen at left posterior recording sites. Here, Holz and co-workers speculated that this reversed effect might indicate the detection of a discrepancy between mental template and a presented item which might in turn trigger a more detailed local processing of sensory input. In the other study, however, the effect was not only right-lateralized but occurred on both the left- and right-hemispheric region of interest (Sauseng et al., 2008). Here, it was reported that in a visuospatial attention task, the increase of theta to gamma phase synchronization around 150 ms after target-onset was always larger contralateral than ipsilateral to target presentation in the validly cued hemifield. This was interpreted as a neural correlate of the matching of memory content with incoming sensory input, modulated by a top-down attentional process. This is supported by the idea that cross-frequency phase synchronization could be a candidate mechanism for integrating cognitive functions, such as the representation of sensory information and attentional or executive functions, by connecting the most central network nodes between distributed neuronal networks that support these functions (Palva and Palva, 2018).

An open question is how this proposed neural correlate of memory matching may be modulated when only one of multiple templates is met by matching sensory input. Interestingly, another form of cross-frequency interaction may also be involved during the earlier stage of the retention of multi-item working memory content. Influential computational models propose that separate memory items are represented by separate gamma waves which are nested into a theta wave (Jensen and Lisman, 1998; Lisman and Idiart, 1995) or that each item is coded by an entire gamma burst, i.e. multiple gamma waves, which are nested into a theta wave (Herman et al., 2013; Van Vugt et al., 2014). Thus, it is assumed that to hold in mind multiple templates, these need to be refreshed in a sequential manner. Although our working memory can undoubtedly represent multiple items, a prominent model proposes that the number of templates that can be active at a time is limited to only one (Olivers et al., 2011). This would predict that even though multiple templates coexist, only one of them can interact with sensory input after another. As mentioned earlier, alternatives to these serial models exist, but while parallel processing during selection and preparation may be possible, it is yet also relatively unclear whether this could generalize from paradigms with relatively simple target features (e.g. color) to paradigms utilizing more complex target stimuli (Ort and Olivers, 2020). But in any case, a single mental template should enable a fast and precise memory matching, whereas a larger number of mental templates that could potentially be matched to visual input should come at costs that disable such an early and precise matching process. Thus, visual search for multiple templates can be expected to come along with limitations in the memory matching stage, whether serial or parallel in nature. These limitations should be reflected in a transient theta to gamma phase synchronization in posterior parietal brain areas, if this mechanism is in-

deed involved in integrating top-down controlled mental templates with bottom-up visual processing, as proposed (Sauseng et al., 2010, 2015).

More specifically, on the basis of these abovementioned models, the proposed neural correlate of memory matching should be modulated when only one of multiple templates could be matched to sensory input in the following way: Assuming that we keep multiple templates in mind sequentially, one would assume that upon search display presentation in a given trial, the first, second or n^{th} item in the sequence incidentally matches sensory input. Further assuming that only one of them can interact with sensory input, memory matching should occur relatively early, a bit later or even much later in a given trial, depending on whether the sequence's first, second, or a later mental template could be matched to the current visual input. This means that in conditions where multiple mental templates could be matched to one out of several possible targets appearing on screen, the memory matching mechanism and likewise its neural correlate, is supposed to display more temporal variability across trials. Therefore, lower overall theta to gamma phase synchronization values, which are measured through an index aggregated over trials, are expected than when a single mental template enables a precise matching and thus a temporally aligned theta to gamma phase synchronization is expected.

A sequential matching process would be a rather plausible interpretation of low estimates of cross-frequency phase synchrony in multiple template search. However, if memory matching in a multiple template search happened with great temporal variability and also consistently later than in a single template search, or if there was more temporal variability in theta-gamma phase relations due to other unspecific differences imposed by multiple template search, then low phase synchronization estimates would be expected as well. Low phase synchronization estimates would also be expected if memory matching did not take place at all during multiple template search; however, this would really only be plausible when none out of multiple templates can be matched, such as previously found in non-match trials from other task paradigms (Holz et al., 2010; Sauseng et al., 2008, 2009). Conversely, when assuming that multiple templates can be matched in parallel, but with costs due to mutual competition, then slightly delayed, but high estimates of phase synchrony similar to a single template search would be expected. In any case, limitations in memory matching due to multiple template search should be reflected in a transient theta to gamma phase synchronization in posterior parietal brain areas, if assuming that this mechanism is indeed a neural correlate of memory matching. Not all of these options can be disentangled due to the nature of the theta-gamma phase coupling index, but in any case, if a modulation of the transient cross-frequency interactions between theta and gamma frequencies was observed during multiple template search compared to single template search, this would indicate that the number of activated mental templates that could be matched with sensory input does influence memory matching in visual search.

We designed a visual search paradigm where displays with four abstract symbols were shown to participants, each display containing one target among distractors. Participants had to indicate in which quadrant of the display their target symbol had been presented. We varied the number of mental templates that had to be kept in mind for successfully performing the visual search. In separate experimental blocks, the target could be either one single symbol (i.e. one item had to be held in memory) or one out of a set of three target symbols (i.e. three items would have to be retained). In the single template condition, we expected that around 150–200 ms after search array onset, a transient increase in theta-gamma phase synchronization should arise over right-hemispheric posterior brain areas for targets located in the contralateral hemifield, relative to ipsilateral targets, because this would corroborate evidence from other task paradigms (Holz et al., 2010; Sauseng et al., 2008, 2009). Conversely, such transient increase in phase synchronization should not arise in a condition where three mental templates were required for successful search performance, because a larger number of mental templates that could potentially be matched to visual input would modulate cross-frequency phase interactions.

2. Methods

2.1. Participants

Thirty-five typically developed volunteers participated in the experiment. All gave written informed consent prior to their participation and received financial compensation or course credits upon completion. Four participants had to be excluded from analysis because their percentages of correct responses were in the range of chance level, suggesting they were merely guessing, in at least one condition of interest. Two more participants were excluded based on too noisy EEG recordings. In the remaining sample that was included in the analyses ($n = 29$), mean age was 24.7 years ($SD = 2.8$) and 7 participants were male, 22 were female. All but one were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) and all reported normal or corrected to normal vision. The study was approved by the local Ethics Review Board and conducted according to the Declaration of Helsinki.

2.2. Apparatus

Participants were seated in a comfortable chair in a dimly lit room and were wearing an EEG cap (Easycap®) for registering EEG signals. They had a standard computer keyboard placed on their lap. Their left and right index and middle fingers were placed on four buttons of the numbers block, namely buttons 1, 2, 4, and 5, which were marked by coloured stickers. Each button represented one of four quadrants of a visual search display. Stimuli were presented on a 22-inch Samsung S22C450 monitor with a resolution of 1280 × 1024 and a 75 Hz refresh rate, which was placed centrally and at a distance of 80 cm from an observer. Stimulus presentation was controlled using Presentation 0.71 (Neurobehavioural Systems®), which was synchronized with recording of the EEG signals in BrainVision Recorder 2.0.4 (BrainProducts®).

2.3. Task

We recorded EEG from participants while they completed a visual search task, where they searched for a target stimulus among distractors. At the beginning of each trial (see Fig. 1A), a central fixation cross was presented for a random duration between 600 and 1000 ms, which participants were instructed to fixate during the whole trial. Next, the search display was displayed for a duration of 200 ms, and immediately masked for 1000 ms. The fixation cross remained on the screen for another 1500 ms. The target stimulus was presented equally often in each quadrant of the search display (25% of the trials). Participants indicated in which quadrant of the search display the target stimulus had been presented by pressing the respective button on the numbers block, for upper left (button 4) upper right (button 5), lower left (button 1) or lower right (button 2). They were instructed to respond as accurately as possible, and as soon as possible after presentation of the search display. So accuracy was emphasized over speed. As an intertrial interval, a blank screen was shown for a random duration of 800 to 1200 ms, adding up to a total trial duration of 4500 ms, before the next trial started. Participants were instructed to keep their eyes fixated at the central fixation cross during the whole task.

2.4. Stimuli

All stimuli were presented against black background, with a white fixation cross in the center of the screen (see Fig. 1A). As stimuli, 16 different abstract symbols were created (for code and stimuli, see https://osf.io/wbhnc/). None of these abstract symbols were known to the observers. Thus, participants could not rely on existing semantic

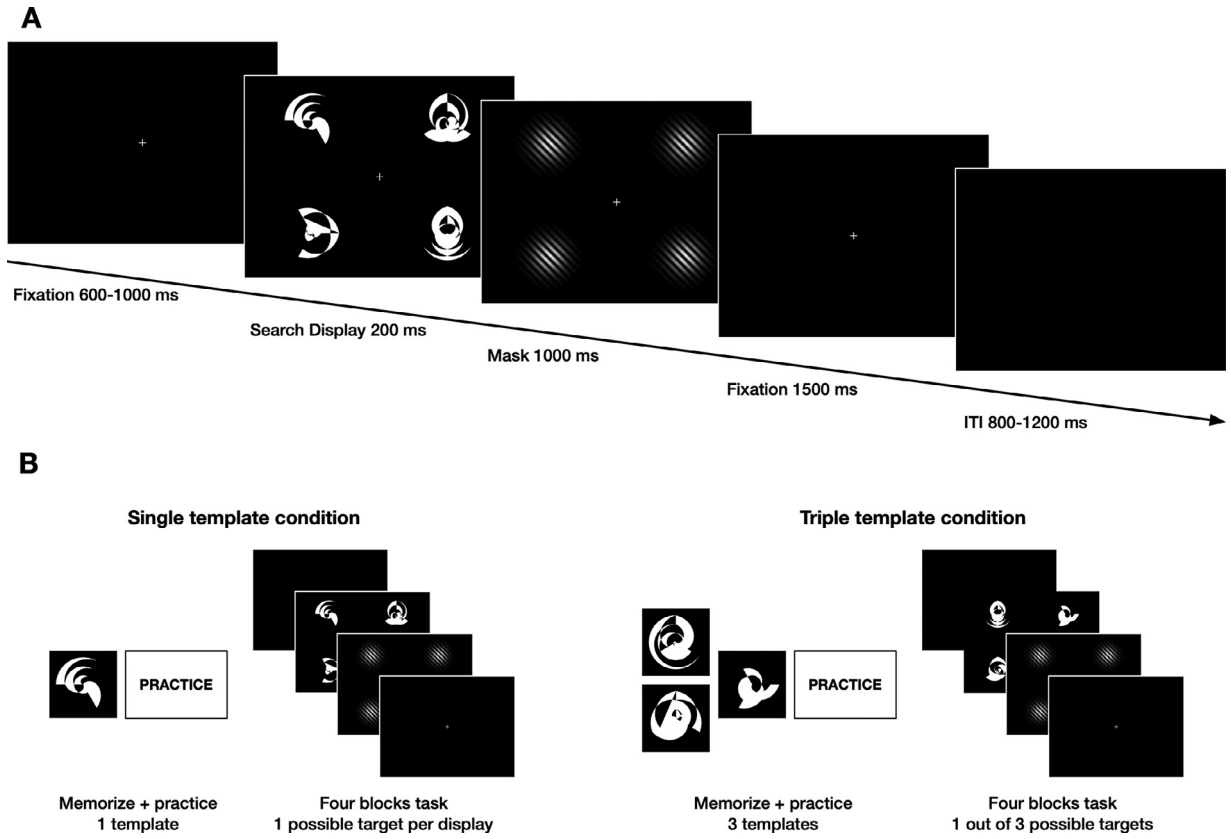

Fig. 1. Illustration of the visual search task. A: Exemplary trial sequence of the visual search task. Trials consisted of a fixation (600–1000 ms), a search display (200 ms), a mask screen (1000 ms), and a fixation (1500 ms); Inter-trial intervals (ITI) showed a blank screen (800–1200 ms). Search displays contained one target among three distractors and participants indicated in which quadrant of the search display the target had been presented by button press. B: Experimental procedure. The experiment comprised two parts with counterbalanced order across the four experimental versions (shown here: version IV). Prior to each part, consisting of four task blocks each, participants memorized and practiced the target(s).

memory contents such as the name of the target feature and we assumed that the search for this kind of complex targets would have relied more on an active attentional template of the visual target(s) in working memory. Four stimuli were used as targets (1–4) and 12 other stimuli as distractors (A-L).

Our paradigm contained two conditions (*Template*; single vs. triple), in which either one or one out of three possible targets was presented among distractors. To counterbalance which target and distractor stimuli appeared in the single vs. triple template conditions, four experimental versions were used (*Version I:*1 and A-F vs. 2, 3, 4 and G-L; *Version II*: 2 and G-L vs. 1, 3, 4 and A-F; *Version III*: 3 and A-F vs. 1, 2, 4 and G-L; *Version IV*: 4 and G-L vs. 1, 2, 3 and A-F). For each template condition, target and distractor stimuli were composed into 48 different search displays. Thus, in the *single template condition*, 12 search displays had the target symbol in the same quadrant, while three distractor symbols, randomly drawn from a subset of 6, were placed into the remaining three quadrants. For the *triple template condition*, a display could contain one out of three possible targets, thus each target was placed in each quadrant four times, accompanied by three randomly drawn distractors. This resulted in a total of 256 search displays being used. Mask screens displayed circular Gabor gratings at the same four locations of the search items, consisting of 9 white and 10 black lines each and oriented vertically (135°).

2.5. Procedure

Our conditions in which the number of possible targets, and thus the number of mental templates to be held in mind, could be either one or three (*Template*; single vs. triple) each consisted of 192 trials, divided into four blocks with 48 trials, such that the experiment comprised eight blocks in total. Whether participants started with the four blocks of the single or of the triple template conditions was counterbalanced across different versions of the experiment (Version I and III: triple, then single; Version II and IV: single, then triple). Version was randomly assigned to a participant and also determined which targets and distractor sets were assigned to which condition (see apparatus and stimuli). The search displays in the single template condition always contained the same target among distractors, whereas and in the triple template condition, one out of three possible targets was presented among distractors for search. In the triple template condition, there are trials where a different or the same target as on the previous trial is presented, however, there is a much lower number of stay trials than switch trials because the paradigm was not designed to contrast these. While this does not leave us with a sufficient number of trials to analyze potential target switch costs after, we provide an overview about potential hypotheses for future studies investigating these in the supplemental materials S9. Within a block, search displays were presented in randomized order. In the triple template condition, targets appeared equally often. Participants took breaks between blocks, resulting in a total of about 40 min to complete the experiment.

In order to familiarize the participants with the targets, a training was completed prior to each condition (see Fig. 1B). During a memorization phase before each practice block, the respective single target or three targets were shown to participants in a printed version, and participants were asked to memorize them well. Practice blocks had fewer trials than the actual experimental blocks and served to make participants familiar with their targets. The same target(s) and distractors as in the respective template condition were displayed here, however, only

with one instead of four stimuli on screen. Upon target presentation, participants decided whether the displayed stimulus was (one of) their target(s) or not. They did so with a button press, where they were asked to press left (no target) and right (target) arrow buttons on the keyboard. At least two memorization phases and practice blocks were completed per condition. If necessary, more were administered, until participants were confident in discriminating between target(s) and distractors and performed well above chance in doing so. Note that the training beforehand was necessary because the target stimuli in our task were displayed briefly and were rather complex (for details, please see below) and unknown to the observers. We intended to build a task that was effortful and where participants could not rely on existing semantic memory contents such as the name of the target feature. We assumed that the search for this kind of complex targets would have relied more on an active attentional template in working memory (Gunseli et al., 2014). For this effortful search, though, it was not possible to ask participants to memorize a trial-by-trial changing target, because they could not rely on one distinct feature, but instead the abstract figure as a whole. Therefore, we kept the target(s) constant in each condition and trained participants beforehand. This makes it possible that participants may have stored those memorized target(s) in long-term memory before the start of our task. We elaborate on this in the discussion.

The whole experiment, including the preparation of the EEG cap, instructions, breaks, training blocks and experimental blocks, took about 2 h.

2.6. EEG data acquisition and preprocessing

EEG was registered from 60 scalp locations with Ag-AgCl electrodes arranged according to the extended 10–10-system in a TMS compatible electrode cap (Easycap®), using a BrainAmp MRplus amplifier (Brain-Products®). Two electrodes were placed above and next to the left eye for recording horizontal and vertical eye movements and blinks. An additional ring-electrode on the tip of the nose was used as a recording reference and the ground electrode was placed at electrode position FPz. Electrode impedances were kept below 15 kΩ. EEG data were digitized at 1000 Hz in a frequency range above 0.016 Hz. A notch filter was set at 50 Hz. Butterworth zero phase filters were used.

EEG data were pre-processed using BrainVision Analyzer 2.0.4 (Brain Products®). Raw data was re-referenced using an average reference of all EEG channels. After filtering with a low-cutoff of 0.5 Hz (48 dB/oct) and a high-cutoff of 100 Hz (48 dB/oct), visual inspection was used for excluding data sections with large artifacts during task breaks. Next, semiautomatic Ocular Correction with Independent Component Analysis (Ocular Correction ICA) was applied to correct for artifacts caused by eye blinks and eye movements. Only trials including a correct response that was given within 3000 ms after search display onset were retained. Data were then segmented into 2000 ms epochs to avoid edge artifacts in later analysis steps, ranging from 1000 ms before to 1000 ms after onset of a search display. Finally, epochs that contained remaining artifacts due to eye movements or muscle activity were rejected manually. On average, the number of trials that remained after these procedures were 75.2 trials (78.3%) for targets on the left side of the screen and 79.3 trials (82.6%) for targets on the right in the Single template condition. In the Triple template condition, on average 54.0 trials (56.2%) remained for left hemifield target positions and 55.2 trials (57.5%) for targets on the right.

2.7. Cross-frequency phase synchronization index

Source-space EEG signals obtained from the brain regions of interest (ROIs; see next section for details) were decomposed using continuous wavelet transformation using Morlet wavelets. In order to extract one lower frequency band that is centered over the typical theta range and comparable to the study by Holz et al. (2010), for several lower frequency bands, wavelet coefficients were extracted with 5 frequency steps ranging from 1 Hz to 12 Hz, using a 5-cycle complex Morlet parameter. Thus, the frequency of interest for theta band activity had a central frequency of 6.50 Hz (bandwith 5.2–7.80 Hz). Both the theta and gamma band activity was derived using the same Morlet parameter, to be able to detect a transient modulation of phase in the gamma frequency range. Activity in several higher frequency bands was extracted with 6 frequency steps ranging from 30 Hz to 80 Hz and with a 5-cycle complex Morlet parameter. The purpose of this was to extract gamma bands that are comparable to the study by Holz et al. (2010) and to cover the whole range from 30 Hz to 80 Hz, but with little overlap to avoid redundancy and to reduce data for statistical analysis. Thus, three of these higher frequency bands were extracted as frequencies of interest for gamma band activity which were centered around 40 Hz (bandwith 32–48 Hz), 60 Hz (bandwith 48–72 Hz), and 70 Hz (bandwith 56–84 Hz).

Next, continuous phase values were extracted from the wavelet coefficients' complex values, for lower and higher frequency bands. To quantify their phase consistency across trials, we calculated the cross-frequency phase synchronization index (PSI), similar to Schack and Weiss (2005) or Palva et al. (2005), through custom-made scripts in MATLAB R2015b. So first, for each trial and sampling point, slow frequency band and high frequency band phase values were multiplied with the central frequency of the other band. Next, the phase differences across these adjusted signals was calculated for each trial and sampling point by subtracting sampling point-wise high frequency from low frequency adjusted signals. This generalized phase difference is described with the equation (where m and n are the central frequencies of the low and high frequency bands, which are multiplied with the instantaneous phase values in the kth trial and at sampling point t for the low and high frequency f_m and f_n, respectively): $\Delta\Phi_k(f_n,\ f_m, t) = m \times \Phi_1^k(f_n,\ t) - n\ \times \Phi_1^k(f_m, t)$. PSIs across trials were calculated as the average vector length of these generalized phase differences, by taking the square root of the sum of the squared sine and cosine values of the phase differences, averaged across trials, yielding an index ranging from 0 to 1, where 1 indicates largest synchrony in phase. From these sampling point-wise PSIs, we then created averaged PSIs for time windows of 50 ms length, starting at stimulus onset up to 450 ms and an averaged PSI for a pre-stimulus time window of 200 ms, starting 200 ms pre-stimulus up to stimulus onset. These were transformed using Rayleigh's Z ($rzPSI = n \times PSI^2$). This was done to account for the number of trials (n) that went into calculation of the index which were overall lower in the triple template condition (only correct, artifact-free trials were entered into the index, see above), since usually, measures of phase-synchronization are sensitive to the difference of trial numbers across conditions used (Cohen, 2014). Note that this yields an index not ranging from 0 to 1, but ranging from 0 to n, where larger values indicate larger synchrony in phase.

2.8. Regions of interest and time of interest

Brain regions of interest (ROIs) for analysis of posterior theta and gamma band activity were identified in source space in order to attenuate effects of volume conduction and to reduce multi-channel EEG data. We therefore transformed EEG data from scalp-level data into voxel-based Low Resolution Electromagnetic Tomography (LORETA) data (Pascual-Marqui et al., 2002) using BrainVision Analyzer 2.0.4 (Brain Products®). Here, a standard brain based on the MNI-305 brain template and a 3-shell spherical head model is used, and the source space comprises the cortical gray matter and hippocampus in the Talairach atlas with 2394 voxels at 7 mm spatial resolution. Based on the literature (Holz et al., 2010; as well as Sauseng et al., 2008), we were interested to compare posterior theta and gamma activity in bilateral posterior ROIs. While we do not assume that these are the only brain areas involved in this task, a source-specific analysis in the study by Sauseng et al. (2008) showed strong effects of cross-frequency phase synchronization in a similar task, with bilateral posterior sources located within extrastriate areas, covering the left and right superior oc-

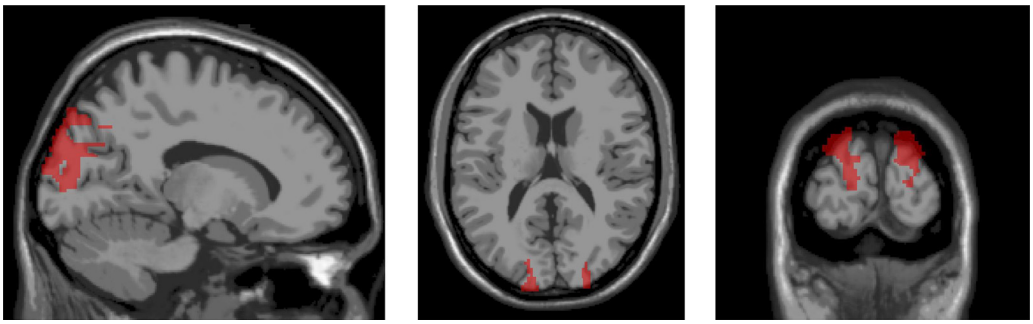

Fig. 2. Illustration of the selected regions of interest (ROIs) in source space. A left middle occipital ROI (centroid at MNI −15, −95, 15) and the homologue right middle occipital ROI (centroid at MNI 15, −95, 15) were selected for all further analyses in source space. Highlighted in red are the left middle occipital gyrus and right middle occipital gyrus.

cipital gyrus for the majority of subjects. Thus, for all further analyses in source space, we manually selected bilateral posterior ROIs in the left and right superior occipital gyrus (see Fig. 2 for a visualization of the left and right superior occipital gyrus, as implemented in the AAL atlas (Tzourio-Mazoyer et al., 2002)): Based on MNI coordinates, we selected two LORETA voxels which are located centrally within superior occipital gyrus for a left superior occipital ROI (centroid at MNI: −15, −95, 15) and the homologue right superior occipital ROI (centroid at MNI: 15, −95, 15). For the source-space EEG signals obtained from the ROIs, we computed cross-frequency phase-synchronization indices (for details, see previous section).

Within these ROIs, we analysed differences between our experimental conditions in the time window of interest. The time window of interest (TOI) was 150–200 ms after visual search display onset, a typical time window found in the previous studies (Holz et al., 2010; as well as Sauseng et al., 2008).

2.9. Event-related potentials

To relate our data to the existing EEG research on visual search, in which the N2pc ERP component has been described as an important neural signature (Eimer, 2014; Luck, 2012), we computed scalp-level grand average ERP waveforms for left and right target locations in both template conditions. These were filtered between 0.5 Hz (48 dB/oct) and 35 Hz (48 dB/oct) and baseline-corrected using a pre-stimulus time window of 200 ms, starting 200 ms pre-stimulus up to stimulus onset. ERPs were averaged for posterior parietal electrodes PO7 and PO8 contra- or ipsilateral relative to target location. Based on visual inspection (see Fig. 3), ERP waves began to differ between contralateral and ipsilateral target presentations from 220 ms onwards, which is in the N2pc latency range. The N2pc, which is consistently found in visual search tasks, is an ERP component exhibiting an enhanced negativity at posterior electrodes contralateral to target presentation and is typically interpreted as an electrophysiological marker of attentional capture. We computed the average N2pc amplitude in the time window 200–350 ms for the difference between contra minus ipsilateral sites relative to target location. Average N2pc amplitudes significantly differed between the template conditions ($t(28)=-3.6$, $p = 0.001$, paired-samples t-test).

2.10. Behavioural data

As a measure of task performance, the percentage of correct responses was computed for each subject and in both template conditions. Additionally, the median across reaction times from trials with a correct response was calculated (note, however, that the task instructions had emphasized accuracy over speed, so reaction times should be interpreted with this in mind).

2.11. Statistical methods

For both the behavioural and the EEG data, statistical analyses were carried out using statistical software R 3.6.1 (R Core Team, 2019) and for data visualization, plots were created using the package ggplot2 3.2.1 (Wickham, 2016). To compare behavioural data from the single template condition vs. triple template condition, two-tailed paired-samples t-tests were used on task accuracy and response times. For the analysis of EEG data, linear mixed effects models (LMMs) were implemented with the lme4 package 1.1.21 (Bates et al., 2007), contrasts matrices were derived using the hypr package 0.1.7 (Rabe et al., 2020; Schad et al., 2019) and model summary tables were produced using the lmerOut package 0.5 (Alday, 2018). As an advantage over traditional repeated-measures ANOVA, LMMs estimate the difference between conditions directly and without the need for post hoc tests instead of only the significance of a difference between conditions. Using LMMs allowed us to model random effects by subject (but as we analyze an aggregated index across trials, we could not include random effects by item as well). They also accommodate shrinkage, such that extreme and therefore less reliable estimates from individual subjects are shrunk towards the grand mean, producing more reliable estimators (see Gelman and Hill (2007) or Pinheiro and Bates (2000) for a general introduction into mixed regression models and Payne et al. (2015) and Alday et al. (2017) for an overview on LMMs, parameter estimation and model fitting, examples of their use for EEG data analyses and further literature recommendations on LMMs). The consistency of theta-gamma phase difference, as measured by the Rayleigh's z-transformed cross-frequency phase synchronization indices (rzPSIs), was analysed for condition differences separately for the left and right posterior ROI (see above for details on the ROIs). This was done because data stemmed from sources located in separate hemispheres and because other studies from our group have previously found lateralized effects of cross-frequency synchronization (see Sauseng et al. (2009) or Holz et al. (2010)). While the whole time series of rzPSIs was inspected descriptively, data were analysed for condition differences exclusively in the time window of interest found in previous studies, 150–200 ms after target onset (see above for details on the TOI) to reduce data for statistical analysis. Here, based on our hypothesis, we were mainly interested in an interaction between template condition and target location or any higher-order interaction involving these two factors. Adding rzPSIs for theta-to-40 Hz, theta-to-60 Hz, theta-to-70 Hz into the model enabled us to assess whether a broadband or rather frequency specific theta-to-gamma band effect were involved. In separate analyses for each ROI, we used a LMM where rzPSIs from that ROI were predicted by the fixed effects COND (Template condition: single, triple), TARG (Target location: contralateral, ipsilateral), CFS (Cross-frequency synchronization: theta-to-40 Hz, theta-to-60 Hz, theta-to-70 Hz), and their interactions. The model included a single random-effects term for the intercept of the individual subjects SUBJ. For LMM modeling, the categorical variables were encoded with sequential difference contrasts

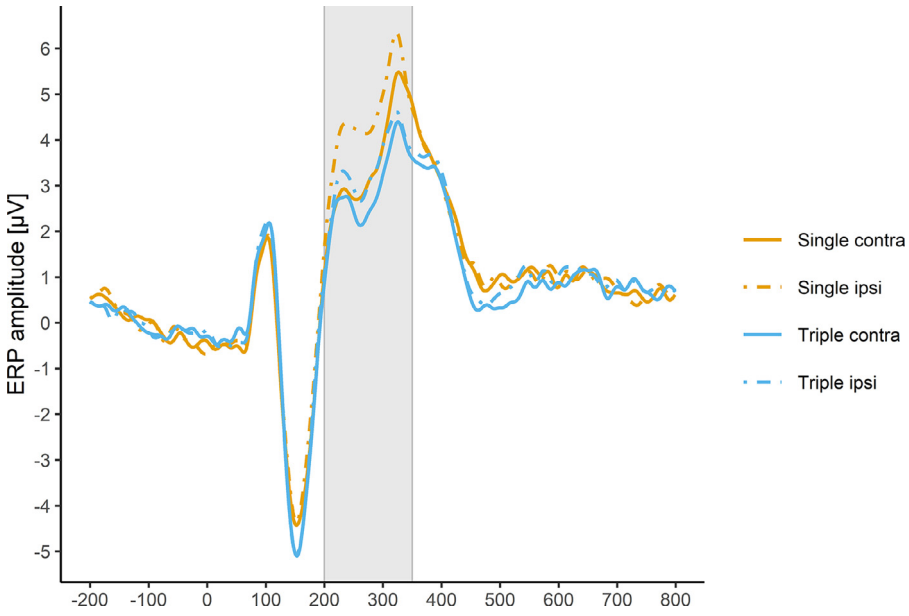

Fig. 3. Event-related potentials (ERPs) averaged for posterior parietal electrodes PO7 and PO8, contra- or ipsilateral relative to target location in both template conditions. The time window for which N2pc amplitudes were computed is illustrated in gray. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(for 2-level predictors COND and TARG: (1/2, −1/2); for 3-level predictor CFS: (−2/3, 1/3, 1/3) and (−1/3, −1/3, 2/3)). Thus, the intercept is estimated as the grand average across all conditions and resulting fixed effect estimates can be interpreted as main effects. For the model summaries we regarded contrast coefficients with absolute t values larger than 1.96 as indicative of a precise estimate. T-values above 1.96 can be treated as approximating the two-tailed 5% significance level since a t-distribution with a high degree of freedom approaches the z distribution (Baayen et al., 2008). The reported models were fit based on restricted maximum likelihood estimation.

2.12. Data and code availability

Data and code needed to reproduce all reported findings are available in our data repository (https://osf.io/h2j6d/).

3. Results

3.1. Behavioural analyses

Task accuracy (measured as the percentage of correct responses) was higher in the SINGLE template condition (M = 86.08%, SD = 14.51%) than in the TRIPLE template condition (M = 63.031%, SD = 11.56%) as indicated by a significant paired samples t-test ($t(28)$ = 5.94, p <0.001, d = 1.76). Similarly, reaction times (computed as the median across correct trial's reaction times) in the SINGLE template condition (M = 698.03 ms, SD = 276.14 ms) were significantly faster than in the TRIPLE template condition (M = 888.07 ms, SD = 322.22 ms; t(28) = −3.87, p < 0.001, d = −0.63). Both these results indicate that behavioural task performance was better when participants had to search for one target among distractors than for one out of three possible targets.

3.2. EEG analyses

3.2.1. Theta-gamma phase synchronization in the right hemispheric ROI

Fig. 5 shows single-subject rzPSIs and their group average from the right hemispheric ROI in the time window 150–200 ms after visual search display onset. A summary of model fit for rzPSIs from the right hemispheric ROI in the time window 150–200 ms after visual search display onset and the fixed effects COND (single, triple), TARG (contralateral, ipsilateral), CFS (theta-to-40 Hz, theta-to-60 Hz, theta-to-70 Hz), their interactions as well as the random effect for SUBJ can be seen in table S1.1 in the supplemental materials S1. A visualization of the fixed effects is provided in Fig. 4A. The grand mean rzPSIs have an estimate of 0.8 as represented by the intercept. TARG has an effect (0.062, t = 2.5) indicating that targets located in the contralateral hemifield elicited larger rzPSIs than targets at ipsilateral locations, but there also is an interaction between COND and TARG (0.18, t = 3.6), indicating that this target-related difference is larger in the single than in the triple template condition (see Fig. 4B). Importantly, no other contrast involving the interaction effect between COND and TARG exceeded the threshold of absolute t values larger than 1.96. So this critical effect does not interact with gamma frequency dependent differences, although three contrasts involving the factor CFS yield precise estimates with absolute t values larger than 1.96: One contrast shows that rzPSIS for Theta-to-70 Hz are smaller than for Theta-to-60 Hz (−0.068, t = −2.2), however, there also is an interaction with COND, reflecting that this gamma frequency dependent difference in rzPSIs is smaller for single than triple template conditions (0.15, t = 2.5). The interaction between the other CFS contrast and COND indicates that the difference between rzPSIs for Theta-to-60 Hz and for Theta-to-40 Hz is larger for single than triple template conditions (−0.14, t = −2.3). Essentially, both these interaction effects involving the factor CFS are driven from overall smaller rzPSI estimates in the single compared to the triple condition for Theta-to-60 Hz, whereas the two template conditions have similar RzPSI estimates for Theta-to-40 Hz and Theta-to-70 Hz (see Fig. 4C).

For an illustration of the whole time-series for rzPSIs from the right hemispheric ROI, Fig. 6 shows the descriptives of group average rzPSIs (averaged across theta-to-40 Hz, theta-to-60 Hz or theta-to-70 Hz cross-frequency synchronization) from the right hemispheric ROI for post-stimulus time windows of 50 ms length and for a pre-stimulus baseline.

3.2.2. Theta-gamma phase synchronization for the left hemispheric ROI

For rzPSIs from the left hemispheric ROI in the time window 150–200 ms after visual search display onset (see supplemental materials S2, figure S2.1), a summary of model fit for the fixed effects COND (single, triple), TARG (contralateral, ipsilateral), CFS (theta-to-40 Hz, theta-to-60 Hz, theta-to-70 Hz), interactions between them, and a single random-effects term for the intercept of the individual subjects can be seen in the supplemental materials S2 in table S2.1.

Unlike the results from the right hemispheric ROI, for rzPSIs from the left hemispheric ROI, no contrast exceeded the threshold of absolute t values larger than 1.96. The grand mean rzPSIs have an estimate

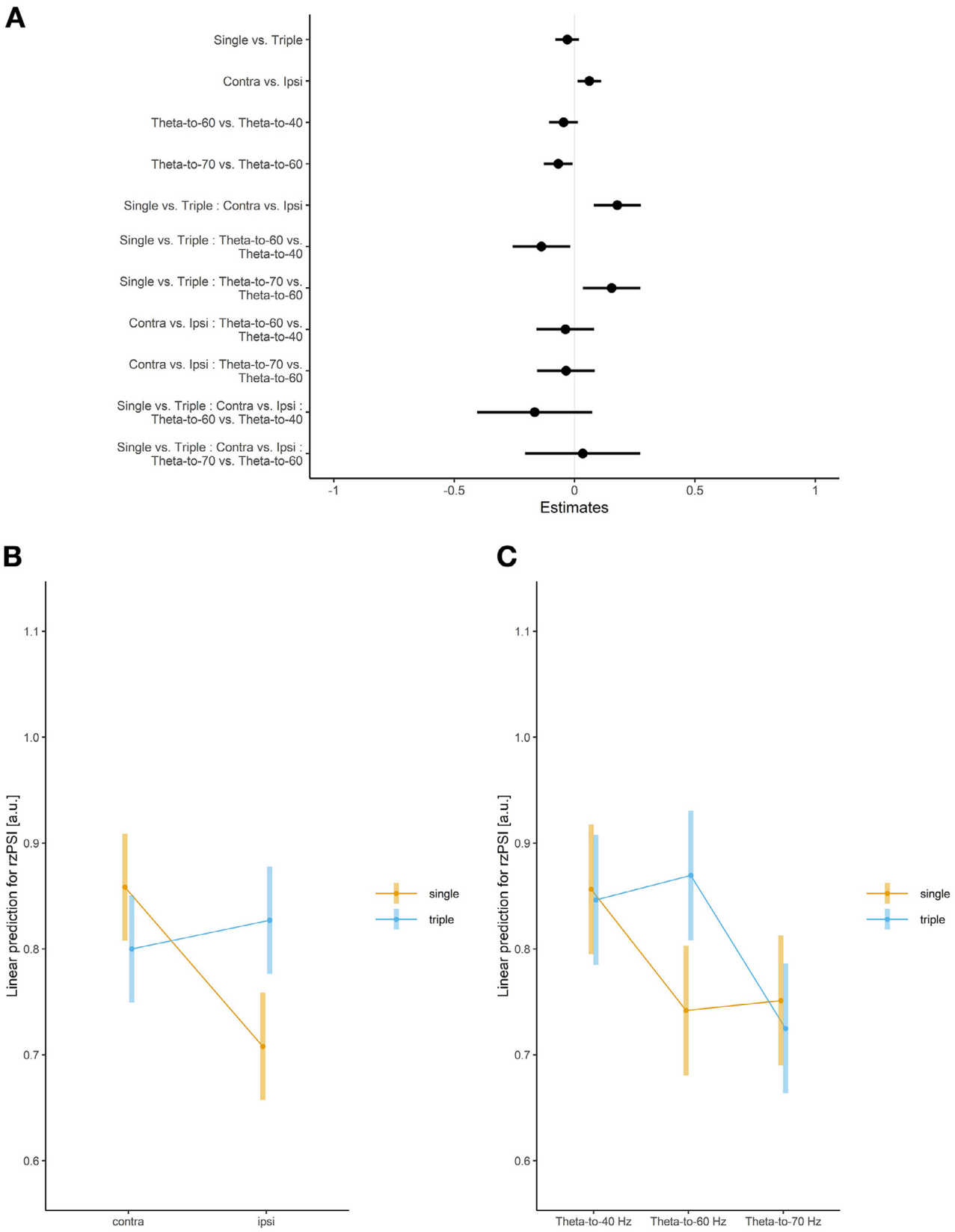

Fig. 4. Visualization of fixed-effect estimates for model fit (A) of the cross-frequency phase synchronization indices (Rayleigh's z-transformed; rzPSIs), measuring the consistency of theta-gamma phase difference, from the right hemispheric ROI in the time window 150–200 ms after visual search display onset. The model includes a random-effects term for the intercept of individual subjects and the fixed effects COND (single, triple), TARG (contralateral, ipsilateral), CFS (Theta-to-40 Hz, Theta-to-60 Hz, Theta-to-70 Hz), and interactions between them.Linear prediction for rzPSIS from the model showing the substantial effects for the interaction contrast between COND and TARG (B) and the interaction contrasts between COND and CFS (C). The substantial main effect TARG is not shown separately due to its involvement in the interaction with COND.

Note: Dots represent values of the estimated coefficients and lines show their standard deviations in panel A. In panels B and C, dots represent estimated marginal means and lines their confidence intervals.

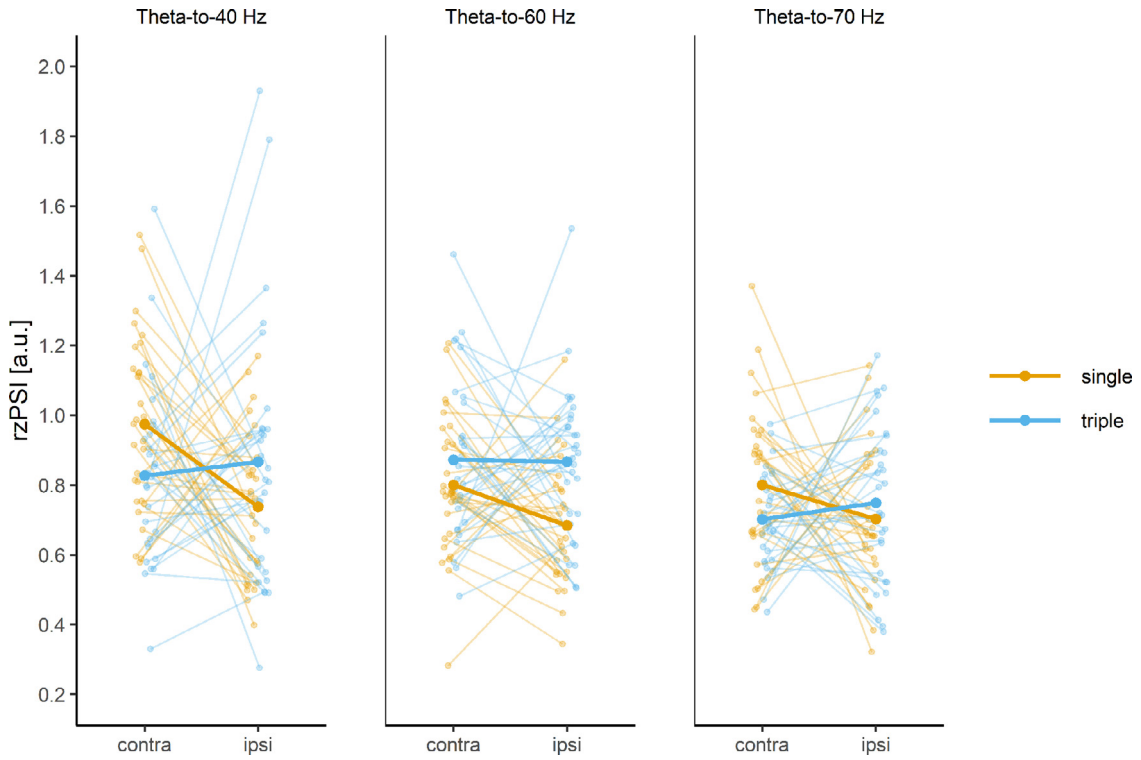

Fig. 5. Cross-frequency phase synchronization indices (Rayleigh's z-transformed; rzPSIs), measuring the consistency of theta-gamma phase difference, from the right hemispheric ROI in the time window 150–200 ms after visual search display onset. RzPSIs are displayed separately for single or triple template conditions (in color), for contralateral or ipsilateral target locations (on the x axis) and for theta-to-40 Hz, theta-to-60 Hz or theta-to-70 Hz cross-frequency synchronization (in separate panels). Single-subject indices (as thin lines) are overlayed by group averages (as thick lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of 0.81 as represented by the intercept. Note that the by subject variation beyond the variability induced by the residual error was estimated as zero, i.e. the random effects matrix was singular for this model. However, since dropping a by-subject random effect of zero will have no effect on the fixed effect estimates, it was kept in the model.

For an illustration of the whole time-series for rzPSIs from the left hemispheric ROI, figure S2.2 in the supplemental materials S2 shows the group average rzPSIs (averaged across theta-to-40 Hz, theta-to-60 Hz or theta-to-70 Hz cross-frequency synchronization) from the left hemispheric ROI for post-stimulus time windows of 50 ms length and for a pre-stimulus baseline.

3.3. Control analyses

We conducted several control analyses in order to investigate whether the critical interaction between COND and TARG that we found for theta-gamma cross-frequency synchronization in the right-hemispheric ROI is frequency-specific and to exclude a spurious effect relying on evoked responses. These were conducted only for the right-hemispheric ROI because the critical effect was exclusively found for this ROI.

First, to control for the possibility that cross-frequency synchronization is rather between gamma and broadband lower frequencies in general than specifically between gamma and the theta frequency range, the same analyses as in the main analysis were carried out, but for cross-frequency phase synchronization indices between gamma frequencies and the alpha frequency range. If alpha-gamma phase synchronization showed the same pattern of results as theta-gamma cross-frequency synchronization, specifically the critical interaction from the main analysis, the effect would not be frequency specific. Next, to control for the possibility of spurious effects of theta-gamma phase synchronization due to simultaneous but unrelated evoked activity in response to probe presentation in both theta and gamma frequency bands, we analysed spectral amplitudes as well as the phase locking factor (PLF) for theta and gamma frequencies. If a simultaneous increase in spectral amplitudes or a simultaneous phase resetting in response to stimulus onset can be found at both theta and gamma frequencies, this could lead to artificial cross-frequency phase synchronization despite the two frequencies not interacting with each other. This would be the case if spectral amplitudes or rzPLFs for theta and gamma frequencies showed the same pattern of results as the main analysis, specifically the critical interaction. Finally, an analysis using surrogate data was performed. For spurious effects that rely on evoked responses, they should occur at a fixed latency, so surrogate data and real data should show the same pattern of rzPSI estimates, whereas for real effects that are not driven by phase-locking to stimulus onset, real data should show larger rzPSIs estimates than surrogate data.

3.3.1. Alpha-gamma phase synchronization for the right hemispheric ROI

To investigate the frequency specificity of the observed interaction between COND and TARG that we found for theta-gamma cross-frequency synchronization in the right-hemisheric ROI in the main analysis, the same analyses were carried out for cross-frequency phase synchronization between gamma frequencies and the alpha frequency range. Thus, the central frequency of interest for this control analysis was at 9.25 Hz (7.40–11.10 Hz) in order to obtain phase estimates from the alpha frequency range. All following analysis steps were identical to the previously described steps for the main analysis of theta-gamma phase synchronization (see methods section for details).

Contrary to the effects observed for the main analysis, in the control analysis for alpha-gamma rzPSIs from the right hemispheric ROI, no contrast exceeded the threshold of absolute t values larger than 1.96. The grand mean rzPSIs have an estimate of 0.8 as represented by the intercept (see supplemental materials S3: figure S3.1 & S3.2 for data visualization and table S3.1 for a summary of model fit).

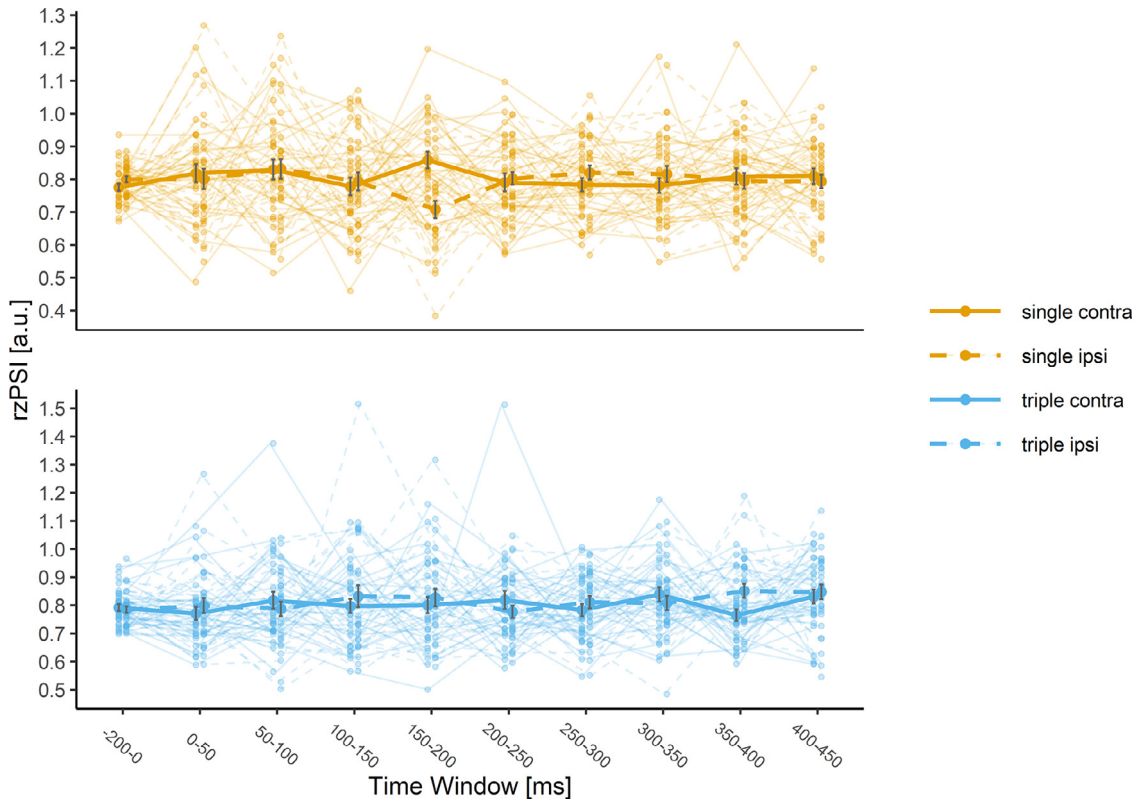

Fig. 6. Cross-frequency phase synchronization indices (Rayleigh's z-transformed; rzPSIs), measuring the consistency of theta-gamma phase difference, from the right hemispheric posterior ROI in windows of 50 ms length, starting at stimulus onset 0 ms up to 450 ms, and in a 200 ms pre-stimulus baseline. Group averaged rzPSIs are shown separately for single or triple template conditions (in color and in separate panels) and for contralateral or ipsilateral target locations (as line-type). Indices are averaged across theta-to-40 Hz, theta-to-60 Hz or theta-to-70 Hz cross-frequency synchronization. Single-subject indices (as thin lines) are overlayed with group averages (as thick lines) and standard errors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3.2. Amplitudes and PLF for the right hemispheric ROI

To control for the possibility of spurious effects of theta-gamma phase synchronization due to evoked activity in response to probe presentation, we further analysed spectral amplitudes for theta and gamma frequencies. Spectral amplitudes were calculated as the wavelet coefficients' real values which were then averaged across trials for the same frequencies of interest as in the main analysis. As for the main analysis, we computed averages of amplitudes for time windows of 50 ms length and for a pre-stimulus time window of 200 ms. We then also calculated the phase-locking factor (PLF; transformed using Rayleigh's Z; rzPLF = n*PLF^2) for theta and gamma frequencies separately. This was done to analyze the inter-trial consistency of phase-locking relative to stimulus onset within both frequency bins. For this, their phase values were extracted as in the main analysis (see methods section for details). PLFs were then calculated as the average vector length of these phase values (Bonnefond and Jensen, 2012; Tallon-Baudry et al., 1996), which were also averaged into time windows and transformed using Rayleigh's Z as in the main analysis.

Thus, for demonstrating that the observed interaction between COND and TARG for theta-gamma cross-frequency synchronization in the right-hemisheric ROI in the main analysis is not an artefact from filtering an evoked response, the same analyses were carried out for theta amplitudes and for gamma amplitudes as well as theta and gamma phase-locking factors from the right hemispheric ROI. While the three gamma bands' spectral amplitudes as well as their phase-locking factors were calculated separately, they were averaged before entering them into the model because the critical effect in the main analysis did not interact with gamma frequency dependent differences. So for gamma frequencies, both these control analyses were conducted for the average of all three gamma bands.

In the control analysis for theta amplitudes, no contrast exceeded the threshold of absolute t values larger than 1.96. The grand mean theta amplitudes have an estimate of 2.4 (see supplemental materials S6: figure S6.1 & S6.2 for data visualization and table S4.2 for a summary of model fit). Similarly, in the control analysis for gamma amplitudes, all contrasts remained below the threshold of absolute t values of 1.96. Here, the intercept indicated that the grand mean gamma amplitudes have an estimate of 3.2 (see supplemental materials S7: figure S7.1 & S7.2 for data visualization and supplemental materials table S7.6 for a summary of model fit). The visualization of the whole time-series from the theta and gamma band amplitudes from the right hemispheric ROI illustrates that there is no simultaneous increase in both bands in response to stimulus onset. In contrast to theta amplitudes, gamma amplitudes did not show any stimulus-locked increase. Note that while these analyses were conducted for te frequencies of interest, an overview of phase locking values for all Morlet wavelets is presented in figure S4.5 of the supplemental materials S4

In the control analysis for theta rzPLFs, the intercept indicated that the grand mean theta rzPLFs have an estimate of 38. The effect of COND (12, t value = 5.8) indicated that theta rzPLFs are larger in single than triple template conditions (see supplemental materials S5: figure S5.1 & S5.2 for data visualization and table S5.1 for a summary of model fit). However, in the control analysis for gamma rzPLFs, no contrast exceeded the threshold of absolute t values larger than 1.96. Here, the grand mean gamma rzPLFs have an estimate of 0.95, as indicated by the intercept (see supplemental materials S5: figure S5.3 & S5.4 for data visualization and table S5.2 for a summary of model fit). When comparing the illustration of the whole time-series from the theta rzPLFs and for gamma rzPLFs from the right hemispheric ROI, it can be seen that

gamma rzPLFs did not show a stimulus-locked resetting of phase. Similar to the amplitudes control analysis, there is no indication for a simultaneous increase of phase-locking of both bands in response to stimulus onset.

3.3.3. Theta-gamma phase synchronization on surrogate data

For the control analysis using surrogate data, the cross-frequency phase differences were calculated between gamma in a given trial and theta shifted for one trial, resulting in trial-shuffled cross-frequency phase synchronization indices (Rayleigh's z-transformed; rzPSIs). Importantly, results for surrogate data are not at all similar to those obtained from the analysis for the real data. The critical interaction between COND and TARG from the main analysis (0.18, t = 3.6, see Fig. 4B) was not reproduced for the analysis on surrogate data (−0.06, t = 1.11). And a main effect TARG as in the main analysis (0.062, t = 2.5) was also not present in the analysis on surrogate data (−0.01, t=−0.48), nor was any other effect from the main analysis. The only substantial effects in the model for surrogate data included the contrast CFSTheta60:Theta40: The model showed both a 3-way interaction effect (−0.31, t= −2.55) and a main effect (−0.09, t = 2.87) for the CFS-Theta60:Theta40 contrast. All other effects were not substantial (t values below 1.96). For comparison with the main analysis on real data, a summary of model fit can be found in supplemental materials S7, including figures for visualization of the surrogate data in the TOI and along the whole time series.

4. Discussion

Cross-frequency synchronization between theta and gamma band EEG activity has been proposed to serve matching processes between prediction and sensation in visual perception (Sauseng et al., 2010, 2015). In this study, we investigated how these electrophysiological correlates of memory matching are affected by the number of activated internal templates which can be compared to incoming sensory information. To perform the visual search task of this experiment, one has to hold in mind a template of a single or of multiple targets' visual properties so that it can be matched with the incoming stimulus. We expected to find stronger transient theta phase to gamma phase synchronization at posterior sites that are contralateral relative to target location compared to ipsilateral targets around 150–200 ms after search display presentation in the single template condition, but less so in the triple template condition.

In line with this, we found stronger theta-to-gamma phase synchronization in this early time window at a ROI in the right middle occipital gyrus, elicited by targets presented in the contralateral hemifield than by ipsilateral targets. An increase in theta to gamma phase synchronization contralateral relative to ipsilateral to target locations is well in line with what can be expected due to the lateralized organization of the visual system. This difference between contra- and ipsilateral target locations was larger in the single template condition than in the triple template condition. Specifically, in the single template condition, theta to gamma phase synchronization was higher for contralateral targets than for ipsilateral targets. This was not the case in the triple template condition. Thus, our data lend support to our hypothesis that memory matching was less precise in conditions where one out of three mental templates had to be matched with a target, whereas single template conditions enabled efficient memory matching.

Note that these effects were only present in the analysis for the right-hemispheric region of interest, whereas the separate analysis for the left hemispheric ROI did not yield any substantial effects. While we find a clearly right-lateralized effect, there are some previous studies reporting bilateral effects of stronger theta-gamma phase synchronization; e.g. in a cued visual attention task (Sauseng et al., 2008). However, in another study, Holz et al. (2010) found a right-lateralized effect of CFS in a visual delayed-match-to-sample task. Similar effects showing a lateralized theta-locked gamma phase synchronization for memory loads 3–4 in visual working memory are also reported by Sauseng et al. (2009). Other studies have also found primarily right-hemispheric brain areas to be relevant for visual search. For example, activity enhancements were reported in bilateral superior parietal cortex, but only extending into the intraparietal sulcus of the right hemisphere during visual search compared to overt orienting, (Nobre et al., 2003) and activation was completely right-lateralized for monitoring functions in visual search (Vallesi, 2014). More evidence for clear right-hemispheric dominance for search organization comes from lesion-studies, for example that lesions in the right parietal, temporal and occipital cortex were related to disorganized search (Ten Brink et al., 2016). This may explain why we only find a larger difference between contra- and ipsilateral target locations in the single template condition than in the triple template condition for right posterior, but not for left posterior regions of interest. While our right-hemispheric results reproduce previous evidence (Holz et al., 2010; Sauseng et al., 2008), the left-hemispheric results from these studies appear to be more variable overall: In the current data, we basically find no effect, whereas previously, both a left-hemispheric reversal of the effect in a visual delayed-match-to-sample task (Holz et al., 2010), as well as a similar effect in the same direction as in right hemisphere in a cued visual attention task (Sauseng et al., 2008) have been reported. Taken together, the left-hemispheric patterns of results seem to depend more on the specific task paradigm at hand. We will therefore focus on discussing the right-hemispheric results in the following.

This evidence from the single template condition in the current visual search paradigm corroborates previous findings showing a higher transient phase synchronization between posterior theta and gamma activity in cases where our expectancies match the actual visual input than in case of a non-match (Holz et al., 2010; Sauseng et al., 2008). Thus, our data from the single template condition fit well into the proposed framework that could well account for the activation of mental templates from working memory and their comparison with sensory input (Sauseng et al., 2010, 2015), which proposes that cross-frequency phase synchronization between theta and gamma frequencies early after target presentation can be regarded as a candidate neural mechanism underlying the matching of mental templates from working memory with sensory input. Here, the typically observed increase of fronto-parietal phase-coupling in the theta band during anticipation of a specified visual target is suggested to reflect the active presentation of a mental template in working memory, controlled by frontal resources and replayed into higher visual areas. Then subsequently, a posterior phase resetting of theta band oscillations is assumed to enable the transient cross-frequency coupling synchronization with high frequency activity in the gamma band range repeatedly found in a time window around 150 ms after target presentation. While potential alternative explanations will be discussed later, converging evidence supporting this view exists, suggesting that frontal low-frequency oscillations are indeed crucially involved in the top-down control during working memory tasks through coherence and cross-frequency interaction in fronto-parietal networks (for recent reviews, see de Vries et al., 2020; Karakaş, 2020; Klink et al., 2020; Palva and Palva, 2018).

Conversely, the triple template condition does not reveal such dynamics early after target presentation. A plausible interpretation of this results is that in the triple template search condition multiple templates are held sequentially in working memory; and that in a given trial depending on whether the sequence's first, second, or third mental template could be matched to the current visual input, memory matching occurred relatively early, a bit later or even much later, leading to overall more temporal variability across trials. This is then reflected in the cross-frequency phase synchronization mechanism investigated here. Based on proposals for a limited capacity of human visual working memory, supposedly around three to four items (Luck and Vogel, 2013), one might expect that likewise, we could maintain up to three or four simultaneous search templates for visual search as well. However, there is evidence that not all working memory items influence the guidance

of selective attention, but that only active memory items function as an attentional template and directly affect perception, whereas accessory memory items have relatively little influence on visual selection (Olivers et al., 2011). The conclusion here is that working memory items generally compete for the status of 'attentional template', which can only be achieved by one item at a time. So, although working memory could store multiple objects, observers could only actively look for one at a time. Thus, multiple-template search should require switching between mental templates or sequentially looking for them. Interestingly, though, Beck et al. (2012) propose that observers can concurrently keep two templates active in simultaneous search because when they explicitly asked participants to simultaneously search for two templates, their gaze frequently switched between them without switch costs. Similarly, Hollingworth and Beck (2016) found that even when multiple templates were kept in mind, a distractor in a visual-search task captured attention more when it matched the template(s), and proposed that multiple templates can guide attention simultaneously; but see also van Moorselaar et al. (2014) or Frătescu et al. (2019) where in contrast, such memory-driven capture was reported only for single templates, demonstrating that this does not hold in all situations. However, evidence showing clear switch costs for selection has been reported when only one out of two potential targets was available, suggesting that observers cannot actively search for multiple objects if they are not able to freely choose the target category (Ort et al., 2017, 2018). This is again well in line with the idea that only one search template at a time has priority and will guide visual attention (Olivers et al., 2011) and Ort and colleagues argue that both lines of evidence can be explained from a reactive versus proactive cognitive control framework (Braver, 2012). In this framework, when multiple targets are all available for search, participants can proactively prepare for any target, resulting in a lack of switch costs. Conversely, when only one of multiple possible targets is present for search, the currently displayed target might not match the target that the participant anticipated. Reactive control would follow this conflict, leading to increased processing times.

This latter case is similar to the current study's triple template condition, where only one of three possible targets was presented for search. While the design of our task does not allow for the analysis of inter-trial switch costs, we do see significantly fewer correct responses as well as behavioural slowing in response times to targets in the triple template blocks compared to targets in single template blocks. Slower and less accurate search performance has also been reported during simultaneous search for two targets compared to search for either target alone, indicating that subjects can probably not perform two simultaneous matching processes (Huang and Pashler, 2007; Menneer et al., 2007). So most likely, in a given trial in the current study's triple template blocks, a currently displayed target possibly did not match the target that the participant anticipated. This means that across trials, the match between memory templates and visual input would occur at varying points in time, which should also be reflected in the neural correlates of memory matching, predicting low estimates of cross-frequency phase synchrony. Conversely, in the single template condition, certainty about the mental template that has to be matched with sensory input was high in each trial and enabled a temporally precise matching process across trials, which predicts higher estimates of cross-frequency phase synchrony. Our data support this interpretation well, showing that theta to gamma phase synchronization, the proposed underlying mechanism of memory matching, was higher for contralateral targets than for ipsilateral targets in the single template condition, whereas this was not the case in the triple template condition. Note that as a measure for theta-gamma cross-frequency phase synchrony, we analysed the consistency of phase difference between the two frequencies over trials (Holz et al., 2010; Palva et al., 2005; Sauseng et al., 2008). This measure does not require the two frequencies to be coupled continuously. High estimates of phase synchrony will be achieved when there is a fixed relation between low and high frequencies across trials, independent of absolute phase difference between them and of phase-locking to stimulus of either of them, whereas low estimates will be achieved when phase relations vary over trials.

To discuss the pattern of results in the triple template condition, one might want to speculate about how the memory matching mechanism investigated here might rely on pre-stimulus working memory retention mechanisms. Generally, cross-frequency interactions between gamma band activity and slower brain waves have frequently been suggested to be involved in multi-item working memory, such as for multi-item working memory retention. A prominent computational model assumes that separate memory items are represented by single gamma waves which are nested into a theta wave (Jensen and Lisman, 1998; Lisman and Idiart, 1995). It is hypothesized that with this mechanism, multiple memory items (gamma waves nested into a theta cycle) can be actively held in parallel in working memory. In the light of this framework, one would assume that before search display presentation, in the triple template condition, the three mental templates would each be represented by separate gamma cycles nested into a theta wave one after another. Thus, upon search display presentation, it would be crucial as to whether the first, second or third item (gamma wave) incidentally matches with the one on the search display, leading to a temporal variability in the range of two gamma cycles. Another theoretical framework which entails cross-frequency synchronization between theta and gamma as the neural basis for multi-item WM retention argues that during retention, each item is coded by an entire gamma burst, i.e. multiple cycles, nested into a theta wave (Herman et al., 2013; Van Vugt et al., 2014). Following these ideas, there would be a temporal variability of memory matching in the triple template condition in the range of two theta cycles, depending on whether visual input matches with the first, second or third item (gamma burst). In this study, grand mean reaction time differences in the triple template condition were longer than reaction times in the single template condition by about 190 ms, which is in the range of a theta cycle. Speculatively, this would fit rather well with the predictions derived from the latter framework, where due to the expected temporal variability of two theta cycles, average reaction times would be expected to be around the length of one theta cycle longer when one out of three potential targets can be matched with visual input. Note, however that our task instructions had not emphasized a speeded but rather an accurate response, so we cannot draw strong conclusions here. To examine these predictions more closely, studies with a more precise measurement of response times would be required.

Although a sequential matching process seems to be a rather plausible interpretation of the observed low estimates of cross-frequency phase synchrony in the triple template condition, there may be alternative explanations to this. For example, a similar pattern of results could be obtained when cross-frequency phase-relations exhibit overall more temporal variability across trials due to differences in the source of EEG activity when several templates have to be processed. Or, for example, low phase synchronization estimates would be expected if memory matching in the triple template conditions happened with great temporal variability and if it happened consistently later than in the single template conditions. Also, an unspecific difference between the conditions, such as larger neural noise could have resulted in low estimates in the triple condition. We cannot rule out these possibilities. Alternatively assuming a parallel mode, would predict that multiple templates interacted in parallel with sensory input; however, this would come at costs due to mutual competition, leading to a delay in target selection (Ort et al., 2019; Ort and Olivers, 2020). For the matching phase, this may mean that when one out of multiple targets must be found, the matching process would happen later than for a single possible target, but consistently, with low temporal variability across trials. In this case, we would have expected to observe a slightly later effect, but with high estimates of phase synchrony similar to those in the single template condition. Descriptively, we find no indication for something like this in our data. Finally, it could be that participants might have had less precise, low fidelity templates in the triple template condition. One possibility is that template fidelity in multi-item retention could influence theta

phase. We recently argued that an increased memory fidelity could be an explanation for the empirically observed increased memory capacity by slowing down theta waves (Vosskuhl et al., 2015; Wolinski et al., 2018): In the light of theoretical models proposing that single visual items are neuronally represented by entire gamma bursts nested into theta waves for multi-item retention (Herman et al., 2013; Van Vugt et al., 2014), an increased memory fidelity could be an explanation for these findings because longer gamma bursts, representing a template with more fidelity, outweigh the slower rate of memory re-activation (Sauseng et al., 2019). Thus, a "let's see if something looks familiar" search mode due to overall lower template fidelity would predict shorter theta cycles than a mode where there is an active top-down set for the target properties. This would predict that theta cycles may have been shorter in the triple, compared to the single template condition. But even if theta frequency was sped up, this should not automatically lead to attenuated theta-gamma phase synchronization. Based on the nature of this measure, only increased temporal jitter should lead to that effect. Therefore, our pattern of results does not support the idea of fidelity differences of the conditions. However, another possibility is that familiarity matching processes could have an entirely different neural signature than template matching processes. Since this should not be reflected in the investigated cross-frequency coupling index, we cannot exclude this possibility.

Yet, we assumed that visual search for the kind of complex targets we used in this study would have relied on an active attentional template in working memory (Gunseli et al., 2014). The abstract symbols that we used as target and distractor stimuli were rather complex and all unknown to the observers. However, since it was not possible to ask participants to memorize a trial-by-trial changing target and, thus, a training beforehand was necessary, it is likely that participants may have stored those memorized target(s) in long-term memory before the start of our task. Given that the task was still relatively difficult (task performance was on average 86% and 63% correct responses in the single and triple condition, respectively), however, we think that rather than being stored passively in long-term memory, it is more likely that the template had to be activated in working memory for successful task performance (Ruchkin et al., 2003). In an ERP study, Gunseli et al. (2014) reported evidence for a larger LPC component when an effortful, as opposed to an efficient search is anticipated, indicating that participants tried maintaining an attentional template in working memory with greater effort. In other words, this suggests that for effortful search an increased working memory effort for maintaining the template in working memory may be required. Based on our participant's feedback and task performance, it seems plausible that our task was experienced as quite challenging; and the strategies that were reported in the personal feedback indicate that they tried maintaining a target template vividly. However, we cannot claim that our task was a pure working memory paradigm, as clear long-term memory involvement exists. Thus, in order to strengthen the argument for matching of templates from working memory, the paradigm could be adjusted to a trial-by-trial target cueing, without prior training in the future. Yet, EEG studies suggest that even in design where targets are not trained beforehand, but changed on a trial-by-trial basis, the attentional template is learned after repeated search for the same target, as evidence for decreased CDA and LPC components with target repetition was found (Carlisle et al., 2011; Gunseli et al., 2014). Based on this, it is proposed that an attentional template which is initially stored in working memory can be transferred to long-term memory when the target is repeated. Additionally, contextual cueing effects in visual search (e.g. Zinchenko et al., 2020) can be explained through storing spatial target-distractor relations as templates in long-term memory after they have been repeatedly encountered. This would mean that even in a search paradigm where targets are cued in each trial, the involvement of long-term memory cannot be entirely excluded.

While the evidence and framework we build on has its focus on how mental templates interact with visual information before and until the match between stimulus-related information and memory contents happens (Sauseng et al., 2010, 2015), memory matching is probably one of several steps that are assumed to take place within the selection stage of visual search (for review, see Eimer (2014) and Ort and Olivers (2020). For example, the 'match-and-utilization model' focuses both on the step of the match between stimulus-related information and memory contents as well as the step of utilization, where the result of this match or mismatch is then 'read out', which could then result in the updating of memory, the selection of behavioural responses and the reallocating of attention (Herrmann et al., 2010). Or, from the point of view of predictive coding theories which assume that top-down predictions are matched to incoming sensory inputs across different levels of the cortical hierarchy, it is assumed that a prediction-error signal is fed forward along the cortical hierarchy and used to update top-down predictions (Friston, 2005). For the template-matching visual input to win the competitive race over other visual input, an increase in attention towards the identity or spatial location of memory-matching visual inputs is quite likely. We cannot exclude that such mechanisms are contributing to the observed effects in our study.

The right-hemispheric effects from our data seem to be specific for theta-gamma phase synchronization since a control analysis for cross-frequency phase synchronization between alpha and gamma did not show similar results. Yet, for alpha-gamma phase synchronization there was an interaction between template condition and target location for the left hemispheric posterior source. However, the direction of this effect (stronger ipsilateral PSI) was contrary to what would be expected due to the lateralized organization of the visual system.

Previous studies have reported similar cross-frequency interaction either between theta and gamma frequencies around 30–50 Hz in a cued visual attention task (Sauseng et al., 2008) or between theta and higher gamma activity (Holz et al., 2010; Sauseng et al., 2009). In the current data from our visual search paradigm, it seems that the difference between right posterior rzPSIs for Theta-to-70 Hz and for Theta-to-60 Hz is smaller for single than triple template conditions; whereas the difference for Theta-to-60 Hz and for Theta-to-40 Hz seems to be larger for single than triple template conditions. However, the critical effect between template condition and target location in the main analysis did not interact with gamma frequency dependent differences. This speaks rather for a broadband gamma effect than a selective effect of theta and a narrow gamma sub-band in the current visual search paradigm. The critical interaction from the main analysis seems to be rather frequency-specific to theta-gamma phase synchronization, however, because contrary to the effects observed for the main analysis, all contrasts remained below threshold in a control analysis with alpha-gamma phase synchronization.

To ensure that differences between conditions were not based on merely different trial counts in the single and triple template condition, PSI values were transformed using Rayleigh's z transform (Cohen, 2014). Naturally, this does not eliminate the difference in signal-to-noise ratio between conditions, which was most likely lower in the triple template condition. Note, however, that this pattern of results was found even though in both conditions, only trials with a correct response for which we assume that successful memory matching must have taken place at some point were used to calculate theta-gamma phase synchronization indices. Additionally, we found that in a control analysis where we drew a random subset of the same number of trials in the condition with fewer trials before calculating rzPSIS on these trial-matched data, results were very similar to those obtained from the main analysis based on all trials. Importantly, the critical interaction between COND and TARG from the main analysis was reproduced and showed the same pattern of results, namely that the single template condition showed larger estimates for contra compared to ipsilateral targets, whereas this was not the case for the triple condition.

Because spurious effects of theta-gamma phase synchronization might arise due to evoked activity in response to probe presentation, we analysed amplitudes and the phase locking factor for theta and gamma frequencies to control for this. If both frequencies showed a si-

multaneous increase in amplitudes or a simultaneous phase resetting in response to stimulus onset, the data might indicate artificial cross-frequency phase synchronization in the absence of true interactions between the two frequencies. However, none of these control analyses showed a simultaneous increase in amplitudes or a simultaneous phase resetting in response to stimulus onset nor a similar pattern of results as the main analysis. Thus, the results from these control analyses rather indicate it being implausible that the observed interaction between COND and TARG for theta-gamma cross-frequency synchronization in the right-hemisheric ROI in the main analysis, is due to an artefact from simultaneous evoked activity in response to probe presentation in both theta and gamma frequency bands. This is also confirmed by a control analysis on surrogate data, demonstrating that trial-shuffled cross-frequency phase synchronization indices did not show similar results to the real data, which should have been the case if the observed effect of theta-gamma phase synchronization 150–200 ms after probe presentation in the real data was generated through an evoked response.

Conclusion

Taken together, our data lend support to the hypothesis that neuronal networks operating at theta and gamma frequency do become more synchronized in phase during an early time window following visual search display onset, when a single template has to be retained compared to triple template conditions. This adds to previous theoretical accounts that have strongly argued for a transient synchronization between theta and gamma phase over posterior electrode sites as a neural correlate of matching of incoming sensory information with memory contents from working memory (Sauseng et al., 2010, 2015). We interpret this as showing that while a single mental template enables precise memory matching, limitations in this matching process occur during multiple template search. These could be explained by sequential attentional templates (Lisman and Idiart, 1995; Olivers et al., 2011; Van Vugt et al., 2014), however, other task paradigms combining multiple template search with the investigation of target switch costs ought to corroborate this. For future studies, it would be interesting to investigate the temporal dynamics of such matching processes during the acquisition and consolidation phase of attentional templates. Studying more naturalistic contexts of template to input matching where, for example, templates are acquired via learning, could further illuminate the involvement of cross frequency interactions in template to input matching.

Declaration of Competing Interest

The authors declare no competing interests.

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Supplementary materials

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References

Alday, P.M. (2018). *lmerOut: LaTeX Output for Mixed Effects Models with LME4*. https://bitbucket.org/palday/lmerout

Alday, P.M., Schlesewsky, M., Bornkessel-Schlesewsky, I., 2017. Electrophysiology reveals the neural dynamics of naturalistic auditory language processing: event-related potentials reflect continuous model updates. ENeuro 4 (6). doi:10.1523/ENEURO.0311-16.2017.

Axmacher, N., Mormann, F., Fernández, G., Elger, C.E., Fell, J., 2006. Memory formation by neuronal synchronization. Brain Res. Rev. 52 (1), 170–182. doi:10.1016/j.brainresrev.2006.01.007.

Baayen, R.H., Davidson, D.J., Bates, D.M., 2008. Mixed-effects modeling with crossed random effects for subjects and items. J. Mem. Lang. 59 (4), 390–412. doi:10.1016/j.jml.2007.12.005.

Bates, D., Sarkar, D., Bates, M.D., Matrix, L., 2007. The lme4 package. R. Package Vers. 2 (1), 74.

Bays, P.M., Husain, M., 2008. Dynamic shifts of limited working memory resources in human vision. Science 321 (5890), 851–854. doi:10.1126/science.1158023.Dynamic.

Beck, V.M., Hollingworth, A., Luck, S.J., 2012. Simultaneous control of attention by multiple working memory representations. Psychol. Sci. 23 (8), 887–898. doi:10.1177/0956797612439068.

Berger, B., Griesmayr, B., Minarik, T., Biel, A.L., Pinal, D., Sterr, A., Sauseng, P., 2019. Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. Nat. Commun. 10 (1), 4242. doi:10.1038/s41467-019-12057-0.

Bonnefond, M., Jensen, O., 2012. Alpha oscillations serve to protect working memory maintenance against anticipated distracters. Curr. Biol. 22 (20), 1969–1974. doi:10.1016/j.cub.2012.08.029.

Braver, T.S., 2012. The variable nature of cognitive control: a dual mechanisms framework. Trends Cogn. Sci. 16 (2), 106–113. doi:10.1016/j.tics.2011.12.010.

Bundesen, C., 1990. A theory of visual attention. Psychol. Rev. 97 (4), 523–547. doi:10.1037/0033-295X.97.4.523.

Bundesen, C., Habekost, T., Kyllingsbæk, S., 2005. A neural theory of visual attention: bridging cognition and neurophysiology. Psychol. Rev. 112 (2), 291–328. doi:10.1037/0033-295X.112.2.291.

Buschman, T.J., Miller, E.K., 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315 (5820), 1860–1862. doi:10.1126/science.1138071.

Buzsáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. Science 304 (5679), 1926–1929. doi:10.1126/science.1099745.

Canolty, R.T., Edwards, E., Dalal, S.S., Soltani, M., Nagarajan, S.S., Kirsch, H.E., Berger, M.S., Barbaro, N.M., Knight, R.T., 2006. High gamma power is phase-locked to theta oscillations in human neocortex. Science 313 (5793), 1626–1628. doi:10.1126/science.1128115.

Carlisle, N.B., Arita, J.T., Pardo, D., Woodman, G.F., 2011. Attentional templates in visual working memory. J. Neurosci. 31 (25), 9315–9322. doi:10.1523/JNEUROSCI.1097-11.2011.

Cohen, M.X., 2014. Analyzing Neural Time Series Data: Theory and Practice. MIT Press.

de Vries, I.E.J., Slagter, H.A., Olivers, C.N.L, 2020. Oscillatory control over representational states in working memory. Trends Cogn. Sci. 24 (2), 150–162. doi:10.1016/j.tics.2019.11.006.

Demiralp, T., Bayraktaroglu, Z., Lenz, D., Junge, S., Busch, N.A., Maess, B., Ergen, M., Herrmann, C.S., 2007. Gamma amplitudes are coupled to theta phase in human EEG during visual perception. Int. J. Psychophysiol. 64 (1), 24–30. doi:10.1016/j.ijpsycho.2006.07.005.

Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18 (1), 193–222. doi:10.1146/annurev.ne.18.030195.001205.

Duncan, J., Humphreys, G.W., 1989. Visual search and stimulus similarity. Psychol. Rev. 96 (3), 433–458. doi:10.1037/0033-295X.96.3.433.

Eimer, M., 2014. The neural basis of attentional control in visual search. Trends Cogn. Sci. 18 (10), 526–535. doi:10.1016/j.tics.2014.05.005.

Engel, A.K., Singer, W., 2001. Temporal binding and the neural correlates of sensory awareness. Trends Cogn. Sci. 5 (1), 16–25. doi:10.1016/S1364-6613(00)01568-0.

Everling, S., Tinsley, C.J., Gaffan, D., Duncan, J., 2006. Selective representation of task-relevant objects and locations in the monkey prefrontal cortex. Eur. J. Neurosci. 23 (8), 2197–2214. doi:10.1111/j.1460-9568.2006.04736.x.

Fell, J., Axmacher, N., 2011. The role of phase synchronization in memory processes. Nat. Rev. Neurosci. 12 (2), 105–118. doi:10.1038/nrn2979.

Frătescu, M., Van Moorselaar, D., Mathôt, S., 2019. Can you have multiple attentional templates? Large-scale replications of Van Moorselaar, Theeuwes, and Olivers (2014) and Hollingworth and Beck (2016). Attention, Percept. Psychophys. 81 (8), 2700–2709. doi:10.3758/s13414-019-01791-8.

Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9 (10), 474–480. doi:10.1016/j.tics.2005.08.011.

Friese, U., Köster, M., Hassler, U., Martens, U., Trujillo-Barreto, N., Gruber, T., 2013. Successful memory encoding is associated with increased cross-frequency coupling between frontal theta and posterior gamma oscillations in human scalp-recorded EEG. Neuroimage 66, 642–647. doi:10.1016/j.neuroimage.2012.11.002.

Friston, K., 2005. A theory of cortical responses. Philos. Trans. R. Soc. B: Biol. Sci. 360 (1456), 815–836. doi:10.1098/rstb.2005.1622.

Gayet, S., Guggenmos, M., Christophel, T.B., Haynes, J.-.D., Paffen, C.L.E., Stigchel, S.V.der, Sterzer, P, 2017. Visual working memory enhances the neural response to matching visual input. J. Neurosci. 37 (28), 6638–6647. doi:10.1523/JNEUROSCI.3418-16.2017.

Gelman, A., Hill, J., 2007. Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge University Press.

Griesmayr, B., Gruber, W.R., Klimesch, W., Sauseng, P., 2010. Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task. Neurobiol. Learn. Mem. 93 (2), 208–215. doi:10.1016/j.nlm.2009.09.013.

Gunseli, E., Olivers, C.N.L., Meeter, M, 2014. Effects of search difficulty on the selection, maintenance, and learning of attentional templates. J. Cogn. Neurosci. 26 (9), 2042–2054. doi:10.1162/jocn_a_00600.

Herman, P.A., Lundqvist, M., Lansner, A., 2013. Nested theta to gamma oscillations and precise spatiotemporal firing during memory retrieval in a simulated attractor network. Brain Res. 1536, 68–87. doi:10.1016/j.brainres.2013.08.002.

Herrmann, C.S., Fründ, I., Lenz, D, 2010. Human gamma-band activity: a review on cognitive and behavioral correlates and network models. Neurosci. Biobehav. Rev. 34 (7), 981–992. doi:10.1016/j.neubiorev.2009.09.001.
Herrmann, C.S., Munk, M.H.J., Engel, A.K, 2004. Cognitive functions of gamma-band activity: memory match and utilization. Trends Cogn. Sci. 8 (8), 347–355. doi:10.1016/j.tics.2004.06.006.
Hollingworth, A., Beck, V.M., 2016. Memory-based attention capture when multiple items are maintained in visual working memory. J. Exp. Psychol. Hum. Percept. Perform. 42 (7), 911–917. doi:10.1037/xhp0000230.
Holz, E.M., Glennon, M., Prendergast, K., Sauseng, P., 2010. Theta-gamma phase synchronization during memory matching in visual working memory. Neuroimage 52 (1), 326–335. doi:10.1016/j.neuroimage.2010.04.003.
Huang, L., Pashler, H., 2007. A Boolean map theory of visual attention. Psychol. Rev. 114 (3), 599–631. doi:10.1037/0033-295X.114.3.599.
Jensen, O., Kaiser, J., Lachaux, J.P., 2007. Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci. 30 (7), 317–324. doi:10.1016/j.tins.2007.05.001.
Jensen, O., Lisman, J.E., 1998. An oscillatory short-term memory buffer model can account for data on the Sternberg task. J. Neurosci. 18 (24), 10688–10699.
Karakaş, S., 2020. A review of theta oscillation and its functional correlates. Int. J. Psychophysiol. 157, 82–99. doi:10.1016/j.ijpsycho.2020.04.008.
Klink, K., Paßmann, S., Kasten, F.H., Peter, J., 2020. The modulation of cognitive performance with transcranial alternating current stimulation: a systematic review of frequency-specific effects. Brain Sci. 10 (12), 932. doi:10.3390/brainsci10120932.
Lba, M., Sawaguchi, T., 2003. Involvement of the dorsolateral prefrontal cortex of monkeys in visuospatial target selection. J. Neurophysiol. 89 (1), 587–599. doi:10.1152/jn.00148.2002.
Lisman, J.E., Idiart, M.A., 1995. Storage of 7 +/- 2 short-term memories in oscillatory subcycles. Science 267 (5203), 1512–1515. doi:10.1126/science.7878473.
Luck, S.J., 2012. Electrophysiological correlates of the focusing of attention within complex visual scenes: n2pc and related ERP components. In: Luck, S.J., Kappenmann, E.S. (Eds.), The Oxford handbook of Event-Related Potential Components. Oxford University Press, pp. 329–360. doi:10.1093/oxfordhb/9780195374148.013.0161.
Luck, S.J., Vogel, E.K., 2013. Visual working memory capacity: from psychophysics and neurobiology to individual differences. Trends Cogn. Sci. 17 (8), 391–400. doi:10.1016/j.tics.2013.06.006.
Menneer, T., Barrett, D.J.K., Phillips, L., Donnelly, N., Cave, K.R, 2007. Costs in searching for two targets: dividing search across target types could improve airport security screening. Appl. Cogn. Psychol. 21 (7), 915–932. doi:10.1002/acp.1305.
Nobre, A.C., Coull, J.T., Walsh, V., Frith, C.D., 2003. Brain activations during visual search: contributions of search efficiency versus feature binding. Neuroimage 18 (1), 91–103. doi:10.1006/nimg.2002.1329.
O'Keefe, J., Recce, M.L., 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3 (3), 317–330. doi:10.1002/hipo.450030307.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113. doi:10.1016/0028-3932(71)90067-4.
Olivers, C.N.L., Peters, J., Houtkamp, R., Roelfsema, P.R, 2011. Different states in visual working memory: when it guides attention and when it does not. Trends Cogn. Sci. 15 (7), 327–334. doi:10.1016/j.tics.2011.05.004.
Ort, E., Fahrenfort, J.J., Olivers, C.N.L, 2017. Lack of free choice reveals the cost of having to search for more than one object. Psychol. Sci. 28 (8), 1137–1147. doi:10.1177/0956797617705667.
Ort, E., Fahrenfort, J.J., Olivers, C.N.L, 2018. Lack of free choice reveals the cost of multiple-target search within and across feature dimensions. Attention, *Percept. Psychophys.* 80 (8), 1904–1917. doi:10.3758/s13414-018-1579-7.
Ort, E., Fahrenfort, J.J., ten Cate, T., Eimer, M., Olivers, C.N., 2019. Humans can efficiently look for but not select multiple visual objects. Elife 8, e49130. doi:10.7554/eLife.49130.
Ort, E., Olivers, C.N.L, 2020. The capacity of multiple-target search. Vis. cogn. 28 (5–8), 330–355. doi:10.1080/13506285.2020.1772430.
Palva, J.M., Palva, S., 2018. Functional integration across oscillation frequencies by cross-frequency phase synchronization. Eur. J. Neurosci. 48 (7), 2399–2406. doi:10.1111/ejn.13767.
Palva, J.Matias, Palva, S., Kaila, K, 2005. Phase synchrony among neuronal oscillations in the human cortex. J. Neurosci. 25 (15), 3962–3972. doi:10.1523/JNEUROSCI.4250-04.2005.
Pascual-Marqui, R.D., Esslen, M., Kochi, K., Lehmann, D., 2002. Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. Methods Find. Exp. Clin. Pharmacol. 24 (Suppl C), 91–95.
Payne, B.R., Lee, C.-.L., Federmeier, K.D., 2015. Revisiting the incremental effects of context on word processing: evidence from single-word event-related brain potentials. Psychophysiology 52 (11), 1456–1469. doi:10.1111/psyp.12515.
Pinheiro, J.C., Bates, D.M., 2000. Mixed-effects Models in S and S-PLUS. Springer.
R Core Team, 2019. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.
Rabe, M.M., Vasishth, S., Hohenstein, S., Kliegl, R., Schad, D.J., 2020. hypr: an R package for hypothesis-driven contrast coding. J. Open Source Softw. doi:10.21105/joss.02134.
Rossi, A.F., Bichot, N.P., Desimone, R., Ungerleider, L.G., 2007. Top down attentional deficits in macaques with lesions of lateral prefrontal cortex. J. Neurosci. 27 (42), 11306–11314. doi:10.1523/JNEUROSCI.2939-07.2007.
Ruchkin, D.S., Grafman, J., Cameron, K., Berndt, R.S., 2003. Working memory retention systems: a state of activated long-term memory. Behav. Brain Sci. 26 (6), 709–728. doi:10.1017/s0140525x03000165.
Sarnthein, J., Petsche, H., Rappelsberger, P., Shaw, G.L., von Stein, A., 1998. Synchronization between prefrontal and posterior association cortex during human working memory. PNAS 95 (12), 7092–7096. doi:10.1073/pnas.95.12.7092.
Sauseng, P., Conci, M., Wild, B., Geyer, T., 2015. Predictive coding in visual search as revealed by cross-frequency EEG phase synchronization. Front. Psychol. 6, 1655. doi:10.3389/fpsyg.2015.01655.
Sauseng, P., Griesmayr, B., Freunberger, R., Klimesch, W., 2010. Control mechanisms in working memory: a possible function of EEG theta oscillations. Neurosci. Biobehav. Rev. 34 (7), 1015–1022. doi:10.1016/j.neubiorev.2009.12.006.
Sauseng, P., Klimesch, W., 2008. What does phase information of oscillatory brain activity tell us about cognitive processes? Neurosci. Biobehav. Rev. 32 (5), 1001–1013. doi:10.1016/j.neubiorev.2008.03.014.
Sauseng, P., Klimesch, W., Gruber, W.R., Birbaumer, N., 2008. Cross-frequency phase synchronization: a brain mechanism of memory matching and attention. Neuroimage 40 (1), 308–317. doi:10.1016/j.neuroimage.2007.11.032.
Sauseng, P., Klimesch, W., Heise, K.F., Gruber, W.R., Holz, E., Karim, A.A., Glennon, M., Gerloff, C., Birbaumer, N., Hummel, F.C., 2009. Brain oscillatory substrates of visual short-term memory capacity. Curr. Biol. 19 (21), 1846–1852. doi:10.1016/j.cub.2009.08.062.
Sauseng, P., Klimesch, W., Schabus, M., Doppelmayr, M., 2005. Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. Int. J. Psychophysiol.: Off. J. Int. Org. Psychophysiol. 57 (2), 97–103. doi:10.1016/j.ijpsycho.2005.03.018.
Sauseng, P., Peylo, C., Biel, A.L., Friedrich, E.V.C., Romberg-Taylor, C, 2019. Does cross-frequency phase coupling of oscillatory brain activity contribute to a better understanding of visual working memory? Br. J. Psychol. 110 (2), 245–255. doi:10.1111/bjop.12340.
Schack, B., Vath, N., Petsche, H., Geissler, H.G., Möller, E., 2002. Phase-coupling of theta-gamma EEG rhythms during short-term memory processing. Int. J. Psychophysiol. 44 (2), 143–163. doi:10.1016/S0167-8760(01)00199-4.
Schack, Baerbel, Weiss, S., 2005. Quantification of phase synchronization phenomena and their importance for verbal memory processes. Biol. Cybern. 92 (4), 275–287. doi:10.1007/s00422-005-0555-1.
Schad, D.J., Vasishth, S., Hohenstein, S., Kliegl, R., 2019. How to capitalize on a priori contrasts in linear (mixed) models: a tutorial. J. Mem. Lang. 110. doi:10.1016/j.jml.2019.104038.
Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., Buzsáki, G., 2008. Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. Neuron 60 (4), 683–697. doi:10.1016/j.neuron.2008.09.014.
Soto, D., Hodsoll, J., Rotshtein, P., Humphreys, G.W., 2008. Automatic guidance of attention from working memory. Trends Cogn. Sci. 12 (9), 342–348. doi:10.1016/j.tics.2008.05.007.
Soto, D., Humphreys, G.W., Heinke, D., 2006. Dividing the mind: the necessary role of the frontal lobes in separating memory from search. Neuropsychologia 44 (8), 1282–1289. doi:10.1016/j.neuropsychologia.2006.01.029.
Soto, D., Humphreys, G.W., Rotshtein, P., 2007. Dissociating the neural mechanisms of memory-based guidance of visual selection. Proc. Natl. Acad. Sci. 104 (43), 17186–17191. doi:10.1073/pnas.0703706104.
Spaak, E., Fonken, Y., Jensen, O., de Lange, F.P., 2016. The neural mechanisms of prediction in visual search. Cereb. Cortex 26 (11), 4327–4336. doi:10.1093/cercor/bhv210.
Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J., 1996. Stimulus specificity of phase-locked and non-phase-locked 40Hz visual responses in human. J. Neurosci. 16 (13), 4240–4249. doi:10.1523/JNEUROSCI.16-13-04240.1996.
Brink, Ten, F., A., Biesbroek, J.M., Kuijf, H.J., Van der Stigchel, S., Oort, Q., Visser-Meily, J.M.A., Nijboer, T.C.W, 2016. The right hemisphere is dominant in organization of visual search-A study in stroke patients. Behav. Brain Res. 304, 71–79. doi:10.1016/j.bbr.2016.02.004.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289. doi:10.1006/nimg.2001.0978.
Vallesi, A., 2014. Monitoring mechanisms in visual search: an fMRI study. Brain Res. 1579, 65–73. doi:10.1016/j.brainres.2014.07.018.
van Moorselaar, D., Theeuwes, J., Olivers, C.N.L, 2014. In competition for the attentional template: can multiple items within visual working memory guide attention? J. Exp. Psychol. Hum. Percept. Perform. 40 (4), 1450–1464. doi:10.1037/a0036229.
Van Vugt, M.K., Chakravarthi, R., Lachaux, J.-.P., 2014. For whom the bell tolls: periodic reactivation of sensory cortex in the gamma band as a substrate of visual working memory maintenance. Front. Hum. Neurosci. 8. doi:10.3389/fnhum.2014.00696.
von Stein, A., Chiang, C., König, P., 2000. Top-down processing mediated by interareal synchronization. PNAS 97 (26), 14748–14753. doi:10.1073/pnas.97.26.14748.
Vosskuhl, J., Huster, R.J., Herrmann, C.S., 2015. Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. Front. Hum. Neurosci. 9, 257. doi:10.3389/fnhum.2015.00257.
Wickham, H., 2016. ggplot2: Elegant graphics for Data Analysis. Springer.
Wolinski, N., Cooper, N.R., Sauseng, P., Romei, V., 2018. The speed of parietal theta frequency drives visuospatial working memory capacity. PLoS Biol. 16 (3), e2005348. doi:10.1371/journal.pbio.2005348.
Yago, E., Duarte, A., Wong, T., Barcelo, F., Knight, R.T., 2004. Temporal kinetics of prefrontal modulation of the extrastriate cortex during visual attention. Cognit. Affect. Behav. Neurosci. 4 (4), 609–617. doi:10.3758/CABN.4.4.609.
Zinchenko, A., Conci, M., Töllner, T., Müller, H.J., Geyer, T., 2020. Automatic guidance (and misguidance) of visuospatial attention by acquired scene memory: evidence from an N1pc polarity reversal. Psychol. Sci. 31 (12), 1531–1543. doi:10.1177/0956797620954815.

Chapter 3

Project II: FM-theta phase dependent parietal TMS effects on working memory

This chapter comprises the manuscript for a research article entitled "Frontal-midline theta phase dependent effects of TMS over parietal cortex on visuospatial working memory performance" (Biel et al., in preparation).

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Frontal-midline theta phase dependent effects of TMS over parietal cortex on visuospatial working memory performance

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Abstract

Working memory (WM) control processes are thought to be implemented in the brain by a distributed fronto-parietal network. They seem to rely on interactions between frontal midline theta oscillations, suggested to play a crucial role for the allocation of cognitive control, and posterior gamma oscillations, linked to local mnemonic processing. There is evidence demonstrating that posterior brain areas can dynamically assess prefrontal cognitive resources though a behaviourally relevant mechanism where depending on task difficulty, bursts of posterior gamma activity cluster into different phases of the FM-theta cycle (Berger et al., 2019). If such dynamic cross-frequency coupling is similarly modulated by a voluntary allocation of cognitive resources, then the level of priority (i.e. prioritizing or non-prioritizing information) should influence the phase of FM-theta to which right posterior gamma amplitude is locked – posterior gamma activity associated with processing of prioritised information nested into the more excitatory FM theta phase (trough), posterior gamma associated with processing of irrelevant information locked to more inhibitory FM theta phases. We therefore hypothesized that in a combined EEG-TMS study where we applied TMS for disrupting posterior brain activity during the retention interval of a visual delayed match to sample task, the impact of posterior TMS on resulting task performance would depend on whether it was delivered to the contralateral task-active (i.e. involved in prioritizing information) or ipsilateral task-inactive (i.e. non-prioritizing) hemisphere and on when TMS was delivered relative to the phase of FM-theta. We tested this in a pilot study and found preliminary evidence that applying TMS at right posterior brain areas resulted in a decrease of task performance during the trough phase for the contralateral prioritized hemifield. For left-hemispheric TMS, results were less clear. We discuss possible explanations for these inconclusive results, give recommendations on methodological considerations and provide fitted linear mixed effects models which can be used for a simulation based power analysis for follow-up studies.

Keywords

Cognitive control; frontal cortex; frontal-midline theta; parietal cortex; theta oscillations; transcranial magnetic stimulation (TMS); working memory

1 Introduction

Working Memory (WM) is known as a limited-capacity system for the transient storage of information and for performing mental operations on this stored information. It is classically though to be comprised of an attentional-control system for central executive processes and two subsidiary systems for the short-term storage of verbal and of visuospatial information (Baddeley, 2000; Baddeley et al., 2011; Baddeley & Hitch, 1974). Studies investigating the neural substrates of these working memory components traditionally related central executive functions to frontal cerebral areas (Collette & Van der Linden, 2002). Converging evidence, however, entails a distributed neuronal network, including the dorso-lateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), and posterior parietal cortices (PPC) for the allocation of cognitive control (Cole & Schneider, 2007; Dosenbach et al., 2008). Thus, an increased activation of medial and dorsal frontal brain areas, as well as interactions between frontal and posterior cortical areas seem to be involved in mnemonic operations in need of cognitive control and resource allocation.

During a variety of cognitive control processes, oscillatory brain activity in the theta band (4-8 Hz) in human medial prefrontal and anterior cingulate cortices, so called frontal midline theta (FM-theta), shows an increase in amplitude, such as during the maintenance and manipulation of information, sustained attention and, more general, cognitive resource allocation (Cavanagh & Frank, 2014; Mitchell et al., 2008; Sauseng et al., 2007, 2010). Theta activity has been shown to have a strong influence on local cortical activity both in the human and animal brain, namely by entraining neuronal spiking and fast oscillatory activity, such as gamma band activity (Canolty et al., 2006; Fell & Axmacher, 2011; O'Keefe & Recce, 1993; Sirota et al., 2008). Thus, neuronal spiking and gamma band oscillations are more likely to occur during the trough phase of maximal excitability of slow oscillatory activity than during its peak phase of minimal excitability (Haegens et al., 2011; Womelsdorf et al., 2010).

Studies using EEG in humans have shown cross-frequency coupling between slow and fast oscillatory activity to be involved in perceptual and working memory processes (Axmacher et al., 2010; Demiralp et al., 2007; Sauseng et al., 2008, 2009; Schack et al., 2002). For instance, Sauseng and colleagues (2009) demonstrated that gamma oscillations over posterior parietal recording sites were locked to the trough of ongoing theta oscillations during the retention of visuospatial information in working memory. Bursts of local gamma band activity were therefore more likely to occur during the theta cycle's phase of maximal excitability than during its phase of minimal excitability.

This kind of neuronal phase coding mechanism has not only been reported on a local scale. There is compelling evidence in rodents that prefrontal and hippocampal theta oscillations entrain local gamma oscillations and neuronal firing in prefrontal and tegmental neurons, which were shown to become phase locked to theta oscillations during working memory (Fujisawa & Buzsaki, 2011; Sirota et al., 2008). In the human brain, Berger and colleagues (2019) demonstrated strong evidence that FM-theta phase might represent a gating mechanism for the allocation of cognitive control, allowing task-relevant posterior cortical areas to access frontal cognitive recourses depending on task demands. EEG results showed that during the maintenance and manipulation of one of four items in visual WM, with increasing task difficulty, posterior gamma bursts were nested closer towards the trough of the FM-theta cycle, while at low task demands, they were nested closer to its peak. Furthermore, performance was shown to significantly decrease in trials in which parietal repetitive transcranial magnetic stimulation (rTMS) had been delivered during the trough of a FM-theta cycle, whereas it was not impaired for other phases. This demonstrated that the functional coupling between FM-theta phase and posterior gamma bursts was indeed behaviourally relevant for WM control functions. Thus, depending on task demand, communication between distant task-relevant regions was facilitated or disrupted during short, periodic time windows, realized through specific adjustments in the coupling between frontal midline theta phase and posterior gamma bursts (Berger et al., 2019).

Whether the clustering of neural activity at task-active posterior brain areas into specific FM-theta phase segments is only influenced by cognitive demands or whether it can also be affected by other factors is yet to be studied. In the current study, we asked whether such a mechanism is influenced by the amount of priority given to respective information, that is, by the voluntary allocation of cognitive resources in WM. In a visuospatial delayed-match-to-sample task, participants had to retain the orientation of bilateral spatially arranged Gabor gratings during a delay period, but were instructed to prioritize one visual hemifield over the other. We expected that depending on whether the contralateral hemifield was prioritized or not prioritized during the retention interval, the level of priority would influence the phase of FM-theta to which neural activity at task-active posterior brain areas is locked, similar to the effects observed for the level of task difficulty in earlier

studies (Berger et al., 2019). We therefore conducted a combined EEG-TMS experiment where young, neurotypical human participants performed the visuospatial WM task while EEG was recorded. To disturb local hemispheric responses to stimuli in the contralateral visual field, both for conditions in which the respective information was prioritized or non-prioritized, we applied a TMS single-pulse during the retention interval of each trial. TMS was applied over left or right posterior brain areas, at the location overlying the region of the intraparietal sulcus (IPS) and task performance was analysed as a function of instantaneous FM-theta phase at which the posterior TMS pulse had been delivered. The IPS is known to show increased activity and increased connectivity to prefrontal cortex during the maintenance and manipulation of visuo-spatial WM contents as well as spatial attention (Bray et al., 2015; Corbetta et al., 2002; Curtis, 2006; Silk et al., 2010; Todd & Marois, 2004).

We hypothesized that the extent to which applying TMS at posterior brain areas would disrupt task performance should depend on when the pulse was delivered with respect to the FM theta phase; and on whether it was delivered to the contralateral task-active (i.e. involved in prioritizing information) or ipsilateral task-inactive (i.e. non-prioritizing) hemisphere. Specifically, we expected that task performance would decrease when the TMS single-pulse was applied at posterior sites contralateral to the prioritized hemifield and fell into trough of the FM-theta cycle because efficient neuronal processing would be interrupted.

2 Method

2.1 Participants

14 students at Ludwig-Maximilians-Universität Munich participated in the experiment. All gave written informed consent for their participation and received financial compensation or course credits. Two participants had to be excluded from analyses due to an excessive amount of horizontal eye movements, and two more because there were not enough trials due to technical issues during recording. Of the remaining sample (n=10), mean age was 24.1 years (*SD* = 2.1), five participants were female, and five male. All but one were right-handed, as assessed by the Edinburgh-Handedness-Scale (Edinburgh Handedness Inventory; Oldfield, 1971). They all reported normal or corrected to normal vision and being free from neurological and psychiatric disorders.

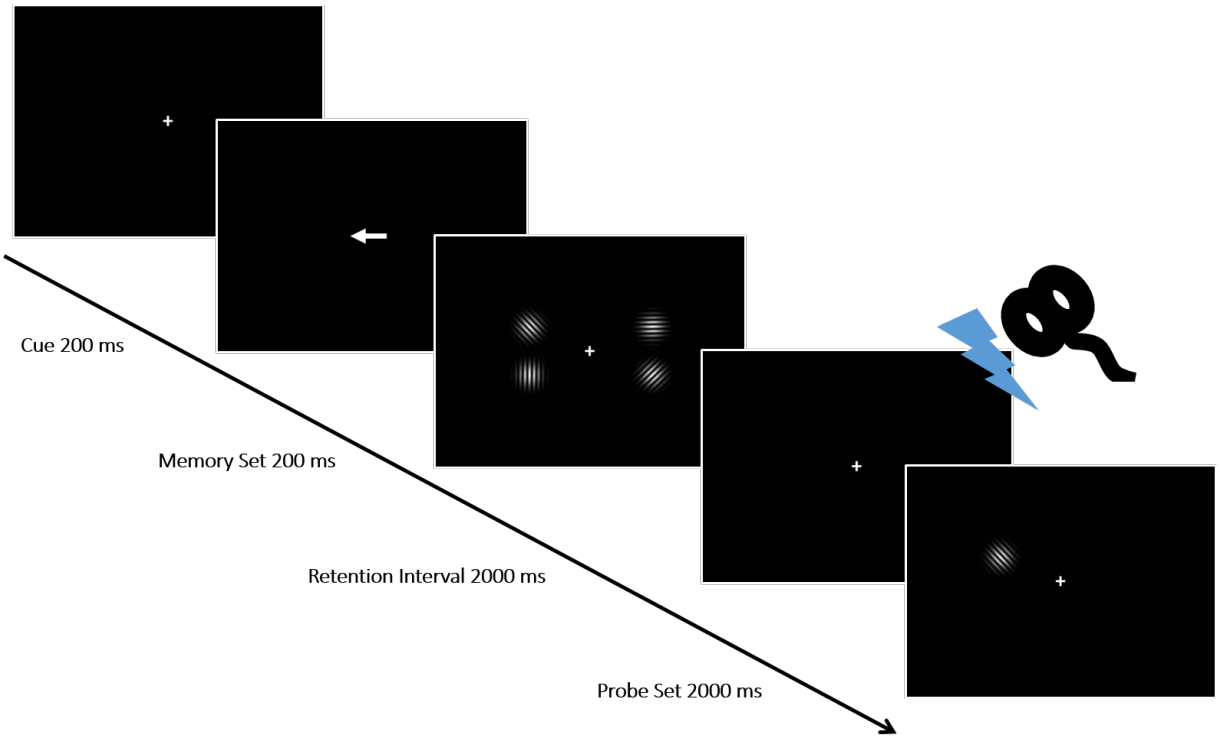

Figure 1 Exemplary trial sequence of the visuospatial delayed match to sample task. *Trials consisted of a cue (200ms), a memory set (200 ms), a retention interval (2000ms), and a probe screen (max. 2000ms or until response); during inter-trial interval a central fixation cross was displayed (1400 to 2000 ms). The task was to indicate whether the probe set matched with the memory set. In each trial, a TMS pulse was applied at a random time point between 500 ms to 1500ms after offset of the memory set during the retention interval.*

2.2 Apparatus and Stimuli

Participants were seated in a comfortable chair in a well-lit room with a standard computer mouse placed on their lap, their right index finger and right middle finger were placed on the left and right mouse button. They were wearing an EEG cap for registration of EEG signals and a TMS coil was placed over posterior parietal brain areas for TMS stimulation (for details see below). Stimuli were presented on a 19-inch CRT View Sonic G90fB monitor with a resolution of 1024 x 768 and a 100 Hz refresh rate, which was set up at a distance of approximately 80 cm from an observer. Stimulus presentation was controlled by Presentation 0.71 (Neurobehavioural Systems, Inc.), which was synchronized with recording of the EEG signals in BrainVision Recorder 2.0.4 (Brain-Products®), where event triggers for screen onsets, TMS pulses, and participants' responses were added.

All stimuli were presented on a black background with a white fixation cross in the centre of the screen (see **Figure 1**). Cue screens contained a central arrow in white colour, pointing either to the left or to the right (covering a visual angle of 4.3°). Four circular Gabor gratings, consisting of 9 white and 10 black lines each, which were either oriented vertically (0°), horizontally (90°) or diagonally (45° or 135°), constituted the memory set screen. The gratings were arranged along the corners of an invisible rectangle, that is with two grating in the left and two in the right visual hemifield (covering a visual angle of 20.5° x 6.4°). Probe screens displayed only one Gabor grating at one of the four possible locations. Orientation of the lines within the probe stimulus either did or did not match with the set stimulus.

2.3 Task

Participants performed a visuospatial delayed match to sample (DMtS) task in which the crucial element was that they had to actively prioritize one visual hemifield over the other. At the beginning of each trial sequence (see **Figure 1**) a central arrow was presented for 200 ms. Participants were instructed to prioritize stimuli in one visual hemifield depending on the direction of this cue, but without ignoring stimuli in the other hemifield, while they encoded the orientation of the four Gabor gratings on the following memory set screen for 200 ms, and while they subsequently maintained these stimulus characteristics for 2000 ms. Within this retention interval, in which participants focused on a central fixation cross, a TMS single-pulse was delivered. Its onset was jittered between 500 and 1500 ms after memory set offset. After this delay interval, a probe screen was displayed for maximally 2000 ms or until button press. In 70% of the trials, the probe stimulus was presented in the prioritized visual hemifield (valid cue), whereas in 30% of trials, it was in the non-prioritized hemifield (invalid cue). Participants then had to indicate whether the probe stimulus and the maintained memory set did (left mouse click) or did not (right mouse click) match with regard to the orientation of the respective Gabor gratings. They were instructed to respond as accurately as possible. Memory set and probe stimuli did or did not match in 50% of the trials each. An inter-trial interval, consisting of a central fixation cross, was presented for a random duration between 1400 and 2000 ms, before the next trial started. Participants were instructed to keep their eyes fixated at the central fixation cross during the whole task.

2.4 Procedure

Two training blocks were carried out at the beginning of the experiment, where only the second one included TMS stimulation during the retention period. Training blocks had fewer trials than the actual experimental blocks. The experiment itself consisted of a total of 300 trials, which were divided in four blocks with 75 trials each. Conditions were presented in randomized order. TMS stimulation during the retention interval of the task was applied over task-relevant posterior brain sites, with the coil centered over EEG electrode sites P3 or P4 for two blocks each; the order of the four blocks was randomized across participants. Participants took breaks between blocks, resulting in a task duration of about 40 minutes. The whole experiment, including the preparation of the EEG cap, determining individual resting motor threshold, instructions, training blocks and experimental blocks, took about 2 hours.

2.5 EEG Data Acquisition

EEG was registered from 30 scalp locations with Ag-AgCl electrodes arranged according to the extended 10-10-system in a TMS compatible electrode cap (Easycap®), using a BrainAmp MRplus amplifier (Brain-Products®). Recording sites were FP1, FP2, F7, F3, AFz, Fz, F4, F8, FC5, FC1, FC2, FC6, T3, C3, Cz, C4, T4, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO3, PO4, O1 and O2. Two electrodes were placed above and next to the left eye for recording horizontal and vertical eye movements and blinks. A ring-electrode on the tip of the nose was used as a reference and the ground electrode was placed at electrode position FPz. Electrode impedances were kept below 20 kΩ. EEG data were digitized at 2500 Hz in a frequency range between 0.016 and 100 Hz. A notch filter was set at 50 Hz.

2.6 TMS protocol

TMS stimulation was done using a PowerMAG 100 research TMS stimulator with a double coil PDM 70 (Mag&More®). During the retention period of each trial, with an onset jittered across trials (see above), a single pulse at 120% of individual resting motor threshold was delivered to the left or right parietal cortex. Stimulation was applied with the coil centered over EEG electrode sites P3 or (see **Figure 2)** in four separate blocks (see above). This position was chosen because in previous TMS studies, applying TMS stimulation over electrode P4 and P3 has been shown effective in order to reach the region of the intraparietal sulcus (Herwig et al., 2003). Mean stimulation intensity was 61.7 (SD=5.4)% of maximal stimulator output. The time of stimulation was during the retention interval of the task, between 500ms to 1500ms after offset of the memory set.

2.7 Data Analysis

EEG data were analyzed using BrainVision Analyzer 2.0.4 (Brain Products®) and Matlab 7.9.0.529 (The Math Works, Inc.). First, visual inspection of the raw data was used for excluding data segments containing large artifacts. Semiautomatic Ocular Correction with Independent Component Analysis (Ocular Correction ICA) was applied to correct for artifacts caused by eye blinks and eye movements. Data were then segmented into epochs starting at 1000 ms before and ending at onset of a TMS single-pulse for four conditions of interest (cue direction: left, right; response: correct, incorrect) per TMS stimulation site (P3, P4). As the number of invalid trials was rather small, only trials in which probe stimuli were displayed in the validly cued hemifield were analyzed. Remaining artifacts due to eye movements or due to muscle activity, were rejected manually. In order to attenuate effects of volume conduction, Laplacian Current Source Density Transformation (CSD) was calculated (order of splines: 4; maximal degree of Legendre polynomials: 10; Lambda: 1 e−5). Then, theta-band activity was calculated with a Continuous Wavelet Transformation using Morlet Wavelets (minimal frequency: 4 Hz, maximal frequency: 4.1 Hz), from which instantaneous phase was then derived in the range +/-Pi for electrode site AFz (see **Figure 2**). The phase of FM-theta at the time point of TMS application was estimated based on the theta phase value 250 ms prior to onset of the TMS single-pulse (=one cycle at the frequency of 4 Hz).

In order to obtain the estimate of task performance as a function of FM-theta phase, trials were sorted into ten equally sized phase bins in the range +/-Pi of the frontal midline theta cyle and the percentage of correct responses was calculated for each of these, separately for all conditions. We labelled these phase bins as phase 1-10, where phases 1 and 10 are during the FM-theta peak and phases 5 and 6 are during the FM-theta trough. The rate of correct responses was calculated for those ten phase bins and per condition. Since the number of invalid trials was quite low (only 30% of trials), only valid trials were included for further analysis.

For statistical analysis, linear mixed effects models (LMMs) were implemented separately for left-hemispheric and right-hemispheric TMS. In these two separate analyses for each hemisphere, we used a LMM where task accuracy was predicted by the fixed effects hemifield (prioritize left vs. prioritize right), phase (10 phase bins labelled as phase 1-10), and their interaction. The model included a single random-effects term for the intercept of the individual subjects. For LMM modeling, the categorical variables were encoded with sequential difference contrasts. Thus, the intercept is estimated as the grand average across all conditions and resulting fixed effect estimates can be interpreted as main effects.

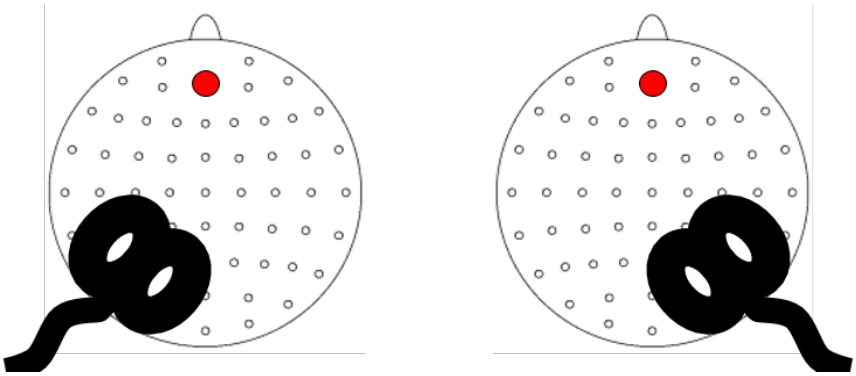

Figure 2. Illustration of electrode sites for TMS stimulation during the retention interval and extraction of FM-theta phase. *TMS was delivered over electrode positions P3 or P4, The phase of FM-theta at the time point of TMS application was estimated based on the phase value of one theta cycle prior to onset of the TMS single-pulse at electrode position AFz (marked in red).*

For the model summaries we regarded contrast coefficients with absolute t values larger than 1.96 as indicative of a precise estimate. T-values above 1.96 can be treated as approximating the two-tailed 5% significance level since a t-distribution with a high degree of freedom approaches the z distribution (Baayen et al., 2008). The reported models were fit based on maximum likelihood estimation. Based on out hypothesis, we expected to observe substantial interaction contrasts between hemifield and the phase bins around the trough of the FM-theta cycle indicating a decrease in performance during the trough relative to the phase bins before or after the trough when the contralateral hemifield was prioritized. For model selection, we therefore used Likelihood ratio χ^2 tests to evaluate the general impact of adding the overall interaction between the factors hemifield and phase into the model compared to a model without their interaction. These were conducted separately for the models of left-hemispheric and right-hemispheric TMS. We followed these up with computing Bayes Factors (BF_{10}), in order to quantify the relative evidence for the full model compared to the model without the interaction effect. For BF_{10} values above 3 or below 0.33, the strength of evidence is regarded as noteworthy, whereas values between 0.33 and 3 are considered as inconclusive evidence for any hypothesis (Jeffreys, 1961; Lee & Wagenmakers, 2014).

Statistical Analyses were carried out using statistical software R 4.04 (R Core Team, 2019). Data was visualised using the ggplot2 package 3.3.3 (Wickham, 2016). Linear mixed effects models (LMMs) were implemented with the lme4 package 1.1.21 (Bates et al., 2007), and model summary tables were produced using the lmerOut package 0.5 (Alday, 2018). Bayes Factors were computed with the BayesFactor package 0.9.12.4.2 (Morey & Rouder, 2018) using default priors.

Results

Overall task performance, as measured by the mean percentage of correct responses, was relatively high across conditions in valid trials, whereas in invalid trials, overall performance was close to chance performance (see **Figure 3**).

In **Figure 4**, task performance in valid trials according to the phase of the frontal midline theta cycle at onset of the TMS single pulse, as measured by the percentage of correct responses in valid trials per FM-theta phasebin, is illustrated for both conditions (left cue, right cue) per TMS site (left posterior, right posterior). In order to analyse the percentage of correct responses according to FM-theta phase and hemifield, we fitted linear mixed models separately per TMS site (left posterior, right posterior). Fixed effects estimates and estimated marginal means are visualized in **Figure 5** (for the full

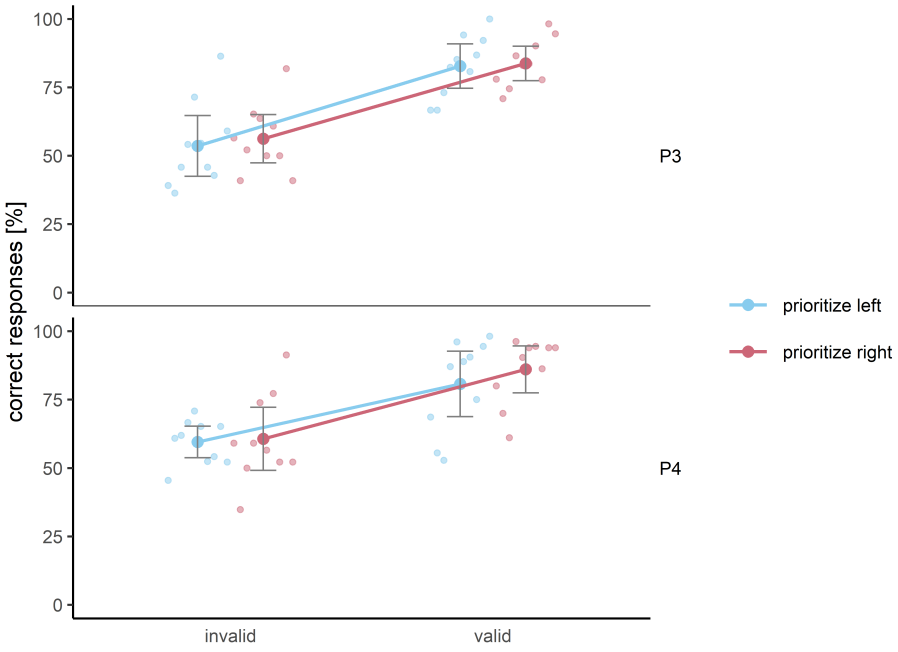

Figure 3. Overall percentage of correct responses. *Single subject task performance is overlayed with group average task performance (thick points indicate the mean and error bars denote the standard error). TMS was delivered over P3 for left hemispheric stimulation (upper panel) or P4 for right hemispheric TMS (lower panel).*

model output, please see supplemental materials Table S1.1 and S1.2).

For the condition where a right posterior TMS single-pulse was delivered during the retention interval, model comparison using a likelihood ratio tests indicated a marginally significant interaction effect between hemifield and phase (χ^2 (9)=15.39, p=0.08). Note, that the additional Bayes factor analysis anecdotally favoured the null hypothesis (BF_{10} = 0.56), which is, however, in the range of inconclusive evidence for either hypothesis. So given that adding the overall interaction effect into the model improved model fit with at least marginal significance and that the Bayes factor did not exclude the H1, we selected the full model with the interaction. Results from the selected linear mixed model (**Figure 5**) indicated a substantial effect for hemifield, signalling overall higher accuracy when the right hemifield was prioritized (hemifield: E=5.5, SE=2.3, t= 2.3). In line with our hypothesis, there was a substantial interaction indicating that this difference was larger in phase bin 6 in the trough phase of the FM-theta cycle than towards the subsequent phase bin 7 of FM-theta (hemifield x phase7 - phase6: E=-29, SE=10, t=-2.8). For the interaction between hemifield and the contrast comparing the phase bin 5 during the FM-theta trough and the preceding phase bin 4, **Figure 4** shows that the pattern of results was along the lines of the expected modulation of task performance by contralateral FM-theta phase at stimulation onset. While descriptively, performance was lower during the trough for left-hemifield prioritization, the interaction contrast was below the t-threshold of 1.96 (hemifield x contrast phase5 - phase 4: E=18, SE=10, t=1.7). No effect involving phase bins during the FM-theta peak was substantial.

For the condition where a left posterior TMS single-pulse was delivered during the retention interval, model comparison using a likelihood ratio tests indicated that the overall interaction effect between hemifield and phase was not significant (χ^2 (9)=10.88, p=0.28), suggesting that adding the interaction effect to the model did not make the model significantly more accurate. This was corroborated by the additional Bayes factor analysis which even indicated substantial evidence favouring the null hypothesis (BF_{10} = 0.188). Based on this, we selected the simpler model without the interaction effect for analysis. Results from the selected linear mixed model showed no substantial effects (**Figure 5**).

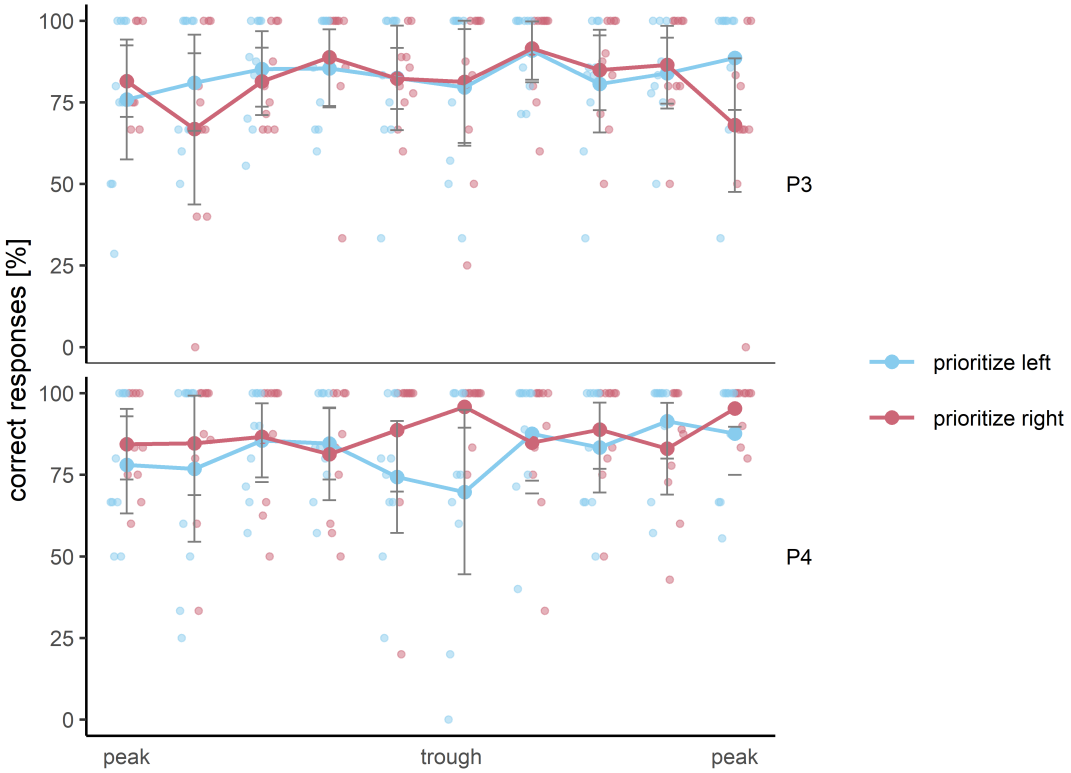

Figure 4. Percentage of correct responses in valid trials, sorted by the phase of FM-theta at TMS onset. *Single subject task performance is overlaid with group average task performance (thick points indicate the mean and error bars denote the standard error) and displayed according to the phase of the frontal midline theta cycle at TMS onset. TMS was delivered over P3 for left hemispheric stimulation (upper panel) or P4 for right hemispheric TMS (lower panel). Note: In the analysis, the ten phase bins are labelled as phase 1 to 10, where phase bins 1 and 10 are during the FM-theta peak, and phase bins 5 and 6 are during the FM-theta trough.*

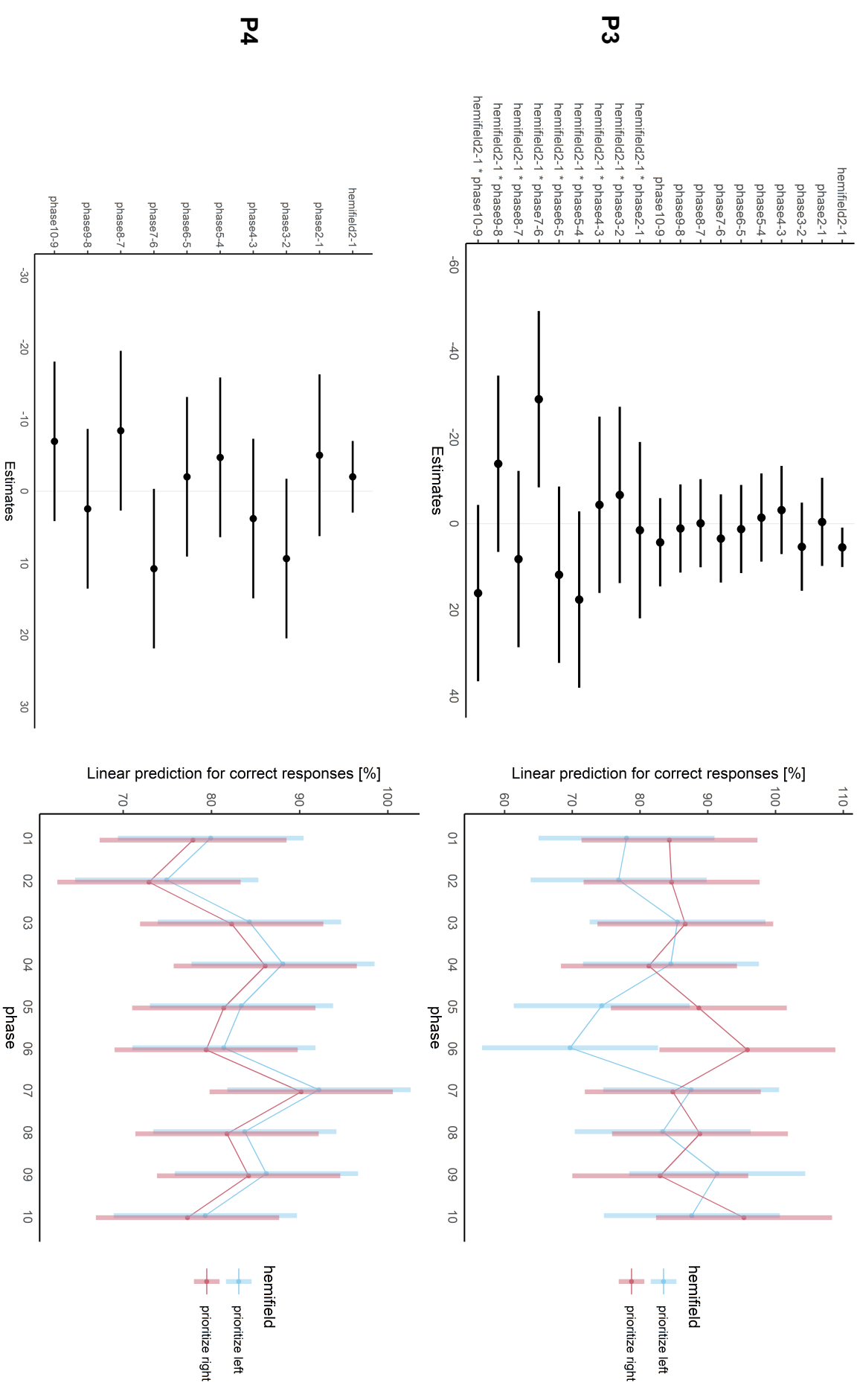

Figure 5. Visualization of fixed-effect estimates and conditional effects estimated by the models for left-hemispheric TMS (P3) and right-hemispheric TMS (P4). Note: Phase bins 1 and 10 are during the FM-theta peak, and phase bins 5 and 6 are during the FM-theta trough.

3 Discussion

We conducted a combined EEG-TMS experiment where we disrupted posterior brain activity by delivering TMS single-pulses during the retention phase of a visuospatial WM task, in which participants were asked to retain the orientation of spatially arranged Gabor patches and prioritize memory items in one visual hemifield over the other. For right-hemispheric posterior TMS, we found that applying TMS at posterior brain areas disrupted task performance depending on when the TMS pulse was delivered with respect to the FM-theta phase and on whether it was delivered to the contralateral task-active (i.e. involved in prioritizing information) or ipsilateral task-inactive (i.e. non-prioritizing) hemisphere. However, while the patterns of results were in line with our hypotheses for right-hemispheric posterior TMS, for left-hemispheric TMS, results were less clear.

For TMS single pulses delivered over right posterior brain sites during the retention interval, we found a substantial interaction between TMS pulses applied close to the trough of FM theta cycle and the prioritized hemifield. This indicated that during the trough of FM-theta relative to the neighbouring FM-theta phase, task performance decreased when the left (contralateral) hemifield was prioritized compared to the right (ipsilateral) hemifield. While this effect was substantial for the trough phase bin compared to the subsequent FM-theta phase bin, for the FM-theta phase preceding the trough phase bins, it did not exceed the significance threshold. However, it was descriptively into the direction as our hypothesis predicted in both cases. Yet, we interpret this as preliminary evidence from a pilot study, given the small sample size (n=10) as well as the results from model comparison: While the overall interaction effect between hemifield and FM-theta phase was at least marginally significant, Bayes factor evidence remained inconclusive. We take this as an indication that it is most useful to interpret the data and model results from right-hemispheric TMS blocks with a focus on planning future studies. Descriptively and based on the contrasts from the linear mixed model, our data are well in line with previous evidence demonstrating that working memory performance under high load conditions was disrupted only when right temporo-parietal TMS was applied near the trough of FM-theta (Berger et al., 2019). This previous study had been based on the observation that right temporo-parietal gamma band activity was nested into frontal-midline theta waves in a working memory task, depending on the level of cognitive control required – specifically, that posterior gamma activity was nested close to the peak phase of FM-theta under low load conditions, but under high load conditions it was aligned close to the trough phase of frontal-midline theta waves (Berger et al., 2019). Given that in the current study, we could demonstrate a FM-theta phase-dependent modulation of task performance through right posterior TMS similar to these effects observed for the level of task difficulty in the study by Berger et al. (2019), we assume that the level of priority (i.e. prioritizing or non-prioritizing information) may have influenced the phase of FM-theta to which right posterior gamma amplitude was locked.

Conversely, results for FM-theta phase-dependent neurostimulation over left posterior left brain areas showed that differential task performance between the prioritized and non-prioritized hemifeld stayed unaffected for the different frontal midline theta phase bins. Adding the interaction into the model had no significant effect and Bayes factor analysis yielded substantial evidence in favour of the model without the interaction. Under the assumption that FM-theta provides an oscillatory gating mechanism by which posterior brain areas can access the required prefrontal cognitive resources, one would not expect that activity in the contralateral task-active (i.e. involved in prioritizing information) areas on the left hemisphere would per se lack such a mechanism. We can only speculate that the oscillatory gating mechanism might be less efficient for left-hemispheric processing, given that visuospatial WM and attentional processing can be expected to predominantly involve right-hemispheric posterior areas, which has been repeatedly found in neuroimaging studies and studies investigating deficit due to parietal lesions (Awh & Jonides, 2001; Corbetta et al., 2002; Driver & Vuilleumier, 2001; Kastner & Ungerleider, 2000).

An underlying assumption of our study was that the level of priority (i.e. prioritizing or non-prioritizing information) would influence the phase of FM-theta to which right posterior gamma amplitude is locked. While this assumption would have to be tested using EEG without TMS, several previous studies have already reported such effects. In a verbal delayed match-to-sample task, the phase of slow oscillatory fronto-medial activity has been found to be synchronized with distributed fast oscillatory activity (Griesmayr et al., 2010). And Pinal and colleagues (2015) demonstrated that during a visual delayed match to sample task, in young adults, but not in older adults, long-range brain networks can be efficiently coupled or decoupled through a mechanism where fast oscillatory activity in posterior areas is nested into the excitatory or the inhibitory phase of slow oscillatory frontomedial activity. In line with this, in another working memory task, depending on task demands, right temporo-parietal gamma band activity was nested

into the peak phase of FM-theta under low load conditions; but under high load conditions it was aligned to the trough phase of frontal-midline theta waves (Berger et al., 2019). But while our data from the right-hemispheric stimulation site can be interpreted in line with this previous EEG evidence, and also corroborate previous evidence that right temporo-parietal TMS applied near the trough of FM-theta was detrimental for working memory performance (Berger et al., 2019), our data from the left-hemispheric TMS condition do not allow this conclusion. But given the inconclusive evidence from the Bayes factor analysis, we wish to stress that evidence from the right-hemispheric TMS condition should be regarded as preliminary evidence as well. We will discuss several possible explanations for these inconclusive results in the following, and give recommendations on methodological considerations which may inform follow-up studies.

In the current study, the onset of posterior TMS single pulses was jittered across trials in a time interval between 500 ms to 1500ms after offset of the memory set. However, cross-frequency phase coupling was previously shown to be predominant during the first half of the delay period (Griesmayr et al., 2010). Possibly, posterior brain activity which was intended to be disturbed with the posterior FM-theta phase dependent neurostimulation, was most pronounced during the first half of the delay period in our data as well. If so, then the amount of trials in which the relevant mechanism was indeed disturbed – that is where a TMS pulse fell into early retention period – was conceivably too small to yield a stronger effect of FM-theta phase-dependent neurostimulation on performance, even in the right-hemisheric TMS condition. Applying TMS primarily in the early time window of the retention interval could be more effective in demonstrating conclusive evidence than in this pilot study.

We chose to apply a single-pulse TMS protocol at 120% of individual resting motor threshold, which could be expected to trigger neuronal oscillations activity or reset the ongoing local neuronal synchronous activity (Berger et al., 2014; Paus et al., 2001; Stamoulis et al., 2011; Taylor et al., 2008). However, it is possible that a TMS triple pulse, which has recently been implemented for a similar paradigm and proven to be effective (Berger et al., 2019), would have been more potent in affecting the interaction between prefrontal and posterior regions than the TMS single-pulse.

The electrode positions P3 and P4 as a stimulation site for applying single TMS pulses are an arguably rough estimate for targeting a specific brain area, for example due to interindividual variability in brain anatomy and to stimulation reaching only a very focal area. The use of neuronavigated TMS, allowing to stimulate the individual's task-relevant brain area (previously derived using source localization in the EEG analysis), could, generally, provide a better spatial resolution and precision for the stimulation of specific regions. Still, electrode positions P3 and P4 have been shown to be an effective site for positioning the TMS coil in order to reach the region of the intraparietal sulcus (Herwig et al., 2003), which is suggested to be involved in visuo-spatial WM and spatial attention (Bray et al., 2015; Corbetta et al., 2002; Curtis, 2006; Silk et al., 2010; Todd & Marois, 2004).

Importantly, results were not due to the complexity/difficulty of the task, since the overall percentage of correct responses was quite comparable between blocks where TMS was applied over the left or right hemisphere or between trials where the left or right hemifield was prioritized and only validly cued trials were analysed according to FM-theta phase. The current task was assumed to be a rather difficult, however, performance in validly cued trials was actually very high across all phases of FM-Theta at TMS onset. In comparison, in the study by Berger et al. (2019), task performance in the most difficult condition of the WM task dropped almost to chance level when TMS stimulation fell into the phase close to the trough of the FM theta cycle. Thus, one could argue that in the current WM task, valid trials were not of a maximal difficulty level and task performance consequently did not drop as severely. Extending this idea, one could raise to question whether with an increased task difficulty (i.e. higher cognitive demands), a more pronounced drop in differential performance could be observed in the same type of hemifield WM task that we used. This is because assuming than under these conditions, the underlying coupling of right posterior gamma bursts to be even closer to the excitatory theta phase when the respective information is prioritized. Whether such a clear-cut, linear combination of task difficulty and prioritization can be made however, is unclear, since the exact functions of such cross-frequency couplings and even more their functional implications for higher cognitive processes are complex, and yet not completely understood. Overall task difficulty may be increased by reducing the contrast of the stimuli. However, it might not (only) be the overall task difficulty, but the choice of strategy for prioritization of one hemifield over the other that could play a role here. Although the task instruction had emphasized that the cued hemifield should be prioritized over the uncued hemifield, but not ignored, we observed that in invalid trials, the overall accuracy (not analysed phase dependent on FM-theta) was close to change level for most participants. Thus, many participants in this study may have chosen to ignore the uncued

hemifield completely, instead of prioritizing it less than the cued hemifield. Increasing the percentage of invalid trials or adding an extended training phase with feedback where participants are required to reach a minimum level of performance in both valid and invalid trials may counteract this potential strategy in the future.

It would be interesting to investigate in further studies, whether a clustering of posterior gamma bursts into specific frontal midline theta phase segments can also be affected by other factors than cognitive demand, of which voluntary allocation of resources by prioritization of information is only one. Based on the current pilot study, follow-up studies investigating whether a FM-theta phase-dependent effect of posterior TMS is affected by the voluntary allocation of cognitive resources can be adequately powered. To estimate the minimal sample size required based on the current findings, the estimated effect sizes from the fitted linear mixed models (i.e. the fixed effects' slopes) can be used for a Monte Carlo simulation based power calculation. This could be realized using the R-package simr (Green & MacLeod, 2016).

4 Conclusion

Based on previous evidence demonstrating that working memory performance under high load conditions was disrupted only when right temporo-parietal TMS was applied near the trough of FM-theta (Berger et al., 2019), we were aiming to demonstrate that this kind of dynamic coupling in a fronto-parietal control network can be influenced by the level of priority given to the respective information. In this pilot study, we found that the extent to which applying TMS at right posterior brain areas disrupted task performance depended on when the TMS pulse was delivered with respect to the FM-theta phase and on whether it was delivered to the contralateral task-active (i.e. involved in prioritizing information) or ipsilateral task-inactive (i.e. non-prioritizing) hemisphere. In line with our hypotheses, we found that a decrease of task performance during the trough phase for the prioritized compared to the non-prioritized hemifield right-hemispheric posterior TMS. For left-hemispheric TMS, results were less clear. The fitted linear mixed effects models can be used for a simulation based power analysis for future studies.

Supplemental materials

Table S1.1. Summary of model fit for TMS over P3
Table S1.2. Summary of model fit for TMS over P4

References

Alday, P. M. (2018). *lmerOut: LaTeX Output for Mixed Effects Models with lme4*. https://bitbucket.org/palday/lmerout

Awh, E., & Jonides, J. (2001). Overlapping mechanisms of attention and spatial working memory. *Trends in Cognitive Sciences*, *5*(3), 119–126. https://doi.org/10.1016/S1364-6613(00)01593-X

Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proceedings of the National Academy of Sciences*, *107*(7), 3228–3233. https://doi.org/10.1073/pnas.0911531107

Baddeley, A. D. (2000). The episodic buffer: A new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417–423. https://doi.org/10.1016/S1364-6613(00)01538-2

Baddeley, A. D., Allen, R. J., & Hitch, G. J. (2011). Binding in visual working memory: The role of the episodic buffer. *Neuropsychologia*, *49*(6), 1393–1400. https://doi.org/10.1016/j.neuropsychologia.2010.12.042

Baddeley, A. D., & Hitch, G. (1974). Working Memory. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (Vol. 8, pp. 47–89). Academic Press. https://doi.org/10.1016/S0079-7421(08)60452-1

Bates, D., Sarkar, D., Bates, M. D., & Matrix, L. (2007). The lme4 package. *R Package Version*, *2*(1), 74.

Berger, B., Griesmayr, B., Minarik, T., Biel, A. L., Pinal, D., Sterr, A., & Sauseng, P. (2019). Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. *Nature Communications*, *10*(1), 4242. https://doi.org/10.1038/s41467-019-12057-0

Berger, B., Minarik, T., Liuzzi, G., Hummel, F. C., & Sauseng, P. (2014). EEG Oscillatory Phase-Dependent Markers of Corticospinal Excitability in the Resting Brain. *BioMed Research International*, *2014*, e936096. https://doi.org/10.1155/2014/936096

Bray, S., Almas, R., Arnold, A. E. G. F., Iaria, G., & MacQueen, G. (2015). Intraparietal Sulcus Activity and Functional Connectivity Supporting Spatial Working Memory Manipulation. *Cerebral Cortex*, *25*(5), 1252–1264. https://doi.org/10.1093/cercor/bht320

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High Gamma Power Is Phase-Locked to Theta Oscillations in Human Neocortex. *Science*, *313*(5793), 1626–1628. https://doi.org/10.1126/science.1128115

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a

mechanism for cognitive control. *Trends in Cognitive Sciences*, *18*(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, *37*(1), 343–360. https://doi.org/10.1016/j.neuroimage.2007.03.071

Collette, F., & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neuroscience and Biobehavioral Reviews*, *26*(2), 105–125. https://doi.org/10.1016/s0149-7634(01)00063-x

Corbetta, M., Kincade, J. M., & Shulman, G. L. (2002). Neural Systems for Visual Orienting and Their Relationships to Spatial Working Memory. *Journal of Cognitive Neuroscience*, *14*(3), 508–523. https://doi.org/10.1162/089892902317362029

Curtis, C. E. (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience*, *139*(1), 173–180. https://doi.org/10.1016/j.neuroscience.2005.04.070

Demiralp, T., Bayraktaroglu, Z., Lenz, D., Junge, S., Busch, N. A., Maess, B., Ergen, M., & Herrmann, C. S. (2007). Gamma amplitudes are coupled to theta phase in human EEG during visual perception. *International Journal of Psychophysiology*, *64*(1), 24–30. https://doi.org/10.1016/j.ijpsycho.2006.07.005

Dosenbach, N. U. F., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, *12*(3), 99–105. https://doi.org/10.1016/j.tics.2008.01.001

Driver, J., & Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition*, *79*(1), 39–88. https://doi.org/10.1016/S0010-0277(00)00124-4

Fell, J., & Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nature Reviews Neuroscience*, *12*(2), 105–118. https://doi.org/10.1038/nrn2979

Fujisawa, S., & Buzsaki, G. (2011). A 4 Hz Oscillation Adaptively Synchronizes Prefrontal, VTA, and Hippocampal Activities. *Neuron*, *72*(1), 153–165. https://doi.org/10.1016/j.neuron.2011.08.018

Green, P., & MacLeod, C. J. (2016). SIMR: An R package for power analysis of generalized linear mixed models by simulation. *Methods in Ecology and Evolution*, *7*(4), 493–498. https://doi.org/10.1111/2041-210X.12504

Griesmayr, B., Gruber, W. R., Klimesch, W., & Sauseng, P. (2010). Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task. *Neurobiology of Learning and Memory*, *93*(2), 208–215. https://doi.org/10.1016/j.nlm.2009.09.013

Haegens, S., Nácher, V., Luna, R., Romo, R., & Jensen, O. (2011). α-Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. *Proceedings of the National Academy of Sciences*, *108*(48), 19377–19382. https://doi.org/10.1073/pnas.1117190108

Herwig, U., Satrapi, P., & Schönfeldt-Lecuona, C. (2003). Using the International 10-20 EEG System for Positioning of Transcranial Magnetic Stimulation. *Brain Topography*, *16*(2), 95–99. https://doi.org/10.1023/B:BRAT.0000006333.93597.9d

Jeffreys, H. (1961). *Theory of probability* (3rd ed). Oxford University Press.

Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience*, *23*, 315–341. https://doi.org/10.1146/annurev.neuro.23.1.315

Lee, M., & Wagenmakers, E. (2014). *Bayesian Cognitive Modeling: A Practical Course*. https://books.google.de/books?hl=de&lr=&id=50tkAgAAQBAJ&oi=fnd&pg=PR10&ots=r4k4Nh7rK3&sig=xK6bnnUkZa9p5yfcZ_q9wQ-qKU4

Mitchell, D. J., McNaughton, N., Flanagan, D., & Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta". *Progress in Neurobiology*, *86*(3), 156–185. https://doi.org/10.1016/j.pneurobio.2008.09.005

Morey, R. D., & Rouder, J. N. (2018). *BayesFactor: Computation of Bayes Factors for Common Designs*. https://CRAN.R-project.org/package=BayesFactor

O'Keefe, J., & Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus*, *3*(3), 317–330. https://doi.org/10.1002/hipo.450030307

Paus, T., Sipila, P. K., & Strafella, A. P. (2001). Synchronization of Neuronal Activity in the Human Primary Motor Cortex by Transcranial Magnetic Stimulation: An EEG Study. *Journal of Neurophysiology*, *86*(4), 1983–1990. https://doi.org/10.1152/jn.2001.86.4.1983

Pinal, D., Zurron, M., Diaz, F., & Sauseng, P. (2015). Stuck in default mode: Inefficient cross-frequency synchronization may lead to age-related short-term memory decline. *Neurobiology of Aging*, *36*(4), 1611–1618. https://doi.org/10.1016/j.neurobiolaging.2015.01.009

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working

memory: A possible function of EEG theta oscillations. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1015–1022. https://doi.org/10.1016/j.neubiorev.2009.12.006

Sauseng, P., Hoppe, J., Klimesch, W., Gerloff, C., & Hummel, F. C. (2007). Dissociation of sustained attention from central executive functions: Local activity and interregional connectivity in the theta range. *The European Journal of Neuroscience*, *25*(2), 587–593. https://doi.org/10.1111/j.1460-9568.2006.05286.x

Sauseng, P., Klimesch, W., Gruber, W. R., & Birbaumer, N. (2008). Cross-frequency phase synchronization: A brain mechanism of memory matching and attention. *NeuroImage*, *40*(1), 308–317. https://doi.org/10.1016/j.neuroimage.2007.11.032

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A. A., Glennon, M., Gerloff, C., Birbaumer, N., & Hummel, F. C. (2009). Brain Oscillatory Substrates of Visual Short-Term Memory Capacity. *Current Biology*, *19*(21), 1846–1852. https://doi.org/10.1016/j.cub.2009.08.062

Schack, B., Vath, N., Petsche, H., Geissler, H. G., & Möller, E. (2002). Phase-coupling of theta-gamma EEG rhythms during short-term memory processing. *International Journal of Psychophysiology*, *44*(2), 143–163. https://doi.org/10.1016/S0167-8760(01)00199-4

Silk, T. J., Bellgrove, M. A., Wrafter, P., Mattingley, J. B., & Cunnington, R. (2010). Spatial working memory and spatial attention rely on common neural processes in the intraparietal sulcus. *NeuroImage*, *53*(2), 718–724. https://doi.org/10.1016/j.neuroimage.2010.06.068

Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., & Buzsáki, G. (2008). Entrainment of Neocortical Neurons and Gamma Oscillations by the Hippocampal Theta Rhythm. *Neuron*, *60*(4), 683–697. https://doi.org/10.1016/j.neuron.2008.09.014

Stamoulis, C., Oberman, L. M., Praeg, E., Bashir, S., & Pascual-Leone, A. (2011). Single Pulse TMS-Induced Modulations of Resting Brain Neurodynamics Encoded in EEG Phase. *Brain Topography*, *24*(2), 105–113. https://doi.org/10.1007/s10548-010-0169-3

Taylor, P. C. J., Walsh, V., & Eimer, M. (2008). Combining TMS and EEG to study cognitive function and cortico–cortico interactions. *Behavioural Brain Research*, *191*(2), 141–147. https://doi.org/10.1016/j.bbr.2008.03.033

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, *428*(6984), 751–754. https://doi.org/10.1038/nature02466

Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. https://ggplot2.tidyverse.org

Womelsdorf, T., Vinck, M., Leung, S. L., & Everling, S. (2010). Selective Theta-Synchronization of Choice-Relevant Information Subserves Goal-Directed Behavior. *Frontiers in Human Neuroscience*, *4*. https://doi.org/10.3389/fnhum.2010.00210

Supplemental materials

Table S1.1. Summary of model fit for TMS over P3

Linear mixed model fit by maximum likelihood

AIC	BIC	logLik	deviance	df.resid
1757	1799	-865	1731	186

Scaled residuals:

Min	1Q	Median	3Q	Max
-4.35	-0.5	0.15	0.7	1.75

Random effects:

Groups	Term	Std.Dev.
SubjectID	(Intercept)	8.7
Residual		17.9

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	82	3	27
hemifield2-1	-2	2.5	-0.79
phase2-1	-5	5.7	-0.87
phase3-2	9.4	5.7	1.7
phase4-3	3.8	5.7	0.67
phase5-4	-4.7	5.7	-0.83
phase6-5	-2	5.7	-0.35
phase7-6	11	5.7	1.9
phase8-7	-8.4	5.7	-1.5
phase9-8	2.4	5.7	0.43
phase10-9	-6.9	5.7	-1.2

Table S1.2. Summary of model fit for TMS over P4

Linear mixed model fit by maximum likelihood

AIC	BIC	logLik	deviance	df.resid
1755	1828	-855	1711	178

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.65	-0.45	0.12	0.62	2.05

Random effects:

Groups	Term	Std.Dev.
SubjectID	(Intercept)	10.6
Residual		16.5

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	85	3.5	24
hemifield	5.5	2.3	2.3
phase2 - phase 1	-0.42	5.2	-0.081
phase3 - phase 2	5.4	5.2	1
phase4 - phase 3	-3.2	5.2	-0.61
phase5 - phase 4	-1.4	5.2	-0.27
phase6 - phase 5	1.2	5.2	0.24
phase7 - phase 6	3.4	5.2	0.66
phase8 - phase 7	-0.099	5.2	-0.019
phase9 - phase 8	1.1	5.2	0.21
phase10 - phase 9	4.3	5.2	0.83
hemifield x phase2 - phase 1	1.5	10	0.14
hemifield x phase3 - phase 2	-6.7	10	-0.64
hemifield x phase4 - phase 3	-4.4	10	-0.42
hemifield x phase5 - phase 4	18	10	1.7
hemifield x phase6 - phase 5	12	10	1.1
hemifield x phase7 - phase 6	-29	10	-2.8
hemifield x phase8 - phase 7	8.2	10	0.79
hemifield x phase9 - phase 8	-14	10	-1.3
hemifield x phase10 - phase 9	16	10	1.5

Chapter 4

Project III: Modulating working memory by multisite theta tACS

The current chapter comprises the manuscript of a research article that is currently under review for publication in the European Journal of Neuroscience, entitled "Modulating verbal working memory with fronto-parietal transcranial electric stimulation at theta frequency: Does it work?" (Biel et al., submitted).

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Elisabeth Sterner: Validation, Investigation, Data Curation, Writing – Review & Editing;

Lukas Röll: Validation, Investigation, Writing – Review & Editing;

Paul Sauseng: Conceptualization, Methodology, Validation, Resources, Writing – Review & Editing, Supervision, Funding acquisition.

Modulating verbal working memory with fronto-parietal transcranial electric stimulation at theta frequency: Does it work?

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Abstract

Oscillatory theta activity in a fronto-parietal network has been associated with working memory (WM) processes and may be directly related to WM performance. In their seminal study, Polanía et al. (2012) (de-)coupled a fronto-parietal theta-network by applying transcranial alternating current stimulation (tACS), and showed that anti-phase tACS led to slower and in-phase tACS to faster response times in a verbal WM task compared to placebo stimulation. In the literature, this 'synchronization-desynchronization' effect has only been partly replicated, and electrophysiological modelling suggests that it might not be the fronto-parietal network that is primarily stimulated during in-phase tACS with a shared return electrode. This provides one possible reason for inconsistency in the literature. In this study, we aimed to reproduce the findings reported by Polanía et al. (2012). We also aimed to investigate whether in-phase theta tACS with multiple close-by return electrodes for focal stimulation of the frontal and the parietal cortex will have at least as much of a facilitatory effect as the in-phase stimulation as indicated by Polania et al. (2012). In a single-trial distributional analysis, we explored whether mean, variation and right-skewness of the response time distribution are affected. Against our hypothesis, we found no 'synchronization-desynchronization' effect by fronto-parietal theta tACS on response times using the same delayed letter discrimination task and stimulation parameters in two experiments, both between-subjects and within-subjects. However, we could show that in a more demanding 3-back task, fronto-parietal in-phase and in-phase focal theta tACS substantially improved task performance compared to placebo stimulation.

Keywords

Connectivity; fronto-parietal network; non-invasive brain stimulation (NIBS);
theta oscillations; transcranial alternating current stimulation (tACS); working memory

1 Introduction

The transient storage of information and flexible usage of this stored information is known as working memory (Baddeley, 2012; Cowan, 2008). There is compelling evidence that activity in a network comprising frontal and parietal cortical regions – called the fronto-parietal working memory network – can be considered as neural signature of working memory processes (D'Esposito & Postle, 2015; Ptak et al., 2017). Synchronous rhythmical activity at theta frequency in this fronto- parietal network, particularly, has been discussed to be associated with working memory processes (Cooper et al., 2015; Sauseng et al., 2005, 2010), and may be directly related to working memory performance (Polanía et al., 2012).

In their seminal study, Polanía et al. (2012) tried modulating fronto-parietal theta-activity and as a consequence impact on working memory performance. In an initial EEG experiment, they had observed increased fronto-parietal phase synchronization in the theta range and that response times were reduced when the phase lag was close to 0°. The authors then used transcranial alternating current stimulation (tACS) at 6 Hz over left prefrontal and parietal cortices either with 0° or 180° phase difference. I.e., the fronto-parietal network was stimulated either in-phase (0°) or anti-phase (180°). Thus, the fronto-parietal network was supposed to be coupled or decoupled, respectively. Polanía et al. (2012) provided evidence that in-phase fronto-parietal theta tACS led to increased working memory performance (faster response times) compared to a placebo stimulation, whereas anti-phase stimulation had detrimental effects on working memory performance (slower response times).

This effect of a phase-dependent modulation of task performance has triggered research on the functional relevance of long-range neuronal coupling. Since then several studies have been published where the authors actively manipulated band-specific coherence within a cortical network using tACS (e.g. Alagapan et al., 2019; Alekseichuk et al., 2017; Helfrich et al., 2014; Kleinert et al., 2017; Polanía et al., 2015; Strüber et al., 2014; van Schouwenburg et al., 2017; Violante et al., 2017). Within the domain of working memory, Violante et al. (2017) were able to partly reproduce the results by Polanía et al. (2012) in one experiment but could not reproduce a behavioural effect in a second experiment, combining tACS-fMRI. Kleinert et al. (2017), however, could not find any significant difference in working memory performance between in-phase and anti-phase fronto-parietal tACS at theta frequency. One reason why there might be inconsistency in attempts to reproduce the findings by Polanía et al. (2012) could be the way the frontal and parietal stimulation electrodes had been referenced. Saturnino et al. (2017) estimated electrical field distribution for different previously published dual-site tACS montages. They could show that using one shared return electrode (e.g. over electrode position Cz) for two stimulation electrodes over frontal and parietal sites in the in-phase stimulation condition led to the strongest stimulation effect under the return electrode. This means that the time varying electrical current patterns from this in-phase stimulation are spatially less confined to the cortical target sites compared to those from the anti-phase stimulation which works without a third reference electrode, such that the conditions do not only differ in their phase relationships. Recently, this was corroborated experimentally using in vivo recordings in nonhuman primates (Alekseichuk et al., 2019). Therefore, Saturnino et al. (2017) proposed in-phase focal stimulation over frontal and parietal cortex where multiple close-by return electrodes can be used to focally stimulate the frontal and the parietal cortex, respectively. This focally induced activity could then be delivered with a 0° phase lag, i.e., in-phase, truly synchronously driving a fronto- parietal theta network and only differing in the relative phase of the applied currents. Similar electrode configurations were used by Schouwenburg (2017), who used three right-lateralised central reference electrodes located in-between the stimulation electrodes over the fronto-parietal locations, or by Helfrich (2014) who surrounded bilateral parietal stimulation electrodes with four surrounding reference electrodes each. As an alternative to surrounding the stimulation electrodes with multiple close-by return electrodes, center-surround ring montages can similarly achieve a better control of current distribution (Bortoletto et al., 2016; Saturnino et al., 2017).

This study aimed to reproduce the findings reported by Polanía et al. (2012). Thus, we hypothesized that compared to placebo stimulation, 0° phase difference (in-phase stimulation) leads to faster response times and 180° phase difference (anti-phase stimulation) would lead to slower response times in a verbal working memory task. Further, we aimed to investigate whether focal fronto-parietal in-phase theta tACS, where the stimulation electrodes are surrounded by multiple close-by return electrodes as suggested by Saturnino et al. (2017), would have at least as much of an facilitatory effect as the in-phase stimulation suggested by Polanía et al. (2012). Based on electrophysiological modelling, the focal stimulation would be supposed to truly and more specifically impact on the fronto-parietal network. Therefore, we expected that focal in-phase fronto-parietal theta tACS should produce an at least as large reduction in response times in a verbal working memory task

compared to placebo stimulation as fronto-parietal in-phase stimulation with a single common return electrode. We investigated these research questions both in a between-subjects experiment, in which participants received one type of stimulation during a single session, and in a within-subjects experiment, in which participants received all types of stimulation in separate sessions. In both experiments, we measured their working memory performance in the same delayed letter recognition task as used by Polanía et al. (2012) and in the within-subjects experiment, we additionally measured their working memory performance in a more difficult 3-back task.

2 Experiment 1: Between-subjects experiment

2.1 *Pre-registration of study protocols*

This experiment was pre-registered on Open Science Framework (OSF repository will be made public upon publication. Anonymous view-only link for peer-review: https://osf.io/4z7wk/?view_only=63290592ea0c424697731b3eae5e62ed)

2.2 *A priori power analysis*

A-priori power analysis for determining sample size for the current experiment was performed with G*Power software (3.1.9.4, Faul et al., 2007). Effect sizes, if not indicated initially in the existing literature, were calculated from the reported statistical indices (Lakens, 2013). Demonstrating a significant effect of fronto-parietal theta tACS on working memory performance, Polanía et al. (2012) reported an effect size of f = .718 in their second experiment and Violante et al. (2017) obtained an effect of f = .923 in their first experiment. Kleinert et al. (2017) did not find any significant effect on working memory performance, nor did Violante et al. (2017) in their second experiment. However, in the latter two experiments, an exact effect size could not be reconstructed from the reported statistical estimates. Therefore, as a rather conservative effect size estimate for the current experiment, we took a third of the mean of the effect sizes reported by Polanía et al. (2012) in experiment 2, and Violante et al. (2017; exp. 1) resulting in f = .2735. Using this estimate of effect size, a significance level of α = .05 and a power of 1-β = .80, power analysis for a mixed 4 (stimulation group) x 2 (test phase) ANOVA suggested a minimal sample size of 44 participants (11 per stimulation group), each being tested twice within the experimental session – pre- and peri-stimulation.

2.3 *Participants*

We tested 48 typically developed volunteers in experiment 1. Participants were recruited by opportunity sampling mainly within the student community of the Ludwig-Maximilians-University Munich, Germany. Inclusion criteria as described in Antal et al. (2017) were applied and the age-range for inclusion was defined as 18 to 40 years. Two participants had to be excluded due to technical issues or being older than the pre-defined age. Thus, the remaining sample consisted of 46 participants (28 female, 18 male, 0 diverse) with a mean age of 21.33 years (SD = 3, range: 19-33 years). 41 of them were right handed, 4 left handed and 1 ambidextrous, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All gave written informed consent prior to their participation and received course credits upon completion. The study was approved by the local Ethics Review Board and conducted according to the Declaration of Helsinki.

2.4 *Task and Stimuli*

Participants performed the same delayed letter recognition task (see Figure 1) as used by Polanía et al. (2012). Three sample letters ("L", "T" and "C") were briefly presented (350 ms) in randomized order and masked for another 1000ms. Then, a numerical cue indicated whether to remember the first, second, or third

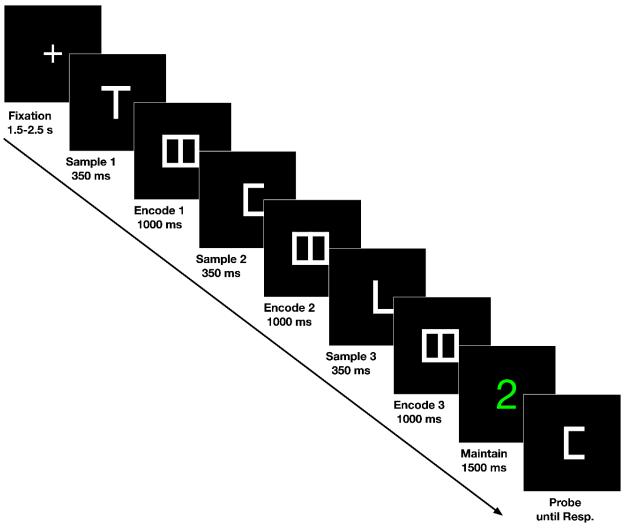

Figure 1. Exemplary trial sequence of the task in experiment 1. The task was the same as in Polanía et al. (2012). After three letters were encoded, a numerical cue indicated whether the first, second or third encoded letter should be maintained. The task was to indicate whether the following probe letter matched with the maintained letter or not. This example shows a match.

of the previously presented letters. After a 1500ms delay interval a probe letter was shown, and participants were asked to indicate as quickly and correctly as possible whether the probe letter matched the letter held in memory. The probe was displayed until a response was registered, but maximally for 2000 ms. Participants responded by pressing one of two buttons with their index finger or middle finger of the right hand to indicate a match or non-match, respectively. Each experimental block consisted of 90 trials with all possible stimulus sequences balanced and randomized in order. Before the start of the proper experiment, participants practiced the task on 18 trials.

Stimuli were presented in white, against a black background. Stimulus presentation was controlled using Presentation 0.71 (Neurobehavioural Systems®) and displayed on a displayed on a 15.4 inch monitor, which was placed centrally and at a distance of 50 cm from an observer.

2.5 Design and Procedure

Participants were randomly assigned to one of four groups: Anti-phase, Sham, In-phase Cz (shared return), or In-phase focal (ring return). They were blind to the kind of tACstimulation they received and to the existence of different groups. During the study session, each of the four participant groups underwent a short practice block and two longer experimental blocks of the task. They completed the first experimental block pre-stimulation (without tACS) and the second experimental block peri-stimulation (with one of the four tACS throughout the block). To ensure that they were comfortable with the stimulation, participants were exposed to a short period of stimulation before the start of the practice block.

2.6 tACS protocols

We used a StarStim device (neuroelectrics®) where stimulation electrodes were placed at EEG-electrode positions F3 and P3 over the dorsolateral prefrontal and the posterior parietal cortex. For In-phase protocols, return electrodes over position Cz (shared return) or over positions F7, Fz, C3, P7, and Pz (ring return) were used. All eight electrodes were mounted, but depending on stimulation protocol, only a subset of electrodes was active (see **Figure 2**). Round sponge electrodes with a diameter of 2.5 cm were used for stimulation. For safety reasons a 5 cm sponge electrode was used over Cz for the shared return. Impedance was kept below 10 kOhm using saline solution.

For Anti-phase stimulation over F3 and P3 (see **Figure 2Fehler! Verweisquelle konnte nicht gefunden werden.**, left) as previously used by Polanía et al. (2012), we delivered tACS at 6Hz at electrode F3 with site P3 as return, such that there was a 180° phase difference between the two sites. Intensity of stimulation was 1000μA. For Sham stimulation, within 30 s anti-phase stimulation (as described above) was ramped-up to 1000 μA, but then ramped-down within another 3 seconds. The stimulator did not deliver any transcranial electric stimulation after that. For In-phase Cz stimulation, the same electrode configuration as by Polanía et al. (2012) was used, i.e. two stimulation electrodes were placed over electrode sites F3 and P3 with a joint return electrode over electrode site Cz. We delivered tACS at 6 Hz with 1000 μA over F3 and P3, and consequently 2000 μA at Cz. There was a 0° phase difference between F3 and P3 stimulation (see **Figure 2**, middle). For the In-phase focal stimulation, we also delivered 0° phase difference tACS at 6 Hz at electrode sites F3 and P3, but four return electrodes were placed at electrode sites F7, Fz, C3, P7 and Pz. To achieve a current source density of stimulation in the dorsolateral prefrontal and the posterior parietal cortex comparable to In-phase Cz stimulation with only one shared return electrode, we delivered tACS at 1500μA intensity over F3 and P3 and 600μA current at each of the return electrodes stimulation (see **Figure 2Fehler! Verweisquelle konnte nicht gefunden werden.**, right).

For each of the active stimulation paradigms there was a 30 second ramp-up phase in the beginning. Then tACS was delivered constantly over the duration of the working memory task (ca. 14 min) and then ramped-down over 3 seconds. Participants were blinded about their stimulation condition. Experimenters were aware of the delivered stimulation condition. To control stimulation, we used NIC2 software (neuroelectrics®) and to model the electric fields in the brain resulting from our stimulation montages, we used the integrated StimViewer software component. Thus, the electric field generated in the cortex during tACS was estimated as described by Miranda et al (2013), using a realistic finite element model derived from MR images (for technical details, please see Miranda et al. (2013)). Figure 2C shows the magnitude of the electric field |E| for the three active stimulation conditions.

2.7 Data processing

To measure working memory performance, we analysed response times to probe items. Only trials with correct responses within the duration of the trial (correct button presses within 2000 ms after onset of the probe item) were included in the analysis. Overall, across participants, this led to an exclusion of 278 out of 8460 trials (3.29%; between 50 and 88 trials per stimulation condition). We checked that all response times were above 150 milliseconds to avoid inclusion of accidental button

presses, and for trials with multiple responses, the first button press was counted, which was not defined in the pre-registration.

The percentage of correct responses was compared between conditions descriptively. Based on the simplicity of the task and the results reported by Polanía et al. (2012), we expected participants to perform close to ceiling.

2.8 *Statistical data analysis*

Aggregated response time data were statistically evaluated using a mixed ANOVA with the within subject

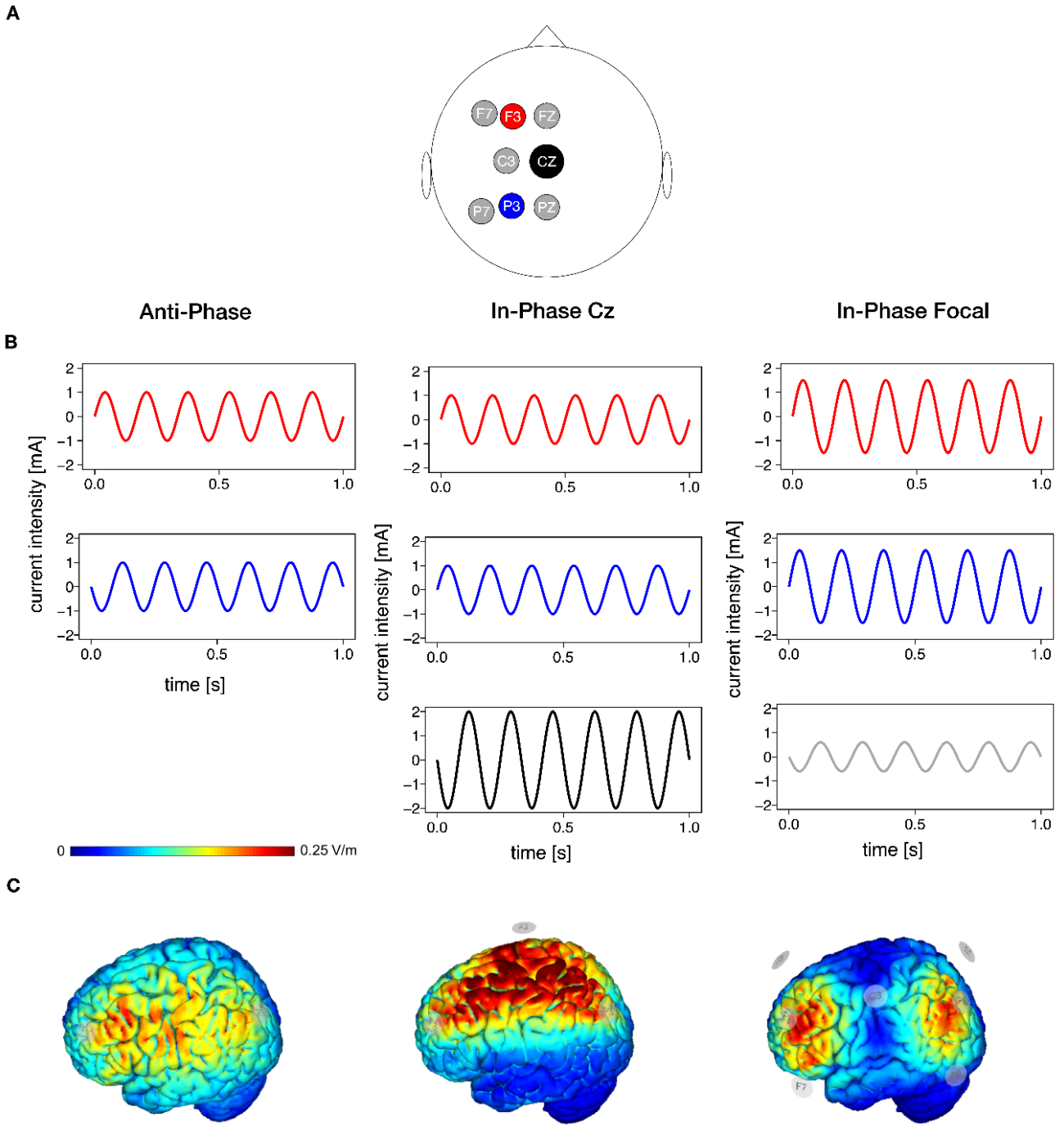

Figure 2. Illustration of electrode montage (A), stimulation protocols (B) and electric field models (C). *All eight electrodes were mounted, but only a subset of electrodes was used depending on stimulation protocol. Stimulation electrodes (red, blue) were centered over F3 and P3 for applying theta (6 Hz) tACS over the dorsolateral prefrontal and posterior parietal cortex. For the Anti-Phase protocol, no additional return electrode was used. For the In-phase protocols, the return electrodes over Cz (black; In-Phase Cz) or over F7, Fz, C3, P7 & Pz (grey; In-Phase Focal) were used.*

factor TESTPHASE (Baseline, Stimulation) and the between subject factor STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal). In contrast to Polanía et al. (2012) who used the mean of response times across trials for their analysis, we calculated the median of response times across trials instead, as response times within subjects were not normally distributed. According to our hypotheses, we expected to find an interaction effect, driven by slower median response times during Anti-phase stimulation, but faster median response times during In-phase stimulation compared to Sham. To investigate whether the Null hypothesis or the alternative hypothesis are more likely, we computed Bayes factors (BF_{10}), quantifying how well H1 predicts the empirical data relative to H0. If BF_{10} values are above 1, they indicate evidence for H1 over H0, whereas values below 1 suggest the opposite. For BF_{10} values above 3 or below 0.33, the strength of evidence is regarded as noteworthy, whereas values between 0.33 and 3 are considered as inconclusive evidence for any hypothesis (Jeffreys, 1961; Lee & Wagenmakers, 2014). We compared the models including the interaction term against the null model that no factor, except the random factor Subject-ID, has an effect.

In addition to the pre-registered analysis on aggregated response times, we also analysed the response time distribution using Bayesian mixed effects models. An advantage of mixed effects regression models is that they allow modelling single trial data, which enabled us to make use of the whole response time distribution instead of collapsing multiple observations into a single summary score for central tendency. For this more sensitive single-trial analysis, we used Bayesian mixed effects models as they allowed us to specify an assumed ex-gaussian distribution, which is well suited for modelling response time distributions that are right-skewed (Balota & Yap, 2011). The ex-gaussian distribution is the convolution of the Gaussian and exponential distribution. Here, the distribution mean is modelled by parameter μ and the standard deviation of the Gaussian component is modelled by parameter σ, which correspond to the localization and variability of the distribution, respectively. The mean of the exponential component is modelled by parameter τ, which corresponds to the right tail of the distribution. Based on our hypotheses, in this distributional analysis, we investigated whether there was an interaction effect of TESTPHASE and STIMULATION condition on the μ parameter, i.e., the location of the distribution. Additionally, we analyzed whether such an interaction would affect the σ parameter, i.e., the spread of the distribution, or the τ parameter, i.e., the right tail of the distribution. We used a Bayesian mixed effects regression model where the same set of predictors were used to model each of the three parameters of the ex-gaussian distribution. The Gaussian's location μ and spread σ, and the exponential component τ were predicted by the fixed effects TESTPHASE (baseline, stimulation), STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal), CODE (Match, Non-match) and their interactions, as well as by TRIAL (continuous covariate). The model included a single random-effects term for the intercept of the individual subjects and parameters σ and τ were fit on the log scale. Categorical covariates were encoded with custom contrasts (STIMULATION (Anti, Sham, InCz, InFo): Sham vs. Anti (-3/4, 1/4, 1/4, 1/4), InCz & InFo vs Sham (-1/2, -1/2, 1/2, 1/2), InFo vs InCz (0, 0, -1/2, 1/2); TESTPHASE (Baseline, Stimulation): Stimulation vs. Baseline (-1/2, 1/2)); CODE (Match, Nonm): Nonm vs. Match (-1/2, 1/2)), and the continuous covariate TRIAL was centred, such that the intercept is estimated as the grand average across all conditions. Thus, resulting fixed effect estimates can be interpreted as main effects. Parameter estimates for a given effect can be interpreted as substantial if their credible intervals do not contain zero.

All analyses were carried out using statistical software R 4.04 (R Core Team, 2019). Data was visualised using the ggplot2 package 3.3.3 (Wickham, 2016). Preregistered ANOVA analyses were completed using the afex package 0.28.1 (Singmann et al., 2021) and Bayes Factors were computed with the BayesFactor package 0.9.12.4.2 (Morey & Rouder, 2018) using default priors. Bayesian mixed effects regression models were implemented with the brms package 2.14.4 (Bürkner, 2017, 2018) using default priors. We ran 4 chains per model, each for 2000 iterations, with a warm-up period of 1000 iterations, and initial parameter values set to 0. If necessary, we increased the number of iterations to 4000 and the treedepth to 15 until the model converged with no divergent transitions (all $\hat{R}$ values < 1.01).

3 Experiment 2: within subjects experiment

3.1 Aims of experiment 2

We investigated the same research questions in a second experiment. Here, we aimed to reproduce the study protocols used by used by Polanía et al. (2012) even more closely. Therefore, we used a within-subjects design like in the study by Polanía and colleagues where participants returned to the lab in multiple sessions. In addition to the delayed letter recognition task, we also administered a more challenging 3-back working memory task (see below). We chose this difficult n-back condition since in a previous study by Kleinert et al

(2017), a 'synchronization-desychronization-effect' had only been partly replicated in a 2-back task, so we chose to increase task difficulty to n=3.

3.2 A priori power analysis

While this follow-up within-subjects experiment 2 was not pre-registered, we closely followed the study protocols from the pre-registered between-subjects experiment 1. The power analysis for a repeated measures ANOVA with 4 levels (stimulation condition) suggested a minimal sample size of 20 participants, each being tested in four separate experimental sessions during the stimulation conditions. As described in experiment 1 and based on previously reported effects in the literature, we again used an estimate of effect size of f = .2735, a significance level of $\alpha = .05$ and a power of $1-\beta = .80$.

3.3 Participants

We tested 23 healthy participants in experiment 2. As in experiment 1, participants were recruited by opportunity sampling mainly within the student community of the Ludwig-Maximilians-University Munich, Germany. Inclusion criteria as described in Antal et al. (2017) were applied and the age-range for inclusion was defined as 18 to 40 years. Two participants did not continue with the study after their first session and one participant had to be excluded due to being older than the pre-defined age range. Thus, the remaining sample consisted of 20 participants (12 female, 8 male, 0 diverse) with a mean age of 24.45 years (SD = 4.74, range: 20-36 years). All of them were right handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All gave written informed consent prior to their participation and received course credits upon completion. The study was approved by the local Ethics Review Board and conducted according to the Declaration of Helsinki.

3.4 Task and Stimuli

In experiment 2a, the experimental paradigm was identical as for experiment 1, namely the same delayed letter recognition task (see **Figure 1**), as described above in detail. In experiment 2b, however, participants completed a 3-back task (see **Figure 3**). For this 3-back task, we used digits 0 to 9 as stimuli, which were sequentially presented in the centre of the screen for 500 ms, with an inter-stimulus-interval of 1000ms. Stimuli were presented equally often. Targets occurred in 25% of trials and were defined as those stimuli where the digit in the current trial was identical to the digit three trials earlier. Participants had to respond by button press whenever a target appeared and to refrain from pressing the button when the stimulus was not a target. Overall, the task consisted of 160 trials. A practice block of 20 trials was completed beforehand. All stimuli were presented in white, against a black background. Stimulus presentation was controlled using Presentation 0.71 (Neurobehavioural Systems®) and displayed on a 15.4 inch monitor, which

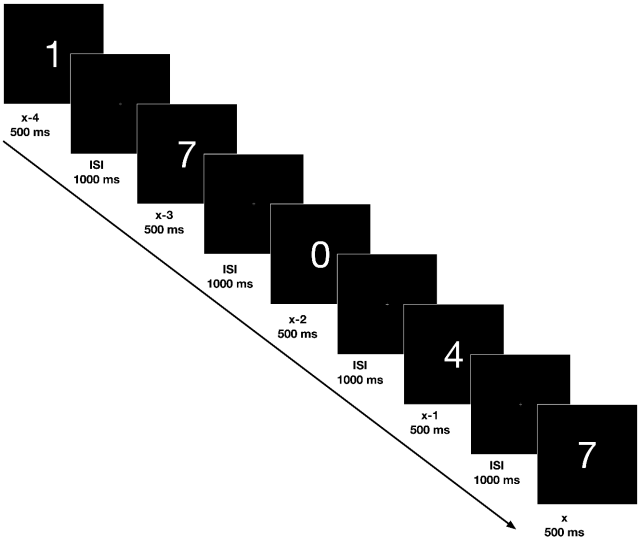

Figure 3. Exemplary trial sequence of the task from experiment 2b. *In this 3-back task, the presented digits had to be continuously remembered and updated. The task was to indicate whether a target was presented on the current trial x, i.e. when the presented digit was identical with the digit which had been presented in trial x-3, so 3 trials before. This example shows a target in the current trial.*

Table 1. Pseudo-randomized order of stimulation protocols across the four sessions.

	Session order I	Session order II	Session order III	Session order IV
Session 1	In-phase Cz	Sham	Anti-phase	In-phase focal
Session 2	In-phase focal	In-phase Cz	Sham	Anti-phase
Session 3	Anti-phase	In-phase focal	In-phase Cz	Sham
Session 4	Sham	Anti-phase	In-phase focal	In-phase Cz

was placed centrally and at a distance of 50 cm from an observer.

3.5 Design and Procedure

In four separate sessions, participants completed all four stimulation conditions (Sham, Anti-phase, In-phase Cz (shared return) or In-phase focal (ring return)). The order of sessions was pseudo-randomized across participants (see table 1). A session took place at least two days but on average around six days after the previous session (average: 5.92 days, SD=3.82). On average, the difference for session 1 to session 2 was 6.19 days (SD = 4.63), for session 2 to session 3 it was 5.81 days (SD=3.34), and for session 3 to session 4 it was 5.76 days (SD = 3.55). In each of the four sessions, participants completed both experiment 2a and experiment 2b. In a pseudo-randomized order, half of the participants started with experiment 2a and the other half with experiment 2b. Both experiments consisted of a short practice block and one longer experimental block. The experimental block was completed peri-stimulation (with one of the four tAC-stimulations throughout the block).

3.6 tACS protocols

We used the same tACS protocols as in experiment 1 (see above and **Figure 2**).

3.7 Data processing

For experiment 2a, accuracy and response time data from the delayed letter recognition task were preprocessed and analysed as in experiment 1. The percentage of correct responses was calculated and compared between conditions descriptively. To measure working memory performance, we analysed response times following probe items. For trials with multiple responses, the first button press was counted and it was checked that all response times were above 150 milliseconds to avoid inclusion of accidental button presses. Trials with incorrect or no responses within the duration of the trial (2 seconds after probe item) were excluded from analysis. Overall, across participants, this led to an exclusion of 222 out of 7560 trials (2.94%; between 52 and 65 trials per stimulation condition).

For data of experiment 2b, all trials of the 3-back task were included in the analysis. Responses (no or yes) were coded as correct or incorrect. For a descriptive analysis of task performance, we computed signal detection theory indices based on the number of hits, misses, correct rejections and false alarms. Discriminability indices were calculated as d' = z(Hit rate) - z(False alarm rate) and response bias indices were calculated as c = -(z(Hit rate) + z(False alarm rate)) / 2, where adjustments for extreme values were applied as implemented in the R package psycho (Makowski, 2018).

3.8 Statistical data analysis

For experiment 2a, in analogy to the pre-registered analysis of experiment 1, aggregated response time data were statistically evaluated using a within-subjects ANOVA with the within subject factor STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal). We expected to find an effect of stimulation condition showing slower median response times during Anti-phase stimulation, but faster median response times during In-phase stimulation compared to Sham. To investigate whether the Null hypothesis or the alternative hypothesis are more likely, we computed the Bayes factor (BF_{10}), comparing the model including the fixed effect against the null model that no factor, except the random factor Subject-ID, has an effect.

Additionally, we again conducted a more sensitive single-trial analysis by analysing the distribution of single-trial response times from experiment 2a using Bayesian mixed effects models with an assumed ex-gaussian distribution. We asked whether there was an effect of STIMULATION on the μ parameter, i.e., the location of the distribution, but also investigated potential effects on the σ parameter, i.e., the spread of the distribution, or the τ parameter, i.e., the right tail of the distribution. For this, the same set of predictors were used to model each of the three parameters of the ex-gaussian distribution. The parameters μ, σ, and τ were predicted by the fixed effects STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal), CODE (Match, Non-match) and their interaction, as well as SESSION (continuous covariate) and TRIAL (continuous covariate). The model included a random-effects term for the intercept of the individual subjects and parameters σ and τ were fit on the log scale. Categorical covariates were encoded with custom contrasts (STIMULATION: Sham vs. Anti (-3/4, 1/4, 1/4, 1/4), InCz & InFo vs Sham (-1/2, -1/2, 1/2, 1/2), InFo vs InCz (0, 0, -1/2, 1/2); CODE: Nonm vs. Match (1/2, -1/2)), and continuous covariates SESSION and TRIAL were centered. As the intercept is estimated as the grand average response times across all conditions, resulting fixed effect estimates can be interpreted as main effects.

For the statistical analysis of data from experiment 2b, for both the discriminability indices and response bias indices, assumptions for repeated-measures ANOVA were violated. Therefore, non-parametric Friedman tests were computed for discriminability and response bias, where we expected to find an effect of the

within subject factor STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal). And to investigate whether the Null hypothesis or the alternative hypothesis are more likely, we computed Bayes factors (BF_{10}), comparing the models including the fixed effect against the null models only including the random factor Subject-ID.

In an additional analysis, single-trial responses (no, yes) from experiment 2b were analysed using a Bayesian logistic mixed-effect regression that separated response bias (overall odds of responding yes) from discriminability (odds of responding yes when a target was presented). Response bias was represented by the intercept, discriminability was coded in the fixed effect CORRRESP (No, Yes), and we examined the interactions of bias and discriminability with STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal), their interaction with SESSION (continuous covariate), as well as their interaction with TRIAL (continuous covariate). The model included a random-effects term for the intercept of the individual subjects. Categorical covariates were encoded with custom contrasts (CORRRESP: Yes vs. No (-1/2, 1/2); STIMULATION: Sham vs. Anti (-3/4, 1/4, 1/4, 1/4), InCz & InFo vs Sham (-1/2, -1/2, 1/2, 1/2), InFo vs InCz (0, 0, -1/2, 1/2)), and the continuous covariates SESSION and TRIAL were centered. Thus, the intercept is estimated as the grand average response bias across all conditions and resulting fixed effect estimates can be interpreted as main effects.

4 Results

4.1 *Results Experiment 1 (Between Subjects)*

Table 2 and **Figure 4** show a descriptive summary of task accuracy (percentage of correct responses) and response times (median across correct trial's RTs). Task

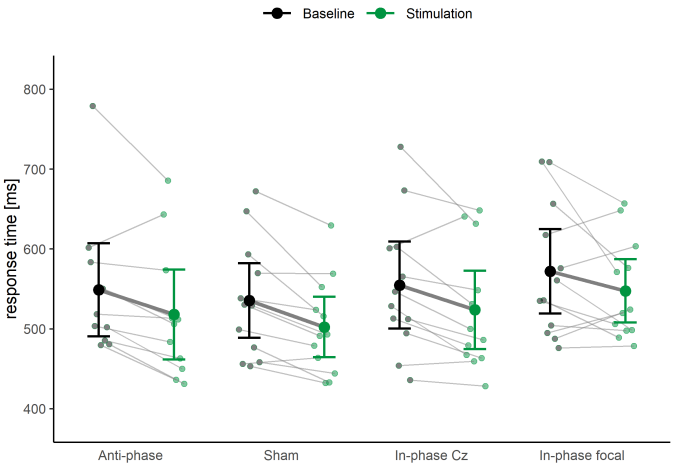

Figure 4. **Response times (RTs) pre-stimulation and peri-stimulation for all four stimulation groups in experiment 1.** RTs were calculated as the median of RTs from correct responses. Individual subjects' scores are overlaid with the group average and 95% confidence intervals as thick lines.

accuracy was overall high (average values in all conditions were above 95%, **Table 2**). For response times, we investigated whether there was an interaction effect of STIMULATION group and TEST PHASE. Results from the pre-registered ANOVA analysis indicated that overall response times were slower during the baseline than during the stimulation phase (TESTPHASE: $F(1,43) = 26.71$, $p < 0.001$, $\eta^2_G = 0.04$). No other effect was significant (STIMULATION: $F(3,43) = 0.62$, $p = 0.6$, $\eta^2_G = 0.04$; STIMULATION x TESTPHASE: $F(3,43) = 0.11$, $p = 0.96$, $\eta^2_G < 0.001$). The Bayes Factor analysis in fact indicated that there was substantial evidence that the null model was more likely to the model including the interaction STIMULATION x TESTPHASE ($BF_{10} = 0.12$). Similarly, there was strong evidence favouring the null model over the model including the interaction and the

Table 2. Overall task accuracy and response times pre-stimulation and peri-stimulation for all four stimulation groups in experiment 1.

STIMULATION	TESTPHASE	N	percent correct		reaction time	
			mean	(SD)	mean	(SD)
Anti-phase	Baseline	11	97.07	(2.12)	548.74	(86.91)
Anti-phase	Stimulation	11	97.88	(2.19)	517.84	(83.76)
Sham	Baseline	12	96.02	(2.25)	535.26	(73.57)
Sham	Stimulation	12	97.96	(1.24)	502.10	(59.67)
In-phase Cz	Baseline	11	96.26	(2.45)	550.12	(88.53)
In-phase Cz	Stimulation	11	96.57	(2.60)	522.93	(80.97)
In-phase focal	Baseline	12	95.09	(5.67)	571.86	(83.44)
In-phase focal	Stimulation	12	96.76	(2.86)	547.40	(62.42)

main effect STIMULATION (BF_{10} = 0.05), but only when including the main effect TESTPHASE along with the main effect STIMULATION the interaction term, then there was decisive evidence that the alternative hypothesis was more likely than the null hypothesis (BF_{10} = 308.28). And the alternative hypothesis was even more likely than the null hypothesis when including TESTPHASE as the only main effect along with the interaction term (BF_{10} = 531.4), which indicates that mainly the large effect of TESTPHASE was influential.

In the additional ex-gaussian regression analysis, we investigated whether there was an interaction effect of STIMULATION group and TESTPHASE on the μ parameter, i.e., the location of the distribution. Additionally, we analysed whether such an interaction affected the σ parameter, i.e., the spread, or the τ parameter, i.e. the right tail of the distribution. The distribution of single-trial response times is shown in **Figure 5**. The Bayesian mixed-effects regression model converged well, yielding R-hat values around 1 and solid posterior predictions. **Table 6** shows the model summary and conditional effects are visualized in **Figure 10Fehler! Verweisquelle konnte nicht gefunden werden.**.

Results of the ex-gaussian regression analysis indicated that for the μ parameter of the ex-gaussian distribution there was no a substantial interaction effect involving STIMULATION group and TESTPHASE. Similar to this, neither the σ parameter nor the τ parameter showed substantial interaction effects involving STIMULATION group and TESTPHASE.

There was a substantial main effect of TESTPHASE on the μ parameter, estimating μ parameter values as faster during the stimulation phase than the previous baseline phase (Stimulation vs. Baseline: B= -26.06, EE=2.37, CI=[-30.65, -21.42]). In non-match trials, μ parameter values were estimated as slower than in match trials (Nonm vs. Match: B=61.75, EE=2.40, CI=[57.10, 66.68]), and this difference was larger in the In-phase focal group than in the In-phase Cz group (InFo vs. InCz x Nonm vs. Match: B=14.05, EE=6.93, CI=[0.12, 27.28]). Across stimulation groups, participants were also estimated as getting faster across trials, i.e. increasing duration of the task (trial: B=-5.18, EE=1.09, CI=[-7.24, -3.04]). Finally, there was a 3-way interaction (InCz & InFo vs. Sham x Stimulation vs. Baseline x Nonm vs. Match: B=22.29, EE=10.46, CI=[2.00,42.54]), indicating that, while the μ parameter values were estimated as faster during the stimulation phase than the previous baseline phase, this difference was similar for both the In-phase stimulation groups and the Sham stimulation group during match trials; but during non-match trials, the In-phase stimulation groups showed an even smaller

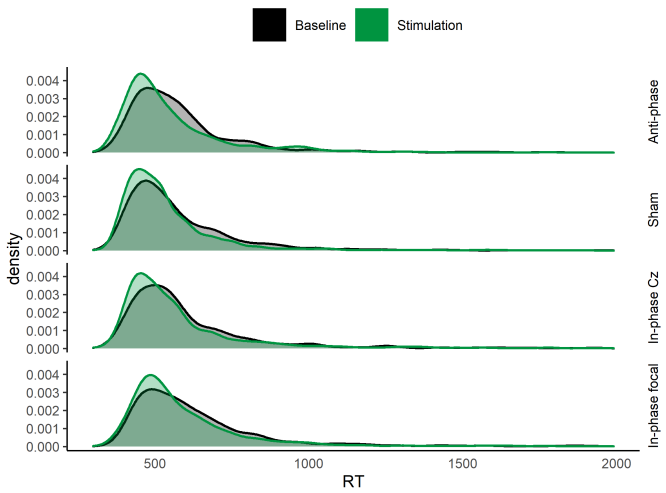

Figure 5. Distribution of single-trial response times (RTs) pre-stimulation and peri-stimulation for all four stimulation groups in experiment 1.

effect of test phase than the Sham group, contrary to what was expected (see **Figure 10**).

Estimates for the σ parameter of the ex-gaussian distribution also showed a substantial main effect of TESTPHASE (Stimulation vs. Baseline: B=-0.12, EE=0.06, CI=-0.24, 0]), showing lower estimates for the stimulation phase than the previous baseline phase. This estimated difference was larger for non-match trials than for match trials (Stimulation vs. Baseline x Nonm vs. Match: B=-0.26, EE=0.11, CI=[-0.48, -0.04]). They were also overall larger for non-match trials than match trials (Nonm vs. Match: B=0.15, EE=0.06, CI=[0.03, 0.27]). Additionally, the σ parameter was estimated to decrease across trials (trial: B=-0.06, E=0.03, CI=[-0.12, -0.01]). Similarly, estimates for the τ parameter of the ex-gaussian distribution were lower for the stimulation phase than baseline phase (Stimulation vs. Baseline: B=-0.09, EE=0.02, CI=[-0.13, -0.04]) and this estimated difference was also slightly larger for non-match trials than for match trials (Stimulation vs. Baseline x Nonm vs. Match: B=0.10, EE=0.04, CI=[0.01, 0.18]). Overall τ parameters were larger for non-match trials than for match trials (Nonm vs. Match: B=0.1, EE=0.03, CI=[0.05, 0.15]).

4.2 Results Experiment 2a (Within Subjects)

Table 3 and **Figure 6** show a descriptive summary of task accuracy (percentage of correct responses) and response times (median across correct trial's response times). Overall, task accuracy was high (the average in all conditions was above 96%, **Table 3**). For response times, we investigated whether there was a main effect of STIMULATION condition. The repeated-measures

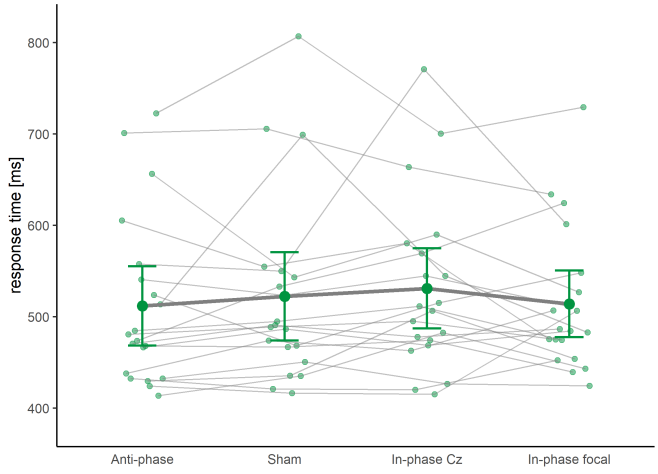

Figure 6. Response times (RTs) peri-stimulation for all four stimulation conditions in experiment 2a. *RTs were calculated as the median of RTs from correct responses. Individual subjects' scores are overlaid with the group average and 95% confidence intervals*

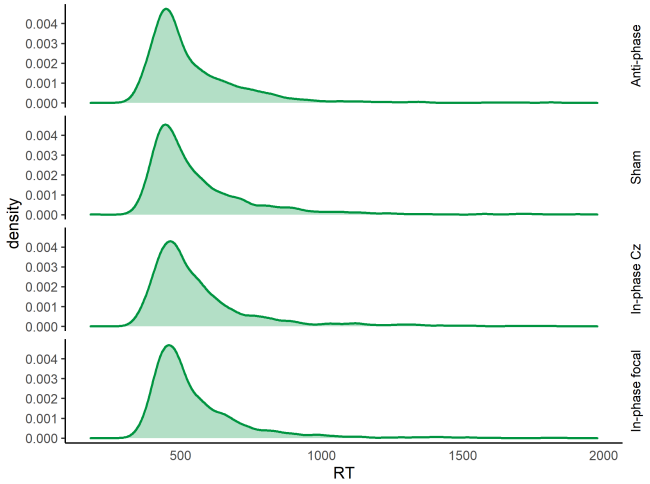

Figure 7. Distribution of single-trial response times (RTs) peri-stimulation for all four stimulation groups in experiment 2a.

ANOVA did not yield a significant effect (STIMULATION: $F(3,60) = 0.87$, $p = 0.46$, $\eta^2_G = 0.008$). The Bayes Factor analysis suggested that there was substantial evidence for the null model being more likely than the model including the effect STIMULATION ($BF_{10} = 0.15$).

In the ex-gaussian regression analysis, we investigated whether there was an effect of stimulation condition on the μ parameter, i.e. the location of the distribution. Additionally, we analysed whether stimulation condition would affect the σ or the τ parameter, the spread or the right tail of the distribution, respectively. The distribution of single-trial response times is visualized in **Figure 7**. The Bayesian mixed-effects model converged well, yielding R-hat values around 1 and solid posterior predictions. The model summary is shown in **Table 7**, conditional effects are visualized in **Figure 11**

Results of the ex-gaussian regression analysis indicated that for the μ parameter of the ex-gaussian distribution, there was a substantial effect indicating that μ parameter values in the Sham condition were estimated as slower than in the Anti-phase condition, contrary to what was expected (Sham vs. Anti: B=7.44, EE=2.87, CI=[1.82, 13.13]). Additionally, the μ parameter was estimated as slower in Non-match trials than in Match trials (Nonm vs. Match: B=55.72, EE=2.07, CI=[51.7, 59.83]); participants were getting faster across sessions (Session: B=-12.13, EE=1.06, CI=[-14.21, -10.02]) and slower with increasing task duration (Trial: B=5.57, EE=1.04, CI=[3.52, 7.6]). However, no other effects involving the factor STIMULATION were substantial for the μ parameter.

For the σ parameter of the ex-gaussian distribution there were no substantial effects involving stimulation condition. Estimates for the σ parameter were smaller for non-match than for match trials (Nonm vs. Match: B=-0.12, EE=0.06, CI=[-0.24, -0.11]) and decreased across sessions (Session: B=-0.14, EE=0.03, CI=[-0.2, -0.08].

Table 3. Overall task accuracy and response times peri-stimulation for all four stimulation conditions in experiment 2a.

STIMULATION	N	percent correct		reaction time	
		mean	(SD)	mean	(SD)
Anti-phase	20	97	(2.01)	511.75	(92.89)
Sham	20	97.17	(2.09)	522.20	(103.21)
In-phase Cz	20	96.44	(3.41)	530.96	(93.93)
In-phase Focal	20	97.22	(2.66)	514.03	(77.82)

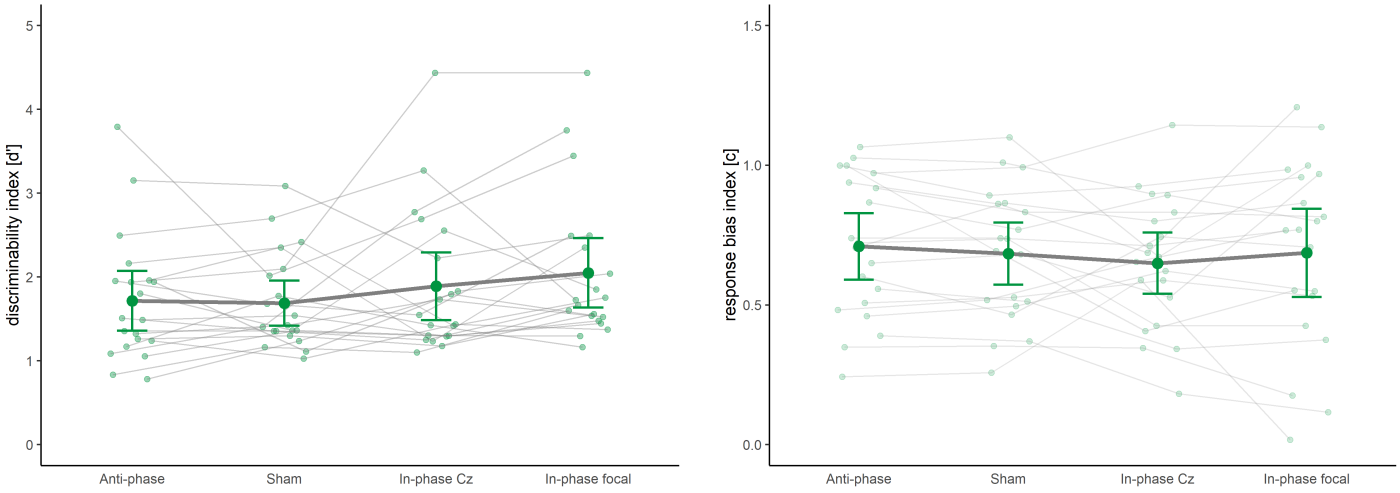

Figure 8. Task performance peri-stimulation for all four stimulation conditions in experiment 2b, measured as discriminability d' (left panel) and response bias c (right panel). *Individual subjects' scores are overlaid with the group average and 95% confidence intervals as thick lines.*

Estimates for the τ parameter of the ex-gaussian distribution were overall larger for Non-match trials than for Match trials (Nonm vs. Match: B=0.13, EE=0.02, CI=[0.09, 0.18]), and this difference was less pronounced in the In-phase conditions compared to the Sham condition (InCz & InFo vs. Sham x Nonm vs. Match: B=-0.11, EE=0.05, CI=[-0.22, -0.01]). And τ estimates also slightly increased across trials (Trial: B=0.06, EE=0.01, CI=[0.04, 0.09]), but no other effects involving stimulation condition were substantial for the τ parameter.

4.3 Results Experiment 2b (Within Subjects)

A descriptive summary of discriminability (d' index) and response bias (c index) is shown in **Figure 8** and **Table 4**. Non-parametric Friedman tests yielded no significant effects for stimulation condition, neither for d' (STIMULATION: χ^2 (3)= 3.76, p=0.29, n=20, Kendall's W=0.06) nor for c (STIMULATION: χ^2 (3)= 0.929, p=0.818, n=20, Kendall's W=0.02). The Bayes Factor analysis for response bias indicated strong evidence favouring the H0 over H1 (BF_{10} = 0.13). However, for the discriminability index, the Bayes Factor indicated that evidence remained inconclusive (BF_{10} = 0.47).

The more sensitive analysis of single-trial responses (no, yes) using a Bayesian logistic mixed-effect regression allowed us to separate response bias (overall odds of responding yes) from discriminability (odds of responding yes when a target was presented), and we investigated their interaction with stimulation condition.

The model converged well, yielding R-hat values around 1 and solid posterior predictions. The model summary is shown in **Table 5** and stimulation effects are visualized in **Figure 9**.

Table 4. Overall task performance peri-stimulation for all four stimulation conditions in experiment 2b, measured as discriminability (d') and response bias (c)

STIMULATION	N	discriminability		response bias	
		mean	(SD)	mean	(SD)
Anti-phase	20	1.71	(0.76)	0.71	(0.25)
Sham	20	1.69	(0.57)	0.68	(0.24)
In-phase Cz	20	1.89	(0.86)	0.65	(0.24)
In-phase Focal	20	2.05	(0.88)	0.69	(0.34)

Results of the logistic regression analysis showed that nonsurprisingly, due to the low number of target trials, there was an overall response bias to respond "no" (intercept: B=-1.2, EE=0.11, CI=[-1.4,-0.98]) which was estimated as slightly decreasing across trials (Trial: B=-0.08, EE=0.03, CI=[-0.14,-0.03]. Discriminability was overall high (Yes vs No: B=3.13, EE=0.06, CI=[3.01,3.24]) and was modulated by stimulation condition such that participants responded yes when a target was presented more often while they received In-phase stimulation (focal as well as with a Cz reference) than during Sham stimulation (Yes vs No x InCz & InFo vs. Sham: B=0.37, EE=0.13, CI=[0.11,0.64]), in line with our a-priori hypotheses. Discriminability also improved across sessions (Yes vs No x Session: B=0.43, EE=0.06, CI=[0.32,0.54]) and decreased across trials (Yes vs No x Trial: B=-0.22, EE=0.06, CI=[-0.33, -0.11]).

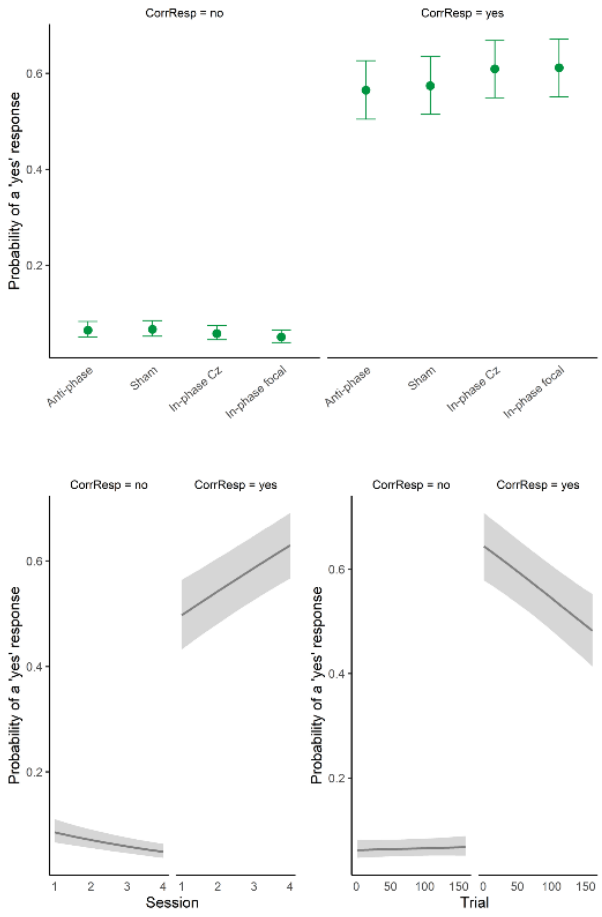

Figure 9. Conditional effects estimated by the model in experiment 2b.

Table 5. Parameters from the model in experiment 2b. *Note. B = estimate, EE = Estimated Error, CI = Credible Interval*

Predictor	B	EE	95% CI		
Intercept	**-1.20**	**0.11**	**-1.40**	**-0.98**	*
Yes vs. No	**3.13**	**0.06**	**3.01**	**3.24**	*
Sham vs. Anti	0.03	0.08	-0.11	0.18	
InCz & InFo vs. Sham	-0.04	0.07	-0.17	0.10	
InFo vs. InCz	-0.07	0.08	-0.23	0.10	
Session (centered)	-0.01	0.03	-0.07	0.04	
Trial (centered)	**-0.08**	**0.03**	**-0.14**	**-0.03**	*
Yes vs. No x Sham vs. Anti	0.01	0.15	-0.29	0.31	
Yes vs. No x InCz & InFo vs. Sham	**0.37**	**0.13**	**0.11**	**0.64**	*
Yes vs. No x InFo vs. InCz	0.15	0.17	-0.18	0.48	
Yes vs. No x Session (centered)	**0.43**	**0.06**	**0.32**	**0.54**	*
Yes vs. No x Trial (centered)	**-0.22**	**0.06**	**-0.33**	**-0.11**	*

Table 6. Parameters from the ex-gaussian regression model in experiment 1. *Note: B = estimate, EE = Estimated Error, CI = Credible Interval*

	mu					sigma					tau				
Predictor	**B**	**EE**	**95% CI**			**B**	**EE**	**95% CI**			**B**	**EE**	**95% CI**		
Intercept	**576.79**	**12.94**	**551.91**	**602.40**	*	**3.33**	**0.04**	**3.24**	**3.42**	*	**4.82**	**0.07**	**4.68**	**4.96**	*
Sham vs. Anti	-13.28	37.2	-85.97	61.62		-0.16	0.13	-0.41	0.08		-0.09	0.20	-0.51	0.30	
InCz & InFo vs. Sham	47.66	31.49	-17.07	104.96		0.07	0.11	-0.14	0.28		0.26	0.18	-0.11	0.61	
InFo vs. InCz	19.30	36.81	-52.09	90.20		0.02	0.13	-0.22	0.28		0.11	0.20	-0.29	0.49	
Stimulation vs. Baseline	**-26.06**	**2.37**	**-30.65**	**-21.42**	*	**-0.12**	**0.06**	**-0.24**	**0.00**	*	**-0.09**	**0.02**	**-0.13**	**-0.04**	*
Nonm vs. Match	**61.75**	**2.40**	**57.10**	**66.68**	*	**0.15**	**0.06**	**0.03**	**0.27**	*	**0.1**	**0.02**	**0.05**	**0.15**	*
Trial (centered)	**-5.18**	**1.09**	**-7.24**	**-3.03**	*	**-0.06**	**0.03**	**-0.12**	**-0.01**	*	-0.01	0.01	-0.04	0.01	
Sham vs. Anti x Stimulation vs. Baseline	9.00	6.14	-3.17	20.83		0.26	0.17	-0.07	0.59		-0.01	0.07	-0.15	0.12	
InCz & InFo vs. Sham x Stimulation vs. Baseline	5.86	5.45	-4.74	16.53		0.24	0.14	-0.03	0.52		0.06	0.05	-0.05	0.17	
InFo vs. InCz x Stimulation vs. Baseline	3.02	7.24	-11.41	17.06		-0.1	0.18	-0.44	0.25		0.02	0.06	-0.11	0.14	
Sham vs. Anti x Nonm vs. Match	0.76	6.66	-12.02	13.71		0.28	0.17	-0.05	0.60		-0.04	0.08	-0.19	0.12	
InCz & InFo vs. Sham x Nonm vs. Match	-1.30	5.83	-12.89	10.01		-0.09	0.14	-0.37	0.19		0.00	0.06	-0.12	0.12	
InFo vs. InCz x Nonm vs. Match	**14.05**	**6.93**	**0.12**	**27.28**	*	0.02	0.18	-0.33	0.36		0.10	0.06	-0.02	0.21	
Stimulation vs. Baseline x Nonm vs. Match	-1.95	4.54	-10.88	7.02		**-0.26**	**0.11**	**-0.48**	**-0.04**	*	**0.10**	**0.04**	**0.01**	**0.18**	*
Sham vs. Anti x Nonm vs. Match x Stimulation vs. Baseline	9.81	11.97	-13.25	33.22		0.23	0.32	-0.42	0.86		0.19	0.13	-0.06	0.44	
InCz & InFo vs. Sham x Stimulation vs. Baseline x Nonm vs. Match	**22.29**	**10.46**	**2.00**	**42.54**	*	-0.12	0.28	-0.64	0.42		0.05	0.10	-0.15	0.25	
InFo vs. InCz x Stimulation vs. Baseline x Nonm vs. Match	15.18	13.87	-12.21	42.34		-0.58	0.33	-1.22	0.07		-0.02	0.11	-0.24	0.21	

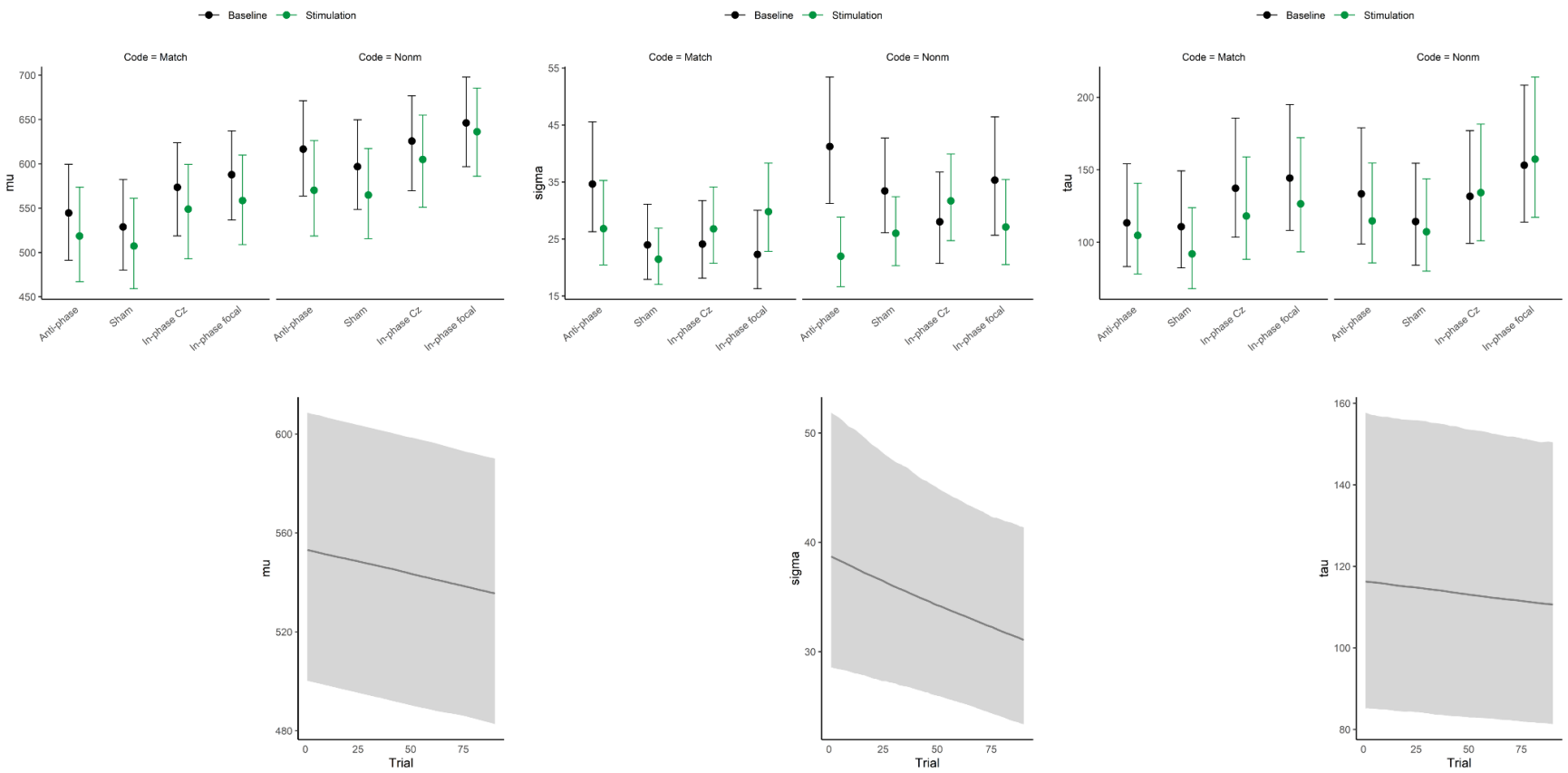

Figure 10. Conditional effects estimated by the ex-gaussian regression model in experiment 1. *Conditional ef-fects are shown for all three parameters of the ex-gaussian distribution*

Table 7. Parameters from the ex-gaussian regression model in experiment 2a. *Note. B = estimate, EE = Estimated Error, CI = Credible Interval*

	mu					sigma					tau				
Predictor	**B**	**EE**	**95% CI**			**B**	**EE**	**95% CI**			**B**	**EE**	**95% CI**		
Intercept	**552.2**	**22.31**	**507.46**	**594.88**	*	**3.23**	**0.1**	**3.02**	**3.43**	*	**4.71**	**0.12**	**4.47**	**4.93**	*
Sham vs. Anti	**7.44**	**2.87**	**1.82**	**13.13**	*	0.05	0.08	-0.11	0.20		0.01	0.03	-0.05	0.08	
InCz & InFo vs. Sham	2.75	2.53	-2.16	7.78		-0.10	0.07	-0.24	0.03		0.03	0.03	-0.02	0.09	
InFo vs. InCz	-5.09	3.12	-11.21	0.95		0.04	0.09	-0.13	0.21		0.01	0.03	-0.06	0.08	
Nonm vs. Match	**55.72**	**2.07**	**51.7**	**59.83**	*	**-0.12**	**0.06**	**-0.24**	**-0.01**	*	**0.13**	**0.02**	**0.09**	**0.18**	*
Session (centered)	**-12.13**	**1.06**	**-14.21**	**-10.02**	*	**-0.14**	**0.03**	**-0.2**	**-0.08**	*	-0.02	0.01	-0.04	0.01	
Trial (centered)	**5.57**	**1.04**	**3.52**	**7.60**	*	-0.03	0.03	-0.09	0.03		**0.06**	**0.01**	**0.04**	**0.09**	*
Sham vs. Anti x Nonm vs. Match	-0.53	5.59	-11.51	10.35		-0.10	0.16	-0.42	0.21		0.04	0.06	-0.09	0.16	
InCz & InFo vs. Sham x Nonm vs. Match	2.61	4.92	-6.95	12.35		0.23	0.14	-0.05	0.50		**-0.11**	**0.05**	**-0.22**	**-0.01**	*
InFo vs. InCz x Nonm vs. Match	-0.58	5.76	-11.77	10.95		0.07	0.17	-0.25	0.40		-0.03	0.06	-0.15	0.10	

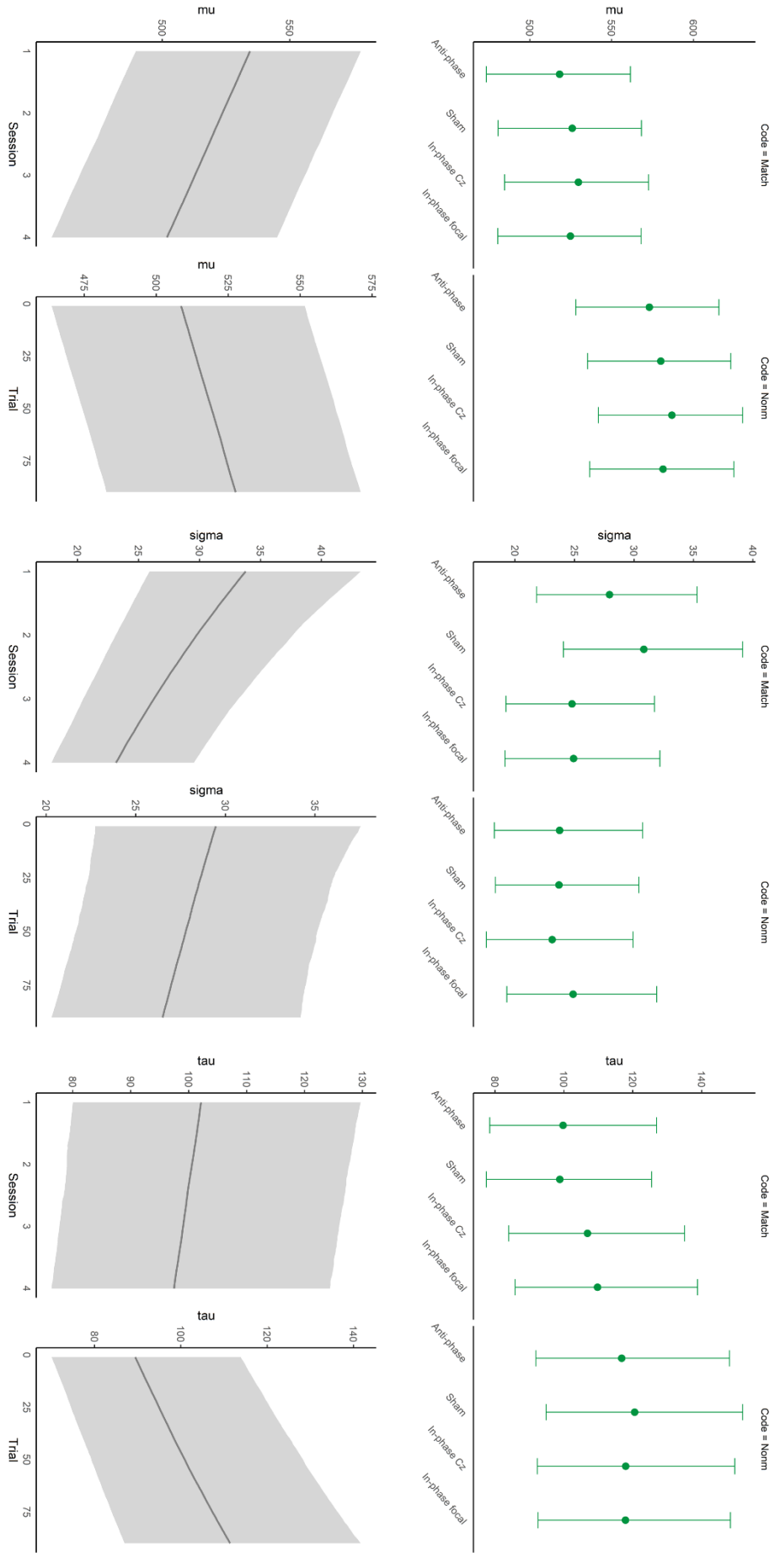

Figure 11. Conditional effects estimated by the ex-gaussian regression model in experiment 2a. *Conditional effects are shown for all three parameters of the ex-gaussian distribution.*

5 Discussion

In this study, we applied transcranial alternating current stimulation (tACS) at theta frequency for exogenously modulating oscillatory activity in a fronto-parietal network that is engaged in working memory performance. We aimed to reproduce the findings reported by Polanía et al. (2012) and to investigate whether a more focal in-phase stimulation, as suggested by electrophysiological modelling (Saturnino et al., 2017), will have at least as much of a facilitatory effect as the in-phase stimulation utilized by Polanía and colleagues. Highlighting the importance of theta oscillations for working memory performance, Polanía et al. (2012) showed that in a left-hemispheric fronto-parietal theta-network, in-phase theta tACS led to shorter response times whereas anti-phase stimulation led to longer response times compared to a placebo stimulation. Against our hypothesis, we found no decrease of response times by an exogenous boost of left-hemispheric fronto-parietal theta coupling nor an increase of response times by an exogenous induction of a 180° relative phase, using the same delayed letter discrimination task and stimulation parameters in two experiments, both between-subjects and within-subjects. Surprisingly, instead of impairment through asynchronous theta tACS, response times in the within-subjects experiment were even slightly faster in the anti-phase stimulation condition than in the sham condition, which is the opposite from what was expected regarding the hypothesized 'synchronization-desynchronization' effect. However, in the same experiment, task performance in a demanding 3-back task (the odds of correctly detecting a target) was substantially improved for in-phase theta tACS compared to the sham condition, which is in line with our a-priori hypothesis, whereas we observed no decrease of performance through anti-phase theta tACS.

Similarly, 'synchronization-desynchronization' effects on response times using fronto-parietal theta tACS have not been or only partly been reproduced in previous studies (Alekseichuk et al., 2017; Kleinert et al., 2017; Violante et al., 2017). Kleinert et al. (2017) reported that their data from a visuospatial delayed match-to-sample task showed no significant differences in response times between the stimulation conditions. Violante et al. (2017) found an effect of tACS condition on response times in the more demanding 2-back task, but not so in the less demanding 1-back task. However, there was only an improvement in the in-phase stimulation group, but no impairment during anti-phase tACS; and this effect was not replicated in a second experiment using simultaneous tACS-fMRI. Similar to this, we observed an improvement of task performance (the odds of correctly detecting a target) for in-phase tACS in the 3-back task in experiment 2b, but no impairment of performance during anti-phase tACS. In contrast to this, Alekseichuk et al. (2017) found that anti-phase theta tACS led to increased response times and reduced accuracy in a 2-back task, whereas in-phase tACS had no beneficial effect.

This could mean that a 'synchronization-desynchronization' effect on response times might be smaller in effect size than previously expected, requiring larger sample sizes than in the current and the aforementioned studies to be detected. However, in this study, a Bayes Factor analysis showed conclusive evidence that the null-hypothesis predicted the empirical data better than the research hypothesis, given the current sample size in the between-subjects experiment (n=46) and the within-subjects experiment (n=20). Additionally, we even conducted a single-trial regression analysis in which we investigated whether there was an effect of stimulation on the location of the response time distribution and also on two additional parameters comprising the variability and the right tail of the distribution. Yet, we did not observe a substantial 'synchronization-desynchronization' effect on either parameter of the response time distribution, nor a trend in that direction. And inconsistent findings have also been reported in the literature using other types of frequency-tuned in-phase or anti-phase stimulation. While it was reported that in-phase alpha-band stimulation over the right frontal and parietal cortex compared to sham stimulation modulated response times and fronto-parietal coherence during a spatial attention task (van Schouwenburg et al., 2017), these effects could not be reproduced in a second study, nor was there a modulation by anti-phase alpha tACS condition (van Schouwenburg et al., 2018).

A common criticism about studies using a single return electrode for two stimulation electrodes is that the phase lag between the two active sites is not the only parameter that varies between in-phase stimulation (using a single return electrode for two stimulation electrodes) and anti-phase stimulation (where the two active stimulation electrodes function as a return for themselves). For example, it has been criticized that between in-phase and anti-phase conditions there could be variations in the direction of current flow (Thut et al., 2017), and it has been pointed out that differences in the overall intensity of stimulation could not be ruled out (Kleinert et al., 2017), potentially leading to the observed differences between conditions. These criticisms have been demonstrated to be very valid using in vivo recordings in the macaque brain (Alekseichuk et al., 2019). And following from electrophysiological modelling (Saturnino et al., 2017), it has been pointed out that for in-phase tACS with a single return electrode for two stimulation electrodes, as used in this study and by previous researchers

(Polania et al., 2012; Kleinert et al., 2017; Violante et al., 2017), it might not be the fronto-parietal network that is primarily stimulated.

Therefore, the central goal of our study was to investigate whether fronto-parietal focal in-phase tACS, for which we positioned multiple close-by return electrodes to focally stimulate the frontal and the parietal cortex, would result in a facilitation of working memory performance. Previously, Schouwenburg et al. (2017) had used three lateral central reference electrodes (C2, C4, C6) located in-between the stimulation electrodes (F4, P4) and others had proposed the use of center-surround ring montages (Bortoletto et al., 2016; Saturnino et al., 2017). We surrounded the stimulation electrodes (F3 and P3) with five return electrodes close-by (F7, Fz, C3, P7, Pz). By modelling the electric field in the brain associated with our stimulation protocols, we confirmed that this montage was capable of producing a focal electric field targeting frontal and parietal cortices. However, for response times in the delayed letter discrimination task, our data neither showed a facilitatory effect of in-phase stimulation (shared return and focal) compared to a sham condition, nor a difference between focal in-phase tACS and in-phase tACS with a shared return electrode or a trend or descriptive difference pointing in that direction.

Since this focal in-phase theta tACS with multiple close-by return electrodes produced no modulation of response times compared to sham stimulation and no benefit over in-phase stimulation with a shared return, it is possible that it might be less effective than suggested by Saturnino and colleagues (2017). One suggestion for future research could be to utilize fully closed ring montages (Bortoletto et al., 2016; Saturnino et al., 2017) instead. However, although we saw no modulatory effect on response times in the letter recognition task what so ever, we did indeed observe a slight improvement of discriminability in the 3-back task during the in-phase theta tACS conditions compared to the sham condition in the single-trial regression analysis, albeit no substantial difference between the focal in-phase stimulation and the in-phase stimulation with a shared return electrode.

So given that we were able to show some facilitatory effect in the more demanding 3-back task, what could be a more plausible and rather general limitation of this study is that the task adapted from Polanía et al. (2012) was a very easy task. This is corroborated by accuracy rates above 95% for the delayed letter recognition task in both experiments, which is close to ceiling. For the 3-back task, however, average discriminability (d') values were between 1.7 and 2, which is not close to ceiling performance, indicating that an improvement of performance would, in general, be possible. This may explain why we find a facilitatory effect of in-phase tACS, but no further detrimental effect. Interestingly, effects of task difficulty or participant characteristics have been previously reported in the literature. For example, previously discussed reports also pointed into the direction that an improvement of reaction times by in-phase theta stimulation was only found in a more demanding 2-back task, but not in the less demanding 1-back task (Violante et al., 2017). Similarly, for gamma tACS, an improvement for a more demanding 3-back task following stimulation has been found, but not in a less demanding 2-back condition (Hoy et al., 2015), or for more complex trials involving logical reasoning (Santarnecchi et al., 2013, 2016). For fronto-temporal theta tACS which had been delivered in-phase, an improvement in working memory accuracy was observed for older adults and only for those younger adults who were low-performing, whereas detrimental effects of anti-phase stimulation could be shown for high-performing younger adults (Reinhart et al., 2019). Similarly, it has also been reported that improved performance in a visual-spatial memory task during in-phase theta tACS between left and right parietal cortex was observed for low-performers, whereas high-performers showed decreased WM performance during anti-phase theta tACS between left and right parietal cortex (Tseng et al., 2018). And such differences between high and low performers regarding their sensitivity for enhancing or detrimental effects due to in-phase or anti-phase tACS were observed for gamma tACS (Tseng et al., 2016). Along with the findings from our study, this evidence underlines that task difficulty and individual performance levels of a given sample might determine whether facilitatory effects through in-phase tACS and detrimental effects of anti-phase tACS will be observed.

While other studies used experimental paradigms and targeted other cortical sites than in the seminal study by Polanía et al. (2012), the approach we used in the current study was very similar to the one by Polanía et al. (2012). One small difference was that repeated sessions within participants occurred with a least five days difference (Polanía et al., 2012) compared to at least two days difference in the current study. However, it is not clear how this would result in an absence of any stimulation effect on response times. Rather, this might contribute to the observed improvement of task performance across sessions (see below for a discussion). One critical difference, however, could be that in the in-phase stimulation condition, we used a slightly larger sponge electrode as a shared return electrode for two stimulation electrodes. We chose this larger electrode to reduce the current density under the reference electrode. Saturnino et al. (2017) demonstrated that using one shared return electrode for

two stimulation electrodes might lead to the strongest stimulation effect under the return electrode and not under the active electrodes placed over fronto-parietal regions. Our in-phase montage aimed to reduce this effect. One could speculate that the increase of working memory performance observed by Polanía et al. (2012) might have been partly driven by a boost of fronto-central theta activity in the in-phase condition, induced through the stronger current density under the central reference electrode location. Particularly frontal-midline theta activity, which has been shown to be essential in working memory processes (Berger et al., 2019), could have been entrained by this kind of stimulation. This might also explain the absence of a modulation of response times during in-phase tACS in our study, where we used the larger return electrode.

In addition to the discussed effects (and nil effects) for stimulation group or stimulation condition, we observed a couple of substantial effects involving covariates. In experiment 1, we observed an effect of test phase, such that average response times, the spread and the right tail of the distribution decreased from the baseline phase to the subsequent phase where stimulation was delivered, reflecting practice effects. Similarly, average response times and their variability in experiment 2a decreased across sessions and discriminability in experiment 2b increased across sessions, indicating that upon repetition of the task, participants improved in performance. However, the training duration in the current study was not much shorter than in a previous study using the same task (Polanía et al., 2012). Still, it could be beneficial to extend the training phase, especially because it has been reported that practice effects across sessions can outweigh effects of tACS or tDCS (Röhner et al., 2018). For the effect of trial, results were a bit more variable. Whereas participants from experiment 1 improved across trials, showing increasingly faster and less variable response times, performance in experiment 2 decremented across trials, with increasingly slower response times in experiment 2a and decreasing discriminability in experiment 2b across trials. This might result from different effects of fatigue between the recruited samples of participants, since study participation was overall more demanding for participants in experiment 2, who returned to the lab four times and completed two task paradigms each session, including the more demanding 3-back task. In both experiments, response times for trials in which the probe did not match the cued memory item were longer, and more skewed; whereas concerning the spread of the response time distributions, they were slightly more variable in experiment 1 or slightly less variable in experiment 2a. But since responses were given by the right index finger for match trials or the right middle finger for non-match trials, this could be simply due to differences in responsiveness of index and middle fingers.

This trivial effect was also involved in several interactions. In experiment 1, for both the variability and the right skewness of the distribution, the difference between stimulation phase and the previous baseline phase was larger for non-match trials than for match trials, which is plausible considering that the middle finger might be less responsive than the index finger. For average response times, the difference between non-match and match trials was larger in the In-phase focal group than in the In-phase Cz group, but this did not interact with test phase. And while average response times were faster during the stimulation phase than during the previous baseline phase, during match trials this difference was similar for both the In-phase stimulation groups and the Sham stimulation group, but during non-match trials, the In-phase stimulation groups showed an even smaller effect of test phase than the Sham group, contrary to what could be expected. Conversely, in experiment 2, only for the right skewness of the distribution, the difference between non-match and match trials was less pronounced in the In-phase conditions compared to the Sham condition. It is possible that all these interaction effects could be driven by differences in electric field strength and spread across motor areas between electrode montages are driven by different motor modulations through the different stimulation montages.

Interestingly, while we could not reproduce a 'synchronization-desynchronization' effect by fronto-parietal theta tACS on response times in a delayed letter recognition task, we could show that in a more demanding 3-back task, in-phase and in-phase focal theta tACS improved discriminability substantially compared to a sham condition. A 'synchronization-desynchronization' effect through in-phase or anti-phase tACS was reproduced, at least partly, both for working memory by fronto-parietal theta tACS (Alekseichuk et al., 2017; Röhner et al., 2018; Tseng et al., 2018; Violante et al., 2017), but also for other cognitive domains; such as for semantic retrieval performance by fronto-parietal theta tACS (Marko et al., 2019), for executive functions by frontal theta tACS (Reinhart, 2017), for spatial attention by fronto-parietal alpha tACS (van Schouwenburg et al., 2017), or for motion perception through parieto-occipital gamma and alpha tACS (Helfrich et al., 2014; Salamanca-Giron et al., 2020; Strüber et al., 2014). Especially those studies reporting an improvement in working memory performance for older adults and low-performing individuals (Reinhart & Nguyen, 2019; Tseng et al., 2016, 2018) are quite promising for future therapeutic applications. However, it is challenging that results have

been relatively inconsistent so far. And, intriguingly, behavioral modulation due to anti-phase stimulation has sometimes been characterized by an enhancement effect on performance instead of showing detrimental effects (Salamanca-Giron et al., 2020; Tseng et al., 2016; Yaple & Vakhrushev, 2018). Depending on the actual phase lag between two stimulated brain areas, either in-phase or anti-phase stimulation might be most beneficial. But most likely, a precise tuning of exact phase lag and the precise frequency at which stimulation gets delivered should result in the strongest effects. Thereby phase lag as well as frequency might demonstrate considerable inter-individual differences which would be important to account for in future brain stimulation studies.

Overall, we did not directly reproduce findings originally reported by Polanía et al. (2012) in this study. Nevertheless, the study by Polanía and colleagues is without doubt a milestone article which has had a tremendous influence on non-invasive brain stimulation. It was one of the first studies that tried modulating more complex distributed network activity, beyond mere entrainment of local amplitude of oscillatory activity. This has opened up an entirely new avenue of research aiming on modulating yet more complex oscillatory brain activation patterns, such as cross-frequency coupling (Alekseichuk et al., 2016; Lara et al., 2018; Turi et al., 2020). Moreover, here we demonstrated that the basic mechanism described in Polanía et al.'s (2012) seminal paper can be found when cognitive task demands are high enough. This indicates that phase-sensitive electric brain stimulation can potentially be used for increasing peak performance or for compensating cognitive decline.

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The authors declare no competing interests.

Data availability statement:
The data and analysis scripts that support the findings of this study are openly available in our project repository on Open Science Framework (OSF repository will be made public upon publication. Anonymous view-only link for peer-review: https://osf.io/4z7wk/?view_only=63290592ea0c424697731b3eae5e62ed).

References

Alagapan, S., Riddle, J., Huang, W. A., Hadar, E., Shin, H. W., & Fröhlich, F. (2019). Network-Targeted, Multi-site Direct Cortical Stimulation Enhances Working Memory by Modulating Phase Lag of Low-Frequency Oscillations. *Cell Reports*, *29*(9), 2590-2598.e4. https://doi.org/10.1016/j.celrep.2019.10.072

Alekseichuk, I., Falchier, A. Y., Linn, G., Xu, T., Milham, M. P., Schroeder, C. E., & Opitz, A. (2019). Electric field dynamics in the brain during multi-electrode transcranial electric stimulation. *Nature Communications*, *10*(1), 2573. https://doi.org/10.1038/s41467-019-10581-7

Alekseichuk, I., Pabel, S. C., Antal, A., & Paulus, W. (2017). Intrahemispheric theta rhythm desynchronization impairs working memory. *Restorative Neurology and Neuroscience*, *35*(2), 147–158. https://doi.org/10.3233/RNN-160714

Alekseichuk, I., Turi, Z., Lara, G. A. D., Antal, A., Alekseichuk, I., Turi, Z., Amador de Lara, G., Antal, A., & Paulus, W. (2016). Spatial Working Memory in Humans Depends on Theta and High Gamma Synchronization in the Prefrontal Cortex. *Current Biology*, *26*(12), 1–9. https://doi.org/10.1016/j.cub.2016.04.035

Baddeley, A. D. (2012). Working Memory: Theories, Models, and Controversies. *Annual Review of Psychology*, *63*(1), 1–29. https://doi.org/10.1146/annurev-psych-120710-100422

Berger, B., Griesmayr, B., Minarik, T., Biel, A. L., Pinal, D., Sterr, A., & Sauseng, P. (2019). Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. *Nature Communications*, *10*(1), 4242. https://doi.org/10.1038/s41467-019-12057-0

Bortoletto, M., Rodella, C., Salvador, R., Miranda, P. C., & Miniussi, C. (2016). Reduced Current Spread by Concentric Electrodes in Transcranial Electrical Stimulation (tES). *Brain Stimulation*, *9*(4), 525–528. https://doi.org/10.1016/j.brs.2016.03.001

Bürkner, P.-C. (2017). brms: An R Package for Bayesian Multilevel Models Using Stan. *Journal of Statistical Software*, *80*(1), 1–28. https://doi.org/10.18637/jss.v080.i01

Bürkner, P.-C. (2018). Advanced Bayesian Multilevel Modeling with the R Package brms. *The R Journal*, *10*(1), 395–411. https://doi.org/10.32614/RJ-2018-

017
Cooper, P. S., Wong, A. S. W., Fulham, W. R., Thienel, R., Mansfield, E., Michie, P. T., & Karayanidis, F. (2015). Theta frontoparietal connectivity associated with proactive and reactive cognitive control processes. *NeuroImage*, *108*, 354–363. https://doi.org/10.1016/j.neuroimage.2014.12.028
Cowan, N. (2008). What are the differences between long-term, short-term, and working memory? *Progress in Brain Research*, *169*, 323–338. https://doi.org/10.1016/S0079-6123(07)00020-9
D'Esposito, M., & Postle, B. R. (2015). The Cognitive Neuroscience of Working Memory. *Annual Review of Psychology*, *66*(1), 115–142. https://doi.org/10.1146/annurev-psych-010814-015031
Helfrich, R. F., Knepper, H., Nolte, G., Strüber, D., Rach, S., Herrmann, C. S., Schneider, T. R., & Engel, A. K. (2014). Selective Modulation of Interhemispheric Functional Connectivity by HD-tACS Shapes Perception. *PLOS Biology*, *12*(12), e1002031. https://doi.org/10.1371/journal.pbio.1002031
Hoy, K. E., Bailey, N., Arnold, S., Windsor, K., John, J., Daskalakis, Z. J., & Fitzgerald, P. B. (2015). The effect of γ-tACS on working memory performance in healthy controls. *Brain and Cognition*, *101*, 51–56. https://doi.org/10.1016/j.bandc.2015.11.002
Jeffreys, H. (1961). *Theory of probability* (3rd ed). Oxford University Press.
Kleinert, M.-L., Szymanski, C., & Müller, V. (2017). Frequency-Unspecific Effects of $þeta$-tACS Related to a Visuospatial Working Memory Task. *Frontiers in Human Neuroscience*, *11*(July), 1–16. https://doi.org/10.3389/fnhum.2017.00367
Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00863
Lara, G. A. de, Alekseichuk, I., Turi, Z., Lehr, A., Antal, A., & Paulus, W. (2018). Perturbation of theta-gamma coupling at the temporal lobe hinders verbal declarative memory. *Brain Stimulation*, *11*(3), 509–517. https://doi.org/10.1016/j.brs.2017.12.007
Lee, M., & Wagenmakers, E. (2014). *Bayesian Cognitive Modeling: A Practical Course*. https://books.google.de/books?hl=de&lr=&id=50tkAgAAQBAJ&oi=fnd&pg=PR10&ots=r4k4Nh7rK3&sig=xK6bnnUkZa9p5yfcZ_q9wQ-qKU4
Makowski, D. (2018). The Psycho Package: An Efficient and Publishing-Oriented Workflow for Psychological Science. *Journal of Open Source Software*, *3*(22), 470. https://doi.org/10.21105/joss.00470
Marko, M., Cimrová, B., & Riečanský, I. (2019). Neural theta oscillations support semantic memory retrieval. *Scientific Reports*, *9*(1), 17667. https://doi.org/10.1038/s41598-019-53813-y
Miranda, P. C., Mekonnen, A., Salvador, R., & Ruffini, G. (2013). The electric field in the cortex during transcranial current stimulation. *NeuroImage*, *70*, 48–58. https://doi.org/10.1016/j.neuroimage.2012.12.034
Morey, R. D., & Rouder, J. N. (2018). *BayesFactor: Computation of Bayes Factors for Common Designs*. https://CRAN.R-project.org/package=BayesFactor
Polanía, R., Moisa, M., Opitz, A., Grueschow, M., & Ruff, C. C. (2015). The precision of value-based choices depends causally on fronto-parietal phase coupling. *Nature Communications*, *6*(1), 8090. https://doi.org/10.1038/ncomms9090
Polanía, R., Nitsche, M. A., Korman, C., Batsikadze, G., & Paulus, W. (2012). The Importance of Timing in Segregated Theta Phase-Coupling for Cognitive Performance. *Current Biology*, *22*(14), 1314–1318. https://doi.org/10.1016/j.cub.2012.05.021
Ptak, R., Schnider, A., & Fellrath, J. (2017). The Dorsal Frontoparietal Network: A Core System for Emulated Action. *Trends in Cognitive Sciences*, *21*(8), 589–599. https://doi.org/10.1016/j.tics.2017.05.002
Reinhart, R., Grover, S., Wang, C., & Nguyen, J. (2019). Improving working memory in older adults by synchronizing cortical interactions with alternating current. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *12*(2), 514. https://doi.org/10.1016/j.brs.2018.12.687
Reinhart, R. M. G. (2017). Disruption and rescue of interareal theta phase coupling and adaptive behavior. *Proceedings of the National Academy of Sciences*, *114*(43), 11542–11547. https://doi.org/10.1073/pnas.1710257114
Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience*, *22*(5), 820–827. https://doi.org/10.1038/s41593-019-0371-x
Röhner, F., Breitling, C., Rufener, K. S., Heinze, H.-J., Hinrichs, H., Krauel, K., & Sweeney-Reed, C. M. (2018). Modulation of Working Memory Using Transcranial Electrical Stimulation: A Direct Comparison Between TACS and TDCS. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00761
Salamanca-Giron, R. F., Raffin, E., Zandvliet, S. B., Seeber, M., Michel, C. M., Sauseng, P., Huxlin, K. R., & Hummel, F. C. (2020). Bifocal tACS Enhances Visual Motion Discrimination by Modulating Phase Amplitude Coupling Between V1 and V5 Regions. *BioRxiv*, 2020.11.16.382267.

https://doi.org/10.1101/2020.11.16.382267
Santarnecchi, E., Muller, T., Rossi, S., Sarkar, A., Polizzotto, N. R., Rossi, A., & Cohen Kadosh, R. (2016). Individual differences and specificity of prefrontal gamma frequency-tACS on fluid intelligence capabilities. *Cortex*, *75*, 33–43. https://doi.org/10.1016/j.cortex.2015.11.003
Santarnecchi, E., Polizzotto, N. R., Godone, M., Giovannelli, F., Feurra, M., Matzen, L., Rossi, A., & Rossi, S. (2013). Frequency-Dependent Enhancement of Fluid Intelligence Induced by Transcranial Oscillatory Potentials. *Current Biology*, *23*(15), 1449–1453. https://doi.org/10.1016/j.cub.2013.06.022
Saturnino, G. B., Madsen, K. H., Siebner, H. R., & Thielscher, A. (2017). How to target inter-regional phase synchronization with dual-site Transcranial Alternating Current Stimulation. *NeuroImage*, *163*, 68–80. https://doi.org/10.1016/j.neuroimage.2017.09.024
Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: A possible function of EEG theta oscillations. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1015–1022. https://doi.org/10.1016/j.neubiorev.2009.12.006
Sauseng, P., Klimesch, W., Schabus, M., & Doppelmayr, M. (2005). Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *57*(2), 97–103. https://doi.org/10.1016/j.ijpsycho.2005.03.018
Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Shachar, M. S. (2021). *afex: Analysis of Factorial Experiments*. https://CRAN.R-project.org/package=afex
Strüber, D., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). Antiphasic 40 Hz Oscillatory Current Stimulation Affects Bistable Motion Perception. *Brain Topography*, *27*(1), 158–171. https://doi.org/10.1007/s10548-013-0294-x
Thut, G., Bergmann, T. O., Fröhlich, F., Soekadar, S. R., Brittain, J. S., Valero-Cabré, A., Sack, A. T., Miniussi, C., Antal, A., Siebner, H. R., Ziemann, U., & Herrmann, C. S. (2017). Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. *Clinical Neurophysiology*, *128*(5), 843–857. https://doi.org/10.1016/j.clinph.2017.01.003
Tseng, P., Chang, Y.-T., Chang, C.-F., Liang, W.-K., & Juan, C.-H. (2016). The critical role of phase difference in gamma oscillation within the temporoparietal network for binding visual working memory. *Scientific Reports*, *6*(1), 32138. https://doi.org/10.1038/srep32138
Tseng, P., Iu, K. C., & Juan, C. H. (2018). The critical role of phase difference in theta oscillation between bilateral parietal cortices for visuospatial working memory. *Scientific Reports*, *8*(1), 1–9. https://doi.org/10.1038/s41598-017-18449-w
Turi, Z., Mittner, M., Lehr, A., Bürger, H., Antal, A., & Paulus, W. (2020). θ-γ Cross-Frequency Transcranial Alternating Current Stimulation over the Trough Impairs Cognitive Control. *ENeuro*, *7*(5). https://doi.org/10.1523/ENEURO.0126-20.2020
van Schouwenburg, M. R., Sörensen, L. K. A., de Klerk, R., Reteig, L. C., & Slagter, H. A. (2018). No Differential Effects of Two Different Alpha-Band Electrical Stimulation Protocols Over Fronto-Parietal Regions on Spatial Attention. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00433
van Schouwenburg, M. R., Zanto, T. P., & Gazzaley, A. (2017). Spatial Attention and the Effects of Frontoparietal Alpha Band Stimulation. *Frontiers in Human Neuroscience*, *10*. https://doi.org/10.3389/fnhum.2016.00658
Violante, I. R., Li, L. M., Carmichael, D. W., Lorenz, R., Leech, R., Hampshire, A., Rothwell, J. C., & Sharp, D. J. (2017). Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. *ELife*, *6*, 1–22. https://doi.org/10.7554/eLife.22001
Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. https://ggplot2.tidyverse.org
Yaple, Z., & Vakhrushev, R. (2018). Modulation of the frontal-parietal network by low intensity anti-phase 20 Hz transcranial electrical stimulation boosts performance in the attentional blink task. *International Journal of Psychophysiology*, *127*, 11–16. https://doi.org/10.1016/j.ijpsycho.2018.02.014

Chapter 5

Interim discussion: increasing reproducibility in TBS research

Transcranial brain stimulation (TBS) techniques have gained increasing popularity for modulating or probing brain activity and in turn modulating perceptual, motor, and cognitive functions (Veniero et al., 2019). However, the literature on their efficacy to produce physiological and behavioral changes has been criticized to yield inconclusive results. For example, several meta-analyses on the effects of tDCS found small or even no effects on working memory performance (Hill et al., 2016; Horvath et al., 2015; Mancuso et al., 2016). In addition to small effects, another problem lies in the difficulty to replicate former findings. We also demonstrated this in Project III by our own attempt to reproduce effects of phase-dependent fronto-parietal theta tACS on working memory performance, which we, and others, only partly been able to reproduce (Alekseichuk et al., 2017; Kleinert et al., 2017; Polanía et al., 2012; Violante et al., 2017). This does not necessarily suggest that TBS cannot produce reliable physiological and behavioral changes, but is an example for the general replication crisis in the psychological sciences and the neurosciences (Collaboration, 2012, 2015). It highlights that efforts to work towards open, robust and reproducible science (Munafò et al., 2017) are also highly relevant for TBS research.

Potential threats for reproducibility are, for example, low statistical power, poor quality control, forms of p-hacking (e.g. unplanned optional stopping rules resulting in inflated Type I error rates), hypothesizing after the results are known (HARKing), publications bias, or a lack of data sharing (Munafò et al., 2017). This is acknowledged by various recent initiatives in the TBS community aiming to work towards the goal of increasing reproducibility in the field. They range from research articles providing recommendations and best practices for administration and analysis of TBS projects (Bikson et al., 2018; Westwood, 2020), over special issues publishing and thereby increasing the visibility of TBS studies with non-significant effects and failed replications (Thut et al., 2018), to large collaborations for analyzing the interindividual variability of TBS effects (Corp et al., 2020) or the variability of TBS effects across different labs (The tACS challenge, in preparation).

For obtaining robust and reproducible TBS effects, it has been demonstrated that sufficient statistical power is crucial (Minarik et al., 2016). However, in general, low statistical power due to small sample sizes, small effects, or a combination of these two, is prevalent in neuroscience (Button et al., 2013; Nord et al., 2017; Poldrack et al., 2017). This results both in a low chance to discover effects that are actually true, as well as in overestimating the magnitude of an effect in the low-powered study. In practice, this problem of low statistical power is accompanied by the general publication bias, favouring significant effects for publication. For the field as a whole, basing a-priori power-analyses on such selectively published effects results in an overestimation of effects, which are

actually smaller than reported in the population. This opens the door for subsequent low-powered studies and overall low reproducibility. Critically evaluating significant results, especially when they come from small sample sizes, and aiming for larger sample sizes in future studies is certainly relevant. However, rather than simply increasing sample size categorically, it is more sensible to try improving the effect size estimation (see e.g. a recent editorial in of The Journal of Neuroscience, 2020).

One way to sustainably increasing replicability could be to counteract publication bias and thereby improve estimation of effect sizes. Efforts towards this goal already exist in the TBS community and beyond. For example, non-significant findings and failed replication studies can be published on preprint-servers, and an increasing number of journals offer publishing formats that welcome studies reporting non-significant effects, or offer publishing pre-registered reports. Once publicly available, insights about ineffective TBS duration, intensity, frequency or montage, which would have been otherwise unpublished, could therefore guide the choice of stimulation parameters future research.

However, counteracting publication bias is not the only important aspect to keep in mind. In order for reported results to be useful for planning future studies, it is essential to differentiate between cases where a particular application of TBS had no effect or whether results were merely inconclusive. Yet, through conventional significance testing, comparing a research hypothesis assuming a certain population effect (H1) against the null hypothesis assuming a non-effect in the population (H0), it cannot be determined whether a specific TBS protocol had no effect. While it is possible to provide evidence against the H0 when the test returns a significant result, a non-significant results does not provide evidence for the H0 but it simply cannot reject it.

Luckily, alternative methods for evaluating evidence both for the research hypothesis and for the null hypothesis exist. Bayes factors tests are a powerful tool that allow to conclude whether the data do or do not favor the null hypothesis over the alternative hypothesis (e.g. Dienes, 2011; Kruschke, 2011; Rouder et al., 2009). Therefore, Bayes factors have been proposed to be useful to get the most out of non-significant results (see also Dienes, 2014).

In order to make our contribution to increasing reproducibility and robustness in TBS research, we aimed to demonstrate the usefulness of Bayes factor analyses over conventional significance tests to differentiate between cases where a particular application of TBS had no effect or whether results were merely inconclusive. In Project IV, we conducted a series of simulated TBS experiments with differing sample size and effect size to investigated under which circumstances non-significant findings from conventional significance testing remain inconclusive. Importantly, we demonstrate that reporting Bayesian statistics, but not conventional tests, can help answering whether there is good enough evidence for the null hypothesis in TBS data. We therefore recommend that non-significant effects from TBS studies should be further analysed with Bayes Factors, especially in the case of small samples.

Chapter 6

Project IV: Bayes factors to support non-effects in TBS research

The current chapter comprises a research article that has been published in Frontiers in Psychology in 2018, entitled "Why you should report Bayes factors in your transcranial brain stimulation studies" (Biel & Friedrich, 2018).

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Contributions:

Anna Lena Biel: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, Project administration;

Elisabeth Friedrich: Conceptualization, Methodology, Validation, Writing – Review & Editing, Supervision.

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OPINION
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Why You Should Report Bayes Factors in Your Transcranial Brain Stimulation Studies

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In this commentary, we argue that it is essential to determine whether a non-significant sample effect really indicates that a particular application of transcranial brain stimulation (TBS) had no effect. We point out that non-significant results do not necessarily support a non-effect and show why reporting Bayesian statistics can help answering whether there is good enough evidence for the null hypothesis in your TBS data.

TBS aims to modulate or probe neural activity. However, reports on physiological and behavioral changes often failed to show conclusive results (Hill et al., 2016; Mancuso et al., 2016). There are many possible reasons for such inconsistencies. Recently it has been demonstrated that sufficiently large samples are essential in designing TBS experiments (Minarik et al., 2016). However, a-priori power-analyses are often skewed due to publication bias, where large or statistically significant effects get published more often. Therefore, the actual efficacy of TBS might be overestimated. While it is possible to adjust overestimated effect size for publication bias, insights about ineffective TBS duration, intensity, frequency or montage cannot be taken into account when unpublished. Thus, initiatives such as this Research Topic should encourage researchers to publish their non-significant outcomes in order to make relevant contributions to the field as well.

However, conventional significance testing cannot determine whether non-significant outcomes really indicate that a TBS protocol had no effect. In conventional significance testing, a research hypothesis assuming a certain population effect (H1), is compared against the null hypothesis assuming a non-effect in the population (H0). The probability for getting an observed sample effect is evaluated based on the significance level. If the outcome is below-threshold, one can provide evidence *against* the null hypothesis and accept the research hypothesis – whereas it is never possible to state evidence *for* the null hypothesis.

Bayes factors (BFs) are a powerful tool for evaluating evidence both for the research hypothesis and for the null hypothesis (e.g., Rouder et al., 2009; Dienes, 2011; Kruschke, 2011). In case of a conventional non-significant test, the observed sample effect either truly supports the null hypothesis or was too weak to yield evidence against it. Bayes factor tests, however, are highly useful to inform whether the data do or do not favor the null hypothesis over the alternative. We demonstrate this by simulating a series of fictional TBS experiments.

We assumed that N participants performed a task under two conditions, namely sham and real TBS. Task performance in these TBS conditions would differ by a true population effect dz. This difference in task performance was simulated by selecting N observations from a normal distribution with a mean of dz and a standard deviation of 1. We repeated this fictional experiment 1000 times. Each time, we tested for the effect of condition by comparing the research hypothesis assuming an increase of task performance during real TBS relative to sham TBS conditions (H1: $dz > 0$), against the null hypothesis assuming a non-effect (H0: $dz = 0$). First, we calculated a one-sided one-sample t-test, which is conventionally considered as significant (i.e., H0 is rejected) if p-values fall below 0.05. Next, we calculated a corresponding Bayes factor test which yields a

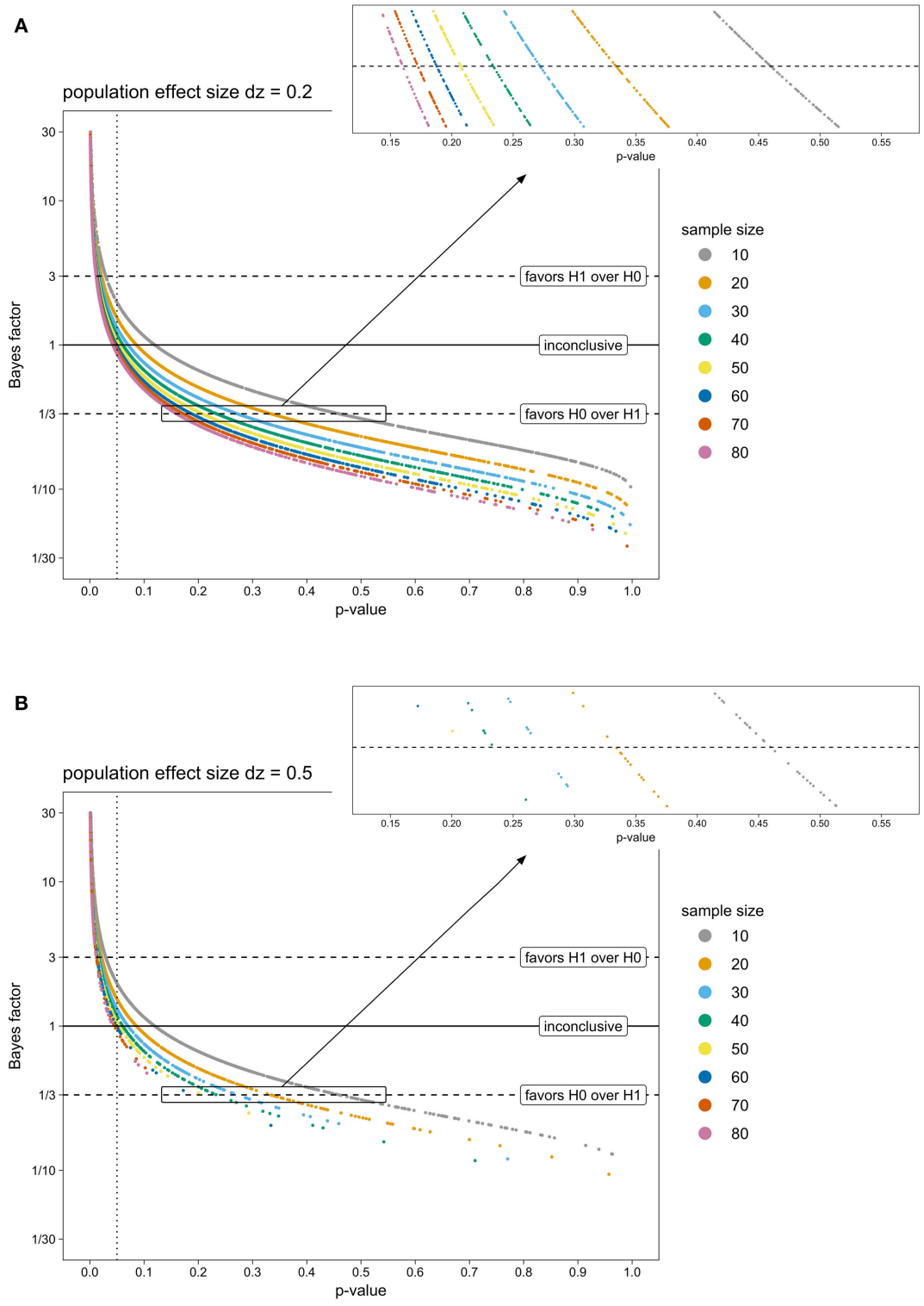

FIGURE 1 | *P*-values from a one-sided one-sample *t*-test and corresponding Bayes factors of simulated TBS experiments, for eight sample sizes (colored points) and two exemplary population effect sizes (**A**: $dz = 0.2$; **B**: $dz = 0.5$). *T*-tests with a *p*-value below 0.05 (dotted line) are conventionally considered as significant and H0 is rejected. BFs above 3 (upper dashed line) indicate evidence for H1 being more likely than H0. BFs below 0.33 (lower dashed line) yield evidence for H0 being favored over H1. BFs between 0.33 and 3 (area between the two dashed lines) are considered as inconclusive, or not more than anecdotal evidence for one of the hypotheses. *Note. BF, Bayes factor; H0, null hypothesis; H1, research hypothesis; TBS, Transcranial Brain Stimulation*.

BF quantifying how well H1 predicts the empirical data relative to H0 (BF_{10}). Here, BFs above 1 indicate evidence for H1 over H0, whereas BFs below 1 suggest the exact opposite. By convention (Jeffreys, 1961; Lee and Wagenmakers, 2014), the strength of evidence for one hypothesis compared to its competing hypothesis is regarded as noteworthy if BFs are above 3 or below 0.33. Thus, BFs between 0.33 and 3 are considered as inconclusive, or only anecdotal evidence for any hypothesis. We conducted this simulation for eight samples differing in sample size ($N = 10$, 20, 30, 40, 50, 60, 70, or 80) and six TBS protocols differing in population effect size compared to sham ($dz = 0$, 0.1, 0.2, 0.3, 0.4, or 0.5). The simulation was run using R (version 3.2.4; R Core Team, 2016) where BFs were computed using default priors by the R package BayesFactor (version 0.9.12-2; Morey and Rouder, 2015), modeling H1 as a Cauchy distribution scaled in standardized effect sizes with scale factor = 0.7 Cohen's *dz* units.

Figure 1 depicts *p*-values and Bayes factors obtained from two exemplary population effect sizes (**Figure 1A**: $dz = 0.2$, **Figure 1B**: $dz = 0.5$). Unsurprisingly, with increasing sample size, more *t*-tests were significant ($p > 0.05$) and more corresponding Bayes factors indicated at least moderate evidence for H0 over H1 ($BF < 0.33$). Similarly, fewer *t*-tests were non-significant and fewer Bayes factors favored the H0 with increasing population effect size.

Interestingly, critical *p*-values, where corresponding BFs fell below 0.33 (i.e., indicating at least moderate evidence for H0 over H1), decreased when sample size increased. For example, for samples of 10 participants, *p*-values as high as 0.45 were associated with BFs being inconclusive ($0.33 > BF > 1$). Only *p*-values beyond 0.45 were indicative for at least moderate evidence supporting H0 ($BF < 0.33$). In contrast, for samples of 80 participants, tests with *p*-values around 0.15 or more could be considered to favor H0 according to BFs. Thus, when small samples were tested, non-significant *p*-values had to be much larger for corresponding BFs to indicate at least moderate evidence for H0 than in the case of larger samples.

This relation between *p*-values, BFs and sample size stayed the same across population effect sizes: Population effect size only influenced how many *t*-tests were non-significant or BF-tests favored the H0 overall, but did not influence the range of non-significant *p*-values where corresponding BFs remained inconclusive.

In line with these described observations from simulated TBS experiments, similar associations between *p*-values and BFs have been established for other statistical tests and other models of H1 (e.g., Dienes, 2014, 2015). Taken together, they illustrate the following: First, non-significant tests with a high *p*-value do not automatically prove the null hypothesis to be true, but might indicate inconclusive evidence. Second, sample size heavily influences the threshold of critical *p*-values where Bayes factors indicate that the null hypothesis is more likely than the research hypothesis.

Thus, we conclude that any non-significant findings from conventional significance testing should be supported with evidence from Bayes Factor analyses. This is especially essential in the case of small samples. Of course, Bayesian alternatives to conventional hypothesis testing are not restricted to this case but may be advantageous in many situations. Without entering the debate whether inferential decisions should be based on a purely Bayesian approach (e.g., Dienes and Mclatchie, 2018), we argue that Bayes factor tests may be highly useful for the TBS community by distinguishing between evidence for an (un-)successful TBS protocol and inconclusive evidence. The approach of using Bayes factors to get the most out of non-significant results (Dienes, 2014) is therefore most attractive for the field: Showing the absence of a particular effect of TBS by means of Bayes factor tests may impact on the choice of stimulation parameters more positively than merely reporting conventional non-significant tests.

PRACTICAL RECOMMENDATIONS

- The absence of a particular effect of TBS compared to sham TBS can be demonstrated by reporting Bayes factors favoring H0 (there is no condition difference between sham and real TBS) over H1.
- Similarly, the specificity of an observed TBS effect can be shown by reporting Bayes factors favoring H0 (the control condition does not differ from zero) over H1.
- For non-significant *t*-tests, corresponding Bayes factors for *p*-values as high as 0.45 may indicate inconclusive evidence for either H0 or H1 when testing small samples around 10 subjects.
- For other standard statistical tests (*t*-tests, ANOVAs, regressions, etc.), there is easy-to use open-source software (JASP Team, 2018) available, providing both conventional tests as well as their Bayesian alternatives.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

Both authors were involved in the conceptualization of the topic. AB conducted the simulation, and prepared and wrote the manuscript. EF edited the manuscript.

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REFERENCES

Dienes, Z. (2011). Bayesian versus orthodox statistics: Which side are you on? *Perspect. Psychol. Sci.* 6, 274–290. doi: 10.1177/1745691611406920

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Front. Psychol.* 5:781. doi: 10.3389/fpsyg.2014.00781

Dienes, Z. (2015). "How Bayesian statistics are needed to determine whether mental states are unconscious," in *Behavioural Methods in Consciousness Research,* ed M. Overgaard (New York, NY: Oxford University Press), 199–220.

Dienes, Z., and Mclatchie, N. (2018). Four reasons to prefer Bayesian analyses over significance testing. *Psychon. Bull. Rev.* 25, 207–218. doi: 10.3758/s13423-017-1266-z

Hill, A. T., Fitzgerald, P. B., and Hoy, K. E. (2016). Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. *Brain Stimul.* 9, 197–208. doi: 10.1016/j.brs,.2015.10.006

JASP Team (2018). *JASP (Version 0.8.5)[Computer software]*. JASP Team.

Jeffreys, H. (1961). *Theory of Probability, 3rd Edn*. Oxford, UK: Oxford University Press.

Kruschke, J. K. (2011). Bayesian assessment of null values via parameter estimation and model comparison. *Perspect. Psychol. Sci.* 6, 299–312. doi: 10.1177/1745691611406925

Lee, M. D., and Wagenmakers, E. J. (2014). *Bayesian Cognitive Modeling: A Practical Course*. Cambridge: Cambridge University Press.

Mancuso, L. E., Ilieva, I. P., Hamilton, R. H., and Farah, M. J. (2016). Does transcranial direct current stimulation improve healthy working memory? A meta-analytic review. *J. Cogn. Neurosci.* 7, 1–27. doi: 10.1162/jocn_a_00956

Minarik, T., Berger, B., Althaus, L., Bader, V., Biebl, B., Brotzeller, F., et al. Sauseng, P. (2016). The importance of sample size for reproducibility of tDCS effects. *Front. Hum. Neurosci.* 10:453. doi: 10.3389/fnhum.2016.00453

Morey, R. D., and Rouder, J. N. (2015). *{BAYESFACTOR}: Computation of Bayes Factors for Common Designs*. R package version 0.9.12-2. Available online at: https://cran.r-project.org/web/packages/BayesFactor/

R Core Team (2016). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. Available online at: http://www.R-project.org/

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., and Iverson, G. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychon. Bull. Rev.* 16, 225–237. doi: 10.3758/PBR.16.2.225

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Chapter 7

General discussion

The goal of this thesis was to investigate brain oscillatory signatures supporting information transfer within or between global and local neural networks involved in human working memory processes. The first section of the General discussion summarizes and interprets the main findings from Project I, an EEG study comparing differences in transient posterior theta-gamma phase synchronization during visual search for one or for multiple mental templates, along with a critical discussion of limitations and implications. The second section introduces the key findings and resulting insights from Project II, a pilot EEG-TMS study on the frontal midline theta phase-dependent effects of TMS over parietal cortex for working memory performance, and discusses implications for follow-up studies. The third section summarizes and interprets the main findings from Project III, a replication study using multisite tACS for either synchronizing or desynchronizing a fronto-parietal theta network in order to modulate verbal working memory performance. Moreover, this section provides an outlook on the reproducibility of effects from TBS in general. In the fourth section, the discussion on reproducibility in TBS research is extended, along with outlining the insights from Project IV, demonstrating the additional value of Bayes factor tests over conventional significance tests based on a series of simulated TBS experiments. This section also gives an outlook on general challenges for reproducible TBS research and discusses solutions with a focus on best practices for statistical data analysis. The General discussion concludes by summarizing the fours projects' achievements in the final section.

7.1 General discussion of Project I

7.1.1 Aims and key results

In Project I, we investigated local cross-frequency phase synchronization (CFS) in the posterior parietal cortex, based on evidence that such CFS between theta and gamma phase is involved when matching mental templates from working memory with visual input (Holz et al., 2010; Sauseng et al., 2008). To investigate how this is affected by the number of activated working memory templates that could be matched, we designed a novel visual search paradigm with complex abstract stimuli where we compared conditions in which participants had to keep either a single or multiple targets' properties in mind for finding the template-matching stimulus. In visual search conditions where a single mental template could be matched, we found a transient theta-gamma CFS around 150ms after search display presentation, in right hemispheric parietal cortex contralateral to target presentation. We did not find this effect in conditions were one out of multiple mental templates was successfully matched to the target.

7.1.2 Interpretation of CFS results

This suggests that neuronal networks operating at theta and gamma frequency became more synchronized in phase when a single mental template could be matched to visual input in comparison to one out of multiple mental templates. On the one hand, the early time window showing this effect falls into the stage of visual search in which information is being selected (see e.g. Eimer, 2014; Ort & Olivers, 2020). It may correspond with the step of matching between stimulus-related information and memory contents (Herrmann et al., 2010; Herrmann et al., 2004) since it precisely replicates time windows from previous studies (Holz et al., 2010; Sauseng et al., 2008). This is consistent with proposals that explain such a transient theta-gamma CFS in posterior areas as a neural correlate of matching between visual input and a top-down controlled mental template (Sauseng et al., 2015; Sauseng et al., 2010). In this framework, it is assumed that an early post-stimulus phase resetting of posterior theta band oscillations allows for a transient CFS with high frequency activity in the gamma range, following after an overall increase of theta phase-coupling in the fronto-parietal network during anticipation of a specified visual target, which was observed in previous EEG studies (Sauseng et al., 2010; Sauseng et al., 2008). Thus, the locally observed transient increase in theta-gamma CFS in posterior areas could reflect information transfer between a global fronto-parietal theta network and a local network operating in the gamma frequency range. On the neuronal level, CFS may enable consistent spike-time relationships between neuronal assemblies oscillating in different frequencies (Palva & Palva, 2018; Sauseng et al., 2010; Sauseng & Klimesch, 2008). Support for this comes from a growing body of research suggesting that frontal low-frequency oscillations play a critical role in top-down control during working memory tasks through coherence and cross-frequency interaction in fronto-parietal networks (for recent reviews, see de Vries et al., 2020; Karakaş, 2020; Klink et al., 2020; Palva & Palva, 2018).

On the other hand, this suggests that, while a single mental template allows for precise memory matching, limitations in this matching process occur during multiple template search. Sequential attentional templates, i.e. the assumption that multiple mental templates need to be refreshed in a sequential manner and that only one of them can interact with sensory input (Lisman & Idiart, 1995; Olivers et al., 2011; van Vugt et al., 2014), could possibly explain these limits. Alternative explanations like differences in the source of EEG activity or larger neural noise when several templates have to be processed, which may have influenced that cross-frequency phase-relations were overall more variable in the triple template condition, cannot be excluded. But since the assumption that templates are being matched sequentially makes direct predictions about expected switch costs between trials with a different or the same target as the preceding trial, future studies may support these predictions by using task paradigms that combine multiple template search with the study of target switch costs.

Conversely, the CFS patterns observed from left-hemispheric posterior regions differ markedly between the current visual search task (the left-hemispheric ROI does not show the same effect as the right-hemispheric ROI), and previous studies (Holz et al., 2010;

Sauseng et al., 2008) using a cued visual attention task (left and right show a similar effect) or a visual delayed-match-to-sample task (left shows the reversed effect). This makes it difficult to interpret all these left-hemispheric CFS patterns. It rather suggests that the CFS patterns of left-hemispheric posterior regions may depend more on the specific task paradigm at hand, whereas the clearly right-lateralized CFS effect in our visual search paradigm is corroborated by evidence that right-hemispheric brain areas are primarily relevant for visual search (Nobre et al., 2003; Ten Brink et al., 2016; Vallesi, 2014).

7.1.3 Limitations, implications and outlook

For future studies, it would be relevant to further investigate the observed limits in memory matching during multiple template search. The assumption that templates are being matched sequentially could be investigated by measuring response times and CFS during multiple template search in a modified task paradigm which allows to contrast switch and stay trials, for example by adapting the task paradigms employed by de Vries et al. (2018), or van Driel et al. (2018). It would also be useful to address a limiting factor of the current task, namely that due to the training phase before the start of our task, participants may have stored templates of the unknown abstract targets in long-term memory. Even though a long-term memory component cannot be excluded, effortful visual search for the kind of complex targets we used in this study, should likely have required an active attentional template in working memory rather than being stored passively in long-term memory (Gunseli et al., 2014; Ruchkin et al., 2003). And whereas a transient posterior theta-gamma CFS, such as the one we observed, is supposed to reflect the matching of a given visual target with a mental template from working memory (Sauseng et al., 2015; Sauseng et al., 2010), in contrast, a matching with a mental template from long-term memory may be explained by an evoked gamma response alone (Herrmann et al., 2010; Herrmann et al., 2004). Future studies could differentiate between both cases by using a task paradigm with varying levels of short-term or long-term memory involvement, where the prediction would be that neural correlates should change accordingly. This could, for example, be manipulated using known, simple stimuli such as shapes or colors that must be held in working memory (e.g. by explicitly changing targets on a trial-by trial basis) or must be retrieved from long-term memory (e.g. by defining targets through familiarity).

Given the converging evidence from the current and previous studies arguing for transient posterior theta-gamma phase synchronization as a neural correlate of matching bottom-up sensory information with top-down controlled mental templates, it would also be interesting to investigate the temporal dynamics of such matching processes during the acquisition and consolidation phase of a mental template. When studying more naturalistic contexts of template to input matching where, for example, templates are acquired via learning, it would be expected that with more learning, a more exact mental template can be established, and that stronger CFS could emerge. This could be investigated using a temporal sequence learning paradigm (Crivelli-Decker et al., 2018; Olson & Chun, 2001). However, single-trial analyses for observing a gradual increase of CFS over

time could not use the CFS index used for assessing the consistency of phase across trials, but would need to use single-trial phase difference, which may require a large number of trials per subject.

7.2 General discussion of Project II

7.2.1 Aims and key results

The kind of transient CFS observed in Project I may be rather suited to enable brief periods of information exchange between long-range and local neural networks involved in matching processes between bottom-up sensory input with top-down expectations (Biel et al., 2021). Other, more sustained, oscillatory dynamics may reflect mechanisms of active top-down control, where the prefrontal cortex coordinates remote brain areas. This could be achieved by rhythmically gating accesses to prefrontal cognitive resources through brief but ongoing windows of opportunity: Our previous study, suggested that posterior brain areas dynamically access prefrontal cognitive resources through a behaviourally relevant mechanism where bursts of posterior gamma activity are nested into different phases of the frontal-midline theta cycle depending on task difficulty (Berger et al., 2019). Next, in Project II we varied the level of priority given to information in working memory (i.e., prioritizing or non-prioritizing information for retention) and delivered TMS over parietal cortey for disrupting local brain activity during the retention interval of a visuospatial delayed match to sample task. We examined the impact on task performance depending on when (relative to the frontal midline theta cycle) and where (contralateral or ipsilateral to the prioritized hemifield) the posterior TMS pulse was delivered. We found that right-hemispheric posterior TMS resulted in decreased task performance for the prioritized left hemifield (contralateral to the stimulation site) when TMS fell into the frontal-midline theta cycle's excitatory phase (i.e. near the trough) relative to the other phases. Importabtly, tis was not found when the right hemifield (ipsilateral to the stimulation site) was prioritized, as predicted by the contralateral organization of the visual system. Yet, the overall interaction effect was relatively small, as also corroborated by a Bayes Factor indicating rather inconclusive evidence. Our results from left-hemispheric posterior TMS showed no overall significant interaction effect and the Bayes Factor analysis substantially favoured the null hypothesis assuming no effect. Due to the small sample size (n=10), we interpret the results as preliminary evidence. As such, the current pilot study will be useful for planning and adequately powering future experiments.

7.2.2 Interpretation of preliminary results

Our results from the right-hemispheric TMS condition corroborate previous evidence which demonstrated that right temporo-parietal TMS delivered near the trough of frontal-midline theta disrupted performance in a similarly difficult visual working memory task (Berger et al., 2019). This suggest that TMS over right posterior cortex selectively

disturbs neural processing which is relevant for successful task performance when applied during the trough of frontal-midline theta. The trough of slow oscillatory activity in the theta to alpha range is known to be associated with the highest spiking rates, as shown by intracranial recordings of local field potentials and spiking rates from nun-human primates, both in somatosensory and prefrontal cortices (Haegens et al., 2011; Siegel et al., 2009). Overall, converging evidence demonstrates that the theta cycle influences and structures neuronal spiking and fast oscillatory activity (Canolty et al., 2006; Fell & Axmacher, 2011; O'Keefe & Recce, 1993; Sirota et al., 2008), where the phase of slow oscillatory activity is thought to provide cyclic excitability windows that influence local cortical activity (Canolty & Knight, 2010; Jensen et al., 2014).

Conversely, left-hemispheric posterior TMS did not show a similar pattern of results. This is contrary to what could be expected. Given that visuospatial working memory and attentional processing have been shown to predominantly involve right-hemispheric posterior-parietal areas (Awh & Jonides, 2001; Corbetta et al., 2002; Driver & Vuilleumier, 2001; Kastner & Ungerleider, 2000), it might be that left-hemispheric parietal areas are less strongly involved which might, in turn, influence associated neural correlates. However, whether these areas are therefore not coupled with prefrontal areas in the same way as the presumably more actively involved right-hemispheric parietal areas, would have to be studied by recording EEG without TMS while participants perform the current task.

In such an EEG study, based on the current pilot data and combined with the existing EEG evidence from previous work (Berger et al., 2019; Griesmayr et al., 2010; Pinal et al., 2015), we would expect that right-hemispheric gamma bursts over task-active parietal brain areas are nested close to the trough of the frontal midline theta cycle when contralateral information is prioritized in working memory, whereas for left-hemispheric posterior gamma activity, we would not expected that to be the case. Importantly, due to the low number of subjects in the present data, these interpretations and predictions must be understood as based on preliminary results.

7.2.3 Recommendations based on this pilot study

Yet, the current study is well suited as a pilot study to inform subsequent research. With the estimated effect sizes from the fitted linear mixed effects models, we provide an ideal basis for a Monte Carlo simulation-based power analysis to plan the required sample size for a follow-up study (Green & MacLeod, 2016). While the generated estimates for the magnitude of the effects from this first exploratory experiment with a small sample size could be inflated or might have wide confidence intervals (Maxwell et al., 2008), by following this exploration-then-estimation procedure (as also suggested in a recent editorial of of The Journal of Neuroscience, 2020), estimates in a second estimation experiment can be expected to provide more precise estimates of these effects. Concerning the TMS protocol, we note that instead of a single TMS pulse, a TMS triple pulse, which has recently been proven to be effective (Berger et al., 2019) and could be applied during the first half of the delay period (Griesmayr et al., 2010) could be more potent in affecting the interaction between posterior and prefrontal regions. For this, it might also be ben-

eficial to further increase overall task difficulty by reducing the contrast of the stimuli, as in the current study, the overall task performance in valdid trials was relatively high. In addition, future study protocols should ensure that the cued hemifield gets prioritized over the un-cued hemifield, but not ignored. Training participants explicitly to reach an above chance level of performance in both valid and invalid trials would therefore be recommended.

7.2.4 Implications and outlook

Generally, the concept of a rhythmic gating based on slow oscillatory phase is supported by a growing number of studies providing correlational as well as causal evidence. In task-relevant sensory or motor areas, for example, it has been shown that working memory contents are locally represented during the preferred phase of slow oscillatory activity in the theta to alpha range (Fuentemilla et al., 2010; Siegel et al., 2009; ten Oever et al., 2020). Similar effects have been reported in visual perception, where attentional sampling has been found to occur at theta frequency in a phase-dependent manner in visual areas (Busch et al., 2009; Hanslmayr et al., 2013; VanRullen, 2016). And phase-dependent effects of TMS during preferred phases of slow oscillatory activity have recently also been demonstrated in the motor domain (Hussain et al., 2021). But especially when a high level of executive control is required, rhythmic gating would rather be expected to rely on prefrontal slow oscillatory phase, given the central role of slow oscillatory activity in the prefrontal cortex for controlling the allocation of cognitive resources for remote, task-relevant brain areas (Cavanagh & Frank, 2014; Helfrich & Knight, 2016; Sauseng et al., 2010; Sauseng & Klimesch, 2008). Recent evidence strongly suggests that for effectively gating access to prefrontal resources, frontal midline theta phase provides rhythmic windows of opportunity, whereby relevant long-range communication can take place during the preferred phase (i.e. the trough), whereas during other non-preferred phases, access to prefrontal resources is denied (Berger et al., 2019; Pinal et al., 2015). Future TMS-EEG studies may therefore probe this mechanism of a rhythmic gating based on prefrontal slow oscillatory phase in different perceptual, cognitive or motor domains for further establishing its behavioural relevance. This could be achieved, for example, by contrasting trials in which either visuospatial information or object information has to be prioritized. As these two types of information are known to be processed in posterior parietal areas (i.e. along the dorsal visual stream) or in temporal brain regions (i.e. along the ventral visual stream), respectively, such paradigms could investigate whether dorsal and ventral stream areas are actively (de-)coupled to frontal midline theta depending on which information is currently prioritized.

7.3 General discussion of Project III

7.3.1 Aims and key results

In Project III, we used multisite tACS at theta frequency to either synchronize or desynchronize a fronto-parietal working memory network in order to modulate verbal working memory performance, as reported by Polanía et al. (2012). We carefully reproduced their behavioural paradigm and tACS protocols: in our pre-registered study, we delivered online theta tACS through two electrodes over left frontal and parietal cortex, either in-phase (with a single shared central return electrode) for synchronous stimulation, or anti-phase for asynchronous stimulation, which we compared to a placebo condition. We employed an additional in-phase focal tACS condition (with five close-by return electrodes) for more localized stimulation of frontal and parietal cortex as suggested by electrophysiological modelling (Saturnino et al., 2017) to compensate for potential confounds related to electrode montage and electric field strength. While we were unable to replicate a 'synchronization- desynchronization' effect by fronto-parietal theta tACS on response times in the same delayed letter recognition task as reported by Polanía et al. (2012), we found that in a more demanding 3-back task, in-phase and in-phase focal theta tACS improved discriminability substantially compared to placebo stimulation.

7.3.2 Interpretation of non-reproduced findings

Overall, these results line up with previous studies, where a 'synchronization- desynchronization' effect of fronto-parietal theta tACS has not been or only partly been reproduced in similar working memory paradigms (Alekseichuk et al., 2017; Kleinert et al., 2017; Röhner et al., 2018; Violante et al., 2017). These relatively inconsistent results are certainly challenging and also prevail in other domains, such as spatial attention (van Schouwenburg et al., 2018; van Schouwenburg et al., 2017). As outlined in Chapter 4 in the interim discussion, a key factor which influences the reproducibility of TBS findings is the sample size, which, along with the true size of an effect, is tightly linked to the probability to detect a true population effect in an experiment (Minarik et al., 2016). Low statistical power due to small sample size, small effect sizes, or both is problematic in neuroscience as a whole (Button et al., 2013; Nord et al., 2017; Poldrack et al., 2017) and publication bias is prevalent in general. When non-significant results remain unpublished or are not publicly available due to selective reporting of only effect sizes from significant tests, the available estimates are likely to be inflated and a sensible estimation of the expected effect size is not trivial. For example, while we based the power analysis in our pre-registered project on the experiments from three studies – some of which did not report effect sizes for their non-significant effects (Kleinert et al., 2017; Violante et al., 2017) – and took a third of the average effect sizes from two experiments (Polanía et al., 2012; Violante et al., 2017), it is possible that the actual effect size is even smaller. However, we took a rather conservative effect size estimate already and even in additional analyses, we found no substantial evidence or trend for a 'synchronization- desynchronization' ef-

fect on response times in the relatively easy delayed letter recognition task, neither in a Bayes Factor analysis nor using a single-trial distributional analysis.

7.3.3 Interpretation of results from the more difficult task

But given that during the difficult 3-back task, we could indeed demonstrate an improvement of working memory performance during in-phase stimulation conditions, interestingly, our study highlights that phase-dependent tACS effects on behavioral performance might be facilitated by a higher level of cognitive demand. More specifically, it might not be high cognitive demand per se, but the right level of cognitive challenge depending on an individual's cognitive capacity. This is suggested by previous studies which could demonstrate that working memory performance improved through an exogeneous boost of neural coherence for older adults and low-performing individuals (Reinhart & Nguyen, 2019; Tseng et al., 2016; Tseng et al., 2018). This essentially indicates that phase-dependent electric brain stimulation can potentially be used for compensating cognitive decline or increasing peak performance, which is quite promising for future therapeutic applications. IT may, for example, be promising for populations showing a reduction of fronto-parietal theta coherence along with lower working memory performance, such as in patients with schizophrenia (Berger et al., 2016; Griesmayr et al., 2014).

7.3.4 Implications and outlook

Despite the discussed inconsistencies in reports aiming to establish the causal relevance of interregional theta coherence, there is correlational evidence that theta phase coherence between human frontal and parietal cortex, which we targeted using tACS in the current study, is associated with verbal working memory (Polanía et al., 2012). It has also been shown during visuospatial working memory (Sarnthein et al., 1998; Sauseng et al., 2005) or task switching (Cooper et al., 2015; Sauseng et al., 2006). Such fronto-parietal phase synchronization has also been shown to increase with increasing working memory load and to be associated with individual working memory capacity (Palva et al., 2010). Thus, correlational research stresses the importance of interregional theta coherence for efficient information transfer within long-range networks during coordinated excitable periods (Cavanagh & Frank, 2014; Fell & Axmacher, 2011; Sauseng & Klimesch, 2008). Polanía et al. (2012) were one of first that tried modulating such distributed network activity, which was instrumental in creating a new field of research using tACS with phase shifted stimulation currents to modulate long-range connectivity. Following this, studies aiming on modulating yet more complex oscillatory brain activation patterns, such as cross-frequency coupling have been published more recently (Alekseichuk et al., 2016; de Lara et al., 2018; Turi et al., 2020).

A challenge is, however, that some studies have reported findings opposing what would be predicted by the idea of externally boosting or impairing network oscillatory coherence through phase shifted tACS (Salamanca-Giron et al., 2020; Tseng et al., 2016; Yaple & Vakhrushev, 2018). Thus, a precise tuning of exact phase lag and the precise frequency for stimuation, based on individual EEG recordings, may be beneficial for future

research. In addition, given that classically used three-electrode montages have been shown to differ in the direction of current flow and overall intensity of stimulation (Alekseichuk et al., 2019), future studies may want to use stimulation setups with the potential for truly focal stimulation of that targeted cortical sites. This can be achieved through multisite electrode montages or fully closed ring montages (Bortoletto et al., 2016; Saturnino et al., 2017), as also explored in the current study, such that these multi-site electrode montages would be recommended in future experiments to avoid potential confounds due to electric field strength.

Finally, besides such methodological considerations, for sustainably increasing the replicability of TBS effect, such as those investigated in the current replication study, efforts to work towards open, robust and reproducible science (Collaboration, 2012, 2015; Munafò et al., 2017; Poldrack et al., 2017) are also highly relevant for TBS research. As discussed in Chapter 4 (Interim), counteracting publication bias through novel publishing formats could improve estimation of effect sizes and thereby increase replicability. Various recent initiatives towards that goal have been estalished in the TBS community (see next section). In addition, using the Bayesian statistical tools may help to get the most out of non-significant results (see Project IV and also Dienes, 2014), such that insights about ineffective TBS parameters could guide the choice of stimulation parameters in future research using tACS with phase shifted stimulation currents to modulate long-range connectivity.

7.4 General discussion of Project IV

7.4.1 Aims and key results

In Project IV, we aimed to show that non-significant findings from TBS studies can inform future research and should therefore be published, especially when the absence of an effect can be convincingly demonstrated. The appropriate statistical tools are essential for this, given that for differentiating between cases where a particular application of TBS had no effect or where results were merely inconclusive, this cannot be determined through conventional significance testing. Using a data simulation approach, we compared conventional significance testing to Bayes factor tests, which allow evaluating evidence both for the research hypothesis and for the null hypothesis (e.g. Dienes, 2011; Kruschke, 2011; Rouder et al., 2009). Our results from a series of 1000 simulated TBS experiments demonstrate that sample size heavily influenced the threshold of critical p-values where corresponding Bayes factors fell below 0.33, i.e., indicating at least moderate evidence that the null hypothesis is more likely than the alternative hypothesis. With larger sample sizes, these critical p-values decreased, but even then, non-significant tests with a high p-value did not automatically correspond with at least moderate evidence for the null hypothesis.

7.4.2 Interpretation of association between p-values and BFs

With data from a series of simulated TBS experiments, we demonstrate that even non-significant tests with a high p-value do not automatically prove the null hypothesis to be true, but might indicate inconclusive evidence, especially in small sample sizes. In the current study, these exact thresholds of associations between p-values and BFs are based on one-sided one-sample t-tests and their Bayesian equivalent, however, for other statistical tests and other models, similar associations between p-values and Bayes factors have been established (Dienes, 2014, 2015). Specifically, our simulations used Bayes factors evaluating evidence for or against the null hypothesis 'this particular active TBS condition does not differ from zero'. When, for example, comparing an active TBS intervention to placebo stimulation, Bayes factor tests could demonstrate whether the null hypothesis 'there is no difference between the sham TBS condition and this particular active TBS condition' is favoured over the alternative hypothesis. Or to prove the specificity of particular active TBS condition, Bayes factor tests could demonstrate whether the null hypothesis 'the control condition does not differ from zero' is favoured over the alternative hypothesis. And conveniently, Bayes Factor analyses for other tests are easy to implement using several open-source software packages providing both conventional statistical tests (t-tests, ANOVAs, regressions, etc.) as well as their Bayesian alternatives (e.g. JASP Team, 2020; Morey & Rouder, 2018; R Core Team, 2021; The jamovi project, 2021, and see the open data and materials in Project III for an example).

7.4.3 Implications

Convincingly demonstrating the absence of a particular effect of TBS may impact on the choice of stimulation parameters more positively than merely reporting conventional non-significant tests, as they provide more information about the effect. Therefore, the use of Bayes factors to support statistical inference may be beneficial both for individual studies (see Project II and III) as well as for the TBS community as a whole.

For example, Bayes factors in Project II allow stronger conclusions than the conventional model comparison, which, in an exploration-then-estimation procedure, is highly useful for planning a follow-up study. In this first exploratory experiment, Bayes factors distinguished between clear evidence for the null hypothesis for the left parietal TMS condition, whereas for the right parietal TMS condition, they indicated rather inconclusive evidence for either hypothesis, given the pilot data (Biel et al., in preparation). This conclusive evidence for a null effect of left posterior TMS can suggest to leave out left posterior TMS in a second estimation experiment, and to instead focus on characterizing the effect of right posterior TMS, given that the evidence was inconclusive and therefore did not exclude the alternative hypothesis.

Prospectively, planned Bayes Factor analyses may counteract inflated Type I error rates due to unplanned optional stopping rules (essentially one form of p-hacking) from conventional null hypothesis significance testing, since Bayes factors allow for sequential sampling plans with pre-defined optional stopping rules until a conclusion about the

presence of an effect is reached (Schönbrodt et al., 2017). Another positive effect in practice may be that studies demonstrating conclusive evidence could be easier to be published in peer-reviewed journals, thereby counteracting publication bias and increasing transparency and openness for the whole field.

7.4.4 Outlook

We recommend that Bayes factor tests should be reported alongside with conventional test, especially with non-significant ones, since gaining this information is most attractive for the TBS community. It enables actual insights about effective or ineffective TBS, intensity, frequency or montage. These can be reached trough simply complementing conventional significance tests with Bayesian statistical analyses.

Naturally, these recommendations are not limited to TBS research. The relevance of best practices and guidelines for statistical data analysis has gained increasing attention in psychological science and neuroscience, such as in research using human electrophysiological and neuroimaging data (Luck & Gaspelin, 2017; Poldrack et al., 2017). For EEG and fMRI data, the fact that these are complex and multi-dimensional entails that researchers have a lot of analytical variability when analysing EEG or fMRI data and can – but also have to – draw many decisions during pre-processing and statistical analysis of the data. The so-called "garden of forking paths" (Gelman & Loken, 2013) is among the central aspects which may pose a threat to robust and reproducible (neuro-)science, even when other biases are well controlled (Munafò et al., 2017). Recently, many initiatives have been formed to in an attempt to investigate the impact of different analysis pipelines across many analysis teams on findings from Neuroimaging data (Botvinik-Nezer et al., 2020), or EEG data (EEG Many Pipelines, in preparation).

Other threats to reproducibility have already been discussed in Chapter 4 and Project IV, such as the prevalence of low statistical power, difficulties in estimating a sensible effect size, publication bias, and p-hacking or questionable research practices in general (Munafò et al., 2017). However, many recent initiatives document a strong and growing awareness for these issues in the neurosciences. For example, collaborative efforts investigating replicability of established effects of tACS (The tACS challenge, in preparation) or of classical EEG findings (Pavlov et al., 2021) across many labs have been recently established, providing relevant contributions to characterize the status quo. And over the last years, the central role of open science practices has been stressed by a number of special issues in electrophysiological and neuroimaging research (Kappenman & Keil, 2017; Poldrack et al., 2020) as well as in neurostimulation research (Thut et al., 2018), inviting studies reporting non-significant effects and attempted or failed replications, as well as papers on the challenges and possible solutions to increase reproducibility.

7.5 Conclusions

This thesis used a multi method approach for investigating brain oscillatory dynamics drawing on slow oscillatory theta activity that are associated with human working memory and selective attentional processes. This included probing their causal relevance for behaviour using a combination of TMS and EEG, reproducing established effects using frequency-specific tACS, and the acquisition of EEG data in a novel task paradigm. Additionally, we explored whether using Bayesian statistics can help establishing increased reproducibility, robustness and openness in transcranial brain stimulation research and beyond.

The current work demonstrates that while visual search for a single mental template enables precise memory matching, limitations in this matching process occur during multiple template search, as reflected by differences in transient phase synchronization between theta and gamma phase over right-hemispheric posterior cortex. Such transient theta-gamma phase synchronization can enable brief periods of information exchange between long-range and local neural networks involved in matching processes between bottom-up sensory input with top-down expectations. Further, more sustained fronto-parietal interaction may be involved in active top-down control, where the prefrontal cortex coordinates remote brain areas, drawing on frontal midline theta phase for rhythmically gating accesses to prefrontal cognitive resources. Here, our pilot data suggests that the voluntary allocation of cognitive resources in visuospatial working might influence such a mechanism: TMS over right parietal cortex, when prioritizing contralateral visuospatial information for working memory maintenance, selectively disrupted performance when it was delivered during the more excitatory phase (i.e. the trough) of the frontal-midline theta cycle. Estimated effect sizes and methodological insights from this can inform follow-up studies. Third, in a pre-registered study using multi-site tACS, we did not reproduce a 'synchronization- desynchronization' effect by fronto-parietal theta tACS on response times. But importantly, we could demonstrate that in a more demanding 3-back task, in-phase and in-phase focal theta tACS improved discriminability substantially compared to placebo stimulation. Thus, an external boost of theta coherence between human frontal and parietal areas, which we targeted in this study, may therefore increase verbal working memory performance if cognitive task demands are high enough. Finally, our work demonstrates that non-significant tests with a high p-value do not automatically prove the null hypothesis to be true, but might indicate inconclusive evidence. We argue that Bayes factor tests are highly useful for the TBS community, providing a simple but effective solution to how non-significant findings from transcranial brain stimulation studies can inform future research.

References

Alekseichuk, I., Falchier, A. Y., Linn, G., Xu, T., Milham, M. P., Schroeder, C. E., & Opitz, A. (2019). Electric field dynamics in the brain during multi-electrode transcranial electric stimulation. *Nature Communications, 10*(1), 2573. https://doi.org/10.1038/s41467-019-10581-7

Alekseichuk, I., Pabel, S. C., Antal, A., & Paulus, W. (2017). Intrahemispheric theta rhythm desynchronization impairs working memory. *Restorative Neurology and Neuroscience, 35*(2), 147–158. https://doi.org/10.3233/RNN-160714

Alekseichuk, I., Turi, Z., Lara, G. A. D., Antal, A., Alekseichuk, I., Turi, Z., Amador de Lara, G., Antal, A., & Paulus, W. (2016). Spatial Working Memory in Humans Depends on Theta and High Gamma Synchronization in the Prefrontal Cortex. *Current Biology, 26*(12), 1–9. https://doi.org/10.1016/j.cub.2016.04.035

Awh, E., & Jonides, J. (2001). Overlapping mechanisms of attention and spatial working memory. *Trends in Cognitive Sciences, 5*(3), 119–126. https://doi.org/10.1016/S1364-6613(00)01593-X

Awh, E., Vogel, E. K., & Oh, S. .-. (2006). Interactions between attention and working memory. *Neuroscience, 139*(1), 201–208. https://doi.org/10.1016/j.neuroscience.2005.08.023

Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proceedings of the National Academy of Sciences, 107*(7), 3228–3233. https://doi.org/10.1073/pnas.0911531107

Baddeley, A. D. (2000). The episodic buffer: A new component of working memory? *Trends in Cognitive Sciences, 4*(11), 417–423. https://doi.org/10.1016/S1364-6613(00)01538-2

Baddeley, A. D., Allen, R. J., & Hitch, G. J. (2011). Binding in visual working memory: The role of the episodic buffer. *Neuropsychologia, 49*(6), 1393–1400. https://doi.org/10.1016/j.neuropsychologia.2010.12.042

Baddeley, A. D., & Hitch, G. (1974, January 1). Working Memory. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (pp. 47–89). Academic Press. https://doi.org/10.1016/S0079-7421(08)60452-1

Bahmani, Z., Clark, K., Merrikhi, Y., Mueller, A., Pettine, W., Isabel Vanegas, M., Moore, T., & Noudoost, B. (2019). Prefrontal Contributions to Attention and Working Memory. *Current Topics in Behavioral Neurosciences, 41*, 129–153. https://doi.org/10.1007/7854_2018_74

Berger, B., Griesmayr, B., Minarik, T., Biel, A. L., Pinal, D., Sterr, A., & Sauseng, P. (2019). Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. *Nature Communications, 10*(1), 4242. https://doi.org/10.1038/s41467-019-12057-0

Berger, B., Minarik, T., Griesmayr, B., Stelzig-Schoeler, R., Aichhorn, W., & Sauseng, P. (2016). Brain Oscillatory Correlates of Altered Executive Functioning in Positive and Negative Symptomatic Schizophrenia Patients and Healthy Controls. *Frontiers in Psychology, 7*. https://doi.org/10.3389/fpsyg.2016.00705

Biel, A. L., Berger, B., Minarik, T., & Sauseng, P. (in preparation). *Voluntary resource allocation in visuospatial working memory is supported by frontal midline theta phase dependent fronto-parietal interaction.*

Biel, A. L., & Friedrich, E. V. C. (2018). Why You Should Report Bayes Factors in Your Transcranial Brain Stimulation Studies. *Frontiers in psychology, 9,* 1125. https://doi.org/10.3389/fpsyg.2018.01125

Biel, A. L., Minarik, T., & Sauseng, P. (2021). EEG cross-frequency phase synchronization as an index of memory matching in visual search. *NeuroImage, 235,* 117971. https://doi.org/10.1016/j.neuroimage.2021.117971

Biel, A. L., Sterner, E., Röll, L., & Sauseng, P. (submitted). *Modulating verbal working memory with fronto-parietal transcranial electric stimulation at theta frequency: Does it work?*

Bikson, M., Brunoni, A. R., Charvet, L. E., Clark, V. P., Cohen, L. G., Deng, Z.-D., Dmochowski, J., Edwards, D. J., Frohlich, F., Kappenman, E. S., Lim, K. O., Loo, C., Mantovani, A., McMullen, D. P., Parra, L. C., Pearson, M., Richardson, J. D., Rumsey, J. M., Sehatpour, P., … Lisanby, S. H. (2018). Rigor and reproducibility in research with transcranial electrical stimulation: An NIMH-sponsored workshop. *Brain Stimulation, 11*(3), 465–480. https://doi.org/10.1016/j.brs.2017.12.008

Bortoletto, M., Rodella, C., Salvador, R., Miranda, P. C., & Miniussi, C. (2016). Reduced Current Spread by Concentric Electrodes in Transcranial Electrical Stimulation (tES). *Brain Stimulation, 9*(4), 525–528. https://doi.org/10.1016/j.brs.2016.03.001

Botvinik-Nezer, R., Holzmeister, F., Camerer, C. F., Dreber, A., Huber, J., Johannesson, M., Kirchler, M., Iwanir, R., Mumford, J. A., Adcock, R. A., Avesani, P., Baczkowski, B. M., Bajracharya, A., Bakst, L., Ball, S., Barilari, M., Bault, N., Beaton, D., Beitner, J., … Schonberg, T. (2020). Variability in the analysis of a single neuroimaging dataset by many teams. *Nature, 582*(7810), 84–88. https://doi.org/10.1038/s41586-020-2314-9

Bundesen, C. (1990). A theory of visual attention. *Psychological Review, 97*(4), 523–547. https://doi.org/10.1037/0033-295X.97.4.523

Bundesen, C., Habekost, T., & Kyllingsbæk, S. (2005). A Neural Theory of Visual Attention: Bridging Cognition and Neurophysiology. *Psychological Review, 112*(2), 291–328. https://doi.org/10.1037/0033-295X.112.2.291

Busch, N. A., Dubois, J., & VanRullen, R. (2009). The Phase of Ongoing EEG Oscillations Predicts Visual Perception. *Journal of Neuroscience, 29*(24), 7869–7876. https://doi.org/10.1523/JNEUROSCI.0113-09.2009

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14*(5), 365–376. https://doi.org/10.1038/nrn3475

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High Gamma Power Is Phase-Locked

to Theta Oscillations in Human Neocortex. *Science, 313*(5793), 1626–1628. https://doi.org/10.1126/science.1128115

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences, 14*(11), 506–515. https://doi.org/10.1016/j.tics.2010.09.001

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences, 18*(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Chaieb, L., Leszczynski, M., Axmacher, N., Höhne, M., Elger, C. E., & Fell, J. (2015). Theta-gamma phase-phase coupling during working memory maintenance in the human hippocampus. *Cognitive Neuroscience, 6*(4), 149–157. https://doi.org/10.1080/17588928.2015.1058254

Christophel, T. B., Klink, P. C., Spitzer, B., Roelfsema, P. R., & Haynes, J.-D. (2017). The Distributed Nature of Working Memory. *Trends in Cognitive Sciences, 21*(2), 111–124. https://doi.org/10.1016/j.tics.2016.12.007

Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage, 37*(1), 343–360. https://doi.org/10.1016/j.neuroimage.2007.03.071

Collaboration, O. S. (2012). An Open, Large-Scale, Collaborative Effort to Estimate the Reproducibility of Psychological Science. *Perspectives on Psychological Science, 7*(6), 657–660. https://doi.org/10.1177/1745691612462588

Collaboration, O. S. (2015). Estimating the reproducibility of psychological science. *Science, 349*(6251). https://doi.org/10.1126/science.aac4716

Cooper, P. S., Wong, A. S. W., Fulham, W. R., Thienel, R., Mansfield, E., Michie, P. T., & Karayanidis, F. (2015). Theta frontoparietal connectivity associated with proactive and reactive cognitive control processes. *NeuroImage, 108*, 354–363. https://doi.org/10.1016/j.neuroimage.2014.12.028

Corbetta, M., Kincade, J. M., & Shulman, G. L. (2002). Neural Systems for Visual Orienting and Their Relationships to Spatial Working Memory. *Journal of Cognitive Neuroscience, 14*(3), 508–523. https://doi.org/10.1162/089892902317362029

Corbetta, M., & Shulman, G. L. (2002). Control of Goal-Directed and Stimulus-Driven Attention in the Brain. *Nature Reviews Neuroscience, 3*(3), 215–229. https://doi.org/10.1038/nrn755

Corp, D. T., Bereznicki, H. G. K., Clark, G. M., Youssef, G. J., Fried, P. J., Jannati, A., Davies, C. B., Gomes-Osman, J., Stamm, J., Chung, S. W., Bowe, S. J., Rogasch, N. C., Fitzgerald, P. B., Koch, G., Di Lazzaro, V., Pascual-Leone, A., & Enticott, P. G. (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration'. *Brain Stimulation, 13*(5), 1476–1488. https://doi.org/10.1016/j.brs.2020.07.018

Cowan, N. (1999). An Embedded-Processes Model of working memory. *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 62–101). Cambridge University Press. https://doi.org/10.1017/CBO9781139174909.006

Cowan, N. (2001). The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences, 24*(1), 87–114. https://doi.org/10.1017/S0140525X01003922

Crivelli-Decker, J., Hsieh, L.-T., Clarke, A., & Ranganath, C. (2018). Theta oscillations promote temporal sequence learning. *Neurobiology of Learning and Memory, 153*, 92–103. https://doi.org/10.1016/j.nlm.2018.05.001

Daume, X. J., Gruber, T., Engel, A. K., & Friese, U. (2017). Phase-Amplitude Coupling and Long-Range Phase Synchronization Reveal Frontotemporal Interactions during Visual Working Memory. *37*(2), 313–322. https://doi.org/10.1523/JNEUROSCI.2130-16.2016

de Lara, G. A., Alekseichuk, I., Turi, Z., Lehr, A., Antal, A., & Paulus, W. (2018). Perturbation of theta-gamma coupling at the temporal lobe hinders verbal declarative memory. *Brain Stimulation, 11*(3), 509–517. https://doi.org/10.1016/j.brs.2017.12.007

Demiralp, T., Bayraktaroglu, Z., Lenz, D., Junge, S., Busch, N. A., Maess, B., Ergen, M., & Herrmann, C. S. (2007). Gamma amplitudes are coupled to theta phase in human EEG during visual perception. *International Journal of Psychophysiology, 64*(1), 24–30. https://doi.org/10.1016/j.ijpsycho.2006.07.005

Desimone, R., & Duncan, J. (1995). Neural Mechanisms of Selective Visual Attention. *Annual Review of Neuroscience, 18*(1), 193–222. https://doi.org/10.1146/annurev.ne.18.030195.001205

D'Esposito, M., & Postle, B. R. (2015). The Cognitive Neuroscience of Working Memory. *Annual Review of Psychology, 66*(1), 115–142. https://doi.org/10.1146/annurev-psych-010814-015031

de Vries, I. E. J., Slagter, H. A., & Olivers, C. N. L. (2020). Oscillatory Control over Representational States in Working Memory. *Trends in Cognitive Sciences, 24*(2), 150–162. https://doi.org/10.1016/j.tics.2019.11.006

de Vries, I. E. J., van Driel, J., Karacaoglu, M., & Olivers, C. N. L. (2018). Priority Switches in Visual Working Memory are Supported by Frontal Delta and Posterior Alpha Interactions. *Cerebral Cortex, 28*(11), 4090–4104. https://doi.org/10.1093/cercor/bhy223

Dienes, Z. (2011). Bayesian Versus Orthodox Statistics: Which Side Are You On? *Perspectives on Psychological Science, 6*(3), 274–290. https://doi.org/10.1177/1745691611406920

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in Psychology, 5*, 781. https://doi.org/10.3389/fpsyg.2014.00781

Dienes, Z. (2015). *How Bayesian statistics are needed to determine whether mental states are unconscious*. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199688890.003.0012

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences, 12*(3), 99–105. https://doi.org/10.1016/j.tics.2008.01.001

Driver, J., & Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition, 79*(1), 39–88. https://doi.org/10.1016/S0010-0277(00)00124-4

Duncan, J., & Humphreys, G. W. (1989). Visual search and stimulus similarity. *Psychological Review, 96*(3), 433–458. https://doi.org/10.1037/0033-295X.96.3.433

EEG Many Pipelines. (in preparation).

Eimer, M. (2014). The neural basis of attentional control in visual search. *Trends in Cognitive Sciences, 18*(10), 526–535. https://doi.org/10.1016/j.tics.2014.05.005

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: Oscillations and synchrony in top–down processing. *Nature Reviews Neuroscience, 2*(10), 704–716. https://doi.org/10.1038/35094565

Enriquez-Geppert, S., Huster, R. J., Figge, C., & Herrmann, C. S. (2014). Self-regulation of frontal-midline theta facilitates memory updating and mental set shifting. *Frontiers in Behavioral Neuroscience, 8*. https://doi.org/10.3389/fnbeh.2014.00420

Eschmann, K. C. J., Bader, R., & Mecklinger, A. (2018). Topographical differences of frontal-midline theta activity reflect functional differences in cognitive control abilities. *Brain and Cognition, 123*, 57–64. https://doi.org/10.1016/j.bandc.2018.02.002

Fell, J., & Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nature Reviews Neuroscience, 12*(2), 105–118. https://doi.org/10.1038/nrn2979

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences, 9*(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011

Fries, P. (2015). Rhythms for Cognition: Communication through Coherence. *Neuron, 88*(1), 220–235. https://doi.org/10.1016/j.neuron.2015.09.034

Fuentemilla, L., Penny, W. D., Cashdollar, N., Bunzeck, N., & Düzel, E. (2010). Theta-Coupled Periodic Replay in Working Memory. *Current Biology, 20*(7), 606–612. https://doi.org/10.1016/j.cub.2010.01.057

Fujisawa, S., & Buzsaki, G. (2011). A 4 Hz Oscillation Adaptively Synchronizes Prefrontal, VTA, and Hippocampal Activities. *Neuron, 72*(1), 153–165. https://doi.org/10.1016/j.neuron.2011.08.018

Gazzaley, A., & Nobre, A. C. (2012). Top-down modulation: Bridging selective attention and working memory. *Trends in Cognitive Sciences, 16*(2), 129–135. https://doi.org/10.1016/j.tics.2011.11.014

Gelman, A., & Loken, E. (2013). *The garden of forking paths: Why multiple comparisons can be a problem, even when there is no "fishing expedition" or "p-hacking" and the research hypothesis was posited ahead of time.*

Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: Effects of task difficulty, type of processing, and practice. *Cerebral Cortex, 7*(4), 374–385. https://doi.org/10.1093/cercor/7.4.374

Green, P., & MacLeod, C. J. (2016). SIMR: An R package for power analysis of generalized linear mixed models by simulation. *Methods in Ecology and Evolution*, *7*(4), 493–498. https://doi.org/10.1111/2041-210X.12504

Griesmayr, B., Berger, B., Stelzig-Schoeler, R., Aichhorn, W., Bergmann, J., & Sauseng, P. (2014). EEG theta phase coupling during executive control of visual working memory investigated in individuals with schizophrenia and in healthy controls. *Cognitive, Affective, & Behavioral Neuroscience*, *14*(4), 1340–1355. https://doi.org/10.3758/s13415-014-0272-0

Griesmayr, B., Gruber, W. R., Klimesch, W., & Sauseng, P. (2010). Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task. *Neurobiology of Learning and Memory*, *93*(2), 208–215. https://doi.org/10.1016/j.nlm.2009.09.013

Gulbinaite, R., van Rijn, H., & Cohen, M. X. (2014). Fronto-parietal network oscillations reveal relationship between working memory capacity and cognitive control. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00761

Gunseli, E., Olivers, C. N. L., & Meeter, M. (2014). Effects of Search Difficulty on the Selection, Maintenance, and Learning of Attentional Templates. *Journal of Cognitive Neuroscience*, *26*(9), 2042–2054. https://doi.org/10.1162/jocn_a_00600

Haegens, S., Nácher, V., Luna, R., Romo, R., & Jensen, O. (2011). -Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. *Proceedings of the National Academy of Sciences*, *108*(48), 19377–19382. https://doi.org/10.1073/pnas.1117190108

Haegens, S., Osipova, D., Oostenveld, R., & Jensen, O. (2010). Somatosensory working memory performance in humans depends on both engagement and disengagement of regions in a distributed network. *Human Brain Mapping*, *31*(1), 26–35. https://doi.org/10.1002/hbm.20842

Hanslmayr, S., Volberg, G., Wimber, M., Dalal, S. S., & Greenlee, M. W. (2013). Prestimulus Oscillatory Phase at 7 Hz Gates Cortical Information Flow and Visual Perception. *Current Biology*, *23*(22), 2273–2278. https://doi.org/10.1016/j.cub.2013.09.020

Harding, I. H., Yücel, M., Harrison, B. J., Pantelis, C., & Breakspear, M. (2015). Effective connectivity within the frontoparietal control network differentiates cognitive control and working memory. *NeuroImage*, *106*, 144–153. https://doi.org/10.1016/j.neuroimage.2014.11.039

Helfrich, R. F., & Knight, R. T. (2016). Oscillatory Dynamics of Prefrontal Cognitive Control. *Trends in Cognitive Sciences*, *20*(12), 916–930. https://doi.org/10.1016/j.tics.2016.09.007

Herman, P. A., Lundqvist, M., & Lansner, A. (2013). Nested theta to gamma oscillations and precise spatiotemporal firing during memory retrieval in a simulated attractor network. *Brain Research*, *1536*, 68–87. https://doi.org/10.1016/j.brainres.2013.08.002

Herrmann, C. S., Fründ, I., & Lenz, D. (2010). Human gamma-band activity: A review on cognitive and behavioral correlates and network models. *Neuroscience and Biobehavioral Reviews, 34*(7), 981–992. https://doi.org/10.1016/j.neubiorev.2009.09.001

Herrmann, C. S., Munk, M. H., & Engel, A. K. (2004). Cognitive functions of gamma-band activity: Memory match and utilization. *Trends in Cognitive Sciences, 8*(8), 347–355. https://doi.org/10.1016/j.tics.2004.06.006

Herrmann, C. S., Strüber, D., Helfrich, R. F., & Engel, A. K. (2016). EEG oscillations: From correlation to causality. *International Journal of Psychophysiology, 103*, 12–21. https://doi.org/10.1016/j.ijpsycho.2015.02.003

Hill, A. T., Fitzgerald, P. B., & Hoy, K. E. (2016). Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations. *Brain Stimulation, 9*(2), 197–208. https://doi.org/10.1016/j.brs.2015.10.006

Holz, E. M., Glennon, M., Prendergast, K., & Sauseng, P. (2010). Theta-gamma phase synchronization during memory matching in visual working memory. *NeuroImage, 52*(1), 326–335. https://doi.org/10.1016/j.neuroimage.2010.04.003

Honkanen, R., Rouhinen, S., Wang, S. H., Palva, J. M., & Palva, S. (2015). Gamma Oscillations Underlie the Maintenance of Feature-Specific Information and the Contents of Visual Working Memory. *Cerebral Cortex, 25*(10), 3788–3801. https://doi.org/10.1093/cercor/bhu263

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimulation, 8*(3), 535–550. https://doi.org/10.1016/j.brs.2015.01.400

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., Schulze-Bonhage, A., & Kahana, M. J. (2003). Gamma oscillations correlate with working memory load in humans. *Cerebral Cortex (New York, N.Y.: 1991), 13*(12), 1369–1374. https://doi.org/10.1093/cercor/bhg084

Hsieh, L. T., & Ranganath, C. (2014). Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. *NeuroImage, 85*, 721–729. https://doi.org/10.1016/j.neuroimage.2013.08.003

Hussain, S. J., Vollmer, M. K., Stimely, J., Norato, G., Zrenner, C., Ziemann, U., Buch, E. R., & Cohen, L. G. (2021). Phase-dependent offline enhancement of human motor memory. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 14*(0). https://doi.org/10.1016/j.brs.2021.05.009

JASP Team. (2020). JASP (Version 0.14.1)[Computer software].

Jensen, O., & Colgin, L. L. (2007). Cross-frequency coupling between neuronal oscillations. *Trends in Cognitive Sciences, 11*(7), 267–269. https://doi.org/10.1016/j.tics.2007.05.003

Jensen, O., Gips, B., Bergmann, T. O., & Bonnefond, M. (2014). Temporal coding organized by coupled alpha and gamma oscillations prioritize visual processing. *Trends in Neurosciences, 37*(7), 357–369. https://doi.org/10.1016/j.tins.2014.04.001

Jensen, O., Kaiser, J., & Lachaux, J. P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences, 30*(7), 317–324. https://doi.org/10.1016/j.tins.2007.05.001

Jensen, O., & Lisman, J. E. (1998). An Oscillatory Short-Term Memory Buffer Model Can Account for Data on the Sternberg Task. *Journal of Neuroscience, 18*(24), 10688–10699. https://doi.org/10.1523/JNEUROSCI.18-24-10688.1998

Jensen, O., Spaak, E., & Zumer, J. M. (2019). Human Brain Oscillations: From Physiological Mechanisms to Analysis and Cognition. In S. Supek & C. J. Aine (Eds.), *Magnetoencephalography: From Signals to Dynamic Cortical Networks* (pp. 471–517). Springer International Publishing. https://doi.org/10.1007/978-3-030-00087-5_17

Jensen, O., & Tesche, C. D. (2002). Frontal theta activity in humans increases with memory load in a working memory task. *European Journal of Neuroscience, 15*(8), 1395–1399. https://doi.org/10.1046/j.1460-9568.2002.01975.x

Kamiński, J., Brzezicka, A., & Wróbel, A. (2011). Short-term memory capacity (7 ± 2) predicted by theta to gamma cycle length ratio. *Neurobiology of Learning and Memory, 95*(1), 19–23. https://doi.org/10.1016/j.nlm.2010.10.001

Kappenman, E. S., & Keil, A. (2017). Introduction to the special issue on recentering science: Replication, robustness, and reproducibility in psychophysiology. *Psychophysiology, 54*(1), 3–5. https://doi.org/10.1111/psyp.12787

Karakaş, S. (2020). A review of theta oscillation and its functional correlates. *International Journal of Psychophysiology, 157*, 82–99. https://doi.org/10.1016/j.ijpsycho.2020.04.008

Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience, 23*, 315–341. https://doi.org/10.1146/annurev.neuro.23.1.315

Kleinert, M.-L., Szymanski, C., & Müller, V. (2017). Frequency-Unspecific Effects of theta-tACS Related to a Visuospatial Working Memory Task. *Frontiers in Human Neuroscience, 11*, 1–16. https://doi.org/10.3389/fnhum.2017.00367

Klink, K., Paßmann, S., Kasten, F. H., & Peter, J. (2020). The Modulation of Cognitive Performance with Transcranial Alternating Current Stimulation: A Systematic Review of Frequency-Specific Effects. *Brain Sciences, 10*(12), 932. https://doi.org/10.3390/brainsci10120932

Kruschke, J. K. (2011). Bayesian Assessment of Null Values Via Parameter Estimation and Model Comparison. *Perspectives on Psychological Science, 6*(3), 299–312. https://doi.org/10.1177/1745691611406925

Lisman, J. E., & Idiart, M. A. (1995). Storage of 7 +/- 2 short-term memories in oscillatory subcycles. *Science, 267*(5203), 1512–1515. https://doi.org/10.1126/science.7878473

Lisman, J. E., & Jensen, O. (2013). The Theta-Gamma Neural Code. *Neuron, 77*(6), 1002–1016. https://doi.org/10.1016/j.neuron.2013.03.007

Luck, S. J., & Gaspelin, N. (2017). How to Get Statistically Significant Effects in Any ERP Experiment (and Why You Shouldn't). *Psychophysiology, 54*(1), 146–157. https://doi.org/10.1111/psyp.12639

Mancuso, L. E., Ilieva, I. P., Hamilton, R. H., & Farah, M. J. (2016). Does Transcranial Direct Current Stimulation Improve Healthy Working Memory?: A Meta-analytic Review. *Journal of Cognitive Neuroscience, 28*(8), 1063–1089. https://doi.org/10.1162/jocn_a_00956

Maxwell, S. E., Kelley, K., & Rausch, J. R. (2008). Sample size planning for statistical power and accuracy in parameter estimation. *Annual Review of Psychology, 59,* 537–563. https://doi.org/10.1146/annurev.psych.59.103006.093735

Minarik, T., Berger, B., Althaus, L., Bader, V., Biebl, B., Brotzeller, F., Fusban, T., Hegemann, J., Jesteadt, L., Kalweit, L., Leitner, M., Linke, F., Nabielska, N., Reiter, T., Schmitt, D., Spraetz, A., & Sauseng, P. (2016). The Importance of Sample Size for Reproducibility of tDCS Effects. *Frontiers in Human Neuroscience, 10,* 453. https://doi.org/10.3389/fnhum.2016.00453

Mitchell, D. J., McNaughton, N., Flanagan, D., & Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta". *Progress in Neurobiology, 86*(3), 156–185. https://doi.org/10.1016/j.pneurobio.2008.09.005

Moore, T., & Zirnsak, M. (2017). Neural Mechanisms of Selective Visual Attention. *Annual Review of Psychology, 68,* 47–72. https://doi.org/10.1146/annurev-psych-122414-033400

Moran, R. J., Campo, P., Maestu, F., Reilly, R. B., Dolan, R. J., & Strange, B. A. (2010). Peak Frequency in the Theta and Alpha Bands Correlates with Human Working Memory Capacity. *Frontiers in Human Neuroscience, 4,* 1–12. https://doi.org/10.3389/fnhum.2010.00200

Morey, R. D., & Rouder, J. N. (2018). *BayesFactor: Computation of Bayes Factors for Common Designs*.

Munafò, M. R., Nosek, B. A., Bishop, D. V. M., Button, K. S., Chambers, C. D., Percie du Sert, N., Simonsohn, U., Wagenmakers, E.-J., Ware, J. J., & Ioannidis, J. P. A. (2017). A manifesto for reproducible science. *Nature Human Behaviour, 1*(1), 1–9. https://doi.org/10.1038/s41562-016-0021

Naghavi, H. R., & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: Shared demands on integration? *Consciousness and Cognition, 14*(2), 390–425. https://doi.org/10.1016/j.concog.2004.10.003

Nee, D. E., & D'Esposito, M. (2018). The Representational Basis of Working Memory. *Current Topics in Behavioral Neurosciences, 37,* 213–230. https://doi.org/10.1007/7854_2016_456

Nobre, A. C., Coull, J. T., Walsh, V., & Frith, C. D. (2003). Brain activations during visual search: Contributions of search efficiency versus feature binding. *NeuroImage, 18*(1), 91–103. https://doi.org/10.1006/nimg.2002.1329

Nord, C. L., Valton, V., Wood, J., & Roiser, J. P. (2017). Power-up: A Reanalysis of 'Power Failure' in Neuroscience Using Mixture Modeling. *Journal of Neuroscience, 37*(34), 8051–8061. https://doi.org/10.1523/JNEUROSCI.3592-16.2017

Oberauer, K. (2009, January 1). Chapter 2 Design for a Working Memory. *Psychology of Learning and Motivation* (pp. 45–100). Academic Press. https://doi.org/10.1016/S0079-7421(09)51002-X

of The Journal of Neuroscience, T. E. B. (2020). Consideration of Sample Size in Neuroscience Studies. *The Journal of Neuroscience, 40*(21), 4076–4077. https://doi.org/10.1523/JNEUROSCI.0866-20.2020

O'Keefe, J., & Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus, 3*(3), 317–330. https://doi.org/10.1002/hipo.450030307

Olivers, C. N. L. (2008). Interactions between visual working memory and visual attention. *Frontiers in Bioscience: A Journal and Virtual Library*, *13*, 1182–1191. https://doi.org/10.2741/2754

Olivers, C. N. L., Peters, J., Houtkamp, R., & Roelfsema, P. R. (2011). Different states in visual working memory: When it guides attention and when it does not. *Trends in Cognitive Sciences, 15*(7), 327–334. https://doi.org/10.1016/j.tics.2011.05.004

Olson, I. R., & Chun, M. M. (2001). Temporal contextual cuing of visual attention. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *27*(5), 1299–1313. https://doi.org/10.1037//0278-7393.27.5.1299

Ort, E., & Olivers, C. N. L. (2020). The capacity of multiple-target search. *Visual Cognition, 28*(5-8), 330–355. https://doi.org/10.1080/13506285.2020.1772430

Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., & Jensen, O. (2006). Theta and Gamma Oscillations Predict Encoding and Retrieval of Declarative Memory. *Journal of Neuroscience, 26*(28), 7523–7531. https://doi.org/10.1523/JNEUROSCI.1948-06.2006

Palva, J. M., Monto, S., Kulashekhar, S., & Palva, S. (2010). Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proceedings of the National Academy of Sciences of the United States of America, 107*(16), 7580–7585. https://doi.org/10.1073/pnas.0913113107

Palva, J. M., & Palva, S. (2018). Functional integration across oscillation frequencies by cross-frequency phase synchronization. *The European Journal of Neuroscience, 48*(7), 2399–2406. https://doi.org/10.1111/ejn.13767

Palva, J. M., Palva, S., & Kaila, K. (2005). Phase Synchrony among Neuronal Oscillations in the Human Cortex. *Journal of Neuroscience, 25*(15), 3962–3972. https://doi.org/10.1523/JNEUROSCI.4250-04.2005

Palva, S., Kulashekhar, S., Hämäläinen, M., & Palva, J. M. (2011). Localization of Cortical Phase and Amplitude Dynamics during Visual Working Memory Encoding and Retention. *Journal of Neuroscience, 31*(13), 5013–5025. https://doi.org/10.1523/JNEUROSCI.5592-10.2011

Pavlov, Y. G., Adamian, N., Appelhoff, S., Arvaneh, M., Benwell, C. S. Y., Beste, C., Bland, A. R., Bradford, D. E., Bublatzky, F., Busch, N. A., Clayson, P. E., Cruse, D., Czeszumski, A., Dreber, A., Dumas, G., Ehinger, B., Ganis, G., He, X., Hinojosa,

J. A., … Mushtaq, F. (2021). #EEGManyLabs: Investigating the replicability of influential EEG experiments. *Cortex*. https://doi.org/10.1016/j.cortex.2021.03.013

Phillips, J. M., Vinck, M., Everling, S., & Womelsdorf, T. (2014). A long-range fronto-parietal 5- to 10-Hz network predicts "top-down" controlled guidance in a task-switch paradigm. *Cerebral Cortex, 24*(8), 1996–2008. https://doi.org/10.1093/cercor/bht050

Pinal, D., Zurron, M., Diaz, F., & Sauseng, P. (2015). Stuck in default mode: Inefficient cross-frequency synchronization may lead to age-related short-term memory decline. *Neurobiology of Aging, 36*(4), 1611–1618. https://doi.org/10.1016/j.neurobiolaging.2015.01.009

Polanía, R., Nitsche, M. A., Korman, C., Batsikadze, G., & Paulus, W. (2012). The Importance of Timing in Segregated Theta Phase-Coupling for Cognitive Performance. *Current Biology, 22*(14), 1314–1318. https://doi.org/10.1016/j.cub.2012.05.021

Poldrack, R. A., Baker, C. I., Durnez, J., Gorgolewski, K. J., Matthews, P. M., Munafò, M. R., Nichols, T. E., Poline, J.-B., Vul, E., & Yarkoni, T. (2017). Scanning the horizon: Towards transparent and reproducible neuroimaging research. *Nature Reviews. Neuroscience, 18*(2), 115–126. https://doi.org/10.1038/nrn.2016.167

Poldrack, R. A., Whitaker, K., & Kennedy, D. (2020). Introduction to the special issue on reproducibility in neuroimaging. *NeuroImage, 218*, 116357. https://doi.org/10.1016/j.neuroimage.2019.116357

R Core Team. (2021). *R: A language and environment for statistical computing*. manual. R Foundation for Statistical Computing. Vienna, Austria.

Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience, 22*(5), 820–827. https://doi.org/10.1038/s41593-019-0371-x

Riddle, J., & Frohlich, F. (2021). Targeting neural oscillations with transcranial alternating current stimulation. *Brain Research*, 147491. https://doi.org/10.1016/j.brainres.2021.147491

Riddle, J., Scimeca, J. M., Cellier, D., Dhanani, S., & D'Esposito, M. (2020). Causal Evidence for a Role of Theta and Alpha Oscillations in the Control of Working Memory. *Current Biology, 30*(9), 1748–1754.e4. https://doi.org/10.1016/j.cub.2020.02.065

Röhner, F., Breitling, C., Rufener, K. S., Heinze, H.-J., Hinrichs, H., Krauel, K., & Sweeney-Reed, C. M. (2018). Modulation of Working Memory Using Transcranial Electrical Stimulation: A Direct Comparison Between TACS and TDCS. *Frontiers in Neuroscience, 12*. https://doi.org/10.3389/fnins.2018.00761

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., Fox, P. T., & Eickhoff, S. B. (2012). Modelling neural correlates of working memory: A coordinate-based meta-analysis. *NeuroImage, 60*(1), 830–846. https://doi.org/10.1016/j.neuroimage.2011.11.050

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychonomic Bulletin & Review, 16*(2), 225–237. https://doi.org/10.3758/PBR.16.2.225

Rouhinen, S., Panula, J., Palva, J. M., & Palva, S. (2013). Load Dependence of and Oscillations Predicts Individual Capacity of Visual Attention. *Journal of Neuroscience, 33*(48), 19023–19033. https://doi.org/10.1523/JNEUROSCI.1666-13.2013

Rouhinen, S., Siebenhühner, F., Palva, J. M., & Palva, S. (2020). Spectral and Anatomical Patterns of Large-Scale Synchronization Predict Human Attentional Capacity. *Cerebral Cortex, 30*(10), 5293–5308. https://doi.org/10.1093/cercor/bhaa110

Roux, F., & Uhlhaas, P. J. (2014). Working memory and neural oscillations: Alpha-gamma versus theta-gamma codes for distinct WM information? *Trends in Cognitive Sciences, 18*(1), 16–25. https://doi.org/10.1016/j.tics.2013.10.010

Roux, F., Wibral, M., Mohr, H. M., Singer, W., & Uhlhaas, P. J. (2012). Gamma-Band Activity in Human Prefrontal Cortex Codes for the Number of Relevant Items Maintained in Working Memory. *Journal of Neuroscience, 32*(36), 12411–12420. https://doi.org/10.1523/JNEUROSCI.0421-12.2012

Ruchkin, D. S., Grafman, J., Cameron, K., & Berndt, R. S. (2003). Working memory retention systems: A state of activated long-term memory. *The Behavioral and Brain Sciences, 26*(6), 709–728. https://doi.org/10.1017/s0140525x03000165

Salamanca-Giron, R. F., Raffin, E., Zandvliet, S. B., Seeber, M., Michel, C. M., Sauseng, P., Huxlin, K. R., & Hummel, F. C. (2020). Bifocal tACS Enhances Visual Motion Discrimination by Modulating Phase Amplitude Coupling Between V1 and V5 Regions. *bioRxiv*, 2020.11.16.382267. https://doi.org/10.1101/2020.11.16.382267

Sarnthein, J., Petsche, H., Rappelsberger, P., Shaw, G. L., & von Stein, A. (1998). Synchronization between prefrontal and posterior association cortex during human working memory. *Proceedings of the National Academy of Sciences of the United States of America, 95*(12), 7092–7096. https://doi.org/10.1073/pnas.95.12.7092

Saturnino, G. B., Madsen, K. H., Siebner, H. R., & Thielscher, A. (2017). How to target inter-regional phase synchronization with dual-site Transcranial Alternating Current Stimulation. *NeuroImage, 163*, 68–80. https://doi.org/10.1016/j.neuroimage.2017.09.024

Sauseng, P., Conci, M., Wild, B., & Geyer, T. (2015). Predictive coding in visual search as revealed by cross-frequency EEG phase synchronization. *Frontiers in Psychology, 6*, 1655. https://doi.org/10.3389/fpsyg.2015.01655

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: A possible function of EEG theta oscillations. *Neuroscience and Biobehavioral Reviews, 34*(7), 1015–1022. https://doi.org/10.1016/j.neubiorev.2009.12.006

Sauseng, P., Hoppe, J., Klimesch, W., Gerloff, C., & Hummel, F. C. (2007). Dissociation of sustained attention from central executive functions: Local activity and interregional connectivity in the theta range. *The European Journal of Neuroscience, 25*(2), 587–593. https://doi.org/10.1111/j.1460-9568.2006.05286.x

Sauseng, P., Klimesch, W., Freunberger, R., Pecherstorfer, T., Hanslmayr, S., & Doppelmayr, M. (2006). Relevance of EEG alpha and theta oscillations during task switch-

ing. *Experimental Brain Research, 170*(3), 295–301. https://doi.org/10.1007/s00221-005-0211-y

Sauseng, P., & Klimesch, W. (2008). What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience and Biobehavioral Reviews, 32*(5), 1001–1013. https://doi.org/10.1016/j.neubiorev.2008.03.014

Sauseng, P., Klimesch, W., Gruber, W. R., & Birbaumer, N. (2008). Cross-frequency phase synchronization: A brain mechanism of memory matching and attention. *NeuroImage, 40*(1), 308–317. https://doi.org/10.1016/j.neuroimage.2007.11.032

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A. A., Glennon, M., Gerloff, C., Birbaumer, N., & Hummel, F. C. (2009). Brain Oscillatory Substrates of Visual Short-Term Memory Capacity. *Current Biology, 19*(21), 1846–1852. https://doi.org/10.1016/j.cub.2009.08.062

Sauseng, P., Klimesch, W., Schabus, M., & Doppelmayr, M. (2005). Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *International Journal of Psychophysiology, 57*(2), 97–103. https://doi.org/10.1016/j.ijpsycho.2005.03.018

Sauseng, P., Peylo, C., Biel, A. L., Friedrich, E. V. C., & Romberg-Taylor, C. (2019). Does cross-frequency phase coupling of oscillatory brain activity contribute to a better understanding of visual working memory? *British Journal of Psychology, 110*(2), 245–255. https://doi.org/10.1111/bjop.12340

Schack, B., Vath, N., Petsche, H., Geissler, H. G., & Möller, E. (2002). Phase-coupling of theta-gamma EEG rhythms during short-term memory processing. *International Journal of Psychophysiology, 44*(2), 143–163. https://doi.org/10.1016/S0167-8760(01)00199-4

Schönbrodt, F. D., Wagenmakers, E.-J., Zehetleitner, M., & Perugini, M. (2017). Sequential hypothesis testing with Bayes factors: Efficiently testing mean differences. *Psychological Methods, 22*(2), 322–339. https://doi.org/10.1037/met0000061

Siebenhühner, F., Wang, S. H., Palva, J. M., & Palva, S. (2016). Cross-frequency synchronization connects networks of fast and slow oscillations during visual working memory maintenance. *eLife, 5*, e13451. https://doi.org/10.7554/eLife.13451

Siegel, M., Donner, T. H., & Engel, A. K. (2012). Spectral fingerprints of large-scale neuronal interactions. *Nature Reviews Neuroscience, 13*(2), 121–134. https://doi.org/10.1038/nrn3137

Siegel, M., Warden, M. R., & Miller, E. K. (2009). Phase-dependent neuronal coding of objects in short-term memory. *Proceedings of the National Academy of Sciences, 106*(50), 21341–21346. https://doi.org/10.1073/pnas.0908193106

Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., & Buzsáki, G. (2008). Entrainment of Neocortical Neurons and Gamma Oscillations by the Hippocampal Theta Rhythm. *Neuron, 60*(4), 683–697. https://doi.org/10.1016/j.neuron.2008.09.014

Soto, D., Hodsoll, J., Rotshtein, P., & Humphreys, G. W. (2008). Automatic guidance of attention from working memory. *Trends in Cognitive Sciences, 12*(9), 342–348. https://doi.org/10.1016/j.tics.2008.05.007

Soto, D., Humphreys, G. W., & Rotshtein, P. (2007). Dissociating the neural mechanisms of memory-based guidance of visual selection. *Proceedings of the National Academy of Sciences, 104*(43), 17186–17191. https://doi.org/10.1073/pnas.0703706104

Tallon-Baudry, C., Bertrand, O., Peronnet, F., & Pernier, J. (1998). Induced -Band Activity during the Delay of a Visual Short-Term Memory Task in Humans. *Journal of Neuroscience, 18*(11), 4244–4254. https://doi.org/10.1523/JNEUROSCI.18-11-04244.1998

Ten Brink, A. F., Biesbroek, J. M., Kuijf, H. J., Van der Stigchel, S., Oort, Q., Visser-Meily, J. M. A., & Nijboer, T. C. W. (2016). The right hemisphere is dominant in organization of visual search-A study in stroke patients. *Behavioural Brain Research, 304*, 71–79. https://doi.org/10.1016/j.bbr.2016.02.004

ten Oever, S., De Weerd, P., & Sack, A. T. (2020). Phase-dependent amplification of working memory content and performance. *Nature Communications, 11*(1), 1832. https://doi.org/10.1038/s41467-020-15629-7

The jamovi project. (2021). jamovi (Version 1.6)[Computer software].

The tACS challenge. (in preparation).

Theeuwes, J., Belopolsky, A., & Olivers, C. N. L. (2009). Interactions between working memory, attention and eye movements. *Acta Psychologica, 132*(2), 106–114. https://doi.org/10.1016/j.actpsy.2009.01.005

Thut, G., & Miniussi, C. (2009). New insights into rhythmic brain activity from TMS-EEG studies. *Trends in Cognitive Sciences, 13*(4), 182–189. https://doi.org/10.1016/j.tics.2009.01.004

Thut, G., Miniussi, C., Cecere, R., Sauseng, P., Benwell, C. S. Y., & Veniero, D. (2018). Introduction to the special issue on Non-Invasive Brain Stimulation Effects on Cognition and Brain Activity: Positive Lessons from Negative Findings. *Frontiers in Psychology*.

Tseng, P., Chang, Y.-T., Chang, C.-F., Liang, W.-K., & Juan, C.-H. (2016). The critical role of phase difference in gamma oscillation within the temporoparietal network for binding visual working memory. *Scientific Reports, 6*(1), 32138. https://doi.org/10.1038/srep32138

Tseng, P., Iu, K. C., & Juan, C. H. (2018). The critical role of phase difference in theta oscillation between bilateral parietal cortices for visuospatial working memory. *Scientific Reports, 8*(1), 1–9. https://doi.org/10.1038/s41598-017-18449-w

Turi, Z., Mittner, M., Lehr, A., Bürger, H., Antal, A., & Paulus, W. (2020). - Cross-Frequency Transcranial Alternating Current Stimulation over the Trough Impairs Cognitive Control. *eNeuro, 7*(5). https://doi.org/10.1523/ENEURO.0126-20.2020

Vallesi, A. (2014). Monitoring mechanisms in visual search: An fMRI study. *Brain Research, 1579*, 65–73. https://doi.org/10.1016/j.brainres.2014.07.018

van van Vugt, M. K., Schulze-Bonhage, A., Litt, B., Brandt, A., & Kahana, M. J. (2010). Hippocampal Gamma Oscillations Increase with Memory Load. *Journal of Neuroscience, 30*(7), 2694–2699. https://doi.org/10.1523/JNEUROSCI.0567-09.2010

van Driel, J., Ort, E., Fahrenfort, J. J., & Olivers, C. N. L. (2018). Beta and theta oscillations differentially support free versus forced control over multiple-target search.

van Moorselaar, D., & Slagter, H. A. (2020). Inhibition in selective attention. *Annals of the New York Academy of Sciences, 1464*(1), 204–221. https://doi.org/10.1111/nyas.14304

VanRullen, R. (2016). Perceptual Cycles. *Trends in Cognitive Sciences, 20*(10), 723–735. https://doi.org/10.1016/j.tics.2016.07.006

van Schouwenburg, M. R., Sörensen, L. K. A., de Klerk, R., Reteig, L. C., & Slagter, H. A. (2018). No Differential Effects of Two Different Alpha-Band Electrical Stimulation Protocols Over Fronto-Parietal Regions on Spatial Attention. *Frontiers in Neuroscience, 12*. https://doi.org/10.3389/fnins.2018.00433

van Schouwenburg, M. R., Zanto, T. P., & Gazzaley, A. (2017). Spatial Attention and the Effects of Frontoparietal Alpha Band Stimulation. *Frontiers in Human Neuroscience, 10*. https://doi.org/10.3389/fnhum.2016.00658

van Vugt, M. K., Chakravarthi, R., & Lachaux, J.-P. (2014). For whom the bell tolls: Periodic reactivation of sensory cortex in the gamma band as a substrate of visual working memory maintenance. *Frontiers in Human Neuroscience, 8*. https://doi.org/10.3389/fnhum.2014.00696

Veniero, D., Strüber, D., Thut, G., & Herrmann, C. S. (2019). Noninvasive Brain Stimulation Techniques Can Modulate Cognitive Processing. *Organizational Research Methods, 22*(1), 116–147. https://doi.org/10.1177/1094428116658960

Violante, I. R., Li, L. M., Carmichael, D. W., Lorenz, R., Leech, R., Hampshire, A., Rothwell, J. C., & Sharp, D. J. (2017). Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. *eLife, 6*, 1–22. https://doi.org/10.7554/eLife.22001

Von Stein, A., & Sarnthein, J. (2000). Different frequencies for different scales of cortical integration: From local gamma to long range alpha/theta synchronization. *International Journal of Psychophysiology, 38*(3), 301–313. https://doi.org/10.1016/S0167-8760(00)00172-0

Vosskuhl, J., Strüber, D., & Herrmann, C. S. (2018). Non-invasive Brain Stimulation: A Paradigm Shift in Understanding Brain Oscillations. *Frontiers in Human Neuroscience, 12*. https://doi.org/10.3389/fnhum.2018.00211

Westwood, S. (2020). Investigating cognitive and therapeutic effects of transcranial electric stimulation (TES): A short guide for reproducible and transparent research. *PsyArXiv*. https://doi.org/10.31234/osf.io/8qms2

Witte, H., Putsche, P., Hemmelmann, C., Schelenz, C., & Leistritz, L. (2008). Analysis and modeling of time-variant amplitude–frequency couplings of and between oscillations of EEG bursts. *Biological Cybernetics, 99*(2), 139–157. https://doi.org/10.1007/s00422-008-0245-x

Wolinski, N., Cooper, N. R., Sauseng, P., & Romei, V. (2018). The speed of parietal theta frequency drives visuospatial working memory capacity. *PLOS Biology*, *16*(3), e2005348. https://doi.org/10.1371/journal.pbio.2005348

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., & Fries, P. (2007). Modulation of neuronal interactions through neuronal synchronization. *Science*, *316*(5831), 1609–1612. https://doi.org/10.1126/science.1139597

Womelsdorf, T., Vinck, M., Leung, S. L., & Everling, S. (2010). Selective Theta-Synchronization of Choice-Relevant Information Subserves Goal-Directed Behavior. *Frontiers in Human Neuroscience*, *4*. https://doi.org/10.3389/fnhum.2010.00210

Yaple, Z., & Vakhrushev, R. (2018). Modulation of the frontal-parietal network by low intensity anti-phase 20 Hz transcranial electrical stimulation boosts performance in the attentional blink task. *International Journal of Psychophysiology*, *127*, 11–16. https://doi.org/10.1016/j.ijpsycho.2018.02.014

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List of publications

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Nowack, L., Finke, K., **Biel, A. L.**, Keller, I., Müller, H. J., & Conci, M. (2021). Attention capture by salient object groupings in the neglected visual field. Cortex, 138, 228–240. https://doi.org/10.1016/j.cortex.2021.02.011

Berger, B., Griesmayr, B., Minarik, T., **Biel, A. L.**, Pinal, D., Sterr, A., & Sauseng, P. (2019). Dynamic regulation of interregional cortical communication by slow brain oscillations during working memory. Nature Communications, 10(1), 4242. https://doi.org/10.1038/s41467-019-12057-0

Sauseng, P., Tschentscher, N., & **Biel, A. L.** (2019). Be Prepared: Tune to FM-Theta for Cognitive Control. Trends in Neurosciences, 42(5), 307–309. https://doi.org/10.1016/j.tins.2019.02.006

Sauseng, P., Peylo, C., **Biel, A. L.**, Friedrich, E. V., & Romberg-Taylor, C. (2019). Does cross-frequency phase coupling of oscillatory brain activity contribute to a better understanding of visual working memory? British Journal of Psychology, 110(2), 245–255. https://doi.org/10.1111/bjop.12340

Biel, A. L., & Friedrich, E. V. C. (2018). Why You Should Report Bayes Factors in Your Transcranial Brain Stimulation Studies. Frontiers in Psychology, 9, 1125. https://doi.org/10.3389/fpsyg.2018.01125

Williams, R. S., **Biel, A. L.**, Dyson, B. J., & Spaniol, J. (2017). Age differences in gain- and loss-motivated attention. Brain and Cognition, 111, 171–181. https://doi.org/10.1016/j.bandc.2016.12.003

Williams, R. S., **Biel, A. L.**, Wegier, P., Lapp, L. K., Dyson, B. J., & Spaniol, J. (2016). Age differences in the Attention Network Test: Evidence from behavior and event-related potentials. Brain and Cognition, 102, 65–79. https://doi.org/10.1016/j.bandc.2015.12.007

Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation "Brain oscillatory correlates in working memory and attentional control processes" selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation "Brain oscillatory correlates in working memory and attentional control processes" is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, 9. Juni 2021

Munich, 9th June 2021 Anna Lena Biel

Declaration of author contributions

Project I

Anna Lena Biel: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, Project administration;
Tamas Minarik: Conceptualization, Writing – Review & Editing;
Paul Sauseng: Conceptualization, Methodology, Validation, Resources, Writing – Review & Editing, Supervision, Funding acquisition.

Project II

Anna Lena Biel: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, Project administration;
Barbara Berger: Conceptualization, Methodology, Software, Formal analysis, Investigation, Validation, Supervision;
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Project III

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