Investigating the spatio-temporal dynamics of human episodic and working memory

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Thesis Abstract

The overall aim of this thesis was to better characterise and understand the role of frontal regions in working memory and the role of the theta rhythm in episodic and working memory. Chapter 1 provides a general background of episodic and working memory with a focus on key cortical regions and oscillatory rhythms.

In Chapter 2, an EEG study is presented in which time-frequency and multivariate decoding analyses implicate fronto-medial theta (FMT) oscillatory activity as the supervisor of posteriorly maintained WM content. In accordance with phase-coding accounts, FMT oscillations decreased with increasing WM load. In Chapter 3, a transcranial direct current stimulation (tDCS) study was conducted to better understand the role of the frontal cortex in working memory and ageing. Specifically, high definition tDCS was applied over the left, right, or bilateral prefrontal cortices to interrogate a framework (HAROLD) that predicts a reduction in the laterality of frontal activation in older adults. In agreement with the HAROLD model, the effect sizes suggested the greatest benefit following bilateral stimulation, although this effect was not significant.

In Chapter 4, the role of theta phase was further investigated in an intracranial dataset employing a continuous encoding/retrieval paradigm. A computational model predicts distinct preferred phases for differentiating encoding and retrieval processes in the hippocampus. In general agreement with this model, the onset of memory-relevant stimuli prompted a phase reset and there was some evidence of a phase difference in the theta band. Notably, condition-specific theta-gamma interactions were observed.

Finally, Chapter 5 summarises the main findings of this thesis and discusses its implications. The results here provide novel insight into the importance of theta activity in both working memory and episodic memory processes. The thesis also highlights the key executive role of frontal regions in WM.

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Ethical Approval

All experiments adhered to the guidelines set forth by the British Psychological Society. All received the required ethical approval from the local ethics committee at the University of Birmingham and the experiment described in Chapter 4 received additional clinical ethical approval from both affiliated hospitals. All participants gave written informed consent to participate in these experiments.

Statement of Authorship

I declare that all the following chapters are my own work. For chapters 2 and 3, all data was collected by the author (O.R). The experimental designs and analysis approaches were conceived by O.R. under the supervision of Kimron Shapiro (K.S) and Bernhard Staresina (B.S.). Code required to run these experiments was written by O.R. except where otherwise specified.

As a result of the COVID-19 pandemic, I was unable to collect data for the sleep stimulation study outlined in Appendix 3. Chapter 4 represents the analysis of an existing intracranial dataset by O.R. One participant's data was collected by O.R. and the rest of the data was collected by other members of the laboratory at the University of Birmingham, as well as by researchers at the University of Madrid. The experimental design and the code required to run the task were conceived by B.S. The implementation of all analyses was conducted by O.R. under the supervision of K.S. and B.S. All analyses employed custom code written by O.R. except where otherwise specified.

All chapters were written by O.R. Chapter 2 represents a reformatting of a manuscript currently under review at Current Biology (entitled "Fronto-medial theta orchestrates posterior maintenance of WM content") and an earlier version was submitted to bioRxiv as a preprint. The manuscript of Chapter 2 was written by O.R. under the supervision of K.S. and B.S.

Chapter 1: General Introduction

1.1 Memory and its Subsystems

As early as William James, subsystems of memory were distinguished into what James referred to as ‘primary’ and ‘secondary’ memory (James, 1891). Both concepts were concerned with the retention of the mind’s contents after a stimulus in the environment had disappeared. The former referred to evanescent memories occurring over brief time periods during which a sensation or thought might temporarily guide action or thought but would otherwise leave awareness. Secondary memory, or ‘proper’ memory, on the other hand represented “the revival in the mind of an image or copy of the original event”, a full recreation of an experience had further back in time than the immediate past. A similar distinction was later formalised into immediate sensation, short-term, and long-term memory storage systems (Atkinson & Shiffrin, 1968). Although these concepts have been modified by years of research (Klein et al., 2002), the distinction of memory into several systems, each system adapted for differing functions or domains of information to be retained, has remained (Nadel & Hardt, 2011; Sherry & Schacter, 1987). What was termed primary memory has largely been subsumed by the concept of working memory (Baddeley, 2003), whereas secondary memory has morphed into long-term declarative memory, further subdivided into episodic and semantic memory (Squire, 2004).

1.2 Working Memory

As Cowan (2017) details, there are various definitions of working memory (WM). There are nevertheless some core features of the concept. Firstly, working memory as a form of memory must provide the ability for an organism to maintain information after the information is no longer being directly perceived. Key features of WM that typically distinguish it from other types of memory are that working memory operates over a limited time duration, on the order of seconds (Shin et al., 2017; Zhang & Luck, 2009), and operates with a limited capacity, ~7 +/-2 items (Cowan, 2010; Fukuda et al., 2010; Luck & Vogel, 2013). Although

these duration and capacity limitations are important, the critical distinction is the emphasis on the ability to manipulate simultaneously stored information. Importantly this distinguishes it from its conceptual predecessor, short-term memory (Atkinson & Shiffrin, 1971), which focused solely on the brief storage of information.

In an early and seminal model (Baddeley, 2003; Baddeley & Hitch, 1974), working memory is accomplished via the interaction within a multi-component cognitive system, consisting of a supervisory component (referred to as the central executive) and several temporary memory storage subsystems. In the initial framework, the authors posited two such sub-systems, the phonological loop and the visuo-spatial sketchpad, both of which were dedicated to short-term storage but which specifically processed auditory or visuo-spatial information respectively. In contrast, the executive component is believed to be responsible for various proposed sub-functions. Although the central executive has been further subdivided into various functions and its exact purview can be considered imprecise (Baddeley, 1998, 2009), it is generally agreed that there exists a distinct component of the WM system responsible for monitoring, updating, and manipulating WM contents whose role is independent of short-term storage (Morris & Jones, 1990).

A typical behavioural task employed to probe working memory function is the N-back task (Gevins et al., 1990; Owen et al., 2005). This task is so-named as a participant is required to continuously encode a trial-specific stimulus and to compare this to the stimulus presented *n* number of trials previously, where an increasing *n* increases the load on the WM system (by increasing the number of items that must be encoded and maintained). Critically this task requires both successful storage of information and the use of this information to make the judgement as to whether the present stimulus is the same as the stimulus to which it is being compared. Thus the task requires successful encoding, updating, dropping, and comparison of a given representation held in WM.

1.3 The Impact of Working Memory

As well as being of academic interest, there are practical justifications for better understanding working memory function. Working memory is highly correlated with several other important cognitive constructs, especially with measures of fluid intelligence or 'g' (Conway et al., 2003). Additionally, WM significantly predicts an individual's level of academic achievement (Alloway & Alloway, 2010). Conversely, working memory deficits are a component of a number of neuropsychological disorders, including autism spectrum disorder (Habib et al., 2019) and attention deficit hyperactivity disorder (Alderson et al., 2013). There also exist several memory disorders whose primary symptoms consist of deficits in working memory and other cognitive processes. The prevalence of these disorders of memory is high across the world and likely to increase (Prince et al., 2013), especially with burgeoning older populations (Sander et al., 2015). In the absence of pathology, working memory functionality has also been shown to decrease precipitously with age, with visual working memory in particular peaking during an individual's mid-20s and declining thereafter (Brockmole & Logie, 2013; Park et al., 2002). Importantly, an individual's level of working memory has been shown to correlate with everyday functioning (Aretouli & Brandt, 2010; Lewis & Miller, 2007).

1.4 Neural Foundations of Working memory

From its first definitions, lesion studies revealed that areas in the prefrontal cortex were shown to play a vital role in working memory (Fuster & Alexander, 1971; Lara & Wallis, 2015). Neuroimaging evidence concurred, finding reliable engagement of frontal areas (Courtney et al., 1998). The modern consensus is that working memory relies on a widespread cortical network (Chai et al., 2018; D'Esposito & Postle, 2015), with a particular emphasis on prefrontal and parietal regions.

Consistent with the critical role of frontal regions in working memory function, age-related changes in behavioural working memory performance are frequently associated with neural

changes in this area. Specifically, Mattay et al. (2006) observed that at higher working memory loads when older adults performed poorer than younger adults, they showed greater prefrontal activation. This was therefore interpreted as compensatory activity. Additionally, Nissim et al. (2017) demonstrated that lower-performance older adults showed significantly reduced cortical surface area in prefrontal regions relative to their higher-performance counterparts. Finally, Wang et al. (2011) observed in non-human primates that neurons active during the delay period of WM showed reduced firing rates with increasing age.

1.5 Frontal Regions and Working Memory

It is not fully understood the degree to which there is functional localisation within the WM network, but it has been posited that frontal activity may resemble the executive component of Baddeley & Hitch's model. That is to say that frontal areas play a supervisory role rather than directly encoding and maintaining working memory representations through their activity (D'Esposito et al., 1995; Lara & Wallis, 2015; Lee et al., 2013; Nee et al., 2013). Specifically, frontal regions may bias and interact with posterior regions in a form of top-down control (Gazzaley & Nobre, 2012; Zanto et al., 2011). Rather than directly coding for a given WM representation, these frontal regions may encode contextual or task-related information (e.g., Warden & Miller, 2010). In agreement with this perspective, the ability to decode stimulus content appears to be largely limited to posterior regions, especially sensory processing areas (D'Esposito & Postle, 2015).

This assertion is not universally accepted, however, and other studies have reported that they are able to show stimulus-specificity from frontal regions. One notable fMRI study (Ester et al., 2015), found that features of remembered content could indeed be decoded from frontal regions. The authors suggest that previous failures to identify this may be explained by content being held by neural means not easily detectable, such as in an activity silent framework. Alternatively it may be that content is in fact held simultaneously in several nodes of the working memory network (Christophel et al., 2017). That is to say that the brain

may ‘hold’ items (show content-differentiating activity), in two or more distinct neural locations, such that the activity at either is sufficient to decode certain stimulus properties. This may explain regional discrepancies in finding stimulus-specific activity but it does prompt the question as to why the brain spends valuable energy maintaining a possibly redundant stimulus code. Explanations could be that different representations are encoded at different levels of abstraction. Alternatively, it could be that multiple copies of a stimulus are maintained in different areas to accomplish different ends.

Work in humans often relies on non-invasive methods such as fMRI and M/EEG, but direct invasive recordings in animals, particularly in non-human primates, also shed light on the role of prefrontal regions in working memory. Such studies generally support the findings in humans that prefrontal areas are critical to working memory functionality (Funahashi et al., 1993; Fuster & Alexander, 1971; Lara & Wallis, 2015; Riley & Constantinidis, 2016). In contrast to decoding work with human data, however, the balance of evidence does perhaps favour the existence of stimulus-selective activity in primate prefrontal regions (Constantinidis et al., 2001; Meyer et al., 2011; Miller et al., 1996; Zaksas & Pasternak, 2006). Thus, the PFC appears implicated in directly maintaining WM representations. This is in opposition to the prevailing view from human data that representations are maintained by early sensory areas, in accordance with the sensory recruitment model (Riggall & Postle, 2012). Mendoza-Halliday et al. (2014), for example, demonstrated during the delay period of a WM task, motion direction-selective firing in lateral PFC but not in middle temporal (MT) area, a region that would be expected to engage in motion-related processing in a non-memory context. The authors suggested that the failure to show such stimulus-selective activity in humans may be due to a lack of resolution when using fMRI. These findings are not unanimous, however. Lara & Wallis (2014) recorded directly from PFC neurons in macaques during a change detection task that required retention of the precise colour of multiple stimuli. The activity of these neurons did not appear to encode the colour of the stimuli and they were instead implicated in organising WM-guided behaviour. Given that this

conflicted with previous evidence of colour coding by PFC, the authors postulated that the degree of precision with which a stimulus must be retained may influence the PFC's precise role in WM maintenance. As with the human data, direct recordings from non-human primates are therefore not incompatible with the idea of distributed storage, with neuronal resources flexibly allocated according to task demands (Lorenc & Sreenivasan, 2021; Salazar et al., 2012).

A related and unresolved question is the purpose of sustained firing activity during working memory maintenance. Initially it was thought that an assembly of neurons representing a specific stimulus would continue firing in the absence of this stimulus and that it was through these continued neuronal spikes that the stimulus code was maintained. However several recent lines of evidence have questioned whether this is the most likely explanation. Detection of persistent activity may have been in part due to averaging over trials, which smeared brief, sporadic high-frequency bursts across time (Lundqvist et al., 2016, 2018). It has recently been suggested that retention of a stimulus may be accomplished by rapid short-term changes in synaptic plasticity (Masse et al., 2019; Stokes, 2015; Zucker & Regehr, 2002). This proposed mechanism has been termed activity-silent working memory. Distinct from the absence of evidence for persistent firing, there is some positive evidence for 'activity-silent' WM content. Namely, Wolff et al. (2017) demonstrated that following a 'pinging' method (Wolff et al., 2015) using an irrelevant stimulus, visual WM content previously undecodable from EEG activity became reactivated. Whether traditional sustained activity and activity-silent traces constitute complementary mechanisms or opposing explanatory theories has yet to be determined (Barbosa et al., 2019).

1.6 Transcranial Current Stimulation and Working Memory

Non-invasive stimulation methods targeting the prefrontal cortex have further reinforced its importance in successful WM function. In addition to work with transcranial magnetic stimulation (TMS) (Balconi, 2013), stimulation studies have been aided by the resurgence of transcranial electrical stimulation largely triggered by Nitsche & Paulus (2000). This research

employed transcranial direct current stimulation (tDCS) in which mild electrical currents were applied across the scalp and were shown to alter the amplitude of motor-evoked potentials. Creating a weak electric field in the brain via this method is believed to increase neuronal excitability via membrane depolarisation (Medeiros et al., 2012). Applying this technique to cognition, an early study found that targeting the left dorsolateral prefrontal cortex (DLPFC) was effective in increasing the accuracy of responses in a visuo-verbal 3-back task (Fregni et al., 2005). The number of studies investigating the potential of tDCS to modulate WM function has increased dramatically since. Several meta-analyses attempting to summarise such work show discrepancies with some suggesting a small beneficial effect of stimulation (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016a; Mancuso et al., 2016), and others judging it unlikely that tDCS has any effect (Hill, Fitzgerald, et al., 2016; Horvath et al., 2015; Medina & Cason, 2017; Nilsson et al., 2017). Whilst much work has employed tDCS, there have also been attempts to instead target rhythmic activity via transcranial alternating current stimulation (tACS). This method relies on similar principles to tDCS but rather than hoping to modulate excitability, tACS involves the application of fluctuating electrical fields which influence the timing of neuronal firing. Specifically, via the process of entrainment, the driving frequency of the exogenous electrical rhythm is thought to be able to influence the frequency and timing of endogenous brain-generated rhythms (Herrmann et al., 2013). Accordingly, tACS has been shown to modulate working memory performance in several paradigms (Abellaneda-Pérez et al., 2020; Hoy et al., 2015; Jaušovec & Jaušovec, 2014; Reinhart & Nguyen, 2019; Vosskuhl et al., 2015).

1.7 Transcranial Current Stimulation Efficacy

Conceptually and empirically, there have been criticisms of the principles underlying transcranial current stimulation, both with direct and alternating currents. Vöröslakos et al (2018) argued that the current is not sufficiently strong to influence activity once it has passed through the scalp; as did Lafon et al (2017). The debate remains unresolved, as other work also employing direct, invasive methods show that stimulation does indeed

modulate neuronal activity (Krause et al., 2019). These findings have themselves been questioned, with the authors commenting that the translation between the primate and the human head resulted in the relative electric field being much stronger than is typically used (Khatoun et al., 2019). Additionally, the degree to which the success of tACS interventions, particularly in the motor cortex, can be attributed instead to entrainment of cutaneous nerve cells remains unclear (Asamoah et al., 2019).

1.8 Working Memory and the Medial Temporal Lobe

In addition to these cortical areas, more recently the role of the medial temporal lobe in working memory has come into question. Despite initial findings that working memory performance was unaffected by lesions to this region, several lesion studies found that patients with damage to the medial temporal lobe were in fact impaired and it was suggested that perhaps WM did indeed recruit the hippocampus (Cabeza, Dolcos, et al., 2002; Graham et al., 2010), although the evidence was not unequivocal (Baddeley et al., 2011). Jeneson & Squire (2012), in reviewing lesion and neuroimaging data, suggested that those studies demonstrating hippocampal involvement were perhaps not exclusively tapping into working memory. They concluded that the focus on the duration of the task obscured the fact that long-term memory processes could be employed to facilitate performance, particularly in cases of high WM load. A more recent framework has also emphasised the possible recruitment of episodic memory processes (Beukers et al., 2021). Whether MTL involvement reflects interaction between memory systems (Lewis-Peacock & Postle, 2008) and whether an exclusively WM-dependent task would elicit hippocampal involvement remains unclear.

1.9 Episodic Memory

As alluded to previously, episodic memory can be distinguished from working memory primarily by its apparent lack of capacity and duration limits. Episodic memory functions over a much longer timescale and can be considered a form of mental time travel in which an individual may consciously re-experience an event in the past (Tulving, 2002). As opposed

to semantic memory, a form of declarative memory that constitutes factual knowledge (Binder & Desai, 2011), it can be thought of as binding together 'what', 'where', and 'when' information together into a coherent memory episode which can be consciously recollected at a later time. Typical tasks requiring episodic memory involve binding together two or more stimuli at an encoding stage and later being cued to retrieve the full memory based on a cue stimulus or presentation of one component of the stimulus pair (Fisher & Craik, 1977).

1.10 Episodic Memory and the Medial Temporal Lobe

In contrast to WM, the medial temporal lobe has long-been seen as a key hub of episodic memory. The medial temporal lobe refers to a set of structures: the hippocampus and entorhinal, perirhinal, and parahippocampal cortices (Squire et al., 2004; Squire & Zola-Morgan, 1991), shown to be critical to human episodic memory processes (Eichenbaum et al., 2007; Eichenbaum, 2013; Ritchey et al., 2015). Specifically, human lesion studies have consistently implicated the hippocampus in memory encoding, recognition, and recall processes (Squire et al., 2007). Neuroimaging work has shown increased activation of the hippocampus and surrounding structures associated with performance on behavioural memory tasks (Wais, 2008) and the amount of information recalled (Rugg et al., 2012).

The precise role of the hippocampus at a computational level remains not fully elucidated. It has been suggested that the hippocampus contributes to episodic memory function by specialised pattern separation and pattern completion accomplished within its subfields (Horner et al., 2015; Knierim & Neunuebel, 2016). The hippocampus receives input from many cortical streams (Montaldi & Mayes, 2010) and may be critical in binding together item and contextual information (Ranganath, 2010). It is generally agreed that the hippocampus is important for rapid encoding of memories which only later migrate to the neocortex and become independent of the hippocampus (McClelland et al., 2020; O'Reilly & Norman, 2002).

1.11 Neural Oscillations

Neural oscillations are rhythmic changes in the electric field potential in the brain. Given that the EEG signal as measured at the scalp is the summation of post-synaptic potentials from tens of thousands of geometrically aligned neurons, this activity represents synchronous activity across large populations of single neurons (Murakami & Okada, 2006). Oscillations are thought to facilitate cortical function through a number of mechanisms (Buzsáki, 2009; Buzsáki & Draguhn, 2004). Neurons possess physiological properties which can bias their responsiveness towards inputs of certain frequencies, thus favouring certain inputs over others. Additionally, inputs can further be selected for based on the timing of these inputs relative to the global, governing oscillation. Specifically, the phase of this overarching electrophysiological activity biases whether voltage-gated channels are likely to be open. Any one neuron's responsiveness is therefore influenced by the period of the oscillation when its membrane potential is closer to its threshold. Indeed it has been shown that the electrophysiological environment in which a neuron is situated does influence its activity (Anastassiou et al., 2011). It has been further suggested that not only are local fluctuations in potential useful for timing responsiveness, but that two or more groups of neurons are able to synchronise the phase of each group's respective rhythmic activity. This may be a means by which the brain ensures neuronal communication only occurs between these neuronal ensembles at the optimal time period of processing, a phenomenon that has been termed communication through coherence (Fries, 2005).

1.12 Working memory and Theta Oscillations

Rhythmic activity at a number of frequencies has been implicated in successful working memory performance, including alpha (8-12 Hz) oscillations (Bonnefond & Jensen, 2012; Foster et al., 2015; Herrmann et al., 2004; Jensen et al., 2002) and activity in the gamma band (>40 Hz) (Howard et al., 2003; Roux et al., 2012; Yamamoto et al., 2014). Activity in the theta (4-8Hz) band, in particular, is reliably observed prominently over fronto-medial EEG channels (Hsieh & Ranganath, 2014).

This theta activity is thought to originate locally in frontal areas (Raghavachari et al., 2006) although theta-related changes have been observed in the BOLD signal in several nodes of the default mode network (White et al., 2013), suggesting theta oscillations may be more widespread. One prominent candidate for an alternative or additional generator could be the hippocampus (Mitchell et al., 2008), where theta is a dominant rhythm. Indeed, the hippocampus consistently shows inter-regional coupling with frontal regions (Colgin, 2011; Gordon, 2011; Young & McNaughton, 2009). Additionally, prefrontal neurons have been shown to demonstrate firing preferences dependent on hippocampal theta phase (Siapas et al., 2005) and theta coherence between the hippocampus and prefrontal cortex is greater in later successfully integrated memory trials (Backus et al., 2016).

Whether locally generated or not, many studies have observed changes in frontal theta activity associated with WM engagement. Of particular significance was the observation that frontal theta activity elicited during the delay period of a Sternberg task increased with the number of to-be-remembered items (Jensen & Tesche, 2002). FMT power changes have since been repeatedly observed in WM-dependent tasks (Hsieh & Ranganath, 2014; Mitchell et al., 2008), especially when the order of items is important to encode (Hsieh et al., 2011) and during successful manipulation of working memory content (Itthipuripat et al., 2013). Additionally, work has revealed the importance of theta phase. In primates during a working memory task, single neurons in the extrastriate visual cortex showed a clear preference for firing during a specific theta phase (Lee et al., 2005)

1.13 Episodic Memory and Theta Oscillations

FMT activity has also been associated with the functioning of episodic memory. In contrasting successful episodic memory encoding events from those that were unsuccessful, several studies have observed elevated theta power (Klimesch et al., 1996; White et al., 2013) at several cortical sites. In addition to these subsequent memory effects, changes in the theta band have also been examined during memory retrieval (Osipova et al., 2006). More frequently implicated in both memory encoding and retrieval is theta activity in the

hippocampus (Colgin, 2013). In parallel with the exploration of its importance in working memory, the theta rhythm has long been investigated in relation to the hippocampus and its functions, especially in spatial navigation and memory (Buzsáki, 2002, 2005; Buzsáki & Moser, 2013). Since its discovery, theta activity was shown to correlate with memory processes (Landfield et al., 1972; Winson, 1978). In a seminal finding, place cells in the hippocampus showed phase precession, firing at distinct phases of an ongoing theta local field potential to encode spatial locations (O'Keefe, 1976).

Despite theta being a well-conserved rhythm across mammalian species (Las & Ulanovsky, 2014), it was initially unclear whether there was an analogous rhythm in the human hippocampus. The development of intracranial recording methods led to increasing evidence that there was indeed a memory-relevant theta rhythm in the human hippocampus (Jacobs & Kahana, 2010; Kahana et al., 2001). Notably, there remains some ambiguity concerning the exact frequency range as human theta may show a slightly different frequency profile (Jacobs, 2014). Specifically, it has been suggested that there exist two functionally distinct frequencies in the theta range, but that the rhythm most analogous to rodent memory-related theta is much lower in frequency around 3 Hz (Goyal et al., 2020). Nevertheless, a recent review corroborates that activity in the theta band in humans is reliably associated with episodic memory formation (Herweg et al., 2020).

1.14 The Functional Role of Theta

In addition to the general advantages of oscillatory activity, more memory-specific explanations have been proposed for how theta activity may facilitate memory function (Nyhus & Curran, 2010). Activity in the theta band may facilitate inter-regional communication (Kopell et al., 2013; Varela et al., 2001; Von Stein & Sarnthein, 2000) given the engagement of wide-ranging cortical regions in both working and episodic memory. In long-term memory, the theta rhythm in particular may be important in the induction of long-term potentiation (LTP) in the hippocampus (McCartney et al., 2004), which is considered a key cellular mechanism of memory (Lynch, 2004; Nicoll, 2017). Specifically, electrical

stimulation at a theta rhythm can induce LTP in hippocampal slices (Capocchi et al., 1992; Larson et al., 1986) and in the hippocampus in vivo (Hölscher et al., 1997). Theta may thus separate encoding and retrieval-related activity to ensure optimal timing of synaptic changes (Hasselmo, 2005; Hasselmo et al., 2002). In working memory, theta oscillations have been further proposed to temporally order discrete representations via nested gamma activity (Jensen & Lisman, 1998; Lisman & Jensen, 2013).

1.15 Thesis Overview

This research aims to better understand some of the spatio-temporal dynamics of the neural activity underlying core mnemonic processes.

Chapter 2 focuses on better characterising the electrophysiological dynamics during working memory maintenance and their relation to maintained content held in WM. In this experiment, visual stimuli of distinct categories were employed to facilitate decoding of specific working memory content. This allowed for an examination of key oscillatory components in conjunction with an information-based measure of content maintenance. Participants completed an N-back task where N was equal either to one or two as well as a delayed match-to-sample (DMS) task. Whilst these tasks were completed, 128 channel EEG was recorded. We were then able to examine changes in theta activity, both at fronto-medial sensors and whether these changes were evident elsewhere on the scalp. Adopting a multivariate decoding approach, we could also decode the category of WM content and identify which channels contributed to this decoding. Finally, we also examined how frontal theta frequency was modulated by an increasing number of to-be-remembered items.

Chapter 3 investigates the importance of the frontal cortex in working memory in older adults. Specifically, I test a proposed model of cognitive ageing known as the HAROLD model, so named as it posits a Hemispheric Asymmetry Reduction in OLDer individuals. There is evidence to suggest that there is functional lateralisation in the working memory system insofar as visuo-spatial and verbal information are preferentially processed in the

right and left dorsolateral prefrontal cortex respectively. The HAROLD model proposes that during ageing this laterality becomes less pronounced. Based on behavioural testing and neuroimaging, it has been suggested that the frontal cortex becomes less selective as a compensatory mechanism to account for age-related physiological changes. Although there is some observational evidence to suggest that this is the case, the argument for this model would be strengthened by acquiring causal evidence. In pursuit of this, older participants (aged 55-80) were stimulated via transcranial direct current stimulation whilst they performed an adaptive visuo-spatial N-back task. All participants experienced a stimulation and sham condition to examine whether, as has been found previously, stimulation of the DLPFC improves working memory performance. Crucially however, making use of novel 'high-definition' stimulation protocols participants were further sub-divided into laterality conditions in which participants were stimulated specifically stimulated over the left, the right, or both cerebral hemispheres. We were then able to test whether bilateral stimulation was more effective in improving working memory performance as compared to the condition wherein only one hemisphere was stimulated.

Chapter 4 reports analyses of intracranial data recordings from the human hippocampus designed to further investigate the role of theta oscillations in memory, in this case episodic memory. I test the predictions of a computational model which suggests discrete roles for the phase of on-going hippocampal theta oscillations in the human hippocampus. Patients awaiting surgery for intractable epilepsy completed a continuous episodic memory task. During encoding trials, patients were required to associate the name of an object with one of four colours. These associations were then tested via retrieval trials presented later in the same block. An object name was again presented with a colour and patients were required to judge whether this object had been presented previously and whether the colour it was now paired with was the same as it was during its respective encoding trial. Critically, before each of these trials began a cue was presented onscreen indicating whether the subsequent trial was to be an encoding trial (where the patient would be required to associate a word

with a colour) or a retrieval trial (where they would be required to recall a previously made association). According to the theta phase model, one could predict that the hippocampus would adopt a preferred encoding or retrieval state dependent on this cue.

Chapter 2: Fronto-medial Theta Orchestrates Posterior Maintenance of WM Content

2.1 Abstract

How does the human brain manage multiple bits of information to guide goal-directed behaviour? Successful working memory (WM) functioning has consistently been linked to oscillatory power in the theta frequency band (4-8 Hz) over fronto-medial cortex (fronto-medial theta, FMT). Specifically, FMT is thought to reflect the mechanism of an executive sub-system that coordinates maintenance of memory contents in posterior regions. However, direct evidence for the role of FMT in controlling specific WM content is lacking. Here we collected high-density Electroencephalography (EEG) data whilst participants engaged in WM-dependent tasks and then used multivariate decoding methods to examine WM content during the maintenance period. Engagement of WM was accompanied by a focal increase in FMT. Importantly, decoding of WM content was driven by posterior sites, which in turn showed increased functional theta coupling with fronto-medial channels. Finally, we observed a significant slowing of FMT frequency with increasing WM load, consistent with the hypothesised broadening of a theta 'duty cycle' to accommodate additional WM items. Together these findings demonstrate that frontal theta orchestrates posterior maintenance of WM content. Moreover, the observed frequency slowing elucidates the function of FMT oscillations by specifically supporting phase-coding accounts of WM.

2.2 Introduction

2.2.1 Subdividing Working Memory

Working memory (WM) is the ability to retain and manipulate information over short delays (Baddeley, 1992). It is thought to rely on at least two functionally distinct sub-systems (Baddeley, 2003). The first is an executive system, which directs cognitive

resources and oversees the prioritisation and readout of representations. This system interacts with the representational system, which directly holds task-relevant informational content. These two systems rely on disparate brain regions, in particular frontal and parietal areas (Bressler & Menon, 2010; Imaruoka et al., 2005; Owen et al., 2005; Vogel & Machizawa, 2004). Importantly, WM requires functional interactions between these systems. A prime mechanism to facilitate inter-regional communication in service of WM is oscillatory activity in the theta range (4-8 Hz) (Sauseng et al., 2010; Von Stein & Sarnthein, 2000).

2.2.2 The Theta-Gamma Model of WM

Specifically, according to an influential computational framework (Jensen & Lisman, 1998; Lisman & Idiart, 1995; Lisman & Jensen, 2013), theta oscillations provide gated processing windows in which neural representations of target information ('WM items') become active. Consistent with this model, non-human primate work has demonstrated that neurons coding for item-related information preferentially fire during particular theta phases (Siegel et al., 2009). Similarly, a recent study using intracranial recordings in humans has shown nesting of stimulus-related gamma activity (>30 Hz) in specific theta phases (Bahramisharif et al., 2018). Theta oscillations may thus constitute the mechanism governing goal-directed interactions between frontal executive and parietal representational subsystems (D'Esposito & Postle, 2015).

2.2.3 Fronto-medial Theta in WM

WM tasks consistently induce theta power increases at fronto-medial sites (fronto-medial theta, FMT) (Hsieh & Ranganath, 2014; Michels et al., 2010; Raghavachari et al., 2001). FMT is generally considered to originate locally in the medial prefrontal and anterior cingulate cortices (Cavanagh & Frank, 2014), based on source-

modelling (Meltzer et al., 2008; Mitchell et al., 2008; Tsujimoto et al., 2006). FMT has been linked to behavioural WM performance (Brzezicka et al., 2018; Maurer et al., 2014), as well as to individual WM capacity (Zakrzewska & Brzezicka, 2014). Consistent with this role for FMT, transcranial magnetic stimulation (TMS) in the theta range improved WM performance (Riddle et al., 2020). Importantly, non-invasive electrophysiological studies have detected fronto-parietal coupling via theta oscillations during WM tasks (Johnson et al., 2017; Dezfouli et al., 2021; Payne & Kounios, 2009). Additionally, experimental induction of fronto-parietal theta coupling via transcranial alternating current stimulation (tACS) increased WM performance (Polanía et al., 2012; Reinhart & Nguyen, 2019). Finally, EEG latency analyses between frontal and parietal regions suggest that the frontal cortex is the driver of these inter-regional interactions (Sauseng et al., 2004).

2.2.4 FMT as the orchestrator of posterior WM representation maintenance

These findings suggest the intriguing scenario that WM content, represented and maintained in posterior/parietal cortex, is orchestrated by frontal control mechanisms via theta oscillations. However, at present it is unclear (i) whether parietal cortex represents individual items held in WM and (ii) whether those parietal WM memoranda are in turn coordinated by FMT. Finally, it is unclear how theta rhythms orchestrate the storage of multiple items, e.g., maintaining two instead of one item in WM. On the one hand, this additional demand may be accommodated by an increase in theta amplitude/power, reflecting the participation of larger neuronal assemblies (Buzsáki & Draguhn, 2004). Conversely, the theta-gamma framework referred to above emphasises a role of oscillatory phase, which allows for separation of individual chunks of information (Lisman & Jensen, 2013). Accordingly, increasing load by requiring maintenance of an additional stimulus might induce a slowing of an

individual's theta frequency - the slower the frequency, the more item-coding assemblies can fire within a given cycle.

2.2.5 Experimental Findings

To answer these questions, we designed a paradigm in which we systematically varied WM demand and decoded the category of a maintained visual stimulus whilst recording high-density EEG. We first show that frontal theta power increases with increased WM engagement. Second, individual items held in WM were decodable from the EEG signal of posterior channels. Intriguingly, the same channels that enabled decoding showed significant coherence in the theta band with the frontal channels identified previously. Finally, we found that theta frequencies slow with an additional to-be-remembered item in WM, consistent with phase-coding accounts of WM maintenance. Together, these results elucidate the role of theta rhythms for linking frontal control mechanisms with posterior content representations during WM maintenance.

2.3 Methods

2.3.1 Software & Analysis Code

All behavioural tasks were created and presented using Matlab 2016b (MATLAB and Statistics Toolbox Release 2016b, The MathWorks, Inc., Natick, Massachusetts, United States) and Psychtoolbox (Version 3.0.16; Brainard, 1997; Kleiner et al., 2007). Analyses were conducted with custom Matlab and R scripts (Version 3.4.3; R Core Team, 2018). EEG analyses were performed with Fieldtrip functions (Version 20210308; Oostenveld et al., 2011). Plots also made use of *boundedline* (Kearney, 2019).

2.3.2 Participants

Thirty-three participants in total were tested. All participants gave written informed consent and all procedures were approved by the University of Birmingham Ethics

Committee. Participants were right-handed, aged between 18 and 35, and had no history of psychological or neurological disorder. Data from two participants were removed for low behavioural performance (see Statistics section for further detail). Data from a further three participants were removed due to poor EEG quality. All analyses therefore focussed on the remaining 28 participants (18 female, mean age of 22.64 years, SD = 3.95, range = 18-33). This sample size provides 80% power to detect a Cohen's d effect size of >= 0.55. WM-induced FMT effects have been observed with similar or smaller sample sizes (e.g., Jensen & Tesche, 2002; Scheeringa et al., 2009).

2.3.3 Subject Exclusion Criterion

Behavioural accuracy was calculated as the proportion of correct responses out of all trials. For outlier analysis, a composite score for each participant was computed by taking the mean accuracy on all three tasks. Outliers were defined as any value more than 1.5 inter-quartile ranges below the lower quartile or above the upper quartile across all participants. As mentioned in the Participants section, this resulted in two participants being removed from subsequent analyses due to outlying low behavioural accuracy.

2.3.3 Procedure

Two behavioural tasks were employed in this experiment: a delayed-match-to-sample (DMS) task and an N-back task featuring two levels of working memory load. Stimuli were 350x350 pixel colour images of one of three categories: object, face, or scene. There were five unique stimuli from each category. The DMS task included all three categories, whereas the N-back task used only the object and the scene stimuli. The additional category in the DMS task was included to facilitate alternative

analyses outside the scope of the results we report here. The stimuli were obtained from the BOSS (Brodeur et al., 2010) and SUN (Xiao et al., 2010) online databases.

After EEG setup was complete, participants performed the first run of the DMS task. Within each run, each unique image (to-be-compared to the probe) was presented six times. Across both runs of the DMS task, each stimulus was therefore presented 12 times. Given the 15 unique stimuli presented, this resulted in a total of 180 trials across the DMS task. For each trial a randomly selected probe image was presented. Following completion of the DMS task, participants completed the N-back task, which consisted of 12 blocks (8x2-back; 4x1-back). Each block contained 36+n trials. At the beginning and the end of each of these blocks, a fixation cross was present on the screen and participants were instructed to focus on the cross and to think of nothing in particular. This period served as a cognitive baseline. A pre-stimulus fixation period was not employed during the task because in the N-back task trials were not discrete. Specifically, any one item needed to be maintained from one trial to another and so there was no time at which participants were not required to hold stimulus content in WM. After completion of the N-back task, participants performed the second run of the DMS task in which each stimulus was again presented six times in a random order. The two runs were performed before and after the N-back task to account for any changes in the EEG signal across the recording session (e.g., signal drift).

2.3.4 Experimental Design and Statistical Analysis

The experimental tasks are illustrated in Figure 2.1. In the Delayed-match-to-sample (DMS) task, participants were asked to focus on a central fixation cross before an image of an object, scene, or face was presented for ≥750 ms. After a delay period of ≥2500 ms, a probe stimulus (randomly selected from the full stimulus set) was

shown for ≥750 ms. In the subsequent response window, an ‘X’ was present on the screen for 750 ms and participants responded using either the left or right arrow key (counter-balanced across participants) to indicate whether the probe’s identity was the same as the first image presented in the trial (i.e., whether it was a ‘match’ or ‘non-match’). In both cases, participants were required to make a response. Here and in the N-back task, identity refers to the unique stimulus. Thus although stimuli of different categories were employed in both tasks, the category of any stimulus had no bearing on the task the participant had been instructed to perform. The duration of the initial stimulus, delay period, and the probe stimulus were all jittered so that trials lasted for the base duration plus 0, 50, 100, or 150 ms. Each trial’s temporal jitter was randomly assigned ensuring that each jitter possibility (including no jitter) was equally represented in each block independent of category.

In the N-back task, participants were presented with an image of an object or a scene for ≥750 ms. An ‘X’ then appeared on the screen for 750 ms during which participants were required to respond ‘match’ or ‘non-match’ with either the left or right arrow key (counter-balanced across participants) to indicate whether the identity of stimulus just seen matched that of the stimulus seen *n* trials back. As before, identity here refers to a singular stimulus meaning that the category of a given stimulus (object/scene) was orthogonal to the task the participants were required to perform. A ‘+’ was then presented for ≥2500 ms. Participants were required to maintain the relevant stimulus (1-back) or stimuli (2-back), so that they could make the N-back match/non-match judgement on the following trial. The stimulus and delay periods were jittered by 0, 50, 100, or 150 ms. As with the DMS task, the possible jitter options were balanced within blocks independent of stimulus category.

2.3.5 EEG setup and Pre-processing

EEG data were collected using a BioSemi system with 128 channels at a 1024 Hz sampling rate. Data were re-referenced offline to the average of the two mastoids. Eye blinks were removed from data using independent components analysis, as implemented by 'runica' in Fieldtrip's *ft_componentanalysis*. Consistently noisy channels were interpolated using a weighted average of neighbours. Data were then high-pass filtered at 0.3 Hz prior to all other analyses.

2.3.6 Time-frequency Calculations

Time-frequency spectra were calculated using Fieldtrip's *mtmconvol* function. Power in frequencies from 2 to 10 Hz (0.5 Hz steps) were computed across the delay period using a Hanning taper. Power was resolved in 50 ms increments. Data were convolved with a variable number of cycles per frequency band. Two cycles were used for frequencies 2-3.5 Hz; 3 cycles for 4-4.5 Hz; 4 cycles for 5-5.5 Hz; and 5 cycles for 6-10 Hz. These power values were averaged across the full delay period and compared between the 1-back task and the DMS task.

Following this analysis, we assessed whether there was a difference in the FMT peak frequency for 1-back vs. 2-back tasks. To this end, spectral power was calculated for all channels that were members of the frontal cluster previously identified. Power was computed for frequencies between 4-8 Hz in 0.2 Hz increments across the full delay period for both conditions for each of these channels. For this analysis, power was calculated via Fieldtrip's *mtmfft* function. Power spectra from individual channels were then averaged. Thus, for the resulting power spectrum of each participant and every trial, local maxima were identified (Matlab function *findpeaks*). The frequency at which the most prominent of these peaks occurred was logged for every trial. These peak frequency values were then

separated into load conditions and averaged across trials. This value was obtained for each participant for 1-back and 2-back trials. Differences in theta peak frequency between the two load conditions were compared via a paired-samples t-test. To obviate the possibility that any difference in these values reflects a shift in the slope of the 1/f component of the EEG signal (Donoghue et al., 2020), the IRASA method (Irregular Resampling Auto-Spectral Analysis; (Wen & Liu, 2016)) was employed to remove the 1/f component from the signal. Additionally, to ensure that this result was not a consequence of any volatility in single-trial power spectra, the analysis was also conducted on smoothed frequency spectra. The spectra were smoothed prior to peak detection via a sliding mean average using the Matlab function *smoothdata*. The degree of smoothing was varied between 2 and 5 elements (approximately 0.2-1.0 Hz window). For all of the preceding peak-based analyses, a trial was discarded if no peak was detected in that trial. Less than 1% of trials were discarded in all variations of this analysis (regardless of whether IRASA or smoothing was employed).

2.3.6 Classification

To decode object vs. scene representations during WM maintenance, multivariate pattern analyses (MVPA) was performed with the MVPA-light toolbox (Treder, 2020). To reduce computational time of classification, data were resampled to 200 Hz. Prior to classification, data in the stimulus, response, and delay periods were smoothed with a running average (100 ms sliding window) and baseline-corrected to the preceding 200 ms. Trials were averaged within exemplar stimuli, as this has been shown to improve decoding performance (Grootswagers et al., 2017). In order to maintain a reasonable trial count this was only done by a factor of ~2. Trials of a given stimulus were randomly assigned to pairs and averaged, resulting in a single

trial with presumed higher signal-to-noise ratio. Remainder trials (in the case of odd trials) proceeded to classification unaveraged. For all classification analyses, linear discriminant analysis (LDA) was employed by taking the voltage values of the EEG channels as features at every time point. Classification was performed on all trials using a k-fold cross-validation procedure in which data were divided into 5 folds (4 training and 1 testing) in 5 iterations. This cross-validation procedure was repeated 5 times. The accuracy values across folds and repetitions were averaged to produce the final classifier performance. Decoding was conducted by training and testing classifiers on each time point of the task to generate a complete time by time temporal generalisation matrix. To examine whether the stimulus period generalised to the delay period, this time by time matrix was averaged across the training time dimension to the period when the stimulus was on the screen (0-750 ms), resulting in a time-series of average classifier accuracy across the testing time dimension (the time axis of the delay period). To determine which channels were most informative to correct classification, we implemented a searchlight approach in which, moving around the channel map of all 128 channels successively, an individual channel and its neighbours (radius = 0.10) were used to classify the data. The searchlight varied in size based on the number of neighbours, but on average the searchlight constituted 5.7 channels. The resultant accuracy for each of the searchlight centres was then tested against chance. Searchlight classification was performed by training and testing during the window in which significant above-chance decoding was observed including all channels (860-1275 ms into the delay period). As mentioned in the results section, when assessing stimulus-to-delay generalisation and when decoding with only those channels that showed the coherence effect, accuracy values were again averaged across this previously defined temporal window of

interest (860-1275 ms). The result of these analyses remained the same when accuracies were averaged or corrected (via cluster-correction) across the full delay period (See Figure A1.1). Finally, we also confirmed stimulus decodability during the DMS task (See Figure A1.4).

2.3.7 Connectivity

To assess load-dependent changes in functional connectivity, cross-spectral densities were computed across the full time period via the Fieldtrip function *mtmconvol* using the same settings as in the time-frequency decomposition described previously. Pairwise channel coherence in the theta range (4-8 Hz) between channel Fz and every other channel was derived in the delay period of the 1-back task and the DMS task. Data from the DMS task were sub-sampled 10 times to accommodate the lower trial count in the 1-back condition (Bastos & Schoffelen, 2016). These sub-sampled coherence maps were averaged before condition contrasts. Note also that, the impact of trial count on coherence precluded the use of the inter-block baseline periods as a comparator for 1-back trials, as there were only 24 inter-block baseline periods. Coherence values were compared statistically between 1-back and DMS conditions via cluster-based permutation tests in the time during the delay period where there was significant decoding above chance (860-1275ms) (Maris & Oostenveld, 2007). As noted in the results section, coherence values from the 1-back task were also averaged across the full 2.5 seconds of the delay period and compared to those from the DMS task.

To determine whether theta coherence was also greater in the 2-back task relative to the DMS task, coherence values were compared with cluster correction (as described above), again averaging across the full delay period. Significant clusters emerged when contrasting both the 1-back task and the 2-back task delay period

with the DMS task, showing increased coherence over central posterior channels. In order to assess whether there was a frequency shift between 1-back and 2-back tasks, coherence values were averaged across channels which were members of both the 1-back and 2-back clusters (as depicted in Figure A1.5A). Coherence values were further averaged over the full delay period. Finally, coherence values from the 1-back task were subtracted from the 2-back task to reveal at which frequency in the theta band coherence was significantly greater in the 2-back task than in the 1-back task. The resulting 2-back – 1-back difference in coherence was then subjected to a paired-samples t-test.

2.3.8 Inferential Statistics

An alpha level of 0.05 was used as the threshold for statistical significance and tests were conducted as 2-tailed. To control for multiple comparisons across dimensions when assessing load-dependent power changes (channel/ frequency/time) or when assessing searchlight classification (channel/time), non-parametric cluster-based permutation testing was employed (Maris & Oostenveld, 2007). Briefly, this is achieved by first testing the spatio-spectro-temporal data via conventional statistics. Clusters are then formed where significant values are adjacent in sensor space, frequency and time. A specific metric of this cluster, e.g. the sum of its t-values, can be compared to a distribution of permuted cluster statistics to determine whether that cluster is statistically significant. This permutation testing was based on the maximum sum of a cluster's t-values, 500 permutations and at least three neighbouring channels constituting a cluster. To control for multiple comparisons otherwise, the Holm correction was employed (Holm, 1979). All statistical details are available in the body text of the results section or in the relevant figure legend. Statistical testing was done via Matlab (MATLAB and Statistics Toolbox Release

2016b, The MathWorks, Inc., Natick, Massachusetts, United States) and R (Version 3.4.3; R Core Team, 2018).

2.4 Results

2.4.1 Oscillatory Mechanisms of WM Maintenance

Our first goal was to confirm the role of fronto-medial theta (FMT) in WM maintenance. We therefore employed a 1-back task, requiring participants to encode, maintain, compare and drop items in a continuous stream of stimuli. As a control condition, we used a Delayed Match-to-Sample (DMS) task, which is similar in its general structure, but crucially different in the level of demand posed on the WM executive (Figure 2.1). Previous work has demonstrated the feasibility of comparing a 1-back task to a variant of the DMS task (the Sternberg task) in order to isolate FMT power (Brookes et al., 2011), arguably due to the enhanced demand to maintain the temporal order of items (Hsieh et al., 2011).

Analysis of behavioural accuracy confirmed increased task difficulty for the 1-back task compared to the DMS task, despite high performance in both tasks (Figure 2.1; 1-back: 94% mean accuracy; SD = 6.59%; DMS: 96% mean accuracy; SD = 3.97%, paired-samples t-test, $t_{(27)} = -2.40$; $p = 0.024$, Cohen's $d = 0.45$).

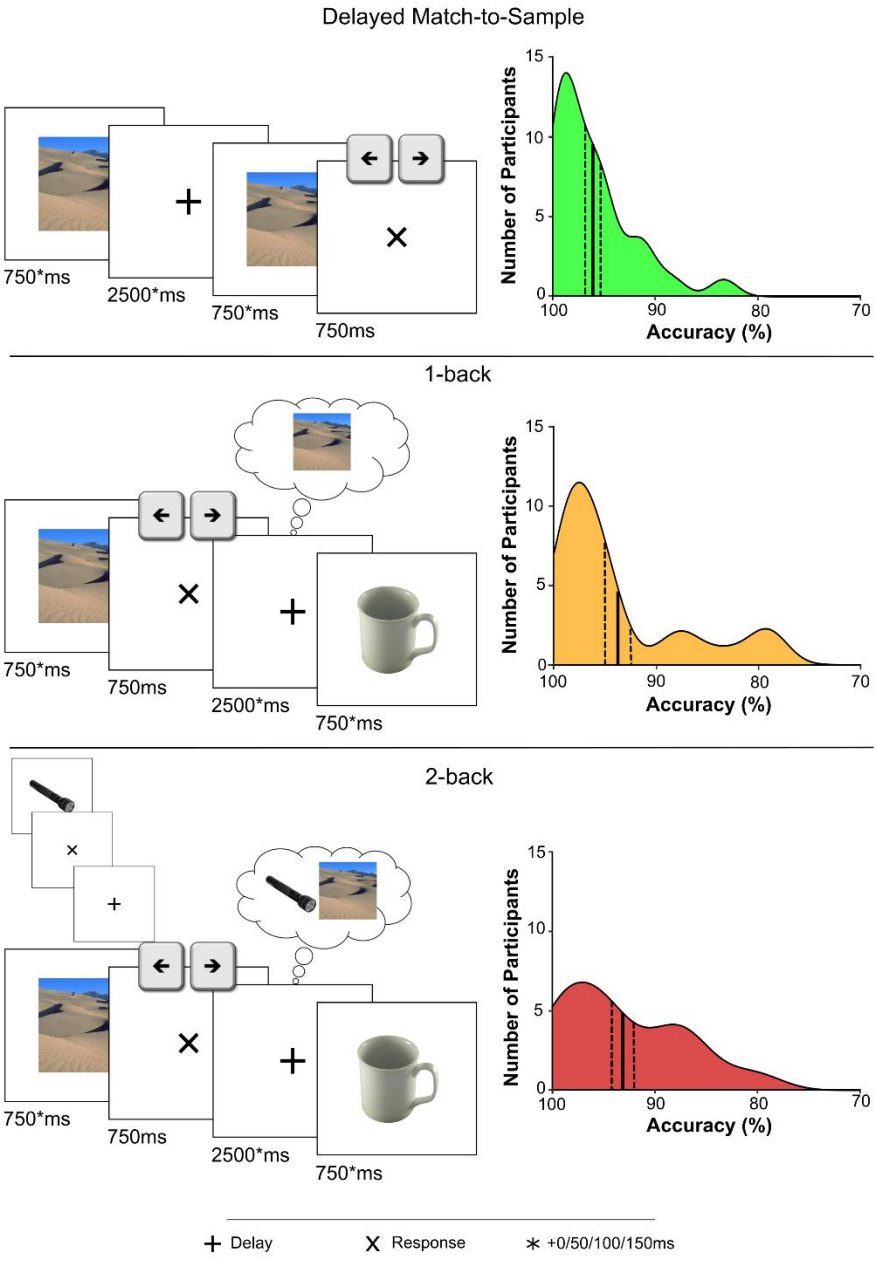

Figure 2.1. **Experimental paradigm and behavioural results.** Trial design (left) and distributions of behavioural accuracy (right) in three WM tasks performed during acquisition of EEG: a delayed-match-to-sample (DMS) task (top), a 1-back task (middle) and a 2-back task (bottom). Solid black lines indicate the mean behavioural accuracy and dashed black lines indicate the standard error of the mean across participants.

To examine oscillatory activity, spectral power was calculated in the delay period of both the 1-back and the DMS tasks, averaging power values across the full 2.5 second delay period. A permutation-based cluster-corrected paired-samples t-test was then conducted on these channel-frequency spectra. Results revealed a

significant cluster in which theta power was greater in the 1-back task as compared to the DMS task. This cluster was centred primarily around 5.5-7 Hz but spanned the entire theta frequency band (4-8 Hz; Figure 2.2A). Collapsing across the 4-8 Hz frequency range illustrates this effect is driven by fronto-medial channels (Figure 2.2B), consistent with previous work identifying fronto-medial sources of WM-related theta oscillations (Onton et al., 2005; Zuure et al., 2020). To determine directly the effect size of this increase, power values were first averaged across the 4-8 Hz range, across the full time period and over significant channels (identified by the cluster-based permutation effect). This recapitulated the result of the cluster test [$t_{(27)}$ = 3.44, p = 0.002] and showed that this effect was in the moderate to large range [Cohen's d = 0.65] (Cohen, 1992). Across participants, the change in FMT from the DMS task to the 1-back task negatively correlated with the change in accuracy [$r_{(27)}$ = -0.40, p = 0.04] - but not with the change in reaction time [$r_{(27)}$ = 0.04, p = 0.62] - between the two tasks. This finding is consistent with previous work (Maurer et al., 2014) and links WM demands (as reflected in reduced overall performance) to FMT power across individuals.

To ensure that the FMT effect we observed does not hinge on the comparison with the DMS task, we contrasted the maintenance period of the 1-back task to a neutral baseline condition. Although a pre-stimulus baseline period was not possible in the 1-back task (in which information must be held between trials), a 10 second inter-block baseline period was acquired before and after each block of the N-back task (see Methods). When power in the delay period was compared to this inter-block baseline, a fronto-medial theta cluster again emerged over frontal channels (see Figure A1.1), similar in topography to comparing the 1-back task to the DMS task (albeit less well-circumscribed).

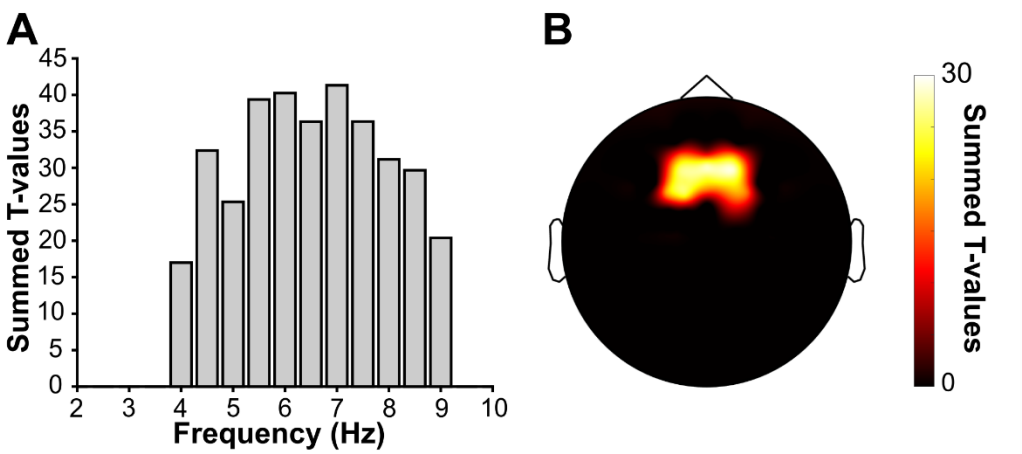

Figure 2.2. WM-induced fronto-medial theta (FMT) power. Cluster-corrected comparison of oscillatory power in the delay period of the 1-back task relative to the same period in the DMS task revealed a significant increase in theta power (4-8 Hz; **A**, summed across significant channels) at fronto-medial channels (**B**, summed across significant frequencies from 4-8 Hz – note the same topography of significant channels emerged when summing across the full 4-9 Hz range).

2.4.2 Decoding Stimulus Category During WM Maintenance

We next addressed the question of when and where WM content is maintained during the delay period. To this end, multivariate pattern classification was applied to the delay period of object and scene trials of the 1-back task. Specifically, the ability to decode stimulus content was assessed via linear discriminant analysis (LDA) in a k-fold cross-validation regimen using – at each time point – the raw EEG signal across channels as features (see method section for additional details). Classifier accuracy was compared to chance (50%) and corrected across time by cluster-based permutation. As shown in Figure 2.3A, this comparison revealed an extended interval of significant above-chance decoding during the delay period, i.e., when no stimulus was visually present. This time window in the delay period (860-1275 ms) was then selected as our temporal region of interest for subsequent delay period

decoding analyses. Importantly however, results using this time period remained the same if decoding accuracies were instead averaged or cluster-corrected across the entire delay period duration (see Table A1.1). Classification was also conducted on the stimulus and response periods, both of which showed periods of accurate decoding across time (Figure 2.2Aii). Although baseline-correcting each epoch individually (with each epoch's preceding 200ms) was used to prevent any spill-over across epochs, classification was also performed with baseline-correcting data only once using the pre-stimulus period. This approach largely replicated the decoding findings as before, showing that decoding accuracy was especially pronounced during the stimulus and delay periods of the 1-back task (see Figure A1.2B i-iii). To further ensure that decodability reflected the goal-directed WM representation of a previously experienced stimulus, we examined the performance of a classifier trained on the stimulus period of the task and tested on the delay period. Above-chance decoding in this case indicates temporal generalisation and therefore reactivation of the stimulus-related pattern. Classifier accuracy was indeed significantly greater than chance [$t_{(27)} = 4.85$, $p < 0.001$, Cohen's $d = 0.92$] (Figure A1.2Aiii).

Previous findings suggest that visual WM content is maintained by posterior sensory rather than frontal executive regions (Sreenivasan et al., 2014). We thus repeated the classification analysis with a searchlight approach, specifically during the delay period where no visual information was on-screen. Classification performance was assessed for each channel, including its immediate neighbours (mean number of neighbours = 5.7) and focussing on the period that showed maximal decoding across time when including all channels (860-1275 ms into the delay period; Figure 2.3A). This approach revealed that stimulus decoding during the delay period was driven

largely by central posterior channels (Figure 2.3B). Examining the unthresholded searchlight statistic (when comparing against chance) corroborated that decoding was driven maximally by posterior channels distinct from the previously identified frontal cluster that showed the theta power increase (See Figure A1.3).

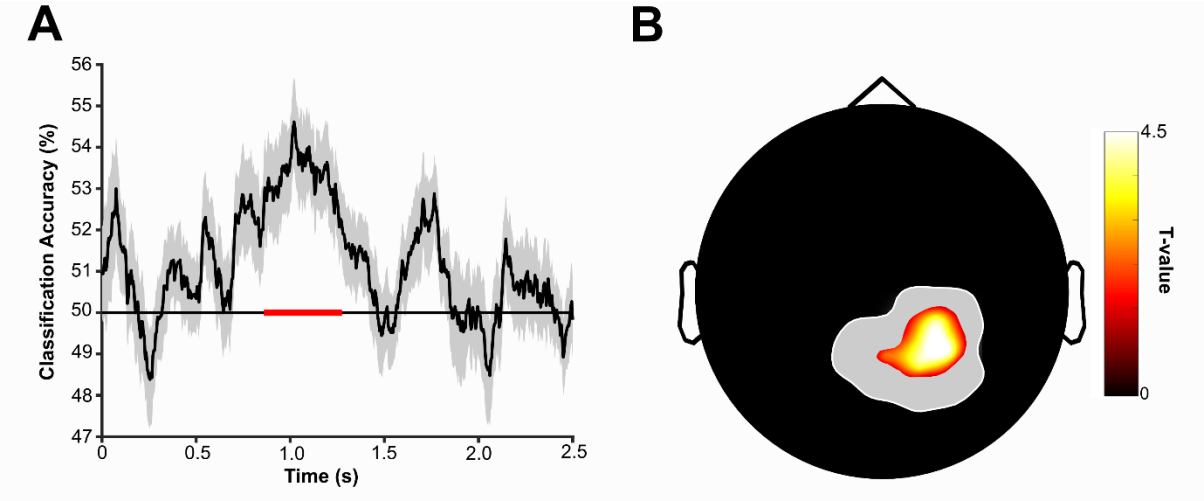

Figure 2.3. Multivariate decoding of WM representations during the 1-back task. A. Decoding (mean +/- SEM across participants) of object vs. scene stimuli across time showed significant above-chance (50%) accuracy in the delay period of the 1-back task (860-1275 ms into the delay period). The depicted delay period reflects the minimum duration, omitting the variable jitter. The solid red line indicates cluster-corrected significance ($p < .05$). **B.** Spatial searchlight decoding during the significant delay period, revealing maximum performance at central-posterior channels (corrected t test vs. chance). The grey outline indicates the maximum extent of the searchlight cluster (i.e., including searchlight centre and its neighbours; see Method section for neighbour definition).

Together, these results suggest that stimulus content maintained in WM can be decoded successfully during the delay period of a 1-back task. The central-posterior topography of maximal decodability (despite WM-load-related theta changes over fronto-medial channels; Figure 2.2B) is consistent with findings from fMRI (Harrison & Tong, 2009) and with the notion of frontal theta as an executive control system that does not directly maintain WM content (D'Esposito & Postle, 2015).

2.4.3 Posterior Channels Are Functionally Coupled With Frontal Theta

We next probed whether regions involved in the maintenance of WM content (Figure 2.3) are coupled to frontal theta rhythms (Figure 2.2). If theta activity does indeed serve as the mediator between frontal executive and posterior representational regions, one would expect increased coherence between these two regions as a result of increased WM engagement. Consequently, we calculated coherence values between channel Fz (representing the centre of the frontal theta cluster previously identified, Figure 2.2B) and every other channel during the portion of the delay period when content could be significantly decoded (i.e., 860-1275 ms, Figure 2.4). Comparison of coherence maps for 1-back vs. DMS tasks revealed a significant central-posterior cluster of increased coherence. Of note and as illustrated in the inset of Figure 2.4, the resulting cluster overlapped markedly with results from our searchlight decoding approach (Figure 3B), suggesting that at least some of the same regions that maintain WM content are coupled to the frontal theta rhythm. Examining the frequency profile of this cluster, it showed maximal coherence at ~7 Hz (results not shown), which matches the peak frequency of the frontal power effect (see Figure 2.2B). A similar cluster (both in frequency and topography) was also present when coherence values were averaged across the full delay period.

To corroborate the regional overlap between (i) coherence with FMT and (ii) stimulus category decoding, we first repeated the classification analysis but used only those channels that showed significant coherence in the theta band with frontal regions. Indeed, this approach yielded significant above-chance decoding [$t_{(27)}$ = 2.70, p = 0.01, Cohen's d = 0.51]. Second, we divided the cluster of significant coherence with FMT into (i) channels that also show significant stimulus category decoding (including any channel that was a member of a significant searchlight cluster, as in

Figure 2.3B and the inset of Figure 2.4) and (ii) channels that do not show significant stimulus category decoding. Direct comparison of peak coherence strength with frontal regions (7 Hz) revealed significantly greater coherence for those channels in which we observed significant stimulus category decoding [$t_{(27)}$ = 2.51, p = 0.018, Cohen's d = 0.47]). Together, these analyses suggest that functional coupling with frontal regions is particularly enhanced in those posterior regions that represent the maintained stimulus category.

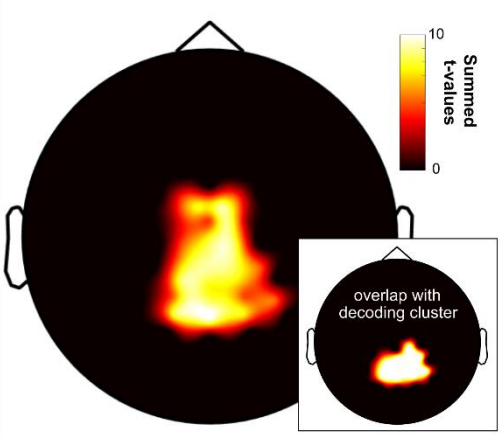

Figure 2.4. Coupling between posterior 'content' channels and frontal theta activity. Taking Fz as the seed channel and comparing 1-back vs. DMS task during the time in the delay period when WM content could be significantly decoded (860-1275 ms) revealed a significant increase in coherence with central-posterior channels in the theta band (4-8 Hz). **Main.** Significant channels, summed across significant frequencies. **Inset.** Overlap with channels contributing to WM content decoding (c.f., Figure 2.3B).

2.4.4 Increasing WM Load Slows Theta Frequency

Given the central role of FMT in coordinating WM, how does an increase in WM load impact theta oscillations? One effect of increased WM load might be an increase in FMT power, perhaps reflecting a greater number and/or level of synchronisation of participating neurons (Buzsáki et al., 2012; Buzsáki & Draguhn, 2004). Indeed, such power increases have been reported before (e.g. Jensen & Tesche, 2002; Meltzer et al., 2008). Another result of increased WM load might be a slowing of the theta rhythm. For instance, the Jensen and Lisman model (Jensen & Lisman, 1998;

Lisman & Jensen, 2013) holds that the ongoing theta cycle governs the serial reactivation item-coding cell assemblies. Thus, the duration of a given theta cycle is the limiting factor in how many items can be successfully maintained. A slowing in frequency would therefore facilitate the maintenance additional items within the same theta cycle. In our study, we tested the effect of increased WM load on FMT by comparing the 1-back task with a 2-back variant (Figure 2.1).

Behaviourally, participants continued to show high accuracy in the 2-back task, although, as with the 1-back task, accuracy was significantly lower in the 2-back relative to the DMS task ($t_{(27)}$ = 3.36, p = 0.002, Cohen's d = 0.63). While there was no significant difference in accuracy between the 2-back and the 1-back tasks ($t_{(27)}$ = 0.816, p = 0.42, Cohen's d = 0.15), the increase in WM load did induce a significant slowing of reaction times (RTs) (paired-samples t-test of 2-back vs. 1-back; $t_{(27)}$ = 3.85, p < 0.001, Cohen's d = 0.73).

We first examined the effects of load (1-back vs. 2-back) and frequency (between 4-8 Hz in 0.5 Hz increments) on power within the theta band over the frontal-medial cluster. Despite previous reports of theta power scaling with WM load (Jensen & Tesche, 2002; Meltzer et al., 2008), we did not find strong evidence for a theta power increase from the 1-back to the 2-back task in the present data. Examining fronto-medial theta power (averaged across the delay period) via a repeated-measures ANOVA revealed no significant main effect of load ($F_{(1,27)}$ = 3.26, p = 0.082, η^2 = 0.12). Unsurprisingly, given the 1/f component present in EEG data (Donoghue et al., 2020), there was a main effect of frequency ($F_{(8,27)}$ = 7.56, p < 0.001, η^2 = 0.28). Importantly however, there was also a significant interaction between frequency and load ($F_{(8,216)}$ = 9.81, p < 0.001, η^2 = 0.36). Follow-up paired t-tests demonstrated that this was driven by a relative power increase in the 2-back condition in the lower theta

range (at the lower end of the theta range at frequencies between 4 and 5.5 Hz [4 Hz, $t_{(27)}$ = 3.29, p_{Holm} = 0.024, Cohen's d = 0.62 ; 4.5 Hz, $t_{(27)}$ = 3.53, p_{Holm} = 0.018, Cohen's d = 0.67; 5 Hz, $t_{(27)}$ = 3.07, p_{Holm} = 0.035, Cohen's d = 0.58], with this difference diminished at higher frequencies [5.5 Hz, $t_{(27)}$ = 2.72, p_{Holm} = 0.066, Cohen's d = 0.51; 6 Hz, $t_{(27)}$ = 2.41, p_{Holm} = 0.12, Cohen's d = 0.46; 6.5 Hz, $t_{(27)}$ = 1.82, p = 0.32, Cohen's d = 0.34; 7 Hz , $t_{(27)}$ = 0.63, p_{Holm} = 1.06 , Cohen's d = 0.12; 7.5 Hz, $t_{(27)}$ = -0.54, p_{Holm} = 0.60, Cohen's d = 0.10; 8 Hz, $t_{(27)}$ = -1.17, p_{Holm} = 0.76, Cohen's d = 0.22]).

To confirm that this change in frequency was indeed a slowing (and thus broadening) of theta oscillations, we defined, for each participant and N-back condition, the peak theta frequency (4-8 Hz) during the delay period. For every trial and for every participant, the frequency at which the most prominent peak in the spectrum occurred was taken. These peak values were averaged by condition resulting in an average theta peak for each condition for each participant. Consistent with the Jensen and Lisman model, a paired t-test revealed a small but highly consistent decrease in peak frequency between the 1-back and 2-back tasks (means: 5.85 Hz vs. 5.77 Hz; $t_{(27)}$ = 5.02, p < 0.001, Cohen's d = 0.95; see Figure 2.5). This peak detection approach should be largely insensitive to the 1/f component of EEG signals, but to ensure that this was the case, and given the possible functional significance of a change in this exponent (Donoghue et al., 2020), the same method was applied to data to which the IRASA algorithm had been applied (Wen & Liu, 2016). The significant slowing effect persisted [means: 6.05 Hz vs. 5.99 Hz; $t_{(27)}$ = 2.84, p = 0.008, Cohen's d = 0.54]. Finally, to rule out the possibility that this finding had occurred due to any volatility in calculating power on the single trial level, the individual trial spectra were smoothed by sliding average (variable window;

0.20-1.00 Hz). Again, significant slowing for 2-back vs. 1-back was observed for all smoothing ranges [t-values ≥ 4.24, p-values < 0.001, Cohen's d values ≥ 0.80].

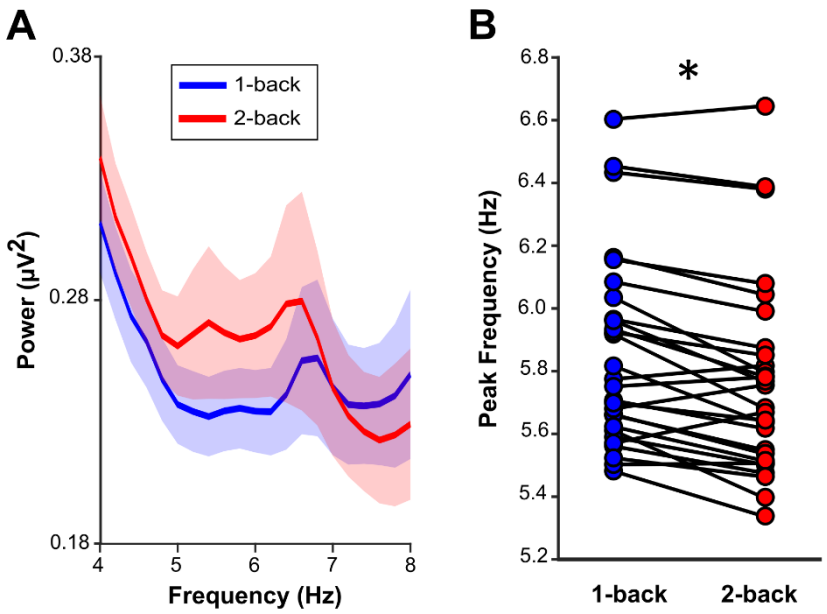

Figure 2.5. Theta frequency slows to accommodate an additional WM item. Raw Mean (+/- SEM) power values in the theta band (4-8 Hz) across participants, averaged across the delay periods of the 1-back task (blue) and the 2-back task (red). Note the relative shift towards lower frequencies for the 2-back task. **B.** Theta peak frequencies for 1-back and 2-back delay periods shown for each participant. Asterisk indicates statistical significance at α = 0.05.

If FMT (and its synchrony with posterior regions that maintain content) is indeed a principal mechanism of WM function, frontal-posterior coherence in the theta band should not only be evident in the 2-back task, but also show a commensurate slowing in frequency. Comparison of the 2-back task to the DMS task indeed revealed a significant central-posterior cluster of increased coherence (See Figure A1.5A inset), similar to that observed when comparing the 1-back task to the DMS task. Importantly, subtracting coherence values in the 1-back task from the 2-back task revealed a relative increase during 2-back maintenance at the lower end of the theta band (See Figure A1.5B), peaking at 5 Hz [$t_{(27)}$ = 2.36, p = 0.026, Cohen's d = 0.45].

2.5 Discussion

2.5.1 Summary of Results

Our study elucidates the dynamic interplay between the two key components of working memory (WM), i.e., an executive control mechanism and the representation of stimulus content. Using a paradigm that manipulated WM demand (Figure 2.1), we found a power increase in fronto-medial theta (FMT) during 1-back tasks relative to a delayed-match-to-sample (DMS) task (Figure 2.2). Multivariate pattern analysis showed that WM content, i.e., whether an individual maintained an object or a scene image, could be decoded successfully during the delay period from central-posterior channels (rather than from those channels showing the theta power effects, Figure 2.3). Importantly, channels that contributed to decoding also showed increased coherence in the theta frequency band with frontal sites sensitive to WM load. Lastly, we found that maintaining an additional item in WM leads to slowing of the FMT rhythm (Figure 2.5), consistent with computational accounts suggesting a broadening of the theta cycle to accommodate multiple WM items.

2.5.2 FMT Couples to Posterior Channels

The finding that WM-induced FMT also governed functional coupling with posterior channels that are most informative to decoding strongly points to a role of FMT in coordinating posterior WM maintenance. This observation unifies a series of recent findings and highlights the importance of theta oscillations as the interlocutor between regional WM sub-systems. Although WM content has been shown to be preferentially decoded from posterior regions, there has been a paucity of evidence to directly associate a measure of WM content with theta activity from frontal regions. That is, there is considerable evidence of FMT as an executive control system in WM (Hsieh & Ranganath, 2014; Riddle et al., 2020) and of posterior localisation of WM content (Christophel et al., 2012; Harrison & Tong, 2009). However, there is little

extant evidence directly connecting WM content with frontal theta activity. Previous work has largely focussed on how frontal theta interacts either with activity in other frequency bands, e.g., gamma activity (Berger et al., 2019), or with neuronal spiking (Crowe et al., 2013; Siegel et al., 2009), neither of which provide a direct read-out of high-level WM content. A recent study which did measure WM content observed modulation of decoding from posterior regions according to a theta/alpha rhythm (ten Oever et al., 2020), but did not link this pattern to frontal activity.

2.5.3 FMT as the WM executive

The topographical dissociation of frontal control mechanisms (Figure 2.2B) vs. posterior content maintenance (Figure 2.3B) dovetails with WM models proposing a domain-general role for prefrontal cortex in executive control (D'Esposito & Postle, 2015). According to the sensory recruitment model, the direct maintenance of content is then accomplished by posterior regions (Scimeca et al., 2018), specifically those that are involved in the processing of the stimulus in a non-WM context. It deserves mention though that other studies have reported content-related WM activity in frontal regions (e.g. Lee & Baker, 2016; Meyer et al., 2011; Riley & Constantinidis, 2016). However, decoding from frontal regions has been proposed to reflect a transformed representation, perhaps representing goal states or action plans rather than stimulus content per se (Christophel et al., 2017; Lee et al., 2013). In the present study, the motor response ('match'/'non-match') was orthogonal to the stimulus category ('object'/'scene') on which the classifier was trained.

2.5.4 Decoding as a measure of WM representations

To what extent do our decoding results reflect actual WM content? While the behavioural task prescribed maintenance of a specific item representation, we here use the superordinate category (i.e., object vs. scene) in our classification regimen.

The rationale for this approach is that although participants most likely indeed maintain individual exemplars (as the labels ‘object’ and ‘scene’ would be insufficient to solve the task), multivariate decoding greatly benefits from higher within-category than between-category similarity of exemplars (i.e., objects being more similar to other objects than to scenes and vice versa) (Norman et al., 2006). The same approach has been used in long-term memory research, where greater decodability of superordinate stimulus categories is harnessed as a proxy for recall of individual items (Jafarpour et al., 2014; Polyn et al., 2005). Likewise, we cannot ascertain which particular features drive decodability of objects vs. scenes (lower-level perceptual vs. higher-level conceptual). Importantly though, using temporal generalisation, we show that the same features that allow discrimination of objects vs. scenes during stimulus encoding are reinstated during the maintenance period (Figure A1.2), tethering decoded WM content to preceding stimulus perception.

2.5.5 Is Decoding Constrained to the Delay Period?

In any case, could decodability of WM content during the delay period reflect a spill-over from the preceding stimulus or response interval? In a recent EEG study in which orientations of a tear drop shape were decoded, there was an initial increase in accuracy after stimulus offset followed by a sustained decline (Bae & Luck, 2018). This pattern more closely resembles the response period in our dataset (Figure 2.3) and is consistent with the finding that decodability rebounds after stimulus offset (Robinson et al., 2019). However, stimulus presentation and maintenance were separated by a minimum of 750 ms in our paradigm (Figure 2.1) and maximum decodability was actually seen from 860 ms to 1275 ms after delay onset, mitigating impacts of preceding stimulus or response windows. Further precluding this explanation is that prior to classification, data were baseline-corrected to the

immediately preceding 200ms (i.e., the final 200ms of the response period was subtracted from the delay period).

2.5.6 WM Load and Theta Power

Assuming that a frontal executive does coordinate WM maintenance via theta oscillations, how does this system respond to increasing task demand? One possibility is a scaling of theta power. Theta power is frequently greater in conditions in which more items must be stored in WM (Gevins et al., 1997; Hsieh & Ranganath, 2014). Furthermore, parametric theta power scaling with conditions of increasing load has previously been observed (Jensen & Tesche, 2002; Meltzer et al., 2008), although not without exception. Payne and Kounios (2009) systematically varied load by presenting 2, 4, or 6 letters, observing an increase in fronto-parietal coherence but not in theta power. Many of these studies employed Sternberg-like paradigms, but studies more comparable to the current paradigm also show some inconsistencies. Brookes et al. (2011) observed robust theta power increases between 0-, 1-, and 2-back tasks, whereas Missonnier et al. (2006) did not find a significant difference between 1- and 2-back conditions. The extent to which the effect of load is influenced by other differences between paradigms, such as stimulus complexity, block length or delay duration, is important to address in future work. In the present study, although FMT power was greater in the 1-back relative to the DMS task, this increase did not extend to the 2-back task.

2.5.7 WM Load and Theta Frequency

An alternative way FMT might respond to WM load is a change in frequency. Indeed, in place of a scaling of FMT power, we provide here the first empirical evidence of a slowing of the FMT rhythm in response to increasing WM load. The magnitude of slowing was moderate, but highly consistent across participants. According to the

Jensen-Lisman model (Jensen & Lisman, 1998; Lisman & Jensen, 2013), slowing of the carrier theta frequency facilitates bursting of additional item-coding cell assemblies in each cycle whilst maintaining phase separation among items. Although a specific slowing in FMT has not previously been demonstrated, Axmacher et al. (2010) did observe, in intracranial hippocampal recordings during a WM (Sternberg) task, a load-dependent reduction of the theta frequency modulating power in the beta/low gamma band. Further indirect evidence for load-dependent theta slowing comes from a series of studies employing transcranial alternating current stimulation (tACS). Modulating the speed of endogenous theta by means of stimulating at a low (3 Hz) or high (7 Hz) theta frequency was shown to improve or impede WM function, respectively (Bender et al., 2019; Vosskuhl et al., 2015; Wolinski et al., 2018). The data here are in agreement with the implication of these stimulation studies - while theta power is critical for WM (as evidenced by the increase in the 1-back relative to the DMS task), the limiting factor in holding multiple items may in fact be the frequency of ongoing theta oscillations. The importance of theta frequency/phase is further supported by recent evidence of phase coding in the human medial temporal lobe. Stimulus-specific cell firing patterns show theta phase precession, whereby stimuli-coding firing occurs at earlier theta phases according to a stimulus' position in a sequence (Reddy et al., 2021). Additionally, when multiple items were maintained in WM, whether a stimulus was in memory or not could be determined by the theta phase to which the relevant cells' firing locked (Kamiński et al., 2020). Nevertheless, the exact functional roles of theta power versus theta phase in WM maintenance should be more systematically explored in future work. In the present case, we observed a change in theta power in response to increased executive WM demand (1-back vs. DMS task) and a change in frequency in

response to an additional to-be-remembered item (2-back vs. 1-back). The use of additional load levels in the N-back task, for example, would further clarify the limits of frequency slowing and whether frequency slowing occurs in lieu of, or in addition to, an increase in power.

2.5.8 Summary and Conclusions

To summarise, we show that frontal theta rhythms orchestrate the maintenance of stimulus representations in posterior brain regions in the service of working memory performance. Increasing the amount of information to be maintained led to a slowing of theta frequency, consistent with the idea that longer duty cycles are needed to accommodate additional items held in working memory.

Chapter 3: Improving Older Adults' Visuo-Spatial Working Memory with Bilateral Prefrontal HD-tDCS

3.1 Abstract

Working memory (WM) is a critical cognitive function that reliably declines with increasing age. A theoretical framework (the HAROLD model) suggests that, to compensate for age-related degeneration, older adults show reduced laterality in WM-related activation of frontal cortical regions. Transcranial direct current stimulation (tDCS) has previously been shown to enhance WM but it is unclear whether stimulation should recreate the youthful activation pattern (laterality) or match the proposed compensatory pattern (bilaterality).

To answer these questions, older adults participated in a double-blind sham-controlled mixed-design experiment. Participants received high definition (HD) tDCS targeting either the left, right, or both hemispheres of the dorsolateral prefrontal cortex (DLPFC) whilst performing an adaptive N-back task. WM capacity, arousal, mood, expectations concerning tDCS, and strategy use were measured.

Despite counterbalancing of real and sham stimulation, a significant order effect was detected whereby participants assigned to stimulation-first showed improvement in both sessions. Nevertheless, in the first session, there was a near-significant effect of stimulation where stimulation improved performance on the adaptive N-back task. A significant block by stimulation interaction suggested that participants benefitted from stimulation in the early-middle portion of the N-back task. Although there was no significant effect of laterality, bilateral stimulation appeared more effective than stimulation of either hemisphere in isolation.

The present findings advocate sufficient washout periods to avoid stimulation-associated learning effects. Nevertheless, the data provide tentative support for the

HAROLD model. Furthermore, the present study demonstrates the feasibility and tolerability of HD-tDCS in an older population.

3.2 Introduction

3.2.1 WM and Ageing

Working memory (WM) defines our ability to maintain and manipulate information in the short-term (Baddeley, 2010) and is tightly associated with everyday function (Aretouli & Brandt, 2010). Working memory ability shows clear degradation with ageing, even in the absence of pathology (Brockmole & Logie, 2013). A number of cross-sectional studies have demonstrated that this decline begins around the age of 20 and occurs across the lifespan (Cansino et al., 2013). Although cross-sectional studies may over-estimate the magnitude of these effects, longitudinal work corroborates the occurrence of a general decline (Singh-Manoux et al., 2012), albeit one that shows significant individual variation (Raz et al., 2010). This age-related decline in working memory ability is particularly pronounced at higher WM loads (Artuso et al., 2017; Pliatsikas et al., 2019), in tasks requiring active manipulation of WM content over those emphasising short-term maintenance (De Beni & Palladino, 2004; Dobbs & Rule, 1989; Reuter-Lorenz & Sylvester, 2009), and in tasks employing visuo-spatial rather than verbal stimuli (Cansino et al., 2013).

3.2.2 Age-associated Compensatory Activity

Concurrent with this behavioural decline, the brain also undergoes physiological changes during ageing, especially in frontal regions. Among other changes reported, there are evident declines in cerebral volume (Resnick et al., 2003; Ritchie et al., 2015) linked to levels of activity (Maillet & Rajah, 2013) and changes in white matter morphology (Ritchie et al., 2015). Thus, although changes in brain activity are reported with ageing, it is important, and not trivial, to distinguish between activity changes which are a result of neurological deterioration versus those changes which

reflect the brain's attempt to compensate for senescence, i.e. to maintain comparable performance with fewer/poorer neurological resources (Cabeza et al., 2018; Grady, 2012; Reuter-Lorenz & Lustig, 2005). One proposed compensatory mechanism adopted by older or ageing brains is the over-recruitment of neuronal populations relative to younger individuals. This can result in similar performance at a low difficulty but when demand is further increased, neural activation is at its maximum, cannot be further increased, and performance is impaired at these levels. This proposal is referred to as CRUNCH, the Compensation-Related Utilization of Neural Circuits Hypothesis (Reuter-Lorenz & Cappell, 2008; Schneider-Garces et al., 2010).

3.2.3 Reduced Asymmetry of WM-associated Frontal Engagement

In working memory specifically, it has been further suggested that hemispheric specificity declines with age. In a seminal study where younger adults showed largely unilateral activation in frontal areas, such as the DLPFC, older adults showed additional activation of the contralateral hemisphere (Cabeza, Anderson, et al., 2002). This has been termed the HAROLD (Hemispheric Asymmetry Reduction in OLDer adults) model. Whilst initially it was unclear whether this reflected an age-related impairment in selectively recruiting required neural resources (the dedifferentiation hypothesis), subsequent work has generally favoured the alternative interpretation: that this change reflects a compensatory mechanism whereby additional neuronal resources are recruited to maintain performance. Cabeza, Anderson, et al (2002) demonstrated using PET scans that older adults who performed better at higher loads also exhibited greater bilateral activity in frontal areas. Similarly, Mattay et al. (2006) utilised fMRI and an N-back task featuring three levels of load. During a 1-back task, older individuals were able to perform

comparably to younger individuals despite showing greater bilateral activation of frontal areas. At higher load levels, performance was significantly worse for older individuals and frontal activation decreased accordingly. More recently, studies employing EEG (Angel et al., 2011) and functional near infrared spectroscopy (fNIRS) (Agbangla et al., 2019; Vermeij et al., 2012, 2014) have corroborated the idea of laterality changes in older adults. The evidence, however, is not unanimous. A recent systematic review has questioned whether there is enough evidence to support the CRUNCH model (Jamadar, 2020) and specifically, if there is indeed a reliable laterality change in response to ageing.

3.2.3 Testing the Compensatory Account with Transcranial Current Stimulation

Assuming that there is a change in laterality, it is challenging to discern whether this truly reflects a compensatory mechanism (Huang et al., 2012; Vallesi et al., 2011). Transcranial current stimulation (tCS) may provide a safe, non-invasive means to causally test such theoretical frameworks and also to examine whether working memory might be improved (Reinhart et al., 2017). The most common version of this type of stimulation is transcranial direct current stimulation (tDCS). As the name suggests, electrodes are applied to the scalp through which a mild (typically 1-2 mA) electrical current is passed. As it was conceived, the electric field generated was thought to modulate activity in the neural tissue underneath and bias neurons towards firing (Nitsche & Paulus, 2000). Recent research suggests this current may also have more complex effects (Chrysikou et al., 2017; Funke, 2013; Medeiros et al., 2012).

3.2.4 Transcranial Current Stimulation and Working Memory

Many studies have targeted WM functionality via tCS, either seeking improvement or to probe the underlying neurophysiology. Meta-analyses largely conclude that tDCS-

related improvement effects are small in magnitude or non-existent (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016a; Hill, Fitzgerald, et al., 2016; Horvath et al., 2015; Medina & Cason, 2017). Nevertheless, a large number of individual studies have reported enhancement of working memory by tDCS targeting the dorsolateral prefrontal cortex (DLPFC) (e.g., Fregni et al., 2005). Additionally, several tDCS studies have successfully shown that older adults are amenable to tDCS-induced improvement (Antonenko et al., 2019; Berryhill & Jones, 2012; Goldthorpe et al., 2020; Summers et al., 2016; Zimerman et al., 2013). Null effects in tDCS studies, and meta-analyses (Nitsche et al., 2015), may be due to significant heterogeneity in methodology, including electrode setup, current strength, duration of stimulation, and when stimulation is applied relative to the task of interest (Woods et al., 2016). One notable advance is the development of what has been termed ‘high definition tDCS’ (Datta et al., 2009). This development largely resulted from an increased demand to understand exactly where in the brain was being stimulated. Modelling the current flow using realistic head models showed that the strength of the electric field was not easily intuited based only on montage setup (Kuo et al., 2013). This has led to a call to model the predicted current flow of a specific setup and also to employ ‘high-definition’ montages. As opposed to conventional bipolar stimulation using a sponge-embedded pair of electrodes (one serving as the anodal and the other as the cathode), newer montages employ multiple (usually around four) cathodal electrodes surrounding a central anode which serve to more precisely guide the electric current (Villamar et al., 2013). This more focal stimulation can reduce one of the sources of variability in stimulation experiments (Datta et al., 2012).

3.2.5 State-dependency of tDCS

According to the generally accepted mechanism of tDCS, it is neuromodulatory (Stagg & Nitsche, 2011). Short-term effects are driven by a depolarisation of the affected tissue which renders action potentials more likely but does not directly induce them as in the case of a method like transcranial magnetic stimulation (TMS). Neurons which are extremely unlikely to fire will therefore not be induced to fire through the action of stimulation. Although aspects of state-dependency have been questioned (Hill et al., 2019), there remains evidence to suggest that task does have a significant impact (Bortoletto et al., 2015; Hsu et al., 2016) on stimulation's effect. Specifically, it has been suggested that stimulation effects are only visible during more difficult tasks (Andrews et al., 2011; Berryhill, 2014; Gill et al., 2015; Jones & Berryhill, 2012). It remains unclear how stimulation interacts with individual variation in cognitive ability, however. Evidence is mixed with some work suggesting that low-performers show greater stimulation-related improvement (Arciniega et al., 2018; Tseng et al., 2012), and others finding that higher education participants may benefit more (Berryhill & Jones, 2012; Hsu et al., 2014). In the present study, prior to stimulation participants completed the change detection task (Luck & Vogel, 1997), from which one can estimate an individual's working memory capacity (Rouder et al., 2011). Additionally, although load can be seen as an objective measure which corresponds to task difficulty, in older populations especially there is significant heterogeneity in cognitive ability (Ghisletta et al., 2012; Pliatsikas et al., 2019). In order to ensure that the task was a similar subjective level of difficulty for everyone and to reduce the risk of any ceiling effect (Furuya et al., 2014), an adaptive N-back task was used in which WM load was modulated according to ongoing performance.

3.2.6 Comparing Bilateral to Unilateral Stimulation

It has yet to be seen whether stimulation could provide evidence for the HAROLD model by comparing bilateral stimulation to unihemispheric stimulation. Although one study has attempted to address this question (Arciniega, Gözenman, Jones, Stephens & Berryhill, 2018), it made use of data from two separate experiments rather than making the comparison directly. Additionally, use of a traditional tDCS setup makes it difficult to stimulate any one area in isolation. Bifrontal stimulation (where the cathodal electrode was placed on the left and the anode on the right) was compared to right-lateralised fronto-parietal stimulation. It is therefore unclear whether the apparent efficacy of the right-lateralised stimulation was due to stimulation of the ipsilateral parietal region or indeed whether performance was impaired in the bilateral stimulation by cathodal stimulation of the opposing hemisphere. Not only is the placement of the cathode non-trivial in terms of current flow (Datta et al., 2008), cathodal stimulation has also has its own physiological effects (Jacobson et al., 2012; Nozari et al., 2014). A separate study (Nissim et al., 2019) also employed ostensibly ‘bilateral’ stimulation in conjunction with a working memory task in older adults, however this also referred to the anode over the left hemisphere and the cathode being placed over the right (at F3 and F4 according to the international 10/20 EEG system (Jasper, 1958)). Conversely, Park et al. (2014) did employ bilateral stimulation (in which each hemisphere was separately stimulated), but did so during 10 WM training sessions over the course of a two-week protocol. Stimulation improved performance on a number of WM tasks relative to sham, but the bilateral montage was not compared to the effect of unilateral DLPFC stimulation.

3.2.7 Hypotheses and Predictions

In the present study, an adaptive working memory task was employed to ensure that each participant was facing a sufficiently challenging task so that any stimulation-induced benefit could be detected. An HD-tDCS set-up was used that could selectively stimulate one or both hemispheres with minimal inter-hemispheric leakage and a within-subjects design was selected to account for inter-individual variability. Firstly, it was predicted that tDCS would improve performance on a WM task relative to sham stimulation. Secondly, the laterality of this stimulation should result in varying degrees of improvement. Specifically, corroborating neuroimaging data, simultaneous stimulation of both hemispheres should be the most effective montage. This would corroborate the idea that, as CRUNCH suggests, the greater degree of recruitment in the contralateral hemisphere is a compensatory mechanism to maintain performance. On the other hand, finding that stimulating both hemispheres results in comparable or reduced performance relative to unilateral stimulation would be more consistent with the account that any asymmetry reduction is a manifestation of brain ageing.

3.3 Methods

3.3.1 Design

This study employed a double-blind mixed design: all participants experienced a sham and a *verum* stimulation session, separated by a washout period of at least one week. Between groups, participants experienced left, right, or bilateral stimulation. Stimulation and sham sessions were counter-balanced within groups. Participants were assigned to laterality and order groups by an experimenter blind to the nature of each condition, maintaining approximate homogeneity of age and gender between these condition groups. To achieve experimenter blinding,

stimulation protocols were set up using the NIC software (Version 2.0.9, Neuroelectrics, Barcelona, Spain) by an independent experimenter.

3.3.2 Participants

Participants were recruited from cohorts associated with the University of Birmingham. Individuals in these cohorts had been contacted through church groups or had previously participated in research at the university. Additional participants were acquired through poster recruitment campaigns in parks, village halls, and around the university campus, and through participant-to-participant word-of-mouth. Participants were compensated £40 for full completion of the study.

Participants were aged between 55 and 75 and were also required to be right-handed. Exclusion criteria constituted any personal or family history of neurological/psychiatric disorder, any personal history of brain injury/trauma, any on-going prescriptions for anti-psychotic or sedative medications, a Montreal Cognitive Assessment (MoCA) score below 26, any form of colour blindness, any electrical pacemaker or other implant, and any participation in a tCS/TMS experiment within the previous 6 months. A total of 24 participants (12M/12F, aged 55-76, mean age = 69) were tested.

Participants were requested to abstain from alcohol for 24 hours and to have no more than one caffeinated drink on experimental days. Participants returned for the second session at approximately the same time as the initial session (morning/afternoon) although time of day, at least as measured by MEP amplitude, is thought to have minimal influence on cortical excitability (Wiethoff et al., 2014).

3.3.3 Measurements

A demographic questionnaire was used to interrogate gender, age, and educational background (primarily assessing years of education). Most participants included had had an assessment on the Montreal Cognitive Assessment (MoCA) in the last 12 months. If this was not the case, a MoCA examination was conducted in the first session. Importantly, the MoCA was used only to exclude participants scoring below the criterion threshold.

General arousal was assessed before and after each session of the N-back task by a psychomotor vigilance task (PVT) in which participants had to respond to the absence of a fixation cross by pressing the space bar as quickly as possible (Roach et al., 2006). The duration of this task was approximately five minutes. This task was used to ensure that any stimulation-induced task improvement was not due to fatigue reduction or generalised improvement in sustained attention, rather than working memory functionality specifically. Notably, tDCS targeting the DLPFC has in previous work been suggested to have stimulant-like properties (McIntire et al., 2017). It should be noted that in one session for one participant, the post-stimulation PVT data was not saved due to technical issues and thus this session was excluded from the PVT analysis.

The mood questionnaire employed in this study asked the participant to report on several aspects of their current mental state on a five point scale (1-5): level of alertness, from extremely sleepy/fighting sleep to extremely alert and wide awake; level of motivation, from very low to very high; expectation that exercises would improve memory, from very low/unlikely to improve to very high probability to improve; and level of sadness, from extremely sad and blue to extremely cheery and optimistic. In addition to these more specific questions, the PANAS (Watson et al.,

1988) was administered before and after stimulation to detect acute changes in mood. tDCS has been shown to ameliorate depressive symptoms (Kalu et al., 2012) but it was not expected from previous stimulation work in older adults, or previous work employing 4x1 HD-tDCS, that there should be any acute mood change in these healthy participants. The level of alertness provided a self-reported measure in addition to the objective behavioural measure provided by the PVT. Motivation and expectation may modulate stimulation responsiveness and performance on the WM task. Frontal stimulation may increase motivation (Soutschek et al., 2018) which could impact performance on a task (Di Rosa et al., 2019; Jones et al., 2015; Krawczyk & D'Esposito, 2013), especially in a challenging, adaptive N-back task. Additionally, Rabipour et al. (2018) reported that manipulation of an individual's expectations concerning tCS modulated the efficacy of stimulation-coupled WM training.

At the end of the session a questionnaire was used to report any side effects on a scale from 1-4 (1, absent; 2, mild; 3, moderate; 4, severe). Participants were questioned on the extent to which they had experienced the following side effects: headache, neck pain, itching, sleepiness, trouble concentrating, acute mood change, fatigue, nausea, muscle twitches (in face or neck), tingling sensation (in head or on scalp), burning sensation (in head or on scalp), light flashes, an uncomfortable feeling (non-specific), and any others that a participant wished to have recorded. Participants also reported whether they believed they had received real stimulation and asked to judge on a scale from 1-7 how confident they felt in this judgement. In the final session, before being debriefed, participants were given a questionnaire asking them to reflect on whether they had used a specific strategy, to describe this strategy in as much detail as they could, and to indicate on a scale from 1 to 10 how

effective they felt this strategy had been (1 indicating that it reduced performance, 10 being that it greatly improved it). Strategy use may alter neural recruitment patterns as well as performance (Sanfratello et al., 2014).

3.3.4 Working Memory Tasks

3.3.4.1 Change Detection Task

In order to estimate WM capacity, the change detection task was employed (Luck & Vogel, 1997; Pashler, 1988). This task was adapted from code freely available at https://github.com/kcsa/change-detection-task. 2, 4, or 6 coloured squares were presented in random positions for 500ms (See Figure 3.1). After a 1000ms fixation period, a single randomly selected item was presented having either changed colour or not (50% of trials). Participants were required to respond with one of two key presses to indicate whether they thought the colour had changed. The primary outcome metric of the change detection task is an estimate of an individual's capacity.

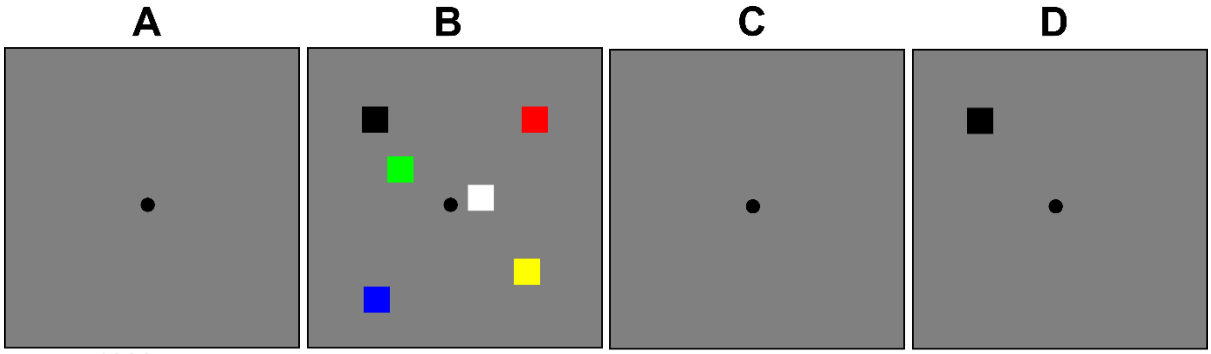

Figure 3.1. Change Detection Task. A. On each trial of the change detection task, fixation spot appeared towards which participants were asked to fixate. **B.** After 1000ms, 2/4/6 coloured squares were presented at random positions and stayed on the screen for 500 ms. **C.** The fixation screen reappeared and participants were required to maintain the previously presented information for 1000ms. **D.** One of the previously present squares of these was randomly chosen and presented as a probe item. On 50% of trials, this square had changed colour and participants were asked to judge whether they thought it had changed or stayed the same by pressing the appropriate key.

3.3.4.2 Adaptive Visuo-Spatial N-Back Task

The working memory task used here was an adaptive visuo-spatial N-back task (see Figure 3.2). The task was adaptive insofar as the task would either reduce in difficulty, stay the same level of difficulty, or increase in difficulty depending on an individual's performance. In this context, the difficulty was defined as the N level. In an N-back task, participants are required to judge whether a given stimulus matches the stimulus N trials previous. The task was made adaptive to rule out any chance of ceiling effects, which have previously been cited as a reason for failure to see a behavioural effect (e.g., Hill et al., 2017). Given the wide age range and expected variance in working memory, an adaptive task was used to ensure maximal engagement of the working memory network.

In the task, participants were presented with a 3x3 grid creating nine regions in which a blue circle could appear. The participant had to report, by pressing one of two keys, whether the circle was in the same region as the one which had been seen 'n' number of trials back. The number of these matches randomly varied between 25-35% of trials in a block. Participants had 1000 ms to respond from when each stimulus appeared. After the stimulus had been on screen for 1000 ms, a fixation break occurred of 1000 ms before the dot appeared again in either the same or a new position. Each block consisted of 20+N trials and at the end of the block performance was calculated to determine whether the difficulty (N level) decreased, remained the same, or increased. The accuracy thresholds used for reducing or increasing the N-back level were 50% and 80% respectively. If a participant's accuracy for the block was between 50-80 %, the N level remained the same for the subsequent block. Participants completed 20 blocks in total, each of which concluded with a 10 second optional break. Task length varied between participants

due to individual differences in the levels of N achieved. As there were 20+N trials in each block, the higher the N level, the more trials there were and the longer the duration, but the task was designed so as to last at least the full 20-minute duration of the stimulation.

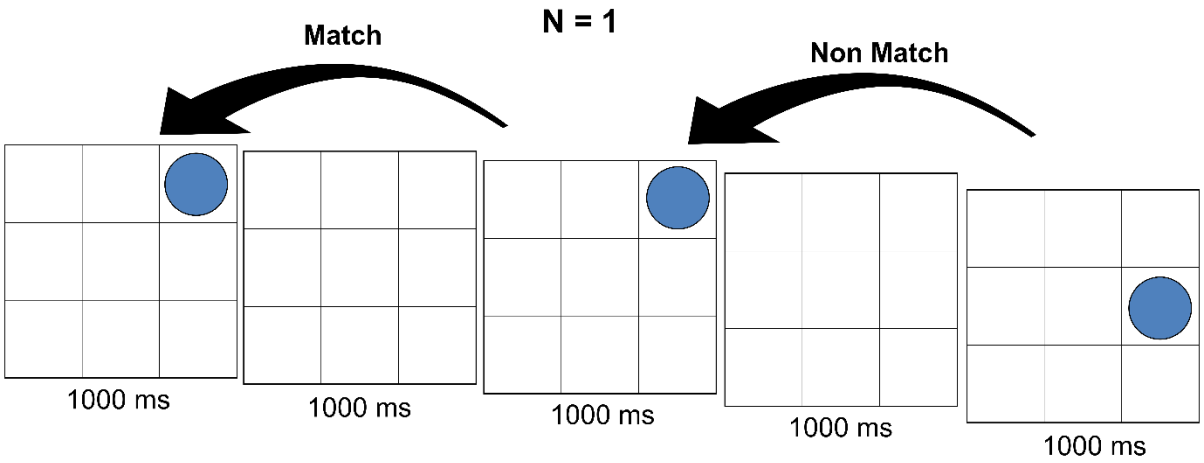

Figure 3.2. Adaptive N-back task. Exemplar trials from the adaptive N-back task when N = 1. Participants were presented with a simple stimulus (blue circle) in one of nine locations in a grid. This stimulus remained on screen for 1000 ms. Participants had 1000 ms to respond using one of two keys whether the circle was in the same location as the trial N (in this case 1) trial(s) previous.

3.3.5 Current Flow Modelling

In order to assess whether the use of the 4x1 electrode array here did indeed result in heightened focality, and therefore better control of laterality, current flow was estimated using SimNIBS (Thielscher et al., 2015). These models were employed to confirm that the electrode montage in the unilateral conditions has indeed resulted in the electric field being constrained to only one hemisphere with minimal overlap and that the DLPFC was being effectively targeted. Such modelling has been validated with intracranial recordings (Huang et al., 2017).

A T1-weighted MRI scan derived from a depository of older individuals' scans was used (Open Access Series of Images (OASIS) data set; Marcus et al., 2010) to create a representative brain mesh. This older brain model was used to better reflect the population used in the present study, rather than the standard head model.

Conductivities assigned were the standard values, as determined by ex vivo studies: white matter 0.126 S/m; grey matter 0.275 S/m; CSF 1.654 S/m; bone 0.010 S/m; scalp 0.564 S/m; spongy bone 0.025 S/m; compact bone 0.008 S/m; eye balls 0.500 S/m; eye region 0.250 S/m; electrode rubber 0.100 S/m; and saline 1.000 S/m. PiStim electrodes (NeuroElectrics, Barcelona, Spain) were represented in the model as 2cmx2cmx1mm with 2mm of conductive gel.

3.3.6 Transcranial Direct Current Stimulation

Electrical stimulation was delivered using two StarStim devices (Neuroelectrics, Barcelona, Spain) being controlled by two computers. In all three stimulation conditions, participants had the same number of electrodes placed on the scalp to promote effective blinding (Figure 3.3). Central stimulation electrodes were placed over F3 and F4 according to the international 10-20 EEG system. Return electrodes were positioned for F3 at Fc1, C3, F7, Fp1 and for F4 and at Fc2, C4, F8, Fp2. Electro-conductive gel (Signa Gel, Parker Laboratories, USA) was used to improve contact between the electrodes and the scalp.

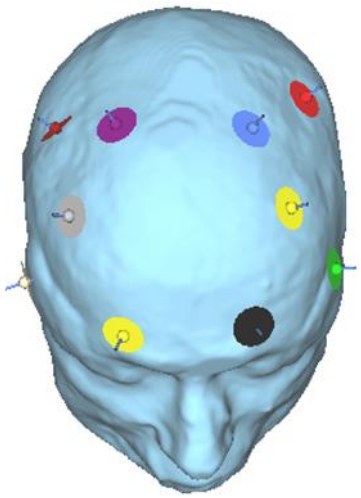

Figure 3.3. Bilateral stimulation montage. The HD-tDCS setup modelled on an average head model in SimNIBS (Thielscher et al., 2015). The two central anodes were placed at positions F3 and F4 with the surrounding electrodes functioning as the cathodes (with the current being split equally between them).

In the bilateral stimulation condition, stimulation was administered through both anodal electrodes simultaneously. Stimulation ramped up and down in the first and last 30 seconds of stimulation. It began simultaneously with the N-back task and lasted for 20 minutes. In the unilateral conditions, the electrode set up was maintained but the inactive side functioned as a sham. In the right-stimulation only condition, for example, stimulation on the left side ramped up for the initial 30 seconds before the current ramped down to zero. In the final 30 seconds, stimulation ramped up and down again. This method of blinding has been effectively used in a number of studies which used conventional tDCS (Gandiga et al., 2006). Despite reports of increased initial sensation from 4x1 HD-tDCS, this blinding method appears to remain effective in studies which have employed a similar setup (Hill et al, 2017). In the sham sessions, both stimulation electrodes functioned as shams in the manner described above.

Impedance was maintained below 15kΩ and stimulation automatically ceased if this threshold was exceeded. In these instances, the experimenter would instruct the participant to pause the task before adjusting the electrode position and/or applying more conductive gel until this impedance was brought below this threshold.

3.3.7 Procedure

Participants were informed that they would be participating in a study investigating memory and transcranial current stimulation. In the first session participants completed a consent form as well as a safety screening and demographic questionnaire, before proceeding to the main experiment (see Figure 3.4). The change detection task was explained to participants and they completed a practice block. No specific accuracy level was required but participants were asked whether they were happy that they understood the task. Participants then completed the

change detection task (See Figure 3.1). Immediately after this, they completed the mood questionnaires and the psychomotor vigilance task for the first time. The electrode cap was placed on their head and prepared for stimulation. The experiment proceeded when impedance checks reported the impedance as below 15 kΩ. An explanation of the N-back task was given to the participant and they completed one block at 1-back and one block at 2-back difficulty. No requisite score was required to continue but corrective feedback was given by the experimenter if it was thought that participants had failed to understand the instructions. The stimulation cap was then put on, electro-conductive gel applied to the electrodes, and the impedances were checked. Stimulation then began concurrently with the initiation of the task. Stimulation ceased after 20 minutes and the N-back task concluded after 20 blocks had been completed. After the task was complete, participants completed the PVT and filled out the mood questionnaire for the second time. Participants were then asked about tDCS side effects and whether, and how confidently, they believed they had received stimulation or not. In the final session, participants were asked about any strategy they employed to accomplish the task during session 1 and session 2.

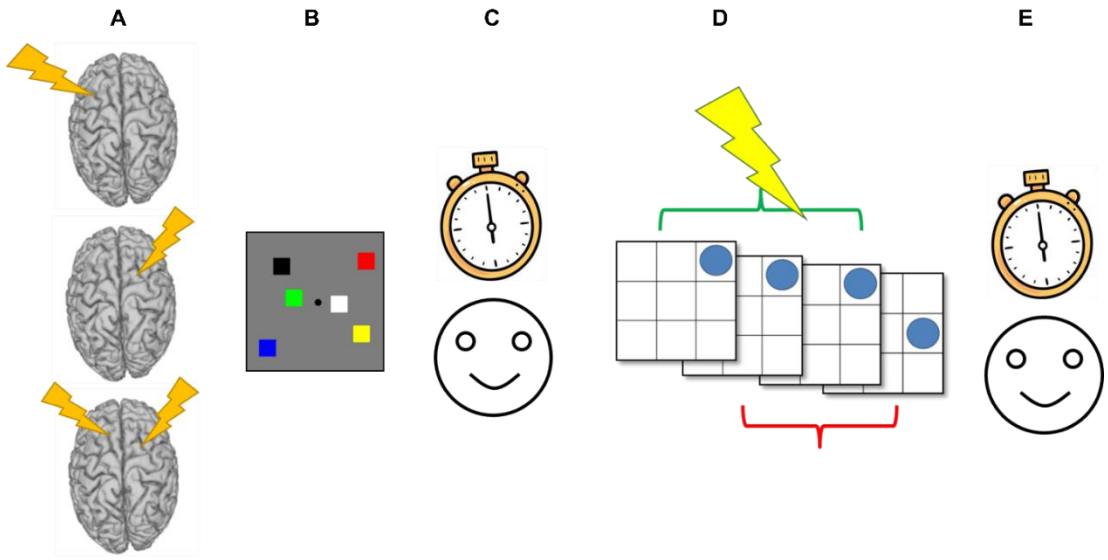

Figure 3.4. Experimental design and procedure. A. Participants were blindly assigned to one of three laterality groups attempting to balance mean age as well as possible They were also assigned to an order group to determine whether they would first experience real or sham stimulation. During each experimental session they were asked to complete the change detection task **(B)**, the PVT (Psychomotor Vigilance Task) and the PANAS mood questionnaire prior to stimulation **(C)**, the adaptive N-back task **(D)**, and the PVT and PANAS after stimulation **(E)**.

3.3.8 Assessing WM Capacity

As the change detection task used here used a single item probe, performance was calculated using the formula as described in (Cowan, 2001; Rouder et al., 2011). K was calculated for each of the three load levels and then averaged to produce a single value for each participant and each session.

3.3.9 Statistics

A 2x3 mixed model ANOVA was employed assessing the effect of session (sham/verum) and stimulation laterality (left/right/bilateral) on working memory performance. Working memory performance was defined as the mean N achieved across the session. Block 1 was excluded from this average given that all participants started at a 1-back task. For single-session analysis, a between-subjects ANOVA was conducting assessing the effect of stimulation laterality (left/right/bilateral) and stimulation group (stimulation/sham). Paired-samples and independent-samples t-tests were used to probe significant effects and interactions.

An alpha of 0.05 was used in all cases to determine statistical significance. Statistical power and required sample sizes were calculated using G*Power (Version 3, Faul et al., 2007). Statistics were conducted in MATLAB (2017b, TheMathworks, USA) and JASP (Love et al., 2019).

3.4 Results

3.4.1 Current Flow Modelling

Current flow models demonstrated precise targeting of the DLPFC (Figure 3.5). The current strength was comparable to (Hill et al., 2017) in which tDCS over the DLPFC elicited a sustained increase in TEP (TMS-Evoked Potential) amplitude. The modified electrode set up here resulted in a peak electric field strength of 0.61 V/m, which was higher than the peak strength in their similar setup modelled on an exemplar younger brain (0.25 V/m). Qualitatively the field strength and distribution were similar, with the DLFPC showing values around 0.3 V/m.

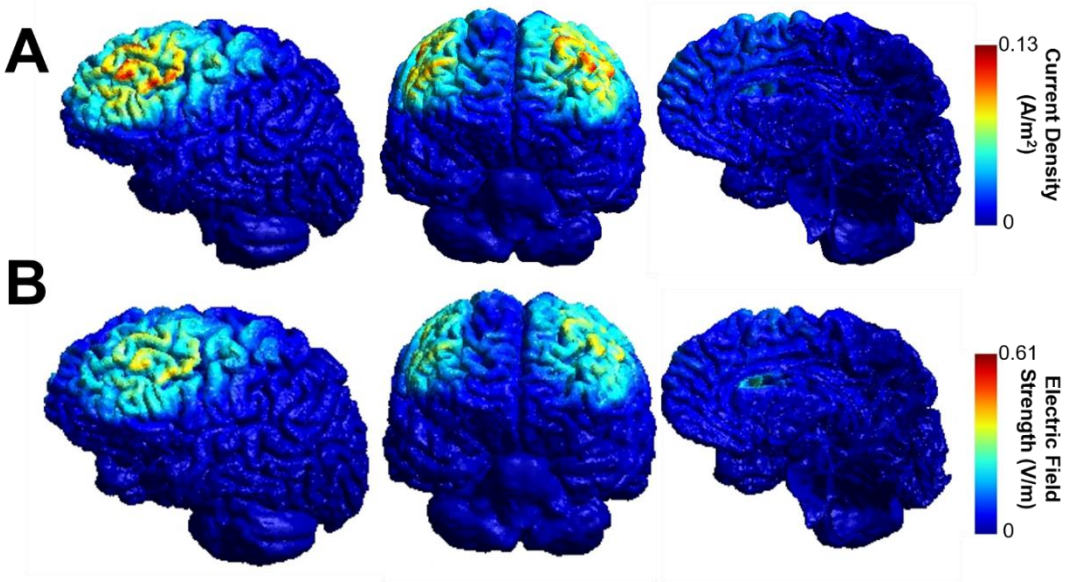

Figure 3.5. FEM calculation of electric field strength modelled for the bilateral montage in an example older brain. A. Estimated current density demonstrating constrained stimulation targeting the DLPFC bilaterally. Current was restricted to the region of interest showing little to no cross-

hemispheric overlap. **B.** Estimated electric field strength on the same example MRI-derived brain mesh.

3.4.2 Order Effect

To assess whether the counterbalancing procedure was effective, a mixed-factor ANOVA was conducted assessing the effect of stimulation (within-subjects) and order group (between-subjects; stimulation-first vs. sham-first). This analysis revealed a main effect of order group [$F_{(1,22)} = 5.18$, $p = 0.033$, $\eta^2 = 0.14$] (See Figure 3.6). There was also a significant interaction between stimulation and order [$F_{(1,22)} = 4.54$, $p = 0.045$, $\eta^2 = 0.04$]. Follow-up independent samples t-tests revealed that WM performance was significantly greater in the stimulation-first group specifically during the sham session of each group (session 2 for stimulation-first, session 1 for the sham-first) [$t_{(22)} = 3.37$, $p = 0.003$, Cohen's $d = 1.38$] rather than during the stimulation session [$t_{(22)} = 0.84$, $p = 0.41$, Cohen's $d = 0.34$]. A paired-samples t-test revealed that the interaction effect was driven by significantly greater performance at session 2 compared to session 1, regardless of stimulation/sham status or order group [$t_{(23)} = 2.18$, $p = 0.04$, Cohen's $d = 0.44$].

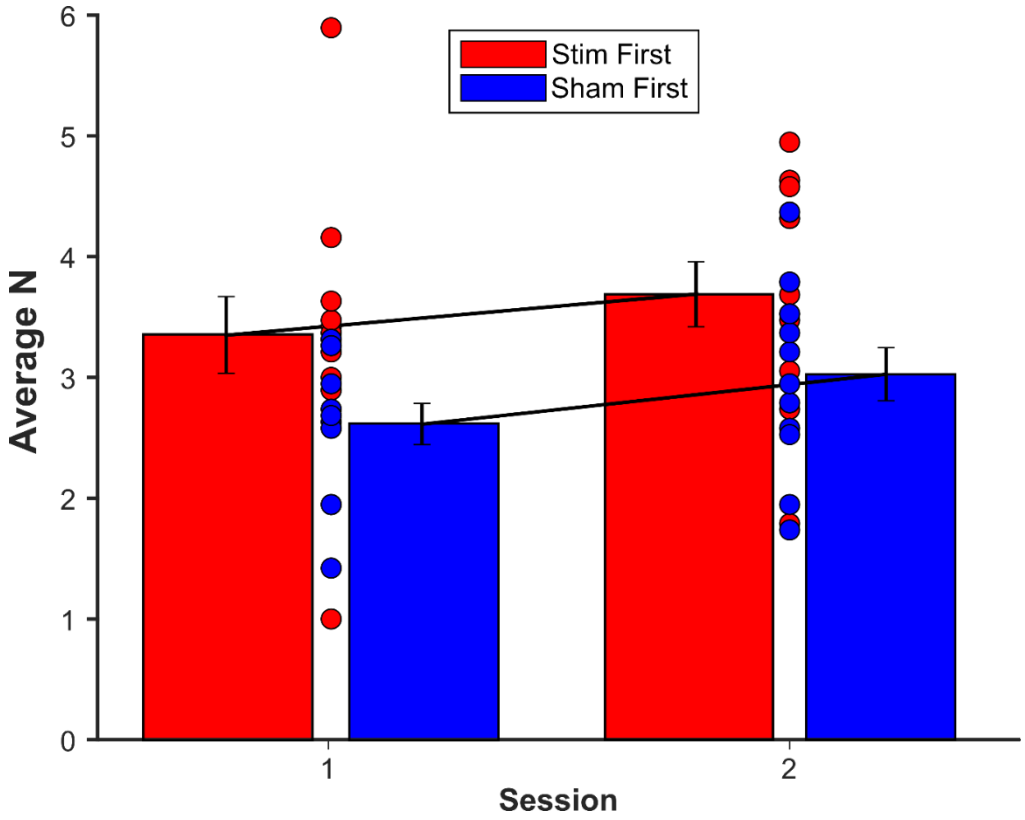

Figure 3.6. Average N across sessions by stimulation-order group. Assessing the effectiveness of the counter-balancing procedure used here revealed a significant order effect in which participants receiving stimulation-first achieved a higher difficulty level (n) across both sessions.

3.4.3 Change Detection Task

To examine the results of the change detection task, each individual's capacity (k) was calculated (Cowan, 2010; Rouder et al., 2011). As this results in a separate k value for each difficulty level of trial (2, 4, or 6 to-be-remembered items), the k value for each trial type was computed before being mean averaged. Theoretically, this k value should be normalised by the number of items so that the values computed at each difficulty level should be comparable. A repeated-measures ANOVA revealed that there was in fact a significant main effect of trial difficulty (whether 2, 4, or 6 items were to be remembered) on an individual's capacity measure (k) [$F_{(2,46)} = 5.14$, $p = 0.010$, $\eta^2 = 0.13$]. Follow-up paired t-tests (averaging across sessions) revealed that this effect of trial difficulty was driven by difficulty level 4, which showed a greater k value compared to difficulty level 2 [$t_{(23)} = 2.76$, $p = 0.010$, Cohen's d =

0.56] and compared to difficulty level 6 [$t_{(23)}$ = 2.67, p = 0.014, Cohen's d = 0.54]. Importantly however, there was no main effect of session [$F_{(1,23)}$ = 0.23, p = 0.63, η^2 = 0.001]. There was also no significant interaction between load and session [$F_{(2,46)}$ = 1.75, p = 0.19, η^2 = 0.12]. Thus, the data suggested that although k as a measure of capacity was not fully independent of trial difficulty, k was a robust measure with no significant difference between values when tested on different sessions. Notably, there was also no significant difference in average capacity between order groups (stimulation-first vs. sham-first) in either session 1 as determined by an independent-samples t-test [$t_{(22)}$ = 0.53, p = 0.60, Cohen's d = 0.22].

3.4.4 Single Session Analysis

To avoid any stimulation-associated learning effect, session 1 was examined in isolation which effectively constituted a between-subjects design single session experiment. In the first session, participants receiving stimulation showed higher working memory performance relative to those receiving sham stimulation(Figure 3.7). We conducted an ANOVA exploring the effect of stimulation (stimulation/sham) and laterality group (left/right/bilateral) on average N achieved. This analysis revealed that the main effect of stimulation approached significance [$F_{(1,18)}$ = 4.08, p = 0.06, η^2 = 0.16]. There was, however, no significant main effect of laterality [$F_{(2,18)}$ = 0.66, p = 0.54, η^2 = 0.05], nor was there a significant interaction between laterality group and stimulation [$F_{(2,18)}$ = 1.10, p = 0.36, η^2 = 0.09]. Although not significantly so, the bilateral group did show the greatest difference between stimulation and sham [$t_{(6)}$ = 1.98, p = 0.10, Cohen's d = 1.98], followed by left-only stimulation [$t_{(6)}$ = 1.55, p = 0.17, Cohen's d = 1.55], with right-only stimulation showing the least stimulation benefit [$t_{(6)}$ = 0.32, p = 0.76, Cohen's d = 0.32]. We note that a post-hoc power analysis conducted using G*Power (Version 3, Faul et al., 2007) revealed that

the required sample size for the beneficial bilateral stimulation effect (bilateral stimulation vs. sham group) to become significant would be an n of 16 (8 per group).

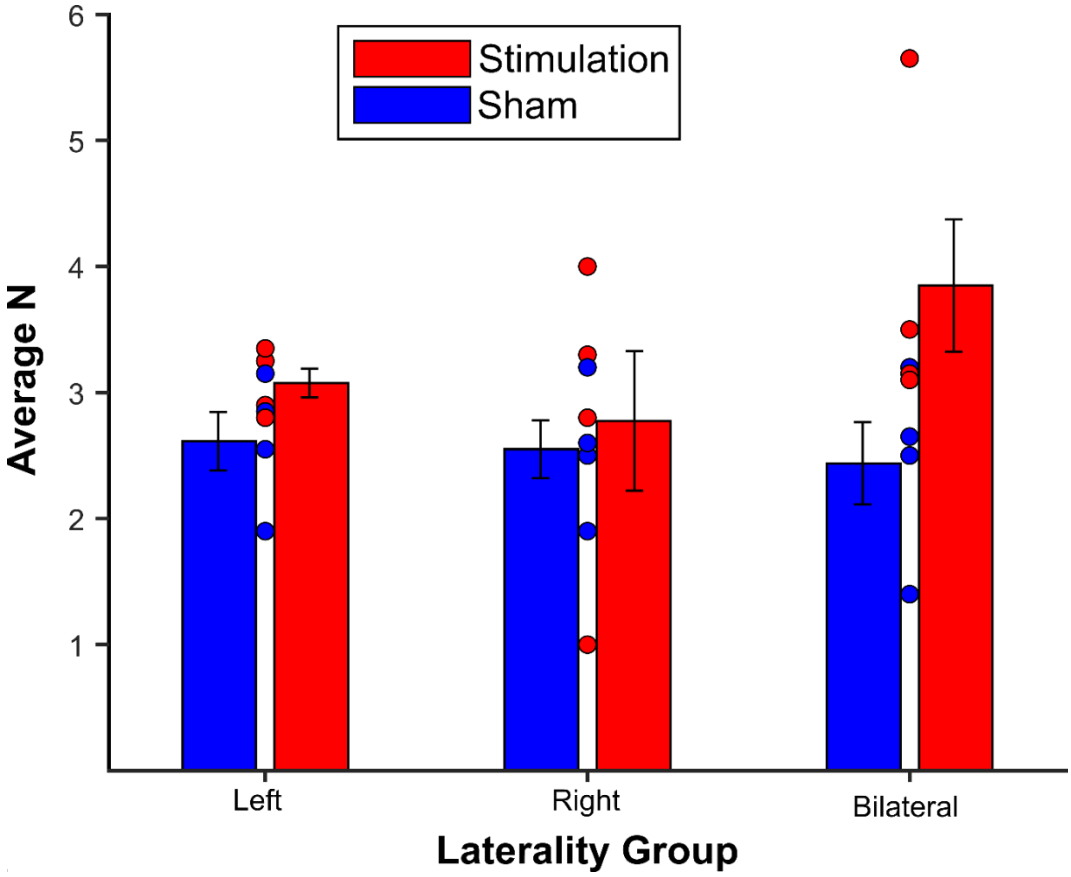

Figure 3.7. Analysing average N in a single-session design. Given the presence of an order effect, data from the second session were discarded and session 1 was analysed in isolation. The group receiving stimulation showed no significant differences in performance neither between laterality groups nor between stimulation groups.

Although this stimulation effect was not significant, we assessed whether the proposed extraneous variables (which the literature had suggested were important but are frequently not examined in such studies) were implicated in this stimulation effect. Specifically, we conducted an ANCOVA on the mean N achieved in session 1, in which the main factors were stimulation, WM capacity, and laterality. We included as covariates self-reported expectation and self-reported strategy use (whether a strategy was reported or not).

As before, there was no significant main effect of stimulation [$F_{(1,15)}$ = 1.25, p = 0.28, η^2 = 0.04], laterality [$F_{(2,15)}$ = 0.97, p = 0.40, η^2= 0.06], or a significant interaction between stimulation and laterality $F_{(2,15)}$ = 0.44, p =0.65, η^2= 0.03]. Notably, there was a significant effect of both strategy use [$F_{(1,15)}$ = 6.00, p = 0.03, η^2= 0.19] and expectation [$F_{(1,15)}$ = 6.70, p = 0.02, η^2= 0.21], although no effect of WM capacity was observed [$F_{(1,15)}$ = 0.68, p 0.42, η^2= 0.02]. Intriguingly, participants who rated their pre-stimulation expectation higher showed lower average performance on the N-back task. In contrast, reported strategy use was associated with higher average performance on the N-back task [two-samples t-test, $t_{(22)}$ = 2.71, p = 0.013, Cohen's d = 1.12]. WM capacity did not directly predict WM performance but it has been suggested that only high capacity participants selectively benefit from stimulation. To examine this interaction, we conducted a median split-analysis dividing the sample into low/high capacity participants. An ANOVA assessing the effect of stimulation and WM capacity (low/high) revealed that there was no significant interaction between stimulation and WM capacity [$F_{(1,20)}$ = 0.77, p = 0.39, η^2= 0.03] suggesting that neither high nor low capacity individuals were more likely to show a stimulation benefit.

3.4.5 Performance across the N-back Task

Although stimulation was expected to improve performance throughout the task (as reflected by mean N across the full task), we also examined how performance changed over time (See Figure 3.8). Specifically, we assessed whether stimulation-induced improvement was constrained to either specific difficulty (e.g. stimulation only improved performance at greater difficulty levels) or a specific portion of the task (e.g. stimulation improved performance only in the early blocks of the task). This analysis was constrained to the first session.

A mixed-factor ANOVA was conducted exploring the between-subjects effect of stimulation and laterality on N and the within-subjects factor of block number. As would be expected, there was a highly significant effect of block [$F_{(19,418)} = 38.93$, $p < 0.001$, $\eta^2 = 0.30$]. As detected when we examined average N achieved, there was a close-to-significant effect of stimulation [$F_{(1,22)} = 4.18$, $p = 0.053$, $\eta^2 = 0.082$]. Importantly, however, there was a significant interaction between block and stimulation [$F_{(19,418)} = 1.97$, $p = 0.01$, $\eta^2 = 0.02$]. Follow-up two-sample t-tests revealed that the difference between stimulation and sham was driven by blocks 4 through to 10 out of the full 20 blocks performed [block 4, $t_{(22)} = 2.35$, $p = 0.03$, Cohen's d = 0.96; block 5, $t_{(22)} = 2.13$, $p = 0.045$, Cohen's d = 0.87; block 6, $t_{(22)} = 3.15$, $p = 0.005$, Cohen's d = 1.29; block 7, $t_{(22)} = 2.53$, $p = 0.019$, Cohen's d = 1.03; block 8, $t_{(22)} = 2.12$, $p = 0.046$, Cohen's d = 0.86; block 9, $t_{(22)} = 2.11$, $p = 0.046$, Cohen's d = 0.86; block 10, $t_{(22)} = 2.18$, $p = 0.040$, Cohen's d = 0.89]. Although the performance of the group receiving stimulation was higher throughout the entire task, after block 10 there was no block where this was significant.

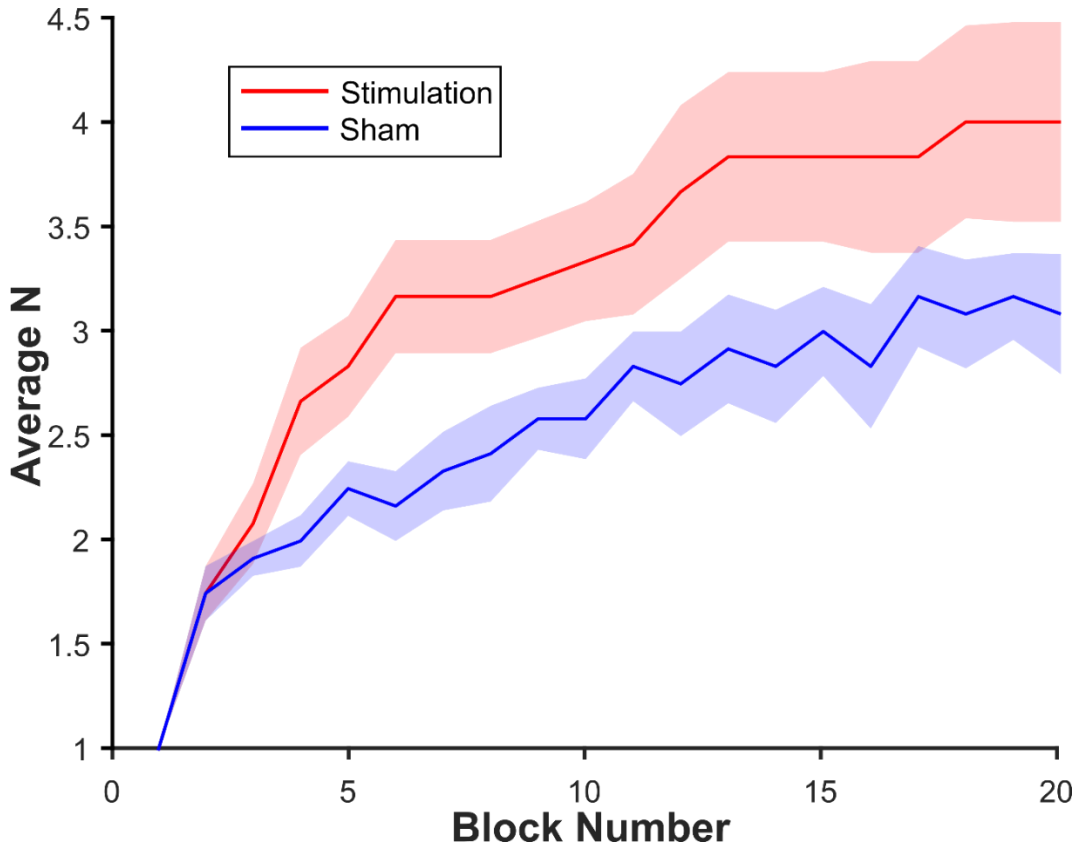

Figure 3.8. The effect of stimulation on average N across the session. Examining session 1, collapsing across laterality groups, participants receiving real stimulation showed improved performance (as manifested by higher N) compared to those receiving sham stimulation. The stimulation group showed significantly higher n from blocks 4-10. Shading indicates standard error of the mean.

3.4.6 Strategy Use

Given that strategy use appeared to modulate WM performance, we further analysed the frequency with which participants spontaneously adopted a strategy and how effective they reported their strategy as being. Firstly, 58.3% of participants reported using a strategy in session 1 and this number increased to 79.17% in session 2. This increase was driven exclusively by participants who did not use a strategy in session 1 adopting a strategy during session 2, i.e. no participants who used a strategy in their first session abandoned using a strategy during the second session. Average self-reported strategy efficacy did not differ between sessions, as determined by a paired-samples t-test of the 14 participants who employed a strategy during both sessions [$t_{(13)} = 0.17$, $p = 0.87$, Cohen's $d = 0.05$].

3.4.7 Arousal and Mood Measures

Several control measures were implemented to ensure that any stimulation-related differences observed were specific to working memory and were not mediated by mood or by improved vigilance. To combat the latter, participants performed a brief psychomotor vigilance task (PVT) before and after the adaptive N-back task (and therefore before and after the transcranial current stimulation was applied). Each subject's average reaction time at the first time point (pre-stimulation) was subtracted from the second time point (post-stimulation). Thus a positive value indicated a slowing and a negative value indicated faster reaction times. These reaction time difference values were then compared between stimulation and sham conditions. For both stimulation and sham conditions, the pre-stimulation to post-stimulation differences were not significantly different [stimulation, $t_{(23)} = 1.27$, $p = 0.22$, Cohen's $d = 0.26$; sham, $t_{(22)} = -0.48$, $p = 0.64$, Cohen's $d = -0.10$]. A paired t-test on these differences between conditions also revealed no significant difference between sham and stimulation sessions [$t_{(22)} = 1.18$, $p = 0.25$, Cohen's $d = 0.25$].

Participants also completed the PANAS questionnaire (Watson et al., 1988) immediately before performing the PVT. For stimulation condition comparisons a mood difference score was computed for both the positive and the negative component of the PANAS. First, we tested whether there was a significant difference between time points for either condition. As with the PVT, there was no significant change in either the positive or the negative component of the PANAS post-stimulation relative to pre-stimulation, although a reduction of negative affect with stimulation did approach uncorrected significance [stimulation, positive affect, $t_{(23)} = 0.80$, $p = 0.43$, Cohen's $d = 0.16$; stimulation, negative affect, $t_{(23)} = -1.94$, $p = 0.06$, Cohen's $d = -0.40$; sham, positive affect, $t_{(23)} = 0.68$, $p = 0.50$, Cohen's $d = 0.14$;

stimulation, negative affect, $t_{(23)}$ = -0.36, p = 0.72, Cohen's d = -0.08]. Additionally, there was no difference in these post-stimulation mood changes relative to pre-stimulation between stimulation and sham conditions for either component of the PANAS [positive affect, $t_{(23)}$ = -0.26, p = 0.80, Cohen's d = 0.05 ; negative affect, $t_{(23)}$ = 1.04, p = 0.31, Cohen's d = 0.22].

Participants were also asked separately to rate on a scale from 1-5 how their current level of alertness, their expectation that the experimental task would improve their working memory, and their level of motivation. In order to examine whether the possible stimulation effect in the first session was due to a group difference in any of these measures, we compared the ratings on each of these measures at the first time-point (T1, pre-stimulation) between the two order groups (stimulation-first vs. sham-first) via Mann-Whitney U tests. These tests revealed a significantly greater degree of self-reported expectation in the sham-first group [ranks = 446.5, p = 0.002], but there was no significant difference in the other measures [alertness, ranks = 621, p = 0.46; motivation, ranks = 622, p = 0.45; sadness, ranks = 606, p = 0.69]. Given that expectation ratings were in fact lower in the group that performed better, this did not appear to be underlying the group difference between stimulation and sham conditions.

3.4.8 Blinding

Although it has been previously reported that HD-tDCS can result in greater cutaneous sensation ratings relative to conventional montages, condition blinding was successfully maintained. A chi-squared test revealed that regardless of whether participants had received verum or sham stimulation, participants were not any more likely to correctly guess which condition they were in [X^2(1, N = 46) = 0.382, p = 0.54]. Additionally, the confidence ratings of this judgement did not differ between

stimulation conditions [Wilcoxon signed rank test, Z = 48, p = 0.51] nor between correct and incorrect responses [Mann Whitney, z = 0.18, p = 0.86]. Wilcoxon signed rank tests indicated that ranks of self-reported side effects did not differ between stimulation and sham conditions [headache, z = 6, p = 0.25; neck pain, z = 75, p =0.63; itching, z = 6, p = 1.00; sleepiness, z = 36.5, p =0.50; concentration, z = 65.5, p = 0.50 ; mood, z = 5, p = 1.00; fatigue, z = 27, p = 0.29; nausea, z = 1.5, p = 1.00; muscle twitching, z = 1, p = 1.00; tingling, z = 56.5, p = 0.96; burning, z = 9, p = 1.00; light flashes, z = 1, p = 1.00; uncomfortable feeling, z = 1, p = 1.00].

3.4.9 Order Group Assignment

Participants were assigned to order group (whether they received verum or sham stimulation first) by an experimenter blind to which group they were being assigned to but attempting to approximately balance years of education and age. This method was effective insofar as between order groups there were no significant difference in years of education [stim-first, mean 15.73 years; sham-first, 15.92 years; $t_{(22)}$ = -0.16, p = 0.88, Cohen's d = 0.18] nor in age [stim-first, mean 69.6 years; sham-first, mean 68.58 years; $t_{(22)}$ = 0.44, p = 0.66, Cohen's d = -0.07].

3.5 Discussion

3.5.1 Summary

To summarise the results, there was no statistically significant benefit conferred by HD-tDCS targeting the DLPFC on performance on an adaptive N-back task. Furthermore, there was no clear benefit of stimulation targeting both hemispheres as compared to stimulation of either the left or the right hemisphere in isolation, as would be predicted by the HAROLD model. There was a significant order effect in which participants who received stimulation during session 1 performing better on the adaptive N-back task relative to those who were stimulated during their second

session. The first session was examined in isolation and participants did show the greatest stimulation benefit in the bilateral stimulation condition but neither the stimulation effect nor this laterality difference were significant. Including the block number (and therefore the timing of the task) as a factor revealed that there was a significant effect of stimulation during the early-middle portion of the task.

3.5.2 Stimulation Order Effect

There are two plausible explanations for the order effect and the finding that the stimulation-first group showed improved WM performance regardless of session. The first explanation is a group effect in which the stimulation group, despite random allocation, contained individuals with higher working memory capacity. The available data suggests that this was not the case. Specifically, there was no group difference in age, years of education, or WM capacity as measured by the change detection task. This argument does however assume that WM capacity is the only factor involved in the performance of the N-back task which is unlikely to be the case. Indeed, as Jaeggi et al. (2010) have discussed, different tasks designed to tap into WM are not uniform. The N-back task, although frequently employed in similar stimulation paradigms shows weak correlations with complex span tasks and is also highly related to fluid intelligence (Andrews et al., 2011; Mashal & Metzuyanim-Gorelick, 2019). The possibility that there was a group difference in a key variable underlying the differential performance cannot be discounted. The alternative explanation for the order effect, however, is that tDCS did in fact improve performance during the first session and participants retained the benefit of stimulation when they returned for the second session.

It should be noted that the primary limitation of this experiment was the sample size which reduced statistical power and may have prevented the detection of a

stimulation benefit. Notably, stimulation did result in higher average performance relative to sham in all three laterality conditions, suggesting that this may have been the case. Small sample sizes pose a particular challenge in tDCS work (Minarik et al., 2016), where effect sizes may be small. Whilst comparable to previous work in the context of the planned analyses, the sample size was largely problematic as a result of the aforementioned learning/order effect detected. This resulted in several analyses being constrained to only the first experimental session, effectively constituting a between-subjects design. Recruitment of the targeted population (55+ years old) can prove challenging, especially in transcranial current stimulation experiments where, for example, metal implants or history of psychological disorder are important exclusion criteria. Future work should, however, strive to adequately power stimulation experiments as well as to avoid tasks prone to learning effects to prevent both spurious null and positive reports of tDCS' efficacy.

3.5.3 Stimulation Washout and Long-term Stimulation Effects

Stimulation benefits accrued during the first session may have enhanced performance in the second session. One week washout periods are considered sufficient (Thair et al., 2017) and conservative given earlier work where periods of an hour were used (Fregni et al., 2005). However the present data suggest that this is not always the case. Notably, this conflicts with the conclusion of a meta-analysis suggesting that there was no benefit in a washout period longer than a week, specifically for stimulation of the DLPFC (Dedoncker et al., 2016b). Several previous studies that applied tCS during cognitive training paradigms across multiple sessions, where stimulation is thought to have a cumulative effect (Ho et al., 2016), suggest that stimulation-related improvements in learning can persist up to six months after the initial training period (Kadosh et al., 2012; Snowball et al., 2013).

The present finding warns that this may not be limited to multiple session training paradigms.

3.5.4 Age and Cortical Excitability

The timing of stimulation effects may be influenced by the population of older adults used here. One relevant finding is from a study examining TMS-derived excitability after 30 minutes of stimulation of the motor cortex via tDCS (Fujiyama et al., 2014). Although older adults did not show a significantly different excitability response overall, excitability in older adults appeared delayed showing difference from sham at 20 and 30 minutes after the end of stimulation, rather than immediately after as was the case in young participants. Furthermore, the timing of stimulation-related effects may also vary as a function of the stimulation montage. Specifically, probing excitability of the DLFPC via TMS-EEG, Hill et al. (2017) revealed a greater P60 response post-stimulation. Crucially, this increase appeared to occur at 5 minutes post-stimulation for the bipolar montage, notably earlier than the HD-tDCS montage where the difference was evident 30 minutes after the end of stimulation. Similarly, Kuo et al. (2013) showed that the excitability increase induced by tDCS of the motor cortex was delayed in the 4x1 (HD) configuration relative to the conventionally setup stimulation. Indeed excitability remained elevated up to 120 minutes post-stimulation in response to HD-tDCS, whereas when receiving conventional stimulation excitability had at this point returned to baseline. Exactly why these two methods may vary in their effects is unclear. Current flow simulations do implicate the orientation of applied electric field. Although both montages produce a combination of tangential (aligned with) and radial (at a right angle to) electric fields relative to the cortical surface, it has been suggested that the proportion and distribution of these varies between the two types of montage (Rahman et al., 2013). Importantly, this is

likely to have functional significance, as radial fields (which may represent a greater proportion in HD-tDCS setups) are more likely to act on axon terminals, thereby modulating synaptic efficacy, whereas tangential fields depolarise the soma of cells.

3.5.5 Stimulation Timing

If improvement is largely accomplished between sessions, is online or offline stimulation most effective? That is to say are the benefits of stimulation on WM previously observed due to the transient depolarisation of neurons or to longer-scale mechanisms such as plasticity induction (Stagg & Nitsche, 2011). In one review, both online and offline stimulation paradigms appeared to showed positive effects (Hill, Fitzgerald, et al., 2016). Another meta-analysis has advocated for the benefit of online over offline paradigms specifically in neuropsychiatric populations (Dedoncker et al., 2016a). Experimentally, Martin et al. (2014) showed that in an adaptive N-back task, participants receiving stimulation during the task performed better when receiving stimulation during the task versus when they received the same stimulation prior to the task. On the other hand, tDCS may still exert effects between sessions. Specifically, Reis et al. (2009) showed that the beneficial effects of tDCS in a motor task were driven by offline (between-day), rather than online (within-day), improvement relative to sham stimulation. The relationship between online and offline remains poorly misunderstood and relatively under-explored (Au et al., 2021). Time-permitting, it may be prudent in future to combine these approaches, by stimulating during the first half of a task, as has been done previously (Ohn et al., 2008), which may capture both online and short-term offline effects.

3.5.6 Testing the HAROLD model

There is limited evidence here to support the HAROLD model. When examining the single-session data, bilateral stimulation did show the greatest stimulation-induced

improvement, but this difference was not significant. In the single-session analysis, the effect size of the stimulation-sham contrast in the bilateral group was suggestive but is limited by the small sample size and large between-subjects variability. Additionally, although bilateral stimulation was numerically the most beneficial, right-only stimulation showed the smallest effect which previous work would suggest is an appropriate montage for visuo-spatial paradigms. Importantly, the present findings do further demonstrate the importance of including measures of strategy use and expectation in similar paradigms, given that these factors significantly modulated WM performance.

3.5.7 Stimulation Parameters

Although null effects are not uncommon in stimulation studies, could the failure to observe a stimulation effect be due to any of the tDCS parameters adopted here? Firstly, participants were stimulated for at least 20 minutes. This stimulation duration has previously been shown to be effective, including when using an older population (Arciniega et al., 2018). Additionally, the electric field achieved by the montage used here was comparable to previous studies in which the current flow has been modelled and reported. Despite claims that an electric field strength of at least 1 V/m is required to alter the internal current (Vöröslakos et al., 2018), previous work has shown a beneficial effect on WM (Kim et al., 2014) and stimulation-induced changes in single-unit activity (Krause et al., 2017, 2019) at lower strengths of approximately 0.3 V/m. Furthermore, a similar setup has been shown to influence cortical excitability (Hill et al., 2017). It is important to note that the current flow modelling derived here used a presumably representative older brain, but that it was not performed for individually derived structural MRI scans as would be optimal (Datta et al., 2011; Filmer et al., 2019; Truong et al., 2014).

3.5.8 Current Dosage

The stimulation montage was designed specifically to achieve a field strength comparable to previous paradigms. It may have been possible to increase the current strength without compromising blinding, however there is some data to suggest that the typical sham method employed here (ramping up and down) may prove ineffective when the current is increased to 2mA (O'Connell et al., 2012). Furthermore, given previous evidence suggesting that HD-tDCS elicits stronger cutaneous sensations (Hill et al., 2017), it seemed prudent not to risk compromising the blinding procedure. The data reported here strongly support that the blinding was sufficient at the current strength employed, but alternative blinding methods (e.g., montages designed to maximise current shunting across the scalp) or topical anaesthetic cream may be necessary with increasing current strength. Participants were unable to judge correctly whether they received real or sham stimulation. Furthermore, self-reported ratings did not differ between real and sham stimulation. We note that an older sample in this case may have been advantageous in ensuring blinding, given reduced tactile (Decorps et al., 2014) and algetic (Tseng et al., 2013) sensitivity in this population. Finally, on the question of whether the current strength could be increased, it remains unclear whether this would have been beneficial. The dose-excitability response to tDCS shows some evidence of non-linearity (Batsikadze et al., 2013; Esmaeilpour et al., 2018; Jamil et al., 2017; Samani et al., 2019). The degree to which this is true in stimulation targeting the prefrontal cortex and whether such non-linearity might be a result of stochastic resonance (Miniussi et al., 2013) or other mechanisms (Ridding & Ziemann, 2010) remains unclear.

3.5.9 Accounting for Inter-individual Variability in WM

Assuming that the parameters adopted here were appropriate, inter-individual variability in responsiveness to stimulation remains high (Guerra et al., 2020; López-

Alonso et al., 2014). Intra-individual reliability may be lower (López-Alonso et al., 2015), although the evidence is somewhat equivocal (Horvath et al., 2016). Nevertheless, it may be helpful in future to determine 'responders' to stimulation before those same participants participate in the paradigm of interest. Additionally, the use of an alternative task to test WM in future work may be appropriate. The rationale behind using an adaptive N-back task was that there was likely to be a significant variability in WM ability, especially among an older population. This variability was indeed evident in the present data. Importantly however, tDCS may only benefit working memory ability when an individual is sufficiently challenged. Thus it was important to ensure that in spite of any variability, participants were sufficiently engaged to ensure that we would see a stimulation effect, as well as to avoid a behavioural ceiling effect. The adaptive N-back task employed here however may be particularly susceptible to learning effects as participants performed better on the second session. A recent tACS study employed a task similar to the change detection task employed here (Bender et al., 2019). Notably, their approach allowed them to detect a stimulation by load interaction in which the stimulation improvement was largely driven at the highest WM load, specifically when 6 (as compared to 4 or 5) items had to be remembered. This did however use a sample of young healthy adults in which there may be less variation. Whilst this does control for the possibility that stimulation effects only occur at high WM load levels, this does not normalise performance between participants. To use the above-mentioned paradigm as an example, if 6 items are not sufficiently challenging for one participant, that individual may be less likely to exhibit a stimulation effect which may occlude any load by stimulation interaction. Another option may be to determine post-hoc when an individual was at their individual ceiling, based on a certain value of d-prime, for

example, and analyse only those trials, or to assess an individual's performance on a specific task prior to stimulation and titrate the task difficulty accordingly.

3.5.10 Probing Working Memory with Transcranial Alternating Current Stimulation (tACS)

Finally, it may be advantageous to test the HAROLD model via transcranial alternating current stimulation (tACS) rather than tDCS. Recently, several studies have successfully shown that transcranial alternating current stimulation (tACS) can modulate working memory performance. Given the proposed role of neural oscillations (especially theta, gamma, and alpha activity) in WM function (Roux et al., 2012), this may provide a more precise and flexible means to influence the brain and its underlying activity (Herrmann et al., 2013; Vosskuhl et al., 2018). Specifically, stimulating with combined theta and gamma rhythms (Alekseichuk et al., 2016), facilitating inter-regional theta coherence (Reinhart & Nguyen, 2019), and slowing the endogenous theta rhythm (Bender et al., 2019; Vosskuhl et al., 2015; Wolinski et al., 2018) have all been shown to improve working memory. If further work demonstrates these to be more reliable than tDCS, hemispheric asymmetry in ageing could be interrogated in this fashion. Furthermore, combining EEG and TMS with tCS to probe cortical excitability (Hill, Rogasch, et al., 2016) or investigating stimulation-induced oscillatory changes, particularly in the theta and gamma band (Hill et al., 2018), may help reduce the reliance on solely behavioural data and thereby help unravel the complexities of transcranial current stimulation.

3.5.11 Conclusions

In conclusion, the data do not provide strong evidence in favour of or against the HAROLD model. We find limited evidence of the efficacy of HD-tDCS targeting the DLPFC in improving performance on an adaptive working memory task.

Encouragingly, HD-tDCS in the present study was exceptionally well-tolerated and did not compromise blinding, supporting its use in future work.

Chapter 4: Encoding and Retrieval State Separation by the Human Hippocampal Theta Rhythm

4.1 Abstract

The hippocampus has been well-studied for its involvement in episodic memory encoding and retrieval. A key challenge in memory is to ensure that encoding and retrieval processes do not become confused. A computational model suggests one mechanism the hippocampus uses to achieve this is to preferentially process encoding and retrieval related information at distinct phases of the ongoing hippocampal theta rhythm.

In the present study, EEG was recorded intracranially while patients performed a continuous encoding/retrieval task in which they were cued when they would be encoding or retrieving the subsequently presented stimulus. Oscillatory power analyses revealed a robust increase in gamma power following stimulus presentation. Both cue and stimulus onsets prompted a phase reset across low frequencies, but a brief phase difference was also observed following the memory cue. Phase-amplitude coupling analyses revealed distinct patterns of theta-gamma coupling depending on whether the cue indicated encoding or retrieval. This condition difference did not reach statistical significance but was consistent with previous rodent data. Gamma power was nested in a different phase of theta depending on the condition, supportive of the original model.

4.2 Introduction

4.2.1 Episodic Memory and the Hippocampus

Episodic memory allows an organism to recall past experiences (Tulving, 2002). The hippocampus and surrounding structures in the medial temporal lobe are critical to the function of this memory system (Dickerson & Eichenbaum, 2010; Squire, 2004, 2009; Squire et al., 2004; Squire & Zola-Morgan, 1991). In humans, observational

studies have implicated the activation of the hippocampal formation in episodic memory (Dickerson & Eichenbaum, 2010; Moscovitch et al., 2016; Squire et al., 2004), and more recently, direct electrical stimulation of the human medial temporal lobe can impair (Jacobs et al., 2016) or improve performance on a memory task (Ezzyat et al., 2017, 2018).

4.2.2 Hippocampal Theta

A dominant feature of electrophysiological recordings from the hippocampus is the theta rhythm, a fluctuation in excitability occurring at a frequency between 4-10 Hz (Colgin, 2013, 2016). Both the hippocampus and its theta rhythm are highly conserved across species (Las & Ulanovsky, 2014; Winson, 1972) and this theta rhythm is highly associated with memory encoding and retrieval processes (Buzsáki & Moser, 2013; O'Keefe, 1993; Vertes, 2005). For example, hippocampal theta power is greater during successful associative learning (Landfield et al., 1972; Seager et al., 2002). Moreover, disruption to generation of the theta rhythm impairs memory processes, whether by lesion (Winson, 1978), pharmacologically (Easton et al., 2012; Givens, 1995), or optogenetically (Kloc et al., 2020). Additionally, a phase reset in the theta range occurs in response to memory-relevant stimuli (Givens, 1997; Mormann et al., 2005) that is thought to provide optimal conditions for the induction of long-term potentiation (Bikbaev & Manahan-Vaughan, 2009; McCartney et al., 2004).

4.2.3 Hippocampal Theta and Human Memory

Although much initial investigation into the hippocampal theta rhythm has been conducted in non-human animals, development in both invasive (Parvizi & Kastner, 2018) and non-invasive methods (Ruzich et al., 2019) have facilitated further investigation within the human hippocampus. Pre-stimulus theta power in the MTL

predicts whether items will later be successfully recalled (Juergen Fell et al., 2011; Guderian et al., 2009). Theta power also facilitates context-binding during encoding (Staudigl & Hanslmayr, 2013). Similarly, subsequent memory effect analyses (where later-retrieved trials are contrasted with later-forgotten trials) suggest that hippocampal theta power is greater during successful episodic memory encoding (Lin et al., 2017; Long et al., 2014). Notably however, the evidence is not unequivocal with some studies, in particular those employing intracranial EEG, reporting an SME-related decrease in theta power, e.g. (Kragel et al., 2017; Solomon et al., 2019).

Neural activity is frequently organised according to the timing relative to this rhythm, both locally and cross-regionally. Theta/delta activity in the hippocampus governs the spike timing of neurons in a number of areas implicated in memory, including the hippocampus, temporal, and parietal cortices (Jacobs et al., 2007; Schonhaut et al., 2020). Phase-locking in the medial temporal lobe during encoding differentiates low-confidence from high-confidence ratings at subsequent retrieval (Rutishauser et al., 2010). In a simultaneous EEG-fMRI study, hippocampal theta was correlated with hippocampal-medial prefrontal cortex connectivity (mPFC) (Herweg et al., 2016), suggesting that hippocampal theta is a key to hippocampal-neocortical communication. Another study employing MEG, corroborated the role of hippocampal theta power and hippocampal-mPFC connectivity in successful memory binding (Backus et al., 2016).

4.2.4 The Function of the Theta Rhythm

What is the functional significance of this theta rhythm? It may function to organise cell assembly activation, facilitate synaptic changes, to optimise inter-regional communication, or serve multiple such functions (Colgin, 2013; Hasselmo, 2005;

Korotkova et al., 2018). The hippocampal theta rhythm results in cyclic fluctuations in excitability. The depolarisation of hippocampal pyramidal cells thereby varies according to a theta rhythm influencing the likelihood of action potentials (Kamondi et al., 1998). Additionally, theta may organise periods in which synaptic efficacy is most labile (Huerta & Lisman, 1993). Finally, theta may also facilitate inter-regional coherence (Buzsáki & Draguhn, 2004; Fries, 2005). Notably, in a number of working memory paradigms, hippocampal cells fire according to theta rhythms detected in the medial prefrontal cortex (Hyman et al., 2010; Hyman et al., 2011), and inter-regional coherence also predicts memory efficacy (Kim et al., 2011). Theta as a low-frequency rhythm may ensure that afferent input arrives at the time of local maximal excitability, ensuring effective communication even between distant regions (Colgin, 2016; Von Stein & Sarnthein, 2000).

4.2.5 Theta as a separator of encoding and retrieval

The phase of theta has been suggested to play a more specific role in memory: that of partitioning discrete memory processes. Since termed the SPEAR model (Separate Phases of Encoding And Retrieval), Hasselmo et al (2002) postulated that opposing theta phases provide discrete optimal time periods during which encoding and retrieval processes are best able to occur. Specifically, at the trough of hippocampal theta (usually measured at the hippocampal fissure), the network dynamics are optimally set up for encoding to occur. This state facilitates long-term potentiation at CA1 between excitatory synaptic connections arising from the entorhinal cortex (Hyman et al., 2003). In contrast, the peak of hippocampal theta serves as an optimal time for retrieval to occur. In this state, input arriving from CA3 region is stronger compared to input arising from the entorhinal cortex. Thus CA1 activity is driven by activity deriving from synapses previously modified during the

encoding phase. These opposite patterns of connectivity ensure that encoding and retrieval processes least likely to be confused.

4.2.6 Evidence for the SPEAR Model

The model was proposed to explain extant behavioural and neurophysiological data, and since its proposal a number of other studies have provided data in support of distinct encoding/retrieval phases according to theta. Lever et al. (2010) showed that the novelty of an environment predicted the theta phase at which cells in the rat hippocampal CA1 fired. Similarly, spiking rates in CA1 showed distinct phase preferences according to whether an item was new or old (Manns et al., 2007), supporting a phase difference between encoding and retrieval periods. Suggestively, administration of scopolamine (which impairs mnemonic accuracy, behaviourally) reduces the magnitude of gamma activity occurring specifically at the theta peak and shifts gamma activity relative to theta phase (Douchamps et al., 2013; Newman et al., 2013). Wang et al. (2020) demonstrated phase precession and procession in forward and backward replay of hippocampal cell firing sequences according to theta phase. Siegle & Wilson (2014) directly tested the Hasselmo model in an optogenetic stimulation experiment. Mice were trained on a spatial memory task with discrete encoding (where mice had to learn the location of a reward) and retrieval portions of the task (where they had to recall this information). Light pulses were delivered in a closed-loop fashion at opposite states of theta phase, with the intention to impede firing of CA1 cells (via inhibitory interneuron activation), during both encoding and retrieval portions of the task. A clear dissociation emerged where inhibition at the peak of theta improved encoding performance (but not retrieval) and the same inhibition at the trough of theta improved retrieval performance (but not encoding).

4.2.7 Hippocampal Theta Phase in Human Episodic Memory

Although working with human subjects precludes directly looking at many neural measures such as LTP, the phase of hippocampal theta appears similarly important to human episodic memory. By flickering auditory and visual stimuli, Clouter et al. (2017) showed that when multisensory information was presented in-phase specifically at a theta rhythm, it was most conducive to successful memory association. Additionally, some of these measures specifically point to phase discriminating between encoding and retrieval. Examining single-trial classifier decision values, Kerrén et al. (2018) showed a fluctuation in decoding evidence specifically at a theta rhythm (~7 Hz). Moreover, this decoding evidence time-series was significantly modulated by hippocampal theta (as measured by MEG), and critically, the maximum category-related evidence (a proxy of reactivation) occurred at distinct phases of the theta oscillation. Response times in memory tasks also occur according to the theta rhythm and at a different phase relative for encoding trials as compared to retrieval trials (ter Wal et al., 2021).

Intracranial data in humans also supports this. At frontal neocortical sites, which show high levels of connectivity with the hippocampus (Mitchell et al., 2008), Rizzuto et al. (2006) detected a reliable reset at the onset of encoding or retrieval states of the task. Importantly regarding the Hasselmo model, after this reset the two conditions showed a phase difference. Recently, single cell recordings from the human hippocampus during a free-recall task provided compelling evidence for the occurrence of encoding/retrieval phase separation in humans (Yoo et al., 2021). Spiking of single neurons in the MTL showed a phase difference between encoding and retrieval that was absent in neurons recorded elsewhere.

4.2.8 Hippocampal Gamma Activity

Another distinct component of rhythmic activity in the hippocampus is activity in the gamma range (> 30 Hz) (Colgin & Moser, 2010; Jacobs & Kahana, 2010). It is an ongoing debate as to the extent to which such high-frequency activity (HFA) in this range reflects enhanced oscillatory activity versus an increase in the rate of spiking amongst large populations of neurons (Burke et al., 2015; Manning et al., 2009). Nevertheless, subsequent memory effect analyses show that increased gamma power in a number of areas, including the hippocampus, is conducive to later subsequent retrieval (Fell et al., 2001; Kucewicz et al., 2014; Long et al., 2014; Sederberg et al., 2007). Additionally, both generation (via optogenetic stimulation; Etter et al., 2019) and entrainment (by visual/auditory flicker; Martorell et al., 2019; Zheng et al., 2020) of hippocampal gamma oscillations in an Alzheimer's mouse model restores previously impaired spatial memory function.

4.2.9 Theta-Gamma Coupling

The multiple rhythms of the hippocampus do not act in isolation and there is good evidence to suggest that by working in concert, synchronous activity at different frequency bands can organise activity at multiple spatial/temporal scales (Canolty & Knight, 2010). The power of high-frequency activity in the gamma band is reliably related to oscillatory activity at lower frequencies via phase-amplitude coupling, especially in the theta range and in the hippocampus (Buzśaki & Wang, 2012; Canolty et al., 2006; Colgin, 2015b; Schomburg et al., 2014), in which the amplitude of higher frequency activity is modulated by the frequency of the slower rhythm. Such phase-amplitude coupling in the human hippocampus is further implicated in successful memory function (Griffiths et al., 2021; Lega et al., 2016; Vivekananda et al., 2021). Notably, Alzheimer's mouse models, which show cognitive deficits, also

show disrupted theta-gamma coupling specifically in the parietal cortex and the hippocampus (Zhang et al., 2016).

4.2.10 Subdividing Activity in the Gamma Band

Memory-related activity does not appear uniform across the gamma range and functionally distinct sub-bands of activity have been proposed in relation to the hippocampus (Buzsáki & Wang, 2012; Colgin, 2016; Colgin et al., 2009). The full hippocampal gamma range is generally divided into slow gamma (30-60 Hz) and faster gamma (60-120 Hz), as well as ultra-fast gamma (>100 Hz), also referred to as sigma. The exact demarcation limits and the terminology employed both vary, by the method used to differentiate distinct gamma sources and by convention (Belluscio et al., 2012; Colgin, 2015b). Nevertheless, distinct patterns of gamma activity may reflect rhythmic activation of different assemblies of neurons in the medial temporal lobe (Butler et al., 2018). Specifically, Colgin et al. (2009) suggested that the action of discrete cell assemblies was evident, reflecting communication between CA1 with either CA3 or with the entorhinal cortex. Functional connectivity between CA1 and CA3 occurred via a slow gamma rhythm (20-50 Hz), facilitating retrieval, whereas CA1 activity at a higher gamma frequency (65-140 Hz) was coherent with activity in the entorhinal cortex, facilitating encoding. Consistent with the Hasselmo framework (in which theta phase distinguishes the two processes), gamma power in these two frequency bands demonstrated a phase difference. Thus the two rhythms may reflect activity relating to encoding (processing input from entorhinal cortex) and retrieval (receiving intra-hippocampal input from CA3) processes, with the former synchronising during the trough and the latter synchronising at the peak.

4.2.11 Hypotheses and Predictions

Despite circumstantial evidence, there remains a lack of direct empirical data to support the hypothesis that in humans encoding and retrieval information is indeed preferentially processed according to theta phase. Furthermore, it remains unclear exactly how the brain may accomplish this. In the present experiment, clinical patients implanted with intracranial electrodes completed a continuous memory paradigm in which encoding and retrieval states were clearly cued. This experiment provided the opportunity to test several key predictions of the Hasselmo framework. Firstly, one would anticipate that following a memory subprocess cue (indicating encoding or retrieval), there would be a phase reset in the theta range. Secondly, following this informative cue the theta rhythm may show a phase difference according to whether encoding or retrieval is required for the task, to ensure that stimulus-related information arrives in the hippocampus at the optimal phase. Finally, given evidence from rodents of cross-frequency interactions subserving inter-regional communication in memory, gamma amplitude may become organised according to the phase of theta activity. Specifically, the power of higher and lower frequency components within the gamma range may be associated with encoding and retrieval processes, respectively, and show increased power at different phases of the theta rhythm.

4.3 Methods

4.3.1 Participants

Participants were clinical patients (5 male, 6 female; aged 14-53 years, mean = 31.9) suffering from medically intractable epilepsy and awaiting surgery in two hospitals (N=8, 4M/4F, Queen Elizabeth Hospital, Birmingham, U.K.; N=3, 1M/2F, La Paz University Hospital Madrid, Spain). As part of the preparation for this surgery all participants were implanted with intracranial depth electrodes. Ethical approval was

granted by the National Research Ethics Service UK and by the Clinical Research Ethics Committee at La Paz University Hospital Madrid, respectively. Two participants lacked any electrode contacts within the hippocampus (see below) and were therefore excluded from electrophysiological analyses, resulting in a final n = 9 (3M/6F; aged 14-53 years, mean = 32.3) for these analyses.

4.3.2. Behavioural analysis

Behavioural accuracy was computed as the proportion of correctly retrieved trials. Average reaction times were computed using a mean average, removing outliers at the participant level. Outlying reaction times were defined as those 3 standard deviations above or below the mean.

4.3.2 EEG Acquisition and Pre-processing

Intracranial EEG (iEEG) was recorded for pre-surgical epilepsy diagnosis in patients using laterally implanted depth electrodes. Electrode shafts contained 5-15 contacts. Data were sampled at 1024 Hz except for one participant whose data were sampled at 256 Hz. Hippocampal contacts were identified based on the post-implantation structural MRI. Two participants did not show electrode contacts within the hippocampus and were therefore excluded from electrophysiological analyses. Contacts with hardware artifacts or excessive epileptic-like activity were discarded based on visual inspection. Data from hippocampal contacts were re-referenced to a white-matter contact on the same electrode and resampled offline to 256 Hz. These white-matter contacts were manually identified according to visual inspection and examination of signal variance. Electrode contacts were further sub-selected based on time-frequency power analysis. Specifically, after time-frequency convolution (as described in the Spectral Power section), power was averaged over 60-110 Hz in the frequency range and averaged before (1.5-0.5 seconds pre-stimulus) and after (0.5-

1.5 seconds post-stimulus) stimulus onset. At the trial level, if there was a significant increase post-stimulus compared to pre-stimulus, this channel was taken forward to subsequent analyses. To maximise the number of participants included (and therefore statistical power), if a participant had no contacts that met this criterion, the contact showing the maximal statistic was taken forward. This was only the case in one participant. The final number of contacts per patient included in all electrophysiological analyses is reported in Table A2.1. In all analyses, only correctly retrieved or successfully encoded (subsequently correct) trials were examined.

4.3.3 Experimental Procedure

Participants performed a continuous encoding and retrieval task using a laptop. Each participant had the task explained to them via written and verbal instructions and then performed a practice block. Depending on performance on this practice block, the difficulty of the experimental task was varied. This difficulty modification was to account for the variability in mnemonic ability in this clinical population. The difficulty was set to one of three levels which determined the number of trials an individual was presented within a single block: either 20, 40, or 60 trials. As participants performed the experiment only when their clinical schedule allowed for it, the number of blocks and trials completed varied by participant. Participants completed on mean average 72 trials (standard deviation = 25) per retrieval condition (intact/rearranged/new; see Memory Task) and double this number of encoding trials.

4.3.4 Memory Task

The paradigm employed here was a continuous memory paradigm in which participants were asked to flexibly encode or retrieve the pairing of a verbal stimulus with one of four colours: red, green, blue, and yellow (See Figure 4.1). Participants

tested in Madrid completed a version of the task translated into Spanish. Importantly, encoding and retrieval trials occurred within the same block. A given trial could require either encoding or retrieval (of material previously encoded in the same block). Each trial began with a temporally jittered pre-stimulus fixation cross indicating the beginning of a trial and lasting 1500 ms ± a randomly assigned temporal jitter (±0/50/100 ms). Subsequently the cue was presented consisting either of the word ‘encoding’ or ‘retrieval’ to instruct the participant which process would be required when the stimuli were presented after this cue left the screen at 2500 ms. Following this the stimulus was presented on the screen. Regardless of whether a trial was an encoding or a retrieval trial, the name of an object was presented centrally.

In an encoding trial, a monochromatic square was presented below, either blue, yellow, red, or green. Participants were required to associate the colour and the object name presented by judging how plausible the association was. For example, a red chair might be judged as ‘high plausibility’ whereas a blue cabbage would likely be judged as either ‘low’ or ‘medium’ plausibility. Participants were encouraged to construct a mental image or scene to judge this plausibility. Participants noted their decision by pressing either the left, right, or down arrow key. The stimulus remained on the screen until a response was made with a minimum duration of 2000ms and a maximum of 10,000 ms.

In a retrieval trial, participants were required to respond whether they had seen the object name before and whether the colour it was now paired with was the same colour as it had been paired with when it was seen before. There were three sub-types of retrieval trial, hereafter referred to as ‘intact’, ‘rearranged’, and ‘new’. These sub-types of retrieval trial were included to further assess the role of the

hippocampus in familiarity and recollection. In an intact trial the word had been seen before and appeared at retrieval paired with the same colour as it had been previously. In a rearranged trial the word had seen before but at retrieval it was paired with a different colour. In a new trial the word had not been seen previously. Participants were required to adjudicate between these three possibilities by pressing the relevant arrow key. As in encoding trials, participants saw the response screen for 2000-10,000 ms but the stimulus disappeared from the screen after a response was made within this constraint.

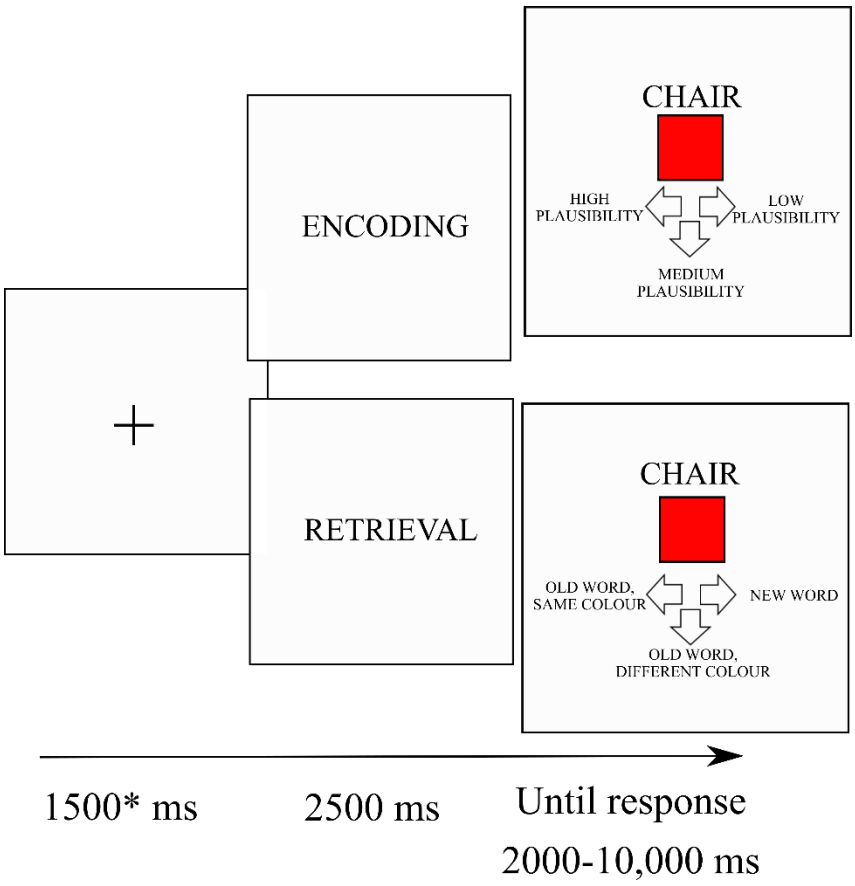

Figure 4.1. Continuous Encoding/Retrieval Memory Task. Each trial of the task began with a pre-stimulus fixation period for 1500ms (temporally jittered by ± 0/50/100 ms). Participants were then presented with a cue to indicate whether the subsequent stimulus was either to be encoded (upper path) or to be retrieved (lower path). After 2500 ms, the cue word was presented accompanied by a colour. In the encoding condition the participant was asked to judge the plausibility of this pairing. In the retrieval condition the participant was asked to judge whether they had seen the cue word before and if so whether the colour it

was now paired with was the same as before. Retrieval trials were evenly divided into intact (old word, same colour), rearranged (old word, new colour), and new (new word) trials.

4.3.4 Software & Analysis Code

The behavioural task was designed and presented using MATLAB (2016b, The MathWorks, Inc., Natick, Massachusetts, United States) and Psychtoolbox (Version 3.0.16; Brainard, 1997; Kleiner et al., 2007). Analyses were conducted using custom MATLAB scripts. Time-frequency analyses employed functions from the Fieldtrip toolbox (Version 20210308; Oostenveld et al., 2011). Circular statistics were conducted using functions from the CircStats toolbox (Berens, 2017). Plots also used the function *boundedline* (Kearney, 2019).

3.4.5 Spectral power

Spectral power was calculated across the full recording in a wide frequency range from 1-110 Hz using the *mtmconvol* function in Fieldtrip. A different level of smoothing was used for lower frequencies (1-29 Hz) compared to higher frequencies (30-110 Hz). Additionally, low frequencies were resolved in 1 Hz increments whereas to avoid redundancy higher frequencies were resolved in 5 Hz increments. For lower frequencies (1-29 Hz), a varying time window was defined for each frequency, using a differing number of cycles by frequency: 2 cycles were used for frequencies 1-2 Hz; 3 cycles for 3-4 Hz; 4 cycles for 5-6 Hz; 5 cycles for 7-8 Hz; 6 cycles for 9-10 Hz; and 7 cycles for 11-29 Hz. For higher frequencies (≥ 30 Hz), a multi-taper approach was employed. Multiple Slepian tapers were employed to achieve a total smoothing of 20 Hz and data were resolved in 400 ms time windows. Time-frequency data for each participant were first normalised across the full recording by z-scoring. Following this z-scoring, artefact rejection was accomplished in an automated subject-specific data-driven fashion. Specifically, the most extreme 10% of power

values were excluded from the data at each frequency. Data were then epoched into trials, with only correct trials proceeding to subsequent analysis.

4.3.6 Phase reset and opposition

Phase angle data were derived from the electrophysiological time series. The complex signal was derived using Fieldtrip's *mtmconvol*. Variable frequency resolution was achieved through a differing number of cycles per frequency band. Two cycles were used for frequencies 2-3.5 Hz; 3 cycles for 4-4.5 Hz; 4 cycles for 5-5.5 Hz; and 5 cycles for 6-12 Hz. Data were resolved in 50 ms timesteps. From this complex signal, the phase angle for each time-frequency point was taken for subsequent phase analyses. A Rayleigh test was conducted for each participant at every time-frequency point. This test examines whether phase angles are uniformly distributed in polar space (Ruxton, 2017). To facilitate comparison, for each participant, the relationship of phase to time in trials of a given condition was disrupted to represent data under the null hypothesis (that there was no reliable phase reset across trials). Each trial of real data was cut at a random timepoint and rearranged so that the first segment became the second segment, thereby disrupting any time-specific phase activity. As the time point of where data were cut varied by trials, this effectively disrupted any across-trial consistency in phase values whilst minimally disrupting phase dynamics within a given trial. Rayleigh z values were then compared for each participant between the unshuffled data and distribution consisting of 1000 permutations of phase-disrupted data. To allow for comparison between participants, at each time-frequency point, the Rayleigh z value was z-scored relative to these permutations. The normalised Rayleigh z value could then be combined across participants using the inverse *normcdf* function (Stouffer et al., 1949; VanRullen, 2016).

To assess whether there was a difference between conditions in average phase angle, phase opposition sum (POS) values were calculated. This measure, related to the phase bifurcation index (PBI), relies on calculating inter-trial coherence (ITC) across trials for each participant and sensor. The relative phase difference can then be calculated according to how consistent the phase when computed for every trial in condition A, condition B, or in both conditions combined. The subtraction of the latter implies (in the case of a positive value) greater consistency in the two conditions separately. If the combination results in less coherence, it implies that there is a reliably different phase in the two conditions that reduces consistency when the two groups are combined (VanRullen, 2016; Wolpert & Tallon-Baudry, 2021). This POS value facilitates comparison across participants, even if the absolute phase angles differ between participants. POS values were derived for real data and phase-disrupted data, as described above for quantifying phase reset. Briefly, the value of POS at each time-frequency point was derived for each participant and normalised relative to 1000 permuted values. These normalised values were then combined across participants and the equivalent p value calculated.

4.3.7 Phase-amplitude coupling

Phase-amplitude coupling (PAC) between theta and gamma band rhythms was calculated according to the Tort method (Tort et al., 2009). This analysis was conducted on data in the 2500 ms period after cue onset, excluding the initial 500 ms to prevent interference from an evoked response that may lead to spurious detection of PAC. Specifically, the signal from full trial data was band-pass filtered around both the low frequency and high frequency separately. These frequencies ranged from 2-12 Hz (0.5 Hz increments; filter width, 1 Hz) for the low (modulating) frequency and

between 30-110 Hz in 1 Hz increments for the high (modulated) frequency range. For the low frequencies, the band pass filter width was 1 Hz. For higher frequencies, given the maximum modulating frequency of 12 Hz, filter width was set to 24 Hz (Aru et al., 2015). This filtering was performed on the full trial period to ensure that no edge artifacts were introduced that might distort phase or amplitude. From the filtered signal, either the phase angle (for the lower frequency) or the amplitude (for the higher frequency) was derived via the Hilbert transform. Trials were subsequently reduced to the time period of interest (-2.0 to 0s relative to stimulus onset). To compare conditions (i.e. encoding vs. retrieval), trials were randomly sub-sampled to ensure the same number of trials between conditions, as data length is known to influence PAC estimates (Aru et al., 2015). Amplitude values across all trials were then binned according to their corresponding phase value (18 bins, 20 degrees per bin). These amplitude values were averaged across these phase bins, normalised, and the resulting distribution compared to a null distribution where amplitude is equal across phase bins. The distance from this null distribution is calculated via the Kullback-Leibler distance to derive the final modulation index (MI). Notably, here we performed a trimmed average to remove spurious or artifactual amplitude values. Specifically, the most extreme 10% of values (above the 90^{th} percentile) from each phase bin were removed prior to averaging to accomplish a trimmed average, as was performed in the analysis of spectral power.

To determine whether phase-amplitude coupling differed from the null hypothesis under which there was no relationship between theta phase and gamma, block resampling was conducted. Specifically, phase data were staggered by one trial relative to the amplitude data. For each condition, trial 1 of the phase data was shunted to the position of the final trial. The new ‘trial 1’ phase data therefore in

reality constituted trial 2. Cutting the data at a single point minimally distorts underlying phase-amplitude dynamics (Aru et al., 2015) and offsetting the phase/amplitude data by one trial constitutes a conservative comparison. The final comparison to detect significance in the phase-amplitude coupling was conducted by comparing real PAC values for each participant against PAC values under the trial-shuffled data using a cluster-based permutation paired samples t-test.

In order to plot the preferred phase of gamma activity, i.e. in which phase bin was gamma amplitude maximal, gamma amplitudes were normalised by dividing the amplitude in each bin by the sum of amplitude values across all phase bins. After this normalisation was performed, gamma amplitudes across the phase bins were averaged across electrode contacts and then participants.

Phase-amplitude coupling was also assessed by an alternative method determining the instantaneous phase consistency between theta phase and the envelope of high-frequency gamma oscillations (Canolty et al., 2006). This method relies on combining the phase of low-frequency data and the amplitude of the envelope of higher frequency amplitude data. The phase and amplitude data were derived as in the Tort method described above. In place of phase-binning the amplitude data, phase and amplitude data were combined and the vector length of the resultant complex signal was acquired. The final value was compared to trial-shuffled data, offset by one trial in the same manner as described for the Tort method above. This comparison between real and shuffled data was performed via a cluster corrected paired t-test as in the Tort method above.

4.3.8 Statistics

To facilitate statistical analysis in several comparisons, surrogate distributions were generated. In these cases, 1000 permutations were used for each comparison point

(e.g. each time-frequency point). The real value was compared to this surrogate distribution and converted into a z-score. The value for each electrode was normalised in this way before being averaged across electrodes. These normalised averages were combined across participants and combined p-values (representing the probability of real values relative to permutation-derived distributions) were calculated according to Stouffer et al. (1949), as cited in VanRullen (2016). In all statistical comparisons, an alpha value of 0.05 was used to determine statistical significance. To correct for multiple comparisons (e.g., when looking at power at multiple time-frequency points), permutation-based cluster correction was employed. Briefly, this corrects for the number of comparisons conducted when assessing time-frequency data by comparing a specific cluster metric to the same metric under permuted conditions. The maximum sum of a cluster's t-values was used to determine the cluster statistic. All statistics were performed at the group level (across-subjects).

4.4 Results

4.4.1 Memory performance

Participants were able to successfully retrieve the association made during the encoding phase with relatively high accuracy (Figure 4.2). Mean accuracy in all conditions was > 80 % [intact, 84 %; rearranged, 80 %; new, 94%]. Paired t-tests revealed that accuracy on new trials was significantly higher than both intact [$t_{(10)}$ = 4.58, p = 0.001] and rearranged trials [$t_{(10)}$ = 3.01, p = 0.013]. Although participants demonstrated higher accuracy on intact trials as compared to rearranged trials, this difference was not statistically significant [$t_{(10)}$ = 1.35, p = 0.21]. Participants' mean reaction times (RT) were also slower on rearranged trials compared to intact trials, but this difference only approached statistical significance [$t_{(10)}$ = 2.23, p = 0.05]. Participants were slower to respond in rearranged and intact trials as compared to

new trials but neither of these comparisons were statistically significant [intact vs. new, $t_{(10)} = 1.27$, $p = 0.23$; rearranged vs. new, $t_{(10)} = 2.07$, $p = 0.07$].

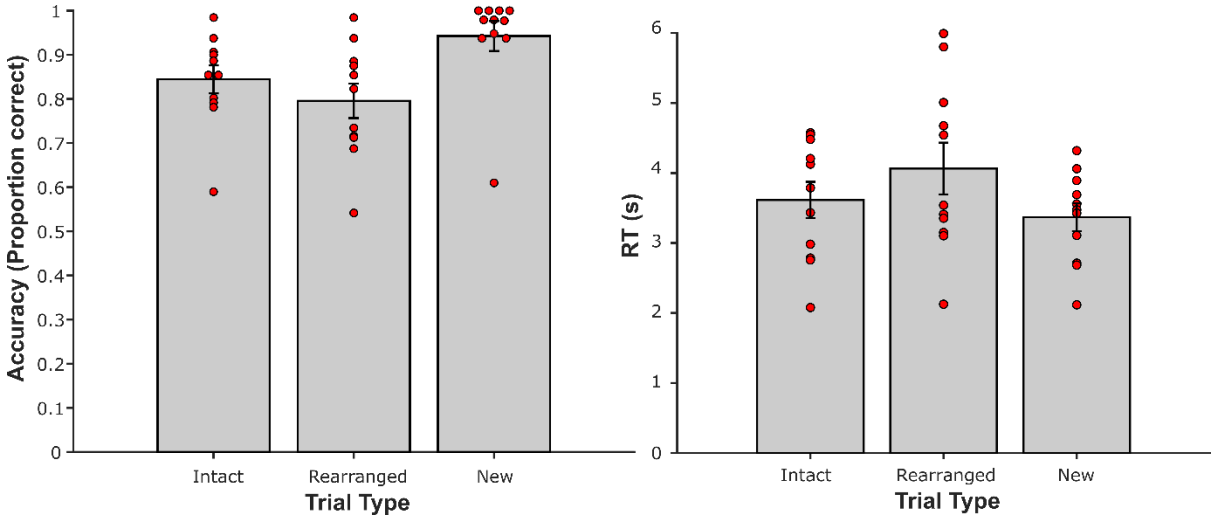

Figure 4.2. Behavioural performance on the associative memory task. A. Participants were able to successfully retrieve previously encoded associations with a high degree of accuracy. Participants were significantly more accurate in the 'new' condition compared to both other types of retrieval trial. **B.** Participants were close-to-significantly slower on rearranged trials compared to intact trials.

4.4.2 Oscillatory Power

To examine which frequency bands appeared involved in memory encoding and retrieval, normalised power from all correct trials was averaged independent of condition. Changes were evident in the theta, alpha/beta, and gamma ranges (See Figure 4.3A; Figure A2.1 for the full time-frequency spectra by condition). To ascertain which frequency bands appeared to respond to both cue and stimulus onset, power values were statistically compared to the pre-cue baseline period (corresponding to 3-2.5 seconds prior to stimulus onset). This comparison was conducted as a paired samples t-test with permutation-based cluster correction (correcting across time). Activity in the gamma range (60-110 Hz) showed an increase after both the cue and stimulus onsets in all conditions relative to the pre-cue baseline, however in all conditions only the post-stimulus increase survived correction for multiple comparisons (Figure 4.3B). All conditions showed a brief

increase in theta activity (3-9 Hz) following both the onset of the cue and the stimulus, however in no cases did this increase achieve statistical significance. Power in the alpha/beta range (10-15 Hz) showed a non-significant decrease. Averaging across these three frequency bands individually (theta/alpha-beta/gamma), there was no significant difference between any condition comparisons after correcting for multiple comparisons across time, despite differing memory demands (i.e., encoding vs. source memory vs. familiarity).

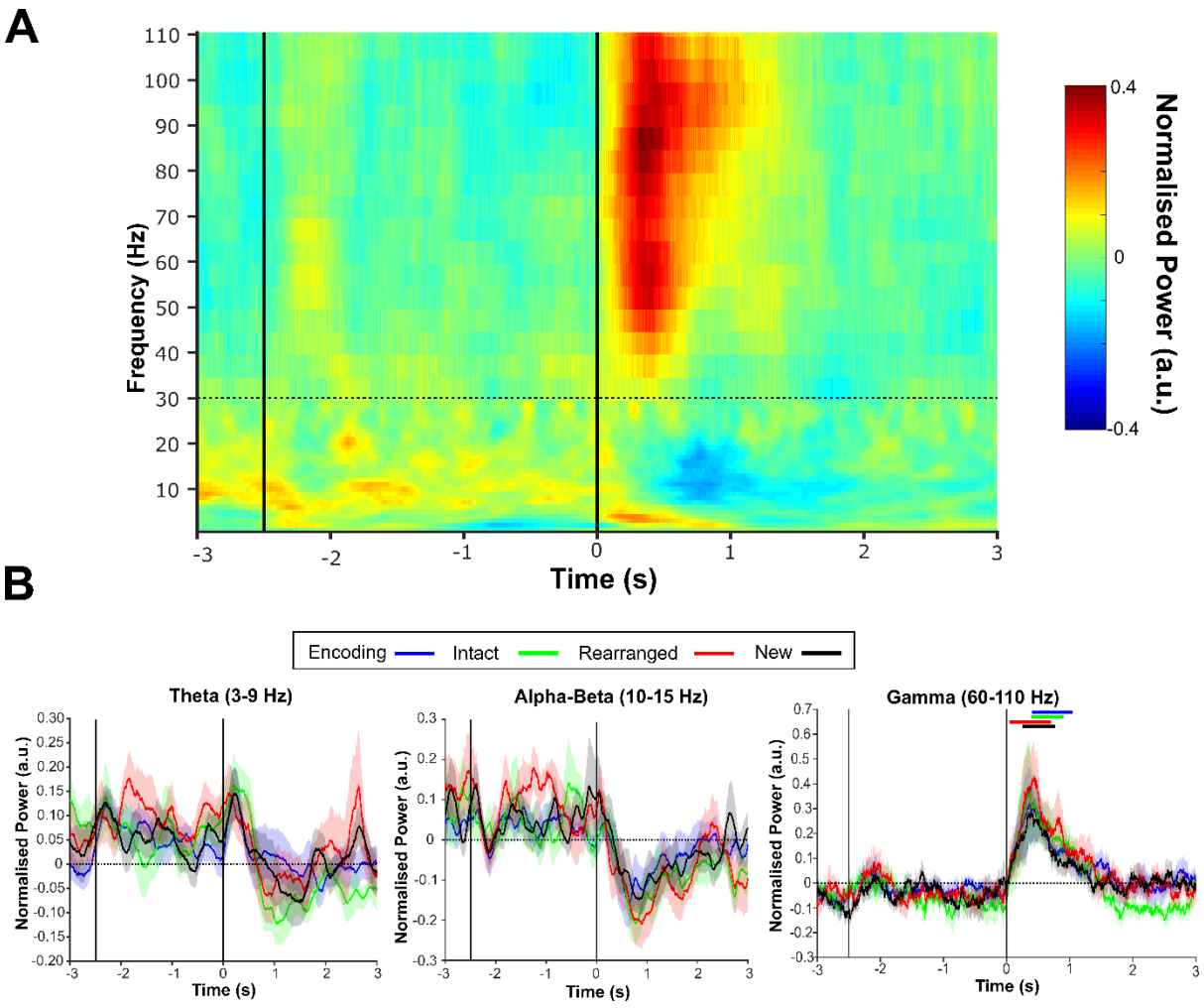

Figure 4.3. Stimulus-locked power changes over the trial. Vertical black lines indicate onset of encoding/retrieval cue (-2.5 s) and stimulus (0 s). **A.** Time-frequency representation indicating oscillatory changes occurring in all conditions. **B.** Collapsing across frequency bands of interest revealed increases in the theta range, reduced alpha-beta power, and increases in broadband gamma power. Solid horizontal lines indicate cluster-corrected

significance when comparing with the pre-stimulus baseline period. No significant differences between any of the experimental conditions were detected after correcting for multiple comparisons.

4.4.3 Phase Reset and Opposition

If theta phase does indeed differentiate between encoding and retrieval processes, the hippocampal theta rhythm may show a phase reset at this frequency. Phase consistency was computed via Rayleigh's z score for a frequency range from 2-12 Hz across the full trial period and contrasted with a permuted distribution (Figure 4.4). As anticipated, and consistent with the literature, there was evidence of a phase reset at low frequencies following both the cue and stimulus onsets (at -2.5 seconds and 0 seconds relative to stimulus onset, respectively). Phase resets occurred primarily within the theta range (~2-8 Hz).

Although this finding of phase reset suggests that, as expected, the task elicited hippocampal involvement, if the Hasselmo SPEAR model is correct in suggesting that encoding or retrieval processes are separated by the phase of hippocampal theta, following this phase reset, one might expect a significant phase difference between the two conditions. A phase opposition measure (the Phase Opposition Sum, POS (VanRullen, 2016)) was derived to determine whether this was the case. Briefly, this measure compares the inter-trial consistency of phase values (by examining mean complex vector length) when examining two conditions individually vs. when the trials from these two conditions are combined. If trials in each condition cluster around a specific phase value that differs between them, the combination of groups should result in a lower degree of consistency. Calculating POS values at each frequency and timepoint revealed several significant clusters of phase divergence following the onset of the cue (Figure 4.4). The largest cluster emerged following the cue onset at the same time as the phase reset observed in Figure 4.4A.

Calculating the average difference in phase angle revealed that across significant time-frequency points, encoding trials were on average ~242 degrees out of phase with retrieval trials. Notably, the clusters of significant phase divergence were present at both proposed theta rhythms previously observed (i.e., both at 'slow theta' (2-5 Hz) and 'fast theta' (5-9 Hz)), although the latter showed brief clusters less aligned with time periods of phase reset.

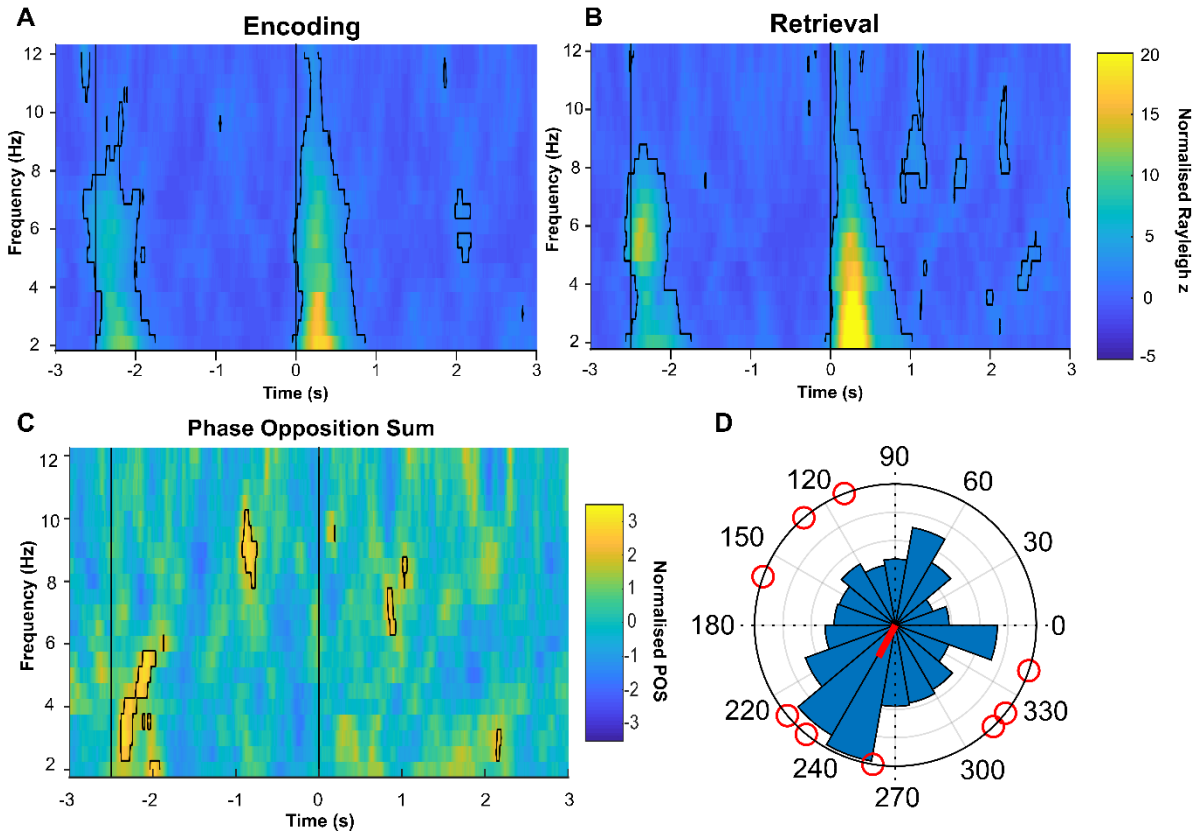

Figure 4.4. Cue and stimulus evoked phase changes. Rayleigh z tests revealed significant phase reset following the onset of the stimulus and the cue in both encoding **(A)** and retrieval **(B)** trials. Black outlines indicate cluster-corrected significance. **C.** Following this reset, phase opposition values were significantly greater than a permuted distribution, particularly at low frequencies (~2-6 Hz) following the cue onset. Black outlines indicate statistical significance. **D.** Participants showed an average phase difference of 242° between encoding and retrieval conditions. Red circles indicate the average phase difference for each participant. The polar histogram depicts the relative distribution of phase difference angles at all significant time-frequency points for all participants and all contacts.

4.4.4 Phase-amplitude Coupling

Is there evidence of theta-gamma coupling within the human hippocampus, as has been reported previously? Furthermore, is there evidence of distinct gamma bands showing this coupling in accordance with Colgin et al. (2009)? Taking a wide range of low-frequency values (2-12 Hz) to account for different definitions of hippocampal theta, we assessed whether the phase at these frequencies modulated the amplitude of higher frequency oscillations. Phase-amplitude coupling was assessed according to the method detailed in Tort et al. (2009) for low (2-12 Hz) and high (30-110 Hz) frequency ranges. Comparing the resultant modulation index (MI) values against those that would be expected by chance revealed significant clusters of phase-amplitude coupling in the high theta range following both the encoding and retrieval cue (Figure 4.5). The modulating frequency was similar between conditions: 8.5-12 Hz in encoding, 7-9.5 Hz in retrieval. The frequency range of the modulated signal varied between conditions encoding (87-99 Hz) and retrieval (54-69 Hz). Each participant's MI comodulogram was further smoothed via a sliding average (to account for inter-individual variability in precise theta frequency; smoothing window length of 1.5 Hz). This smoothing corroborated the idea that a similar theta frequency modulated higher-frequency activity in both conditions (encoding 6-12 Hz, retrieval, 7-10 Hz).

Comparing MI values between encoding and retrieval directly, there was significantly greater phase-amplitude coupling in encoding trials (low frequency range, 6.5-9.5 Hz; high frequency range, ~80-100 Hz), however this cluster did not survive multiple comparison correction (see Figure A2.2). Given variability in PAC estimation methods, PAC was also calculated according to an alternative method (assessing phase-phase consistency between low frequency phase data and high frequency

amplitude envelope (Canolty et al., 2006)). The results were largely replicated using this method (See Figure A2.3). Both conditions showed significant clusters of theta-gamma amplitude coupling. As with the Tort method, encoding trials showed theta-gamma phase-amplitude coupling with higher frequency activity, although the effect did show a broader band of modulated activity. Retrieval trials showed coupling at a similar theta frequency (comparable to results using the Tort method and comparable to encoding trials) but at a lower frequency in the gamma band.

The difference in frequency between the theta-modulated gamma clusters did not seem to be driven by a difference in power. To ensure that this was not being obscured by frequency smoothing via multi-tapering, power was calculated in a higher resolution fashion. Power was calculated using a single Hanning taper and the 1/f signal component removed via IRASA (Wen & Liu, 2016). Averaging across low gamma (50-70 Hz) and high gamma (80-100 Hz), there was no significant difference between encoding and retrieval trials either during the post-cue period [low gamma, $t_{(8)} = 0.81$, $p = 0.44$, Cohen's $d = 0.27$; high gamma, $t_{(8)} = 1.04$, $p = 0.33$, Cohen's $d = 0.35$] nor during the post-stimulus period [low gamma, $t_{(8)} = -0.65$, $p = 0.53$, Cohen's $d = -0.22$; high gamma, $t_{(8)} = -0.52$, $p = 0.62$, Cohen's $d = -0.17$]. Additionally, no significant condition difference was present at any frequency comparing each increment from 50-110 Hz.

The modulation index (MI) value generated by the Tort method indicates deviance from a uniform phase bin distribution, thus suggesting that gamma power is modulated by theta phase, but it does not indicate whether the gamma modulation is the same between these two conditions. Gamma amplitude distributions from the initial phase of the PAC calculation were derived from the significant clusters emerging in each condition. These amplitude values were normalised (dividing bin

amplitude by the sum across bins) and then averaged across channels and participants. Plotting these distributions (See Figure 4.5B) suggested that following the retrieval cue power at the lower gamma cluster increased selectively around the peak of theta oscillations. In contrast, following the encoding cue, gamma power clustered closer to the trough. Comparing normalised gamma power at each phase bin via paired t-tests revealed significantly greater power in encoding trials at phase bin centres -2.61 radians [$t_{(8)}$ = 3.00, p = 0.017, Cohen's d = 0.56] and -2.27 radians [$t_{(8)}$ = 2.40, p = 0.043, Cohen's d = 0.50]. Although retrieval trials showed greatest gamma power difference relative to encoding trials at the phase bin encompassing 0 radians (suggesting maximal gamma power at the theta peak), this difference was not statistically significant [$t_{(8)}$ = -2.22, p = 0.058, Cohen's d = 0.50].

As an alternative method to quantify the degree of phase discrepancy between coupling in the two conditions, the peak phase bin for each participant was determined (i.e., which phase bin showed the maximal normalised gamma power). Peak values for each condition were subtracted to generate a phase difference between conditions. At the participant level, these phase difference values did not significantly depart from uniform distribution around the circle [Rayleigh z test, z = 0.35, p = 0.72]. Notably however, differences did not significantly cluster around 0° as would be expected if there were no condition difference [v test, v = 0.92, p = 0.33]. Thus it is possible that low participant count and therefore statistical power may have made it challenging to detect such an effect. In retrieval trials, the theta phase preference of gamma amplitude showed a statistically significant deviation from circular uniformity [Rayleigh z test, z = 4.04, p = 0.013] and a significant preference for 0° [v test, v = 6.01, p = 0.002]. In contrast, the theta phase preference

in encoding trials did not significantly differ from circular uniformity [Rayleigh z test, z = 1.08, p = 0.35].

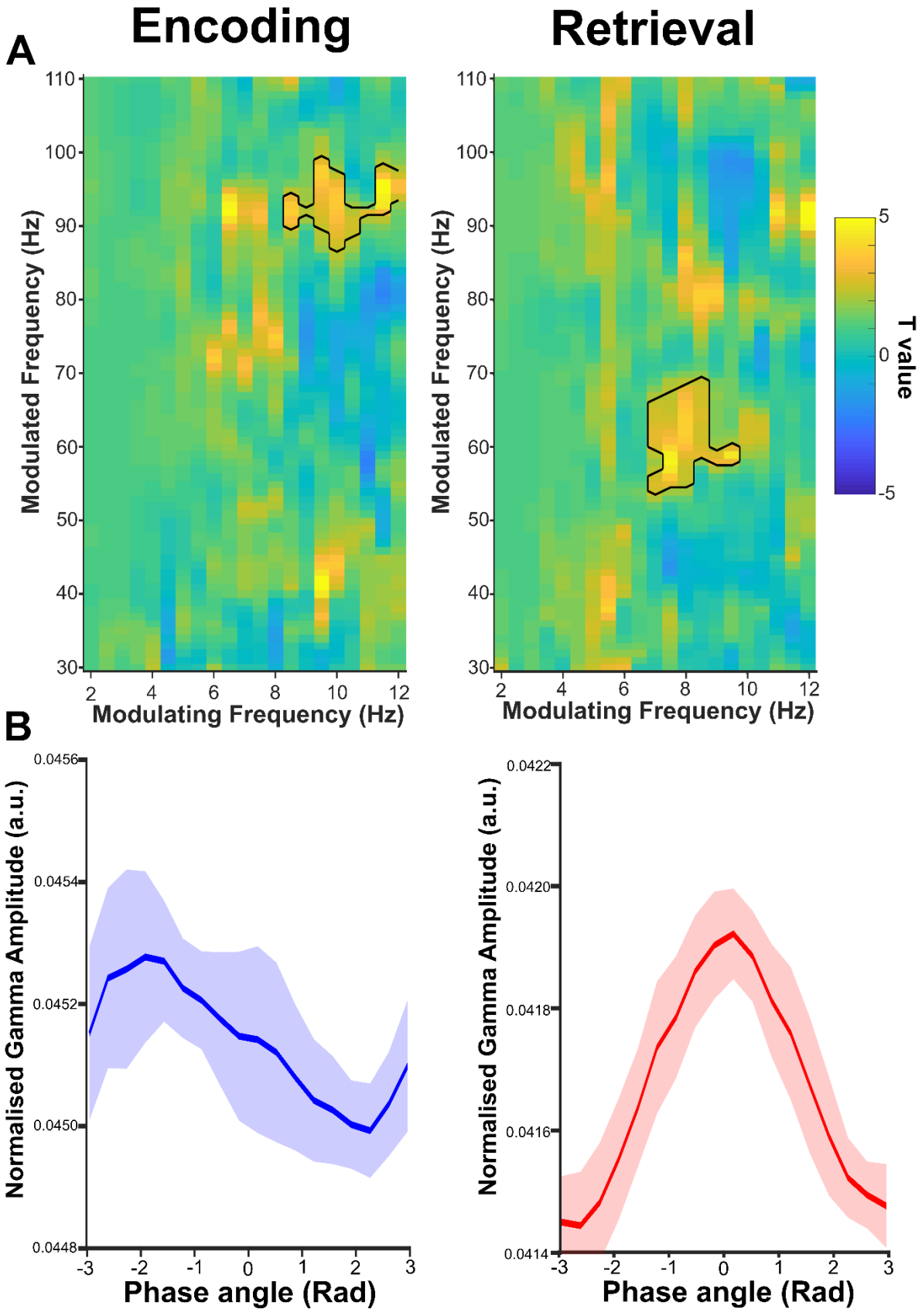

Figure 4.5. Phase-amplitude coupling analyses reveal process-specific theta-gamma interactions. A. Although a significant cluster of phase-amplitude coupling (modulated by ~8-10 Hz) was detected following cue for both encoding and retrieval data, in the encoding condition the modulated frequencies were higher than in the retrieval condition (~85-100 Hz vs. ~50-70 Hz). **B.** Normalised gamma amplitude values were averaged within each of the two significant clusters identified. This result suggested a distinct preferred phase between encoding and retrieval conditions. Phase angles in radians indicate the centre of a given phase bin. Shading indicates the standard error of the mean across participants.

PAC was also calculated in the period following stimulus onset. Specifically, theta-gamma PAC was determined in the 2.5 seconds following stimulus onset (excluding the initial 500 ms to prevent interference of the evoked response). This was conducted for all four condition subtypes (intact/rearranged/new/encoding trials). No significant clusters emerged when comparing comodulograms against chance except for rearranged trials (See Figure A2.4.). In this condition phase at a similar modulating frequency (5.5-6.5 Hz) modulated power at a range close to the post-cue retrieval pattern, albeit in a cluster extending higher in frequency (65-85 Hz). When comparing comodulograms between all condition pairings, no significant clusters emerged.

4.5 Discussion

4.5.1 Summary

To summarise, the oscillatory dynamics of the intracranially recorded hippocampal signal were investigated during a cued encoding/retrieval task. All participants performed the task with high behavioural accuracy, suggesting largely intact mnemonic ability despite the participants' epileptic status. As expected, participants were significantly more accurate in new trials where the task only required recognition and successful rejection of a new stimulus, as compared to intact/rearranged trials where source memory (i.e., memory of the associated stimulus) was required. Although accuracy was not impaired, participants were close-to-significantly slower on rearranged trials compared to intact trials.

A significant increase in gamma power was seen in all experimental conditions following stimulus onset, but this did not significantly differ between conditions. A significant phase reset occurred at low frequencies in response to both the cue and stimulus onsets. After the cue onset low-frequency activity also showed significantly different phase clustering depending on whether it was the encoding or retrieval condition. Finally, phase-amplitude coupling was calculated in the period after both the cue and stimulus onset. Significant clusters of PAC emerged in both encoding and retrieval trials after the cue suggesting that gamma activity was modulated by the phase of theta activity (~6-10 Hz). Notably, the frequency of modulated activity varied within the gamma range according to whether the cue was indicating encoding or retrieval.

4.5.2 Memory-related Power Changes

Significant power increases were evident in the gamma range following stimulus onset. This increase is nevertheless consistent with the involvement of high-frequency activity in this range in both encoding and retrieval (Burke et al., 2014; Johnson & Knight, 2015; Long et al., 2014). Despite the conceptual distinction (Wixted & Mickes, 2010) between recognition and recollection and the suggested differential involvement of the hippocampus (Wixted & Squire, 2010), there was no significant difference in the magnitude of the power response between new trials (which can be correctly responded to using only familiarity) and intact/rearranged trials (which require recollection of the previously paired stimulus). Previous work showed that instances of successful recollection of an associated stimulus relative to recognition-only trials exhibited greater hippocampal gamma power (Staresina et al., 2016). Although the same general pattern was demonstrated here (insofar as intact and rearranged trials showed a greater stimulus-locked gamma power increase

relative to new trials), this difference was small in magnitude and not statistically significant. Thus, despite significantly faster and more accurate responses in new trials, the initial gamma response of the hippocampus was similar. Indeed, there is some evidence suggesting that the hippocampus similarly involved in recognition as it is in recollection (Merkow et al., 2015).

Although power in the theta range increased following the onset of both the encoding/retrieval cue and the memory stimulus, neither increase was statistically significant. The lack of a significant power effect in the theta range is broadly consistent with conflicting previous reports from human intracranial data that observe both power increases (Lin et al., 2017; Miller et al., 2018) and decreases (Fellner et al., 2019; Long & Kahana, 2015). Importantly, previously reported theta power effects are frequently derived from subsequent memory effect (SME) analyses (Fellner et al., 2019; Long et al., 2014). Such comparisons capture all activity distinguishing between later-remembered and later-forgotten trials which may not be limited to episodic memory processes (Herweg et al., 2020). Given the low number of error trials, such a contrast was not assessed here.

Although it has been suggested that a lack of theta power effects in intracranial data may be in part due to variable re-referencing methods (Herweg et al., 2020), this is unlikely to be the case here. Intracranial EEG data are often re-referenced in a bipolar fashion where each contact is re-referenced to a neighbouring electrode. Importantly, this constitutes a form of spatial filter. Any component of the signal that is present in both an electrode and its neighbour will be subtracted out, leaving components unique to the to-be-referenced channel (Michelmann et al., 2018). Given that low-frequency oscillations would be more likely to appear on multiple channels, it may be that theta activity is vulnerable to being subtracted. However

here contacts were re-referenced to nearby white matter contacts that should share any electrode-wise noise but are not located as nearby and should show reduced activity (Li et al., 2018; Mercier et al., 2017). This renders it less likely that any theta activity was erroneously removed from the data, however contacts located in white matter may still detect signal via volume conduction from other areas. Assuming that no theta component was removed in this way, it may be that power changes are less robust. Phase, as opposed to the power, may be the more important component of theta oscillations given its involvement in inducing LTP (Hölscher et al., 1997).

4.5.2 Theta Phase Reset

Phase reset has previously been observed in the medial temporal lobe in response to memory-relevant stimuli (Fell et al., 2008; Mormann et al., 2005). Although the phase reset observed here is consistent with these prior findings, its frequency profile (reducing power with increasing frequency) does suggest it could reflect an event-related response (ERP) in the hippocampus, rather than a theta-specific resetting. Its frequency is unlike that observed in Rizzuto et al (2006), for example, in which a significant phase difference was observed specifically around 8 Hz and absent in lower frequencies. It should be noted that the criteria for detecting phase reset in the present study were more stringent than studies in which statistics are conducted at the electrode level. Performing the comparison at the subject level, as was conducted here, requires there to be a reliable phase reset at a similar frequency across all hippocampal contacts and all participants.

The phase reset observed here occurred in the absence of a significant increase in power at the same frequencies which has historically been cited as evidence of a phase reset account over the evoked explanation. However, whether an increase in power, i) can always be detected in the presence of an evoked component, and ii) is

never detected in the case of phase reset, is dubious (Sauseng et al., 2007; Sauseng & Klimesch, 2008). The generation of such an ERP may be mediated, at least partially, by oscillatory reset (Helfrich & Knight, 2019; Xu et al., 2016) but the present data do not provide clear evidence for or against this account.

4.5.3 Theta Phase Divergence

Following evidence of this reset there was a significant difference in phase between encoding and retrieval trials at two proposed functional theta bands, namely 3-7 Hz and at 7-10 Hz. Periods of phase difference were brief, with the longest duration occurring after the encoding/retrieval cue for ~ 500ms. Rizzuto et al. (2006) previously observed a phase difference centred on 8 Hz detectable for up to 500 ms after stimulus onset and interpreted this in favour of the Hasselmo framework. In contrast, the primary cluster of phase divergence was detected at the lower end of the theta range (~3-4 Hz).

The phase difference observed here was approximately 240 degrees. Although the initial model suggested that the encoding/retrieval would occur in perfect anti-phase (i.e., 180 degree separation), this difference was intended to describe the difference in synaptic efficacy rather than neuronal spiking/high-frequency activity. Indeed, the theta phase difference observed in spiking activity in rats was significantly smaller (Manns et al., 2007). Similarly, in human single-unit data (Yoo et al., 2021), this difference was 98°. Crucially, the experiment was designed to probe cued encoding/retrieval and it was in response to this cue, rather than stimulus onset, that the measure of phase difference showed significance. After stimulus onset, evidence of such a phase divergence was largely absent. It might be expected that in a paradigm where the onset of memory-relevant stimulus was predictable (as was the case here, given that the interval between cue and stimulus was not jittered), this

phase difference should occur in anticipation of stimulus onset to ensure that stimulus information was processed during at the optimal time relative to theta phase. Alternatively, the cue might prompt a phase reset after which the theta rhythm remains consistently out of phase between conditions. This did not appear to be the case here, and thus arguing only from the phase effects presented here, there is limited evidence of phase-specific segregation of encoding/retrieval-related processing.

Recently, Kota et al. (2020) contrasted hits vs. misses in an associative task and showed that during periods of significant phase reset, encoding and retrieval conditions showed a differing mean phase but this was greater in electrode contacts located in the posterior hippocampus relative to anterior sites, consistent with some proposed theories of functional segregation (Strange et al., 2014). In the present study, the sample size and variable electrode coverage precluded exploration of how phase reset/divergence effects might vary according to the hippocampus' longitudinal axis.

4.5.4 Theta-gamma Phase-amplitude Coupling

The evidence of significant phase-amplitude coupling (PAC) corroborate previous reports of theta-gamma interactions in the hippocampus in which gamma amplitude is significantly modulated by the phase of activity in the theta range (Colgin, 2015b; Vivekananda et al., 2021). Notably, in the present case this was observed in the period following a cue forewarning future encoding or retrieval. Intriguingly, the pattern of gamma amplitude did resemble the scheduling of encoding/retrieval by theta phase put forward by Hasselmo (2002), although it should be stressed that the difference in theta phase preference was not statistically significant. This was driven by a reliable preferred phase of theta-modulated gamma power in encoding trials,

but a less robust preference in retrieval trials. Importantly, the optimal encoding/retrieval phase will vary according to specifically where in the hippocampus the theta rhythm is recorded (Bragin et al., 1995; Buzsáki, 2002).

4.5.4.1 Theta Frequency

Gamma power was modulated by activity at the higher range of theta (~6-11 Hz). Several previous studies have suggested that two distinct hippocampal theta components (at ~3 Hz and ~8 Hz) reflect distinct rhythms, the former of which is associated with memory and the latter more so with navigation (Goyal et al., 2020). In contrast, a number of studies have found memory-related effects in the hippocampus at the higher end of the theta band (closer to 8 Hz than 3 Hz, (Bahramisharif et al., 2018; Griffiths et al., 2021)). Additionally, in Watrous et al. (2013) a widespread coherence effect in response to retrieval centred on the higher end of theta (7-10 Hz) for temporal order information, vs. 1-4 Hz for spatial information. Rizzuto et al. (2006) detected a phase reset occurred at around 8 Hz, however this was detected at neocortical sites. Fronto-medial theta (FMT) may be related to the theta rhythm in the hippocampus (Mitchell et al., 2008) but the latter is more reliably seen around 7-8 Hz (Hsieh & Ranganath, 2014). It is important to note that although the theta rhythm is frequently referred to as a unitary phenomenon, there exist multiple putative generators of theta activity and these rhythms may be serving distinct functions (Buzsáki, 2002; López-Madrona et al., 2020). Determining functional distinctions between different frequencies within the traditionally defined theta band of 4-10 Hz may require further systematic exploration.

4.5.4.2 Gamma Frequency

In addition to being consistent with the Hasselmo model of theta activity, the finding of two distinct gamma rhythms synchronising to distinct phases of the hippocampal

theta rhythm according to the task requirement mirrors previous rodent data (Colgin, 2015a; Colgin et al., 2009). Specifically, high gamma (65-140 Hz) activity was associated with encoding processes whereas low gamma (25-50 Hz) was implicated in retrieval. These distinct coupling patterns were speculated to facilitate communication between CA1 and the entorhinal cortex (in the case of encoding and low gamma) and the CA3 sub-region of the hippocampus (in the case of retrieval and high gamma). The frequency at which these theta-gamma effects occurred is broadly consistent with previous work and pre-existing functional subdivisions of the gamma band, especially in the hippocampus. The majority of such data is derived from rodent work, in which the threshold between low and high gamma power is typically defined ~50-60 Hz (Bieri et al., 2014; Colgin & Moser, 2010; Nakazono et al., 2019; Zheng et al., 2020). Taking a data-driven approach, Lopes-dos-Santos et al. (2018) observed distinct gamma components at 22, 35, and 54 Hz during retrieval activity, whereas an 80 Hz component was associated with encoding-like behaviour. In one study utilising human intracranial data (Griffiths et al., 2019), an encoding/retrieval power difference was observed when low gamma was defined as 40-50 Hz and high gamma as 60-80 Hz. Thus, the frequency of the gamma effects observed here are slightly higher than has previously been observed. Additionally, it should be noted that there was no power difference between slow/fast gamma in the present data as in Griffiths et al. (2019). In the present case in response to encoding/retrieval demands, gamma activity did not significantly increase but instead became selectively clustered during a specific phase of theta activity.

4.5.4.3 PAC timing relative to encoding/retrieval

In the present study, the time period in which theta-gamma PAC was detected preceded the onset of the memory-relevant stimuli, whereas previous theta-gamma

effects have been shown upon encountering novel/familiar stimuli or when asked to bind together information into a coherent memory episode (Griffiths et al., 2021). Hippocampal gamma activity may reflect cell assembly reactivation directly coding for a mnemonic representation (Colgin & Moser, 2010; Griffiths & Fuentemilla, 2020; Lisman & Jensen, 2013), but in the present case during the post-cue period the exact identity of what must be retrieved or encoded has yet to be made clear. It is therefore somewhat surprising that this theta-gamma effect did not persist following the onset of the stimulus, except for a minor cluster detected in rearranged trials. Additionally, it is interesting to speculate as to why this condition was the only one to show post-stimulus theta-gamma PAC, given that rearranged trials differed from intact trials (requiring retrieval under conditions of visual interference) and new trials (requiring precise recollection rather than recognition). Importantly however, no condition comparisons reached statistical significance, precluding any robust inferences.

4.5.5 Limitations

Given that the robustness of PAC estimation relies on the length of the data, PAC was not examined on single trials. A growing body of evidence, however, posits that distinct coupling occurs on distinct theta cycles, i.e. that gamma activity of different frequency is clustered within different theta waves (Lopes-dos-Santos et al., 2018). Furthermore, advances in assessing PAC with greater temporal resolution may assist in understanding the temporal evolution of theta-gamma coupling pre- and post- encoding/retrieval (Martínez-Cancino et al., 2019).

Additionally, although the primary window of interest was the window between the cue (indicating whether a trial was to require encoding or retrieval), determination of how the present findings may differ (power/phase/phase-amplitude effects) when

response-locking the data may be of interest. Further linking these data to behaviour may also prove fruitful. Although the number of error trials was low (largely precluding correct vs. incorrect analyses), taking slower response times as a proxy of confidence/memory strength may help elucidate the memory-specificity of these effects.

A further limitation of the analyses here, is that to maximise statistical power hippocampal contacts were identified but were not further sub-classified by hemisphere or by their relative position in the hippocampus which may have masked meaningful intra-hippocampal distinctions (Persson & Söderlund, 2015).

4.5.6 Further work

One possibility for future examination of this data set is to explore a multivariate measure of memory reactivation. Specifically, should it be possible to decode which of the four colours a specific word stimulus was paired with using the signal from extrahippocampal/neocortical channels, it would be of interest to observe whether this was linked in a phase-specific manner to hippocampal theta. It has been suggested that hippocampal theta facilitates hippocampal-neocortical information exchange. If indeed this is the case, one would anticipate a phase difference between decoding accuracies, i.e., reactivation of colour information should occur out of phase between encoding and retrieval conditions or at a latency consistent with half a theta cycle.

Furthermore, these findings may prove informative to establishing stimulation paradigms. Particularly compelling evidence could be application of theta-nested gamma stimulation as has been administered previously in a working memory paradigm (Alekseichuk et al., 2016). Traditionally, the medial temporal lobe has

represented a challenging target to stimulate, with efforts primarily relying on stimulating neocortical regions showing high connectivity with the hippocampus (Thakral et al., 2020) or implantation of deep brain stimulation electrodes (Ezzyat et al., 2018). However, a novel non-invasive stimulation paradigm, relying on summation of overlapping electrical fields, may in the future provide a means to stimulate deeper structures like the hippocampus in healthy participants (Grossman et al., 2017). Alternatively, indirectly driving the hippocampus at a theta frequency using rhythmic TMS may further provide a means to test the role of phase on encoding/retrieval processes (e.g., Hermiller et al., 2019).

4.5.7 Conclusions

In conclusion, this experiment further characterises the role of hippocampal rhythms in episodic memory processes. Specifically, the present data corroborate the role of hippocampal gamma oscillations in both encoding and retrieval of memory associations. We also provide some support for the distinguishing of encoding and retrieval by hippocampal theta phase and theta-gamma interactions.

Chapter 5: General Discussion and Conclusions:

5.1 Overview of General Discussion

In the discussion, I first summarise the main findings of this thesis. I then consider how the findings fit into existing conceptual frameworks and the extent to which they agree with previous literature. I elaborate on the proposed characterisation of frontal sites in the WM network as supervisory regions in which stimulus representations are not directly held, but instead provide top-down control to other regions. Secondly, the theta rhythm is discussed, particularly the degree to which the data in Chapters 3 and 4 elucidate what functional role it may play in working and episodic memory as well as its relationship to activity at higher frequencies (namely in the gamma band). Finally, I discuss how the methodologies in this thesis advance the field, the limitations of the present work, and I posit some suggestions for interesting future avenues of exploration.

5.2 Summary of Findings

To summarise, this thesis comprised three experiments conducted to elucidate the mechanisms of and test existing frameworks of human memory.

Chapter 1 discussed the contemporary understanding of two types of memory: episodic memory and working memory. Within in this framework, the role of the frontal cortex in working memory was detailed. The evidence for the involvement of theta oscillations in both memory systems was also discussed.

Chapter 2 detailed an EEG experiment aimed at elucidating the role of fronto-medial theta (FMT) oscillations in working memory (WM). As predicted, frontal theta oscillations exhibited greater power in response to increasing WM demand. Taking the site of FMT as a seed channel, increased WM engagement also increased coherence with posterior channels. It was these same posterior channels that a

classifier could use to be successfully distinguish between the semantic category of maintained content. Finally, by adding an item to be remembered, the frontal theta rhythm showed a significant slowing in accordance with a proposed framework of theta-gamma interactions.

Following on from this demonstration of the importance of frontal regions in working memory, in Chapter 3 a further experiment was conducted to test an existing theory of cognitive ageing. The HAROLD model has been proposed to explain a reported reduction in laterality of WM-related frontal activation observed in older adults. The degree to which this laterality reduction occurs however is disputed. Moreover, it is unclear whether this truly reflects a compensatory mechanism or occurs as a consequence of cognitive ageing. Comparing the laterality of tDCS was, however, largely inconclusive as there was no significant benefit of stimulation on an adaptive N-back task. Notably, this analysis was made more challenging by the presence of a significant order effect in which participants assigned to receive stimulation in their first session performed significantly better on the task during both sessions.

Finally, in Chapter 4 to further investigate the role of theta oscillations and theta phase in human memory, the predictions of an existing framework were tested using recordings from intracranially implanted electrodes and an episodic memory task. According to an influential computational model, encoding and retrieval processes in memory may be preferentially accomplished in the hippocampus according to the phase of ongoing theta rhythms. Gamma power increased following all memory conditions. Although a phase reset and subsequent phase difference occurred after the memory cue, it was shorter-lived than previously observed effects. Following the encoding/retrieval cue, significant phase-amplitude coupling was detected. Gamma power was significantly modulated by the phase of activity in the high theta range

(~6-11 Hz). Gamma power showed a phase preference according to whether an encoding or retrieval cue was presented (suggesting functional distinction within this band), but this difference was not statistically significant.

5.3 Frontal Localisation of the WM executive

Two of these three experimental chapters further corroborate the importance of frontal regions in WM. Chapter 2 detailed how frontal regions respond to WM demand and load. Chapter 3 further targeted the dorsolateral prefrontal cortex with a non-invasive method of stimulation and found some evidence that this may improve performance on a working memory task. To what extent does the data presented here support the idea that the frontal cortex represents the action of the WM executive rather than a site of WM storage?

5.3.1 Dissociating the WM Executive and WM Storage

In Chapter 2, a clear dissociation was evident between frontal channels that responded to WM demand and those whose signal contained information relevant to the WM representation maintained. The data presented in Chapter 2 are consistent with both the notion that prefrontal regions serve an executive role (D'Esposito et al., 1999; Postle et al., 1999) and sensory recruitment model (Scimeca et al., 2018) in which frontal regions primarily supervise representation maintenance in the regions in which the modality of information would be processed in a non-WM context. Specifically, training a classifier on the encoding portion of the task demonstrated that the pattern of activity generalised to the subsequent maintenance of the same stimulus content. Whilst many studies have observed an absence of stimulus-related activity in frontal regions, some studies suggest stimulus-specific WM representations are in fact maintained directly by frontal regions. Ester et al. (2015),

for example, detected orientation-specific (thus stimulus feature coding) activity using an inverted encoding model where classification with a support vector machine was unable to decode this orientation. Nevertheless, the majority of studies do not detect frontal stimulus-specific activity. Higher and lower level cortices may both serve to represent a given item in WM in a distributed fashion (Christophel et al., 2017). Specifically, frontal regions may code for a more abstract/verbal version of a maintained item or such activity may reflect a transformed representation used to inform a subsequent WM-guided action. The data in Chapter 2 are not inconsistent with this suggestion. Importantly in Chapter 2, and unlike other paradigms, the decoding was conducted by training on the category of maintained content which did not represent the primary feature of the stimuli required to complete the task. Thus the significant decoding observed is unlikely to reflect a task-guided action plan. Dissociating these in future experiments may be desirable to facilitate interpretation of the type of representation maintained (task-guided vs. purely stimulus-driven).

To the extent that there was a benefit of bilateral frontal stimulation in Chapter 3 (which would require replication with a greater sample size), further experimentation is required to establish whether this reflects improved function of the WM executive as opposed to a generalised improvement across WM sub-processes, including maintenance. Future experiments dissociating action of the WM executive (e.g., updating) as opposed to short-term storage will be of interest. A recent TMS study provided some causal evidence showing that rhythmic TMS was effective in improving WM updating, specifically when stimulation was conducted according a theta rhythm at frontal sites (Riddle et al., 2020). Similarly, frontal TMS selectively disrupts action of the WM executive (Postle et al., 2006). It remains unclear however whether tDCS is also exerting its effects through enhancement of the frontal

executive and/or FMT activity and the extant evidence is mixed. One study suggested that tDCS did increase subsequent theta power (Miller et al., 2015), however this increase was also present in delta and alpha bands. This power increase was also constrained to a resting state period immediately after stimulation and absent during a subsequent sustained attention task. Zaehle et al. (2011) showed that frontal stimulation elicited significantly enhanced power in theta and alpha/beta bands accompanied by behavioural improvement, however this difference was localised to parieto-occipital channels. Hoy et al. (2013) showed a theta power increase during an N-back task following frontal tDCS at both 1 mA and 2 mA compared to sham stimulation. However, this effect and the behavioural enhancement (reduced RT) was limited to a 2-back task and absent in a 3-back task, casting some ambiguity on its interpretation. Frontal stimulation has been shown to modulate TEP (TMS Evoked Potential) amplitude (Hill et al., 2017), and also to modulate subsequent resting state power when simultaneous frontal and parietal stimulation was employed (Hill et al., 2018). In neither case, however, were these changes accompanied by behavioural improvement.

In contrast, data from a combined tDCS-cognitive training paradigm using an N-back task is suggestive. Improvement in the task was accompanied by increased frontal-posterior theta synchrony and increased frontal-posterior theta-gamma coupling (Jones et al., 2017, 2020). Further work will be necessary to uncover the oscillatory changes that accompany tDCS-induced WM improvement and i) if frontal tDCS selectively modulates the action of the WM executive and ii) if the neural mechanism by which this occurs is indeed related to FMT.

5.3.2 Activity-silent WM Maintenance

One open question concerning WM function is the recently postulated phenomenon of ‘activity-silent’ WM. Initially, it was broadly believed that WM maintenance required continuous firing during the delay period. Evidence for an alternative mechanism of maintenance has stemmed predominantly from Wolff et al. (2015) who demonstrated that latent WM representations (required for the task, but not immediately relevant), originally undetectable, became decodable via a ‘pinging’ of an irrelevant stimulus. The authors suggested that representations can be held in an ‘activity-silent’ fashion. According to the activity-silent framework, rather than being maintained by persistent cell firing, representations may instead be held in temporary patterns of short-term plasticity (Stokes, 2015), undetectable via (and therefore ‘silent’ to) EEG. However, it has been questioned whether evidence for activity-silent WM can instead be interpreted through hippocampal/episodic memory recruitment (Beukers et al., 2021). Moreover, whether representations were truly silent in the original paper by (Wolff et al., 2015) has also been challenged (Barbosa et al., 2021). Importantly, I cannot definitively rule out the possibility that the dissociation in Chapter 2 (i.e., a lack of frontal decoding) was driven by an activity-silent coding scheme employed in frontal regions but not in posterior regions.

5.3.3 Frontal Theta Facilitates Inter-regional Communication in WM

Although a parsimonious explanation of theta oscillations is that they are a useful rhythm by which to coordinate local neural activity (Buzsáki & Draguhn, 2004), the theta rhythm may be particularly suited to facilitate inter-regional communication. Specifically, two regions displaying a coherent overarching rhythm provides a temporal structure in which any afferent communication occurring between them is able to do so during an optimal time window (Sauseng et al., 2010; Sauseng &

Klimesch, 2008). As a lower frequency rhythm, theta may be better-suited to facilitate such long-distance synchrony (Von Stein & Sarnthein, 2000). The coherence effect in Chapter 2 suggests that this may be the case. As well as synchronising activity according to the theta rhythm, this may further ensure that high frequency activity can be synchronised over relatively long cortical distances. Consistent with this idea, Daume et al. (2017) identified significantly enhanced phase-amplitude coupling locally in the inferotemporal cortex where it was presumed that the WM content was being directly encoded. This same region showed enhanced synchrony with frontal regions in a frontal-posterior direction. Thus the authors suggested that low-frequency synchronisation in the theta range could indirectly ensure coordination of high-frequency activity. Similarly, Berger et al. (2019) showed that temporal/parietal gamma amplitude was nested according to the rhythm of frontal-medial theta oscillations during a working memory task. Intriguingly, the phase of nested gamma activity appeared to differ between high and low load condition.

5.4 Theta Phase Coding

To what extent does theta phase appear more important than theta power in the function of episodic and working memory? The results of Chapters 2 and 4 may be marshalled as evidence of phase-coding according to a theta rhythm. That is not to say that power is unimportant (as with no power, any phase would be meaningless), but it may be that phase is the more critical factor in either limiting WM capacity or ensuring successful memory encoding/retrieval. In Chapter 2, in response to an additional to-be-remembered item, theta frequency slowed significantly. Most notably, this shift in the dominant theta frequency occurred in the absence of a change in overall theta power. Indeed, this may explain variable reports of theta

power scaling parametrically with WM load. It is difficult to conceive of an experiment that could directly dissociate power from frequency, but recent tACS experiments in which theta oscillations are significantly slowed are certainly suggestive (Bender et al., 2019; Wolinski et al., 2018). Further tailoring the tACS protocol to an individual's theta frequency in a similar paradigm may help resolve the role of frequency and power. Specifically, if frequency/phase is the critical factor, matching-frequency stimulation should enhance the amplitude of endogenous theta activity but critically, it should be less effective than frequency-slowing stimulation.

Similarly, in Chapter 4, encoding and retrieval-related gamma power appeared to show a preference for distinct phases of theta. There was however no statistically significant increase in theta power. This builds on an increasing amount of evidence in both animal and human data suggesting that these two processes are indeed separated according to theta phase (Hasselmo et al., 2002; Hasselmo & Eichenbaum, 2005) and that theta phase may be the more important component, given its role in facilitating long-term potentiation (McCartney et al., 2004).

5.5 Theta-Gamma Coupling

As well as implicating the importance of theta phase in memory mechanisms, Chapters 2 and 4 are both elucidatory in highlighting theta-gamma interactions. Whilst in Chapter 2 I did not directly examine activity in the gamma range, the finding that theta oscillations slowed significantly with an increasing number of to-be-remembered items is indirectly highly suggestive of a theta-gamma relationship. Specifically, the slowing effect observed is a direct prediction of a model of theta-gamma coupling suggesting that organisation of gamma oscillations within theta phase codes the order of WM items. Slowing theta in this manner means that there

is a wider time window in which, communication between coupled neuronal groups can occur under optimal conditions. Cell assemblies representing a specific item in working memory can thereby synchronise at a gamma frequency at discrete, separable phases of the underlying theta oscillation (Jensen & Lisman, 1998; Lisman & Jensen, 2013).

5.5.1 Do Theta-Gamma Interactions Occur Consistently Across Cycles?

One intriguing question that remains unanswered is whether distinct cell assemblies fire according to a gamma frequency during different cycles of theta activity. The theta-slowing effect demonstrated here is consistent with both the canonical theta-gamma model (Lisman & Jensen, 2013) and with a proposed variant model (Herman et al., 2013; Kopell et al., 2013). In the canonical model, slowing of the theta wave allows for a greater number of distinct cell assemblies to fire whilst maintaining a distinct theta phase. The alternative model suggests that an individual WM 'item' is only reactivated on a single theta cycle. Much of the extant evidence is consistent with this alternative account (Sauseng et al., 2019), including recent stimulation studies in which the slowing of theta frequency improves working memory (Bender et al., 2019; Wolinski et al., 2018) and the WM load-induced slowing observed in Chapter 2. Under the variant model, as the theta rhythm slows, the temporal window of excitability is extended and a given cell assembly coding for a particular item is able to fire for longer. This increased gamma bursting may ensure a higher fidelity representation, thereby improving WM performance. There are data less easily reconciled with this variant of the model however. Bahramisharif et al. (2018) found stimulus-selective activity differentiated by preferred phase angle, which would not be the case in the variant model. Additionally, the ratio of theta/gamma frequencies predicts WM capacity (Kamiński et al., 2011), consistent with multiple items being

represented during the same theta cycle. However, the reliability of this finding has been since questioned (Malenínská et al., 2021).

Such questions concerning single-cycle dynamics may be amenable to investigation. Lopes-dos-Santos et al. (2018) successfully employed independent components analysis to identify four distinct gamma components that varied on a cycle-to-cycle basis. This was further corroborated by Zhang et al. (2019) using an alternative method. The authors concurred that the majority of theta cycles showed phase-amplitude coupling consistent with one specific gamma component, suggesting that the hippocampus can switch rapidly (cycle-by-cycle) between differing theta-gamma states.

5.5.2 The Memory Function of Theta-Gamma Coupling

In this thesis, I have presented data indicating the importance of theta-gamma interactions in both working memory at frontal sites (Chapter 2) and in an episodic memory task at hippocampal sites (Chapter 4). Is there evidence either way to suggest that theta-gamma interactions serve the same or similar functions in episodic and working memory and in different neural regions?

Theta-gamma interactions in working memory appear to be driven largely by the need to maintain the temporal order of serially presented items in addition to the items' identity. In paradigms where the order of items is less necessary to complete the behavioural task, theta-gamma coupling is reduced accordingly (Brooks et al., 2020; Rajji et al., 2017). Similarly, FMT power increases in response to the requirement of order information (Hsieh et al., 2011). However, theta-gamma PAC has been investigated primarily in multi-item WM where multiple stimuli must be encoded and maintained. It remains largely an open question whether phase-amplitude coupling is completely absent when only one item is maintained or indeed

whether one would expect this, given that theta could still constitute an efficient means to organise single-item maintenance.

In an episodic sequence memory task in which the sequence order of item presentation was directly probed, theta-gamma interactions also appeared to facilitate temporal ordering of stimuli (Heusser et al., 2016). Gamma power distributions by phase showed distinct phase separation of items as would be predicted. Although the task was not a task designed to recruit WM, the serial presentation and binding of items likely required some degree of WM maintenance. In the experiment in Chapter 4 in which theta-gamma changes were observed, the order of items was not tested but the verbal stimulus (the object name) always preceded the paired colour and this was also the case at retrieval. It may be impossible to fully remove the component of temporal ordering from many episodic memory paradigms and indeed the distinction between episodic memory and working memory is unlikely to be as hard a line as the labels imply, especially considering the proposed episodic buffer within some models of working memory (Baddeley, 2012). Suggestively though, Griffiths et al. (2021) showed that theta gamma PAC occurred most prominently after participants were cued to bind together multiple pieces of information into a coherent episodic memory, despite the requirement to maintain multiple stimuli prior to this binding period. Similarly, Köster et al. (2018) showed that increased PAC was specific to mnemonic binding.

Theta-gamma PAC may also reflect inter-regional communication (Buzsáki & Wang, 2012; Canolty & Knight, 2010; Lisman & Jensen, 2013). Theta-gamma interactions are prevalent in the hippocampus, where they are thought to reflect local routing of information to sub-regions of the medial temporal lobe (Colgin, 2015b). Chapter 4 provides tentative support insofar as the condition difference in gamma frequency

and preferred phase was consistent with previous rodent data, although it should be stressed that this difference at the subject level was not statistically significant. Additionally, determining whether this truly reflects functional coupling between CA1 and CA3/entorhinal cortex will require analysis of precise and dense recordings of the human MTL. A recent study does suggest cross-regional PAC interactions are prevalent throughout the human hippocampus (Wang et al., 2021). Theta-gamma coupling may also facilitate long-distance cross-regional interplay in working memory, especially between the hippocampus and prefrontal cortex (Tamura et al., 2017) and in frontal-posterior interactions (Reinhart & Nguyen, 2019).

To conclude, it remains unclear the extent to which theta-gamma interactions serve differing functions across memory systems. Coupling between low and high frequencies may represent a brain-wide efficient communication mechanism (Canolty & Knight, 2010; Lisman, 2005) and may serve several functions simultaneously. Carefully designed experiments will be needed to clarify the importance of such interaction in episodic memory and working memory, as well as such (presumably memory-related) occurrences during REM sleep (e.g., Bandarabadi et al., 2019).

5.6 Methodological Advances

5.6.1 Multivariate Decoding

Combining a multivariate decoding method with conventional time-frequency analyses proved fruitful in Chapter 2 by providing an information-based measure of mnemonic content that could be related to oscillatory activity. Multivariate decoding methods have been used in fMRI research for some time (Haynes & Rees, 2006) and they are more recently being adopted in the analysis of electrophysiological data

(EEG/MEG/iEEG) (Grootswagers et al., 2017). Although not fully novel, the results of combining multivariate decoding with conventional statistics in memory research can facilitate the distinguishing of content/stimulus-related activity from memory-general processes. This approach has been employed in several previous studies (e.g., Cairney et al., 2018; Kerrén et al., 2018) and this thesis further corroborates its utility.

5.6.2 High-definition tDCS

Chapter 3 employed high-definition transcranial direct current stimulation (HD-tDCS). The number of studies employing this method is increasing, however there are still a number of studies employing conventional bipolar montages where it is less clear where precisely the current is affecting the brain (Datta et al., 2009; Dmochowski et al., 2011). Studies should ideally model the current flow of stimulation montages to ensure that the correct neuroanatomy is being targeted and, ideally, construct and use individualised head models (Datta et al., 2011). The data presented in Chapter 3 also advocate for the inclusion of several relevant extraneous variables that have historically been neglected. Although factors such as mood, general arousal, and expectation surrounding tCS did not significantly affect WM performance, participants who reported using a strategy did perform significantly better than those who did not suggesting that this should be considered or controlled for in future research examining stimulation and WM.

5.7 Limitations

5.7.1 Sample characteristics

A primary limitation of the present thesis is the sample sizes involved, particularly in Chapter 2 and Chapter 4. Older adults represent a less studied population in

stimulation work and are more difficult to recruit compared to undergraduate age students. Simultaneously, older adults represent a population in especial need of interventional methods that may assist in preserving cognitive function into older age. Unfortunately, using stringent exclusion criteria (as in the present case) can exclude older adults who are more likely to fit one of the exclusion criteria, e.g. history of psychological disorder, metal implants. In Chapter 4, data recording directly from the hippocampus is difficult to acquire. Collection of this dataset took advantage of a clinical population in whom electrodes had been implanted for clinical reasons. As a clinical population, there is the concern that the conclusions cannot be generalised to a healthy population, however participants generally performed well on the task suggesting that mnemonic ability was sufficient to complete the task.

5.7.2 Measuring WM using the N-back task

In chapters 2 and 3, the N-back task was used to probe working memory ability. The N-back task has been frequently used in cognitive neuroscience (Owen et al., 2005) facilitating comparison with previous literature. However, the task does correlate weakly with other measures of working memory, such as complex span tasks (Jaeggi et al., 2010; Redick & Lindsey, 2013). Similarly, Miller et al. (2009) showed that accuracy on the N-back task showed a greater correlation with processing speed rather than with another WM task (the reverse digit span task). Planned analyses in Chapter 2 were constrained by the order effect, suggesting that an adaptive N-back task in particular may be susceptible to learning effects. Although the task was designed to ensure that participants were similarly challenged regardless of variation in working memory capacity, this likely exacerbated this effect. Other tasks may be better suited to examining the various sub-processes of WM. A task comparable to the change detection task, as in Luck & Vogel (1997),

may be more useful in probing working memory and unravelling the different functional components of WM, particularly with the addition of retro-cues that indicate selective dropping or updating of WM contents or requiring some rearrangement/manipulation of WM contents.

5.7.3 The Use of tDCS

tDCS has a diverse range of effects (Chase et al., 2020; Stagg & Nitsche, 2011). In the event of a successful intervention (whereby WM ability is improved), it can be unclear as to exactly the implications are regarding both the means of improvement (which can impede replicability) and the inferences that can be made regarding WM function. Combining tDCS with other neuroimaging methods, such as MEEG/EEG (Neuling et al., 2015), TMS-EEG (Hill, Rogasch, et al., 2016), and fMRI (Esmaeilpour et al., 2020) may prove useful in helping to understand its effects. Alternatively, utilising tACS may confer the advantage of providing mechanistic insight into WM functionality (Vosskuhl et al., 2018). Alekseichuk et al. (2016), for example, elegantly demonstrated the role of theta-gamma coupling in working memory by stimulating using a theta-nested gamma waveform. Manipulating this waveform and assessing its effect on the behavioural improvement allowed the researchers to show that, to improve WM, i) gamma oscillations had to be nested during the peak of theta and ii) the optimal frequency appeared to be 80 Hz.

Given concerns that the current is insufficiently strong to influence endogenous activity (Vöröslakos et al., 2018), future work employing non-invasive electrical stimulation may benefit from adopting increased current strength, taking advantage of recent demonstrations that transcranial current stimulation remains safe when using current strengths up to 3-4 mA (Khadka et al., 2020; Samani et al., 2019; Shinde et al., 2021).

5.8 Suggestions for Future Work

5.8.1 Inducing Inter-regional Synchrony with tACS

There are various promising future avenues in which to take the present body of work. As mentioned above, it may prove advantageous to employ tACS rather than tDCS. Manipulating parameters of tACS would facilitate the probing of several outstanding theoretical questions. For example, following on from the finding in Chapter 2, a clear prediction would be that disrupting or enhancing frontal-posterior coherence will modulate WM performance. Indeed, Polanía et al. (2012) used tACS to drive the DLPFC and posterior parietal cortex at a theta frequency. Critically, the two sites were stimulated in phase or in anti-phase. As anticipated, in-phase stimulation improved performance and stimulation at anti-phase impaired performance. This was replicated in a tACS-fMRI experiment (Violante et al., 2017). Furthermore, Reinhart & Nguyen (2019) observed impaired long-distance synchronisation in older adults that was amenable to strengthening via tACS and, notably, single-site stimulation of the prefrontal cortex on its own was insufficient to improve performance. Adopting a multi-regional synchronous approach may prove a better way of testing the HAROLD model, as probed in Chapter 3. If the bilateral stimulation benefit observed in Chapter 3 is robust, synchronising frontal and posterior regions at a theta rhythm bilaterally should benefit working memory function to a greater extent than doing so unilaterally.

5.8.2 Multi-frequency Stimulation to Interrogate Theta-Gamma Coupling

The theta slowing effect shown in Chapter 2 is highly suggestive of theta-gamma coupling as a key mechanism of multi-item working memory. To further interrogate the interplay between theta and gamma rhythms, it would be of interest to make use of tACS using a combined waveform consisting of both a theta and a gamma

component, as in Alekseichuk et al. (2016). In a series of experiments, both the frequency and the phase of a nested gamma component could be manipulated. Although the authors tested the influence of nesting the gamma at the peak or the trough of theta, a similar design could probe theta-gamma coupling more precisely. Specifically, a specific item in a sequence of to-be-maintained items could be targeted by nesting the gamma component according to the item's position in the order. For example, one could predict that if six items were to be remembered, stimulation in which the gamma component is nested at a later phase position should selectively benefit retention of the items towards the end of the sequence.

5.8.3 Non-invasively Stimulating the Hippocampus

Although hippocampal theta is more challenging to target, as mentioned in the discussion of chapter 4, a new method that relies on the envelope of overlapping high-frequency fields may facilitate targeting of deeper sub-cortical structures like the hippocampus (Grossman et al., 2017). Should it prove possible to successfully entrain the hippocampal theta rhythm, one could present the stimulus either at the peak or trough of the entrained oscillation. A clear prediction is that a stimulus is better encoded at the trough vs the peak of the oscillation, but better recalled at the opposite phase. One important ambiguity to resolve is the frequency of hippocampal theta in relation to human memory. In Chapter 4, the theta-gamma effect was detected at ~7-10 Hz at the higher range of theta into the alpha band. Although this is not fully inconsistent with previous research, other experiments have suggested that activity at the lower end of theta into the delta range (~3 Hz) in humans is most similar to memory-associated type 1 theta in rodents (Foo & Bohbot, 2020; Jacobs, 2014). Stimulation at the two proposed frequencies at ~3 Hz and ~8 Hz the higher and lower end may provide a means to clarify this. Furthermore, it may prove

necessary to better understand and differentiate between rhythmic activity at a near-theta frequency linked to respiration (Bandarabadi et al., 2019; Hammer et al., 2021; Tort et al., 2018).

5.9 Final Conclusions

In several experiments and employing various neuroscientific methods (EEG/tDCS/iEEG), this thesis aimed to further understanding of key mechanisms of human memory. Frontal regions were shown to play a critical, executive role in organising posteriorly held WM representations that were detectable via multivariate decoding methods. This inter-regional interplay was accomplished by frontal-posterior theta coherence. Further exploring the role of the frontal cortex, tDCS was used to selectively manipulate the laterality, providing some evidence to suggest that bilateral tDCS may represent an effective montage to manipulate WM. Finally, this thesis provides some support from human data for a proposed function of the hippocampal theta rhythm in an episodic memory task.

This thesis represents an expansion on previous literature regarding transcranial current stimulation and the role of theta activity in both working and episodic memory, interrogating and providing support for several conceptual frameworks.

References

Abellaneda-Pérez, K., Vaqué-Alcázar, L., Perellón-Alfonso, R., Bargalló, N., Kuo, M. F., Pascual-Leone, A., Nitsche, M. A., & Bartrés-Faz, D. (2020). Differential tDCS and tACS Effects on Working Memory-Related Neural Activity and Resting-State Connectivity. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2019.01440

Agbangla, N. F., Audiffren, M., Pylouster, J., & Albinet, C. T. (2019). Working memory, cognitive load and cardiorespiratory fitness: Testing the CRUNCH model with near-infrared spectroscopy. *Brain Sciences*. https://doi.org/10.3390/brainsci9020038

Agnew, H. W., Webb, W. B., & Williams, R. L. (1966). THE FIRST NIGHT EFFECT: AN EEG STUDYOF SLEEP. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.1966.tb02650.x

Alderson, R. M., Kasper, L. J., Hudec, K. L., & Patros, C. H. G. (2013). Attention-deficit/hyperactivity disorder (ADHD) and working memory in adults: A meta-analytic review. *Neuropsychology*. https://doi.org/10.1037/a0032371

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*. https://doi.org/10.1016/j.cub.2016.04.035

Alloway, T. P., & Alloway, R. G. (2010). Investigating the predictive roles of working memory and IQ in academic attainment. *Journal of Experimental Child Psychology*. https://doi.org/10.1016/j.jecp.2009.11.003

Anastassiou, C. A., Perin, R., Markram, H., & Koch, C. (2011). Ephaptic coupling of cortical neurons. *Nature Neuroscience*. https://doi.org/10.1038/nn.2727

Anderer, P., Klösch, G., Gruber, G., Trenker, E., Pascual-Marqui, R. D., Zeitlhofer, J., Barbanoj, M. J., Rappelsberger, P., & Saletu, B. (2001). Low-resolution brain electromagnetic tomography revealed simultaneously active frontal and parietal sleep spindle sources in the human cortex. *Neuroscience*. https://doi.org/10.1016/S0306-4522(01)00028-8

Andrews, S. C., Hoy, K. E., Enticott, P. G., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Improving working memory: The effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2010.06.004

Andrillon, T., Nir, Y., Staba, R. J., Ferrarelli, F., Cirelli, C., Tononi, G., & Fried, I. (2011). Sleep spindles in humans: Insights from intracranial EEG and unit recordings. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2604-11.2011

Angel, L., Fay, S., Bouazzaoui, B., & Isingrini, M. (2011). Two hemispheres for better memory in old age: Role of executive functioning. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_00104

Antonenko, D., Hayek, D., Netzband, J., Grittner, U., & Flöel, A. (2019). tDCS-

induced episodic memory enhancement and its association with functional network coupling in older adults. *Scientific Reports*. https://doi.org/10.1038/s41598-019-38630-7

Antony, J. W., Ferreira, C. S., Norman, K. A., & Wimber, M. (2017). Retrieval as a Fast Route to Memory Consolidation. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2017.05.001

Antony, J. W., Schönauer, M., Staresina, B. P., & Cairney, S. A. (2019). Sleep Spindles and Memory Reprocessing. In *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2018.09.012

Arciniega, H., Gözenman, F., Jones, K. T., Stephens, J. A., & Berryhill, M. E. (2018). Frontoparietal tDCS benefits visual working memory in older adults with Low working memory capacity. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2018.00057

Aretouli, E., & Brandt, J. (2010). Everyday functioning in mild cognitive impairment and its relationship with executive cognition. *International Journal of Geriatric Psychiatry*. https://doi.org/10.1002/gps.2325

Artuso, C., Cavallini, E., Bottiroli, S., & Palladino, P. (2017). Updating working memory: memory load matters with aging. *Aging Clinical and Experimental Research*. https://doi.org/10.1007/s40520-016-0581-y

Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., Singer, W., & Vicente, R. (2015). Untangling cross-frequency coupling in neuroscience. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2014.08.002

Asamoah, B., Khatoun, A., & Mc Laughlin, M. (2019). tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nature Communications*. https://doi.org/10.1038/s41467-018-08183-w

Astori, S., Wimmer, R. D., & Lüthi, A. (2013). Manipulating sleep spindles - expanding views on sleep, memory, and disease. In *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2013.10.001

Atkinson, R. C., & Shiffrin, R. M. (1968). Human Memory: A Proposed System and its Control Processes. *Psychology of Learning and Motivation - Advances in Research and Theory*. https://doi.org/10.1016/S0079-7421(08)60422-3

Atkinson, R. C., & Shiffrin, R. M. (1971). The control of short-term memory. *Scientific American*. https://doi.org/10.1038/scientificamerican0871-82

Au, J., Katz, B., Moon, A., Talati, S., Abagis, T. R., Jonides, J., & Jaeggi, S. M. (2021). Post-training stimulation of the right dorsolateral prefrontal cortex impairs working memory training performance. *Journal of Neuroscience Research*. https://doi.org/10.1002/jnr.24784

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 of the United States of America*. https://doi.org/10.1073/pnas.0911531107

Backus, A. R., Schoffelen, J. M., Szebényi, S., Hanslmayr, S., & Doeller, C. F. (2016). Hippocampal-prefrontal theta oscillations support memory integration. *Current Biology*. https://doi.org/10.1016/j.cub.2015.12.048

Baddeley, A. (1992). Working memory. *Science*. https://doi.org/10.1126/science.1736359

Baddeley, A. (1998). The central executive: A concept and some misconceptions. *Journal of the International Neuropsychological Society*. https://doi.org/10.1017/S135561779800513X

Baddeley, A. (2003). Working memory: Looking back and looking forward. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1201

Baddeley, A. (2009). Fractionating the Central Executive. In *Principles of Frontal Lobe Function*. https://doi.org/10.1093/acprof:oso/9780195134971.003.0016

Baddeley, A. (2010). Working memory. In *Current Biology*. https://doi.org/10.1016/j.cub.2009.12.014

Baddeley, A. (2012). Working memory: Theories, models, and controversies. *Annual Review of Psychology*. https://doi.org/10.1146/annurev-psych-120710-100422

Baddeley, A. D., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation - Advances in Research and Theory*. https://doi.org/10.1016/S0079-7421(08)60452-1

Baddeley, A., Jarrold, C., & Vargha-Khadem, F. (2011). Working memory and the hippocampus. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_00066

Bae, G. Y., & Luck, S. J. (2018). Dissociable decoding of spatial attention and working memory from EEG oscillations and sustained potentials. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2860-17.2017

Bahramisharif, A., Jensen, O., Jacobs, J., & Lisman, J. (2018). Serial representation of items during working memory maintenance at letter-selective cortical sites. *PLoS Biology*. https://doi.org/10.1371/journal.pbio.2003805

Balconi, M. (2013). Dorsolateral prefrontal cortex, working memory and episodic memory processes: Insight through transcranial magnetic stimulation techniques. In *Neuroscience Bulletin*. https://doi.org/10.1007/s12264-013-1309-z

Bandarabadi, M., Boyce, R., Herrera, C. G., Bassetti, C. L., Williams, S., Schindler, K., & Adamantidis, A. (2019). Dynamic modulation of theta-gamma coupling during rapid eye movement sleep. *Sleep*. https://doi.org/10.1093/sleep/zsz182

Bar, E., Marmelshtein, A., Arzi, A., Perl, O., Livne, E., Hizmi, E., Paz, R., Sobel, N., Dudai, Y., & Nir, Y. (2020). Local Targeted Memory Reactivation in Human Sleep. *Current Biology*. https://doi.org/10.1016/j.cub.2020.01.091

Barakat, M., Doyon, J., Debas, K., Vandewalle, G., Morin, A., Poirier, G., Martin, N., Lafortune, M., Karni, A., Ungerleider, L. G., Benali, H., & Carrier, J. (2011). Fast

and slow spindle involvement in the consolidation of a new motor sequence. *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2010.10.019

Barbosa, J., Stein, H., Martinez, R., Galan, A., Adam, K., Li, S., Valls-Solé, J., Constantinidis, C., & Compte, A. (2019). Interplay between persistent activity and activity-silent dynamics in prefrontal cortex during working memory. *Nature Neuroscience*. https://doi.org/10.1101/763938

Barbosa, J., Lozano-Soldevilla, D., & Compte, A. (2021). Pinging the brain with visual impulses reveals electrically active, not activity-silent, working memories. *PLOS Biology*, *19*(10), e3001436.

Bastos, A. M., & Schoffelen, J. M. (2016). A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. In *Frontiers in Systems Neuroscience*. https://doi.org/10.3389/fnsys.2015.00175

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2012.249730

Batterink, L. J., Creery, J. D., & Paller, K. A. (2016). Phase of spontaneous slow oscillations during sleep influences memory-related processing of auditory cues. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3175-15.2016

Belluscio, M. A., Mizuseki, K., Schmidt, R., Kempter, R., & Buzsáki, G. (2012). Cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.4122-11.2012

Bender, M., Romei, V., & Sauseng, P. (2019). Slow Theta tACS of the Right Parietal Cortex Enhances Contralateral Visual Working Memory Capacity. *Brain Topography*. https://doi.org/10.1007/s10548-019-00702-2

Berens, P. (2017). CircStat: A MATLAB Toolbox for Circular Statistics. *JournalofStatisticalSoftware*.

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*. https://doi.org/10.1038/s41467-019-12057-0

Berryhill, M. E. (2014). Hits and misses: leveraging tDCS to advance cognitive research. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2014.00800

Berryhill, M. E., & Jones, K. T. (2012). tDCS selectively improves working memory in older adults with more education. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2012.05.074

Beukers, A. O., Buschman, T. J., Cohen, J. D., & Norman, K. A. (2021). Is Activity Silent Working Memory Simply Episodic Memory? In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2021.01.003

Bieri, K. W., Bobbitt, K. N., & Colgin, L. L. (2014). Slow and Fast Gamma Rhythms

Coordinate Different Spatial Coding Modes in Hippocampal Place Cells. *Neuron*. https://doi.org/10.1016/j.neuron.2014.03.013

Bikbaev, A., & Manahan-Vaughan, D. (2009). Relationship of hippocampal theta and gamma oscillations to potentiation of synaptic transmission. In *Frontiers in Neuroscience*. https://doi.org/10.3389/neuro.01.010.2008

Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2011.10.001

Bódizs, R., Kis, T., Lázár, A. S., Havrán, L., Rigó, P., Clemens, Z., & Halász, P. (2005). Prediction of general mental ability based on neural oscillation measures of sleep. *Journal of Sleep Research*. https://doi.org/10.1111/j.1365-2869.2005.00472.x

Bonnefond, M., & Jensen, O. (2012). Alpha oscillations serve to protect working memory maintenance against anticipated distracters. *Current Biology*. https://doi.org/10.1016/j.cub.2012.08.029

Bortoletto, M., Pellicciari, M. C., Rodella, C., & Miniussi, C. (2015). The interaction with task-induced activity is more important than polarization: A tDCS study. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2014.11.006

Bragin, A., Jando, G., Nadasdy, Z., Hetke, J., Wise, K., & Buzsaki, G. (1995). Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *The Journal of Neuroscience*, *15*(1), 47 LP – 60. https://doi.org/10.1523/JNEUROSCI.15-01-00047.1995

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*. https://doi.org/10.1163/156856897X00357

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2010.04.004

Brockmole, J. R., & Logie, R. H. (2013). Age-related change in visual working memory: A study of 55,753 participants aged 8-75. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2013.00012

Brodeur, M. B., Dionne-Dostie, E., Montreuil, T., & Lepage, M. (2010). The bank of standardized stimuli (BOSS), a new set of 480 normative photos of objects to be used as visual stimuli in cognitive research. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0010773

Brookes, M. J., Wood, J. R., Stevenson, C. M., Zumer, J. M., White, T. P., Liddle, P. F., & Morris, P. G. (2011). Changes in brain network activity during working memory tasks: A magnetoencephalography study. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.10.074

Brooks, H., Goodman, M. S., Bowie, C. R., Zomorrodi, R., Blumberger, D. M., Butters, M. A., Daskalakis, Z. J., Fischer, C. E., Flint, A., Herrmann, N., Kumar, S., Mah, L., Mulsant, B. H., Pollock, B. G., Voineskos, A. N., Rajji, T. K., Lourenco, L., Gallagher, D., Golas, A., … Verhoeff, N. P. L. G. (2020). Theta–

gamma coupling and ordering information: a stable brain–behavior relationship across cognitive tasks and clinical conditions. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-020-0759-z

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition*. https://doi.org/10.1016/j.bandc.2014.01.008

Brzezicka, A., Kamiński, J., Reed, C. M., Chung, J. M., Mamelak, A. N., & Rutishauser, U. (2018). Working memory load-related theta power decreases in dorsolateral prefrontal cortex predict individual differences in performance. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_01417

Burke, J. F., Long, N. M., Zaghloul, K. A., Sharan, A. D., Sperling, M. R., & Kahana, M. J. (2014). Human intracranial high-frequency activity maps episodic memory formation in space and time. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.06.067

Burke, J. F., Ramayya, A. G., & Kahana, M. J. (2015). Human intracranial high-frequency activity during memory processing: Neural oscillations or stochastic volatility? In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2014.09.003

Butler, J. L., Hay, Y. A., & Paulsen, O. (2018). Comparison of three gamma oscillations in the mouse entorhinal–hippocampal system. *European Journal of Neuroscience*. https://doi.org/10.1111/ejn.13831

Buzsáki, G. (2002). Theta oscillations in the hippocampus. In *Neuron* (Vol. 33, Issue 3, pp. 325–340). Cell Press. https://doi.org/10.1016/S0896-6273(02)00586-X

Buzsáki, G. (2005). Theta rhythm of navigation: Link between path integration and landmark navigation, episodic and semantic memory. In *Hippocampus*. https://doi.org/10.1002/hipo.20113

Buzsáki, G. (2009). Rhythms of the Brain. In *Rhythms of the Brain*. https://doi.org/10.1093/acprof:oso/9780195301069.001.0001

Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3241

Buzsáki, G., & Draguhn, A. (2004). Neuronal olscillations in cortical networks. In *Science*. https://doi.org/10.1126/science.1099745

Buzsáki, G., & Moser, E. I. (2013). Memory, navigation and theta rhythm in the hippocampal-entorhinal system. In *Nature Neuroscience*. https://doi.org/10.1038/nn.3304

Buzsáki, G., & Wang, X.-J. (2012). Mechanisms of Gamma Oscillations. *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev-neuro-062111-150444

Buzśaki, G., & Wang, X. J. (2012). Mechanisms of gamma oscillations. In *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev-neuro-062111-150444

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/s41583-018-0068-2

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage*. https://doi.org/10.1006/nimg.2002.1280

Cabeza, R., Dolcos, F., Graham, R., & Nyberg, L. (2002). Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *NeuroImage*. https://doi.org/10.1006/nimg.2002.1063

Cairney, S. A., Guttesen, A. á. V., El Marj, N., & Staresina, B. P. (2018). Memory Consolidation Is Linked to Spindle-Mediated Information Processing during Sleep. *Current Biology*. https://doi.org/10.1016/j.cub.2018.01.087

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbare, N. M., & Knight, R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science*. https://doi.org/10.1126/science.1128115

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

Cansino, S., Hernández-Ramos, E., Estrada-Manilla, C., Torres-Trejo, F., Martínez-Galindo, J. G., Ayala-Hernández, M., Gómez-Fernández, T., Osorio, D., Cedillo-Tinoco, M., Garcés-Flores, L., Beltrán-Palacios, K., García-Lázaro, H. G., García-Gutiérrez, F., Cadena-Arenas, Y., Fernández-Apan, L., Bärtschi, A., & Rodríguez-Ortiz, M. D. (2013). The decline of verbal and visuospatial working memory across the adult life span. *Age*. https://doi.org/10.1007/s11357-013-9531-1

Capocchi, G., Zampolini, M., & Larson, J. (1992). Theta burst stimulation is optimal for induction of LTP at both apical and basal dendritic synapses on hippocampal CA1 neurons. *Brain Research*. https://doi.org/10.1016/0006-8993(92)91715-Q

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

Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working memory from the psychological and neurosciences perspectives: A review. In *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2018.00401

Chase, H. W., Boudewyn, M. A., Carter, C. S., & Phillips, M. L. (2020). Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. In *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0499-9

Christophel, T. B., Hebart, M. N., & Haynes, J. D. (2012). Decoding the contents of

visual short-term memory from human visual and parietal cortex. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.0184-12.2012

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

Chrysikou, E. G., Berryhill, M. E., Bikson, M., & Coslett, H. B. (2017). Editorial: Revisiting the effectiveness of transcranial direct current brain stimulation for cognition: Evidence, challenges, and open questions. In *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2017.00448

Clemens, Z., Fabó, D., & Halász, P. (2005). Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience*. https://doi.org/10.1016/j.neuroscience.2005.01.011

Clemens, Z., Fabó, D., & Halász, P. (2006). Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2006.04.035

Clouter, A., Shapiro, K. L., & Hanslmayr, S. (2017). Theta Phase Synchronization Is the Glue that Binds Human Associative Memory. *Current Biology*. https://doi.org/10.1016/j.cub.2017.09.001

Cohen, J. (1992). A power primer. *Psychological Bulletin*. https://doi.org/10.1037/0033-2909.112.1.155

Colgin, L. L. (2011). Oscillations and hippocampal-prefrontal synchrony. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2011.04.006

Colgin, L. L. (2013). Mechanisms and functions of theta rhythms. In *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev-neuro-062012-170330

Colgin, L. L. (2015a). Do slow and fast gamma rhythms correspond to distinct functional states in the hippocampal network? *Brain Research*. https://doi.org/10.1016/j.brainres.2015.01.005

Colgin, L. L. (2015b). Theta-gamma coupling in the entorhinal-hippocampal system. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2014.08.001

Colgin, L. L. (2016). Rhythms of the hippocampal network. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn.2016.21

Colgin, L. L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M. B., & Moser, E. I. (2009). Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature*. https://doi.org/10.1038/nature08573

Colgin, L. L., & Moser, E. I. (2010). Gamma oscillations in the hippocampus. In *Physiology*. https://doi.org/10.1152/physiol.00021.2010

Constantinidis, C., Franowicz, M. N., & Goldman-Rakic, P. S. (2001). The sensory nature of mnemonic representation in the primate prefrontal cortex. *Nature Neuroscience*. https://doi.org/10.1038/85179

Conway, A. R. A., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2003.10.005

Courtney, S. M., Petit, L., Haxby, J. V., & Ungerleider, L. G. (1998). The role of prefrontal cortex in working memory: Examining the contents of consciousness. *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.1998.0334

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

Cowan, N. (2010). The magical mystery four: How is working memory capacity limited, and why? *Current Directions in Psychological Science*. https://doi.org/10.1177/0963721409359277

Cowan, N. (2017). The many faces of working memory and short-term storage. *Psychonomic Bulletin and Review*. https://doi.org/10.3758/s13423-016-1191-6

Cox, R., Hofman, W. F., de Boer, M., & Talamini, L. M. (2014). Local sleep spindle modulations in relation to specific memory cues. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.05.028

Cox, R., Schapiro, A. C., Manoach, D. S., & Stickgold, R. (2017). Individual differences in frequency and topography of slow and fast sleep spindles. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2017.00433

Crowe, D. A., Goodwin, S. J., Blackman, R. K., Sakellaridi, S., Sponheim, S. R., MacDonald, A. W., & Chafee, M. V. (2013). Prefrontal neurons transmit signals to parietal neurons that reflect executive control of cognition. *Nature Neuroscience*. https://doi.org/10.1038/nn.3509

Curcio, G., Ferrara, M., Piergianni, A., Fratello, F., & De Gennaro, L. (2004). Paradoxes of the first-night effect: A quantitative analysis of antero-posterior EEG topography. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2003.12.018

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Scott, A., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature*. https://doi.org/10.1038/378279a0

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain and Cognition*. https://doi.org/10.1006/brcg.1999.1096

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

Datta, A., Baker, J. M., Bikson, M., & Fridriksson, J. (2011). Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimulation*.

https://doi.org/10.1016/j.brs.2010.11.001

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., & Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2009.03.005

Datta, A., Elwassif, M., Battaglia, F., & Bikson, M. (2008). Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2560/5/2/007

Datta, A., Truong, D., Minhas, P., Parra, L. C., & Bikson, M. (2012). Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2012.00091

Daume, J., Gruber, T., Engel, A. K., & Friese, U. (2017). Phase-amplitude coupling and long-range phase synchronization reveal frontotemporal interactions during visual working memory. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2130-16.2016

De Beni, R., & Palladino, P. (2004). Decline in working memory updating through ageing: Intrusion error analyses. *Memory*. https://doi.org/10.1080/09658210244000568

De Gennaro, L., & Ferrara, M. (2003). Sleep spindles: An overview. In *Sleep Medicine Reviews*. https://doi.org/10.1053/smrv.2002.0252

Decorps, J., Saumet, J. L., Sommer, P., Sigaudo-Roussel, D., & Fromy, B. (2014). Effect of ageing on tactile transduction processes. In *Ageing Research Reviews*. https://doi.org/10.1016/j.arr.2013.12.003

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016a). A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. In *Brain Stimulation*. https://doi.org/10.1016/j.brs.2016.04.006

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016b). The effect of the interval-between-sessions on prefrontal transcranial direct current stimulation (tDCS) on cognitive outcomes: a systematic review and meta-analysis. In *Journal of Neural Transmission*. https://doi.org/10.1007/s00702-016-1558-x

Dezfouli, M. P., Davoudi, S., Knight, R. T., Daliri, M. R., & Johnson, E. L. (2021). Prefrontal lesions disrupt oscillatory signatures of spatiotemporal integration in working memory. *Cortex*. https://doi.org/10.1016/j.cortex.2021.01.016

Di Rosa, E., Brigadoi, S., Cutini, S., Tarantino, V., Dell'Acqua, R., Mapelli, D., Braver, T. S., & Vallesi, A. (2019). Reward motivation and neurostimulation interact to improve working memory performance in healthy older adults: A simultaneous tDCS-fNIRS study. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2019.116062

Dickerson, B. C., & Eichenbaum, H. (2010). The episodic memory system: Neurocircuitry and disorders. In *Neuropsychopharmacology*. https://doi.org/10.1038/npp.2009.126

Diekelmann, S., & Born, J. (2010). The memory function of sleep. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn2762

Dmochowski, J. P., Datta, A., Bikson, M., Su, Y., & Parra, L. C. (2011). Optimized multi-electrode stimulation increases focality and intensity at target. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2560/8/4/046011

Dobbs, A. R., & Rule, B. G. (1989). Adult age differences in working memory. *Psychology and Aging*. https://doi.org/10.1037/0882-7974.4.4.500

Donoghue, T., Haller, M., Peterson, E. J., Varma, P., Sebastian, P., Gao, R., Noto, T., Lara, A. H., Wallis, J. D., Knight, R. T., Shestyuk, A., & Voytek, B. (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience*. https://doi.org/10.1038/s41593-020-00744-x

Douchamps, V., Jeewajee, A., Blundell, P., Burgess, N., & Lever, C. (2013). Evidence for encoding versus retrieval scheduling in the hippocampus by theta phase and acetylcholine. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.4483-12.2013

Easton, A., Douchamps, V., Eacott, M., & Lever, C. (2012). A specific role for septohippocampal acetylcholine in memory? *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2012.07.022

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. In *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev.neuro.30.051606.094328

Eichenbaum, H. (2013). What H.M. taught Us. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_00285

Esmaeilpour, Z., Marangolo, P., Hampstead, B. M., Bestmann, S., Galletta, E., Knotkova, H., & Bikson, M. (2018). Incomplete evidence that increasing current intensity of tDCS boosts outcomes. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2017.12.002

Esmaeilpour, Z., Shereen, A. D., Ghobadi-Azbari, P., Datta, A., Woods, A. J., Ironside, M., O'Shea, J., Kirk, U., Bikson, M., & Ekhtiari, H. (2020). Methodology for tDCS integration with fMRI. In *Human Brain Mapping*. https://doi.org/10.1002/hbm.24908

Ester, E. F., Sprague, T. C., & Serences, J. T. (2015). Parietal and Frontal Cortex Encode Stimulus-Specific Mnemonic Representations during Visual Working Memory. *Neuron*. https://doi.org/10.1016/j.neuron.2015.07.013

Etter, G., van der Veldt, S., Manseau, F., Zarrinkoub, I., Trillaud-Doppia, E., & Williams, S. (2019). Optogenetic gamma stimulation rescues memory impairments in an Alzheimer's disease mouse model. *Nature Communications*. https://doi.org/10.1038/s41467-019-13260-9

Ezzyat, Y., Kragel, J. E., Burke, J. F., Levy, D. F., Lyalenko, A., Wanda, P., O'Sullivan, L., Hurley, K. B., Busygin, S., Pedisich, I., Sperling, M. R., Worrell, G. A., Kucewicz, M. T., Davis, K. A., Lucas, T. H., Inman, C. S., Lega, B. C., Jobst, B. C., Sheth, S. A., … Kahana, M. J. (2017). Direct Brain Stimulation Modulates Encoding States and Memory Performance in Humans. *Current Biology*. https://doi.org/10.1016/j.cub.2017.03.028

Ezzyat, Y., Wanda, P. A., Levy, D. F., Kadel, A., Aka, A., Pedisich, I., Sperling, M. R., Sharan, A. D., Lega, B. C., Burks, A., Gross, R. E., Inman, C. S., Jobst, B. C., Gorenstein, M. A., Davis, K. A., Worrell, G. A., Kucewicz, M. T., Stein, J. M., Gorniak, R., … Kahana, M. J. (2018). Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. *Nature Communications*. https://doi.org/10.1038/s41467-017-02753-0

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. https://doi.org/10.3758/BF03193146

Fell, J., Ludowig, E., Rosburg, T., Axmacher, N., & Elger, C. E. (2008). Phase-locking within human mediotemporal lobe predicts memory formation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2008.07.021

Fell, J., Ludowig, E., Staresina, B. P., Wagner, T., Kranz, T., Elger, C. E., & Axmacher, N. (2011). Medial temporal theta/alpha power enhancement precedes successful memory encoding: Evidence based on intracranial EEG. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3668-10.2011

Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Schaller, C., Elger, C. E., & Fernández, G. (2001). Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. *Nature Neuroscience*. https://doi.org/10.1038/nn759

Fellner, M. C., Gollwitzer, S., Rampp, S., Kreiselmeyr, G., Bush, D., Diehl, B., Axmacher, N., Hamer, H., & Hanslmayr, S. (2019). Spectral fingerprints or spectral tilt? Evidence for distinct oscillatory signatures of memory formation. *PLoS Biology*. https://doi.org/10.1371/journal.pbio.3000403

Filmer, H. L., Ehrhardt, S. E., Shaw, T. B., Mattingley, J. B., & Dux, P. E. (2019). The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2019.04.026

Finelli, L. A., Ackermann, P., & Borbély, A. A. (2001). Individual "fingerprints" in human sleep EEG topography. *Neuropsychopharmacology*. https://doi.org/10.1016/S0893-133X(01)00320-7

Fisher, R. P., & Craik, F. I. M. (1977). Interaction between encoding and retrieval operations in cued recall. *Journal of Experimental Psychology: Human Learning and Memory*. https://doi.org/10.1037/0278-7393.3.6.701

Fogel, S. M., & Smith, C. T. (2006). Learning-dependent changes in sleep spindles and Stage 2 sleep. *Journal of Sleep Research*. https://doi.org/10.1111/j.1365-2869.2006.00522.x

Fogel, S. M., & Smith, C. T. (2011). The function of the sleep spindle: A physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2010.12.003

Foo, S., & Bohbot, V. D. (2020). Theta rhythm across the species: Bridging inconsistencies with a multiple memory systems approach. *Behavioral Neuroscience*. https://doi.org/10.1037/bne0000440

Foster, D. J. (2017). Replay Comes of Age. *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev-neuro-072116-031538

Foster, J. J., Sutterer, D. W., Serences, J. T., Vogel, E. K., & Awh, E. (2015). The topography of alpha-band activity tracks the content of spatial working memory. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00860.2015

Frauscher, B., von Ellenrieder, N., Dubeau, F., & Gotman, J. (2015). Scalp spindles are associated with widespread intracranial activity with unexpectedly low synchrony. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.10.048

Fregni, F., Boggio, P. S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M. A., Rigonatti, S. P., Silva, M. T. A., Paulus, W., & Pascual-Leone, A. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental Brain Research*. https://doi.org/10.1007/s00221-005-2334-6

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

Fujiyama, H., Hyde, J., Hinder, M. R., Kim, S. J., McCormack, G. H., Vickers, J. C., & Summers, J. J. (2014). Delayed plastic responses to anodal tDCS in older adults. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2014.00115

Fukuda, K., Awh, E., & Vogel, E. K. (2010). Discrete capacity limits in visual working memory. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2010.03.005

Funahashi, S., Chafee, M. V., & Goldman-Rakic, P. S. (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*. https://doi.org/10.1038/365753a0

Funke, K. (2013). Quite simple at first glance - complex at a second: Modulating neuronal activity by tDCS. In *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2013.260661

Furuya, S., Klaus, M., Nitsche, M. A., Paulus, W., & Altenmüller, E. (2014). Ceiling effects prevent further improvement of transcranial stimulation in skilled musicians. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1170-14.2014

Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term

memory. *Science*. https://doi.org/10.1126/science.173.3997.652

Gais, S., Mölle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.22-15-06830.2002

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2005.12.003

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

Gebodh, N., Esmaeilpour, Z., Adair, D., Chelette, K., Dmochowski, J., Woods, A. J., Kappenman, E. S., Parra, L. C., & Bikson, M. (2019). Inherent physiological artifacts in EEG during tDCS. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.10.025

Gevins, A. S., Bressler, S. L., Cutillo, B. A., Illes, J., Miller, J. C., Stern, J., & Jex, H. R. (1990). Effects of prolonged mental work on functional brain topography. *Electroencephalography and Clinical Neurophysiology*. https://doi.org/10.1016/0013-4694(90)90035-I

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*. https://doi.org/10.1093/cercor/7.4.374

Ghisletta, P., Rabbitt, P., Lunn, M., & Lindenberger, U. (2012). Two thirds of the age-based changes in fluid and crystallized intelligence, perceptual speed, and memory in adulthood are shared. *Intelligence*. https://doi.org/10.1016/j.intell.2012.02.008

Gill, J., Shah-Basak, P. P., & Hamilton, R. (2015). It's the thought that counts: Examining the task-dependent effects of transcranial direct current stimulation on executive function. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2014.10.018

Givens, B. (1995). Low Doses of Ethanol Impair Spatial Working Memory and Reduce Hippocampal Theta Activity. *Alcoholism: Clinical and Experimental Research*. https://doi.org/10.1111/j.1530-0277.1995.tb01580.x

Givens, B. (1997). Stimulus-evoked resetting of the dentate theta rhythm: Relation to working memory. *NeuroReport*. https://doi.org/10.1097/00001756-199612200-00032

Goldthorpe, R. A., Rapley, J. M., & Violante, I. R. (2020). A Systematic Review of Non-invasive Brain Stimulation Applications to Memory in Healthy Aging. In *Frontiers in Neurology*. https://doi.org/10.3389/fneur.2020.575075

Gordon, J. A. (2011). Oscillations and hippocampal-prefrontal synchrony. In *Current*

Opinion in Neurobiology. https://doi.org/10.1016/j.conb.2011.02.012

Goyal, A., Miller, J., Qasim, S. E., Watrous, A. J., Zhang, H., Stein, J. M., Inman, C. S., Gross, R. E., Willie, J. T., Lega, B., Lin, J. J., Sharan, A., Wu, C., Sperling, M. R., Sheth, S. A., McKhann, G. M., Smith, E. H., Schevon, C., & Jacobs, J. (2020). Functionally distinct high and low theta oscillations in the human hippocampus. *Nature Communications*. https://doi.org/10.1038/s41467-020-15670-6

Grady, C. (2012). The cognitive neuroscience of ageing. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3256

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. In *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2010.01.001

Griffiths, B. J., & Fuentemilla, L. (2020). Event conjunction: How the hippocampus integrates episodic memories across event boundaries. In *Hippocampus*. https://doi.org/10.1002/hipo.23161

Griffiths, B. J., Martín-Buro, M. C., Staresina, B. P., & Hanslmayr, S. (2021). Disentangling neocortical alpha/beta and hippocampal theta/gamma oscillations in human episodic memory formation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2021.118454

Griffiths, B. J., Parish, G., Roux, F., Michelmann, S., van der Plas, M., Kolibius, L. D., Chelvarajah, R., Rollings, D. T., Sawlani, V., Hamer, H., Gollwitzer, S., Kreiselmeyer, G., Staresina, B., Wimber, M., & Hanslmayr, S. (2019). Directional coupling of slow and fast hippocampal gamma with neocortical alpha/beta oscillations in human episodic memory. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1914180116

Grootswagers, T., Wardle, S. G., & Carlson, T. A. (2017). Decoding dynamic brain patterns from evoked responses: A tutorial on multivariate pattern analysis applied to time series neuroimaging data. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_01068

Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S. B., Rudenko, A., Suk, H.-J., Cassara, A. M., Neufeld, E., Kuster, N., Tsai, L.-H., Pascual-Leone, A., & Boyden, E. S. (2017). Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. *Cell*, *169*(6), 1029-1041.e16. https://doi.org/https://doi.org/10.1016/j.cell.2017.05.024

Guderian, S., Schott, B. H., Richardson-Klavehn, A., & Düzel, E. (2009). Medial temporal theta state before an event predicts episodic encoding success in humans. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0900289106

Guerra, A., López-Alonso, V., Cheeran, B., & Suppa, A. (2020). Variability in non-invasive brain stimulation studies: Reasons and results. In *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2017.12.058

Habib, A., Harris, L., Pollick, F., & Melville, C. (2019). A meta-analysis of working memory in individuals with autism spectrum disorders. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0216198

Hammer, M., Schwale, C., Brankačk, J., Draguhn, A., & Tort, A. B. L. (2021). Theta-gamma coupling during REM sleep depends on breathing rate. *Sleep*. https://doi.org/10.1093/sleep/zsab189

Harrison, S. A., & Tong, F. (2009). Decoding reveals the contents of visual working memory in early visual areas. *Nature*. https://doi.org/10.1038/nature07832

Hasselmo, M. E. (2005). What is the function of hippocampal theta rhythm? - Linking bahavioral data to phasic properties of field potential and unit recording data. In *Hippocampus*. https://doi.org/10.1002/hipo.20116

Hasselmo, M. E., Bodelón, C., & Wyble, B. P. (2002). A proposed function for hippocampal theta rhythm: Separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Computation*. https://doi.org/10.1162/089976602317318965

Hasselmo, M. E., & Howard Eichenbaum. (2005). Hippocampal mechanisms for the context-dependent retrieval of episodes. *Neural Networks*. https://doi.org/10.1016/j.neunet.2005.08.007

Haynes, J. D., & Rees, G. (2006). Decoding mental states from brain activity in humans. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1931

Helfrich, R. F., & Knight, R. T. (2019). Cognitive neurophysiology: Event-related potentials. In *Handbook of Clinical Neurology*. https://doi.org/10.1016/B978-0-444-64032-1.00036-9

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*. https://doi.org/10.1016/j.brainres.2013.08.002

Hermiller, M. S., VanHaerents, S., Raij, T., & Voss, J. L. (2019). Frequency-specific noninvasive modulation of memory retrieval and its relationship with hippocampal network connectivity. *Hippocampus*. https://doi.org/10.1002/hipo.23054

Herrmann, C. S., Rach, S., Neuling, T., & Strüber, D. (2013). Transcranial alternating current stimulation: A review of the underlying mechanisms and modulation of cognitive processes. In *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2013.00279

Herrmann, C. S., Senkowski, D., & Röttger, S. (2004). Phase-locking and amplitude modulations of EEG alpha: Two measures reflect different cognitive processes in a working memory task. *Experimental Psychology*. https://doi.org/10.1027/1618-3169.51.4.311

Herweg, N. A., Apitz, T., Leicht, G., Mulert, C., Fuentemilla, L., & Bunzeck, N. (2016). Theta-alpha oscillations bind the hippocampus, prefrontal cortex, and

striatum during recollection: Evidence from simultaneous EEG–fMRI. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3629-15.2016

Herweg, N. A., Solomon, E. A., & Kahana, M. J. (2020). Theta Oscillations in Human Memory. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2019.12.006

Heusser, A. C., Poeppel, D., Ezzyat, Y., & Davachi, L. (2016). Episodic sequence memory is supported by a theta-gamma phase code. *Nature Neuroscience*. https://doi.org/10.1038/nn.4374

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. In *Brain Stimulation*. https://doi.org/10.1016/j.brs.2015.10.006

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2016). TMS-EEG: A window into the neurophysiological effects of transcranial electrical stimulation in non-motor brain regions. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2016.03.006

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2017). Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2017.03.001

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2018). Effects of single versus dual-site High-Definition transcranial direct current stimulation (HD-tDCS) on cortical reactivity and working memory performance in healthy subjects. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2018.06.005

Hill, A. T., Rogasch, N. C., Fitzgerald, P. B., & Hoy, K. E. (2019). Impact of concurrent task performance on transcranial direct current stimulation (tDCS)-Induced changes in cortical physiology and working memory. *Cortex*. https://doi.org/10.1016/j.cortex.2018.11.022

Ho, K. A., Taylor, J. L., Chew, T., Gálvez, V., Alonzo, A., Bai, S., Dokos, S., & Loo, C. K. (2016). The Effect of Transcranial Direct Current Stimulation (tDCS) Electrode Size and Current Intensity on Motor Cortical Excitability: Evidence from Single and Repeated Sessions. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2015.08.003

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*.

Hölscher, C., Anwyl, R., & Rowan, M. J. (1997). Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.17-16-06470.1997

Horner, A. J., Bisby, J. A., Bush, D., Lin, W. J., & Burgess, N. (2015). Evidence for holistic episodic recollection via hippocampal pattern completion. *Nature Communications*. https://doi.org/10.1038/ncomms8462

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*. https://doi.org/10.1016/j.brs.2015.01.400

Horvath, J. C., Vogrin, S. J., Carter, O., Cook, M. J., & Forte, J. D. (2016). Effects of a common transcranial direct current stimulation (tDCS) protocol on motor evoked potentials found to be highly variable within individuals over 9 testing sessions. *Experimental Brain Research*. https://doi.org/10.1007/s00221-016-4667-8

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*. https://doi.org/10.1093/cercor/bhg084

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*. https://doi.org/10.1016/j.bandc.2015.11.002

Hoy, K. E., Emonson, M. R. L., Arnold, S. L., Thomson, R. H., Daskalakis, Z. J., & Fitzgerald, P. B. (2013). Testing the limits: Investigating the effect of tDCS dose on working memory enhancement in healthy controls. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2013.05.018

Hsieh, L. T., Ekstrom, A. D., & Ranganath, C. (2011). Neural oscillations associated with item and temporal order maintenance in working memory. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.0828-11.2011

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

Hsu, T. Y., Juan, C. H., & Tseng, P. (2016). Individual differences and state-dependent responses in transcranial direct current stimulation. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2016.00643

Hsu, T. Y., Tseng, P., Liang, W. K., Cheng, S. K., & Juan, C. H. (2014). Transcranial direct current stimulation over right posterior parietal cortex changes prestimulus alpha oscillation in visual short-term memory task. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.04.069

Huang, C. M., Polk, T. A., Goh, J. O., & Park, D. C. (2012). Both left and right posterior parietal activations contribute to compensatory processes in normal aging. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2011.10.022

Huang, Y., Liu, A. A., Lafon, B., Friedman, D., Dayan, M., Wang, X., Bikson, M., Doyle, W. K., Devinsky, O., & Parra, L. C. (2017). Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. *ELife*. https://doi.org/10.7554/eLife.18834

Huerta, P. T., & Lisman, J. E. (1993). Heightened synaptic plasticity of hippocampal CA1 neurons during a Cholinergically induced rhythmic state. *Nature*. https://doi.org/10.1038/364723a0

Hyman, J. M., Wyble, B. P., Goyal, V., Rossi, C. A., & Hasselmo, M. E. (2003). Stimulation in Hippocampal Region CA1 in Behaving Rats Yields Long-Term Potentiation when Delivered to the Peak of Theta and Long-Term Depression when Delivered to the Trough. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.23-37-11725.2003

Hyman, J. M., Zilli, E. A., Paley, A. M., & Hasselmo, M. E. (2010). Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Frontiers in Integrative Neuroscience*. https://doi.org/10.3389/neuro.07.002.2010

Hyman, J. M., Hasselmo, M. E., & Seamans, J. K. (2011). What is the functional relevance of prefrontal cortex entrainment to hippocampal theta rhythms? In *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2011.00024

Imaruoka, T., Saiki, J., & Miyauchi, S. (2005). Maintaining coherence of dynamic objects requires coordination of neural systems extended from anterior frontal to posterior parietal brain cortices. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2005.01.045

Itthipuripat, S., Wessel, J. R., & Aron, A. R. (2013). Frontal theta is a signature of successful working memory manipulation. *Experimental Brain Research*. https://doi.org/10.1007/s00221-012-3305-3

Jacobs, J. (2014). Hippocampal theta oscillations are slower in humans than in rodents: Implications for models of spatial navigation and memory. In *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2013.0304

Jacobs, J., & Kahana, M. J. (2010). Direct brain recordings fuel advances in cognitive electrophysiology. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2010.01.005

Jacobs, J., Kahana, M. J., Ekstrom, A. D., & Fried, I. (2007). Brain oscillations control timing of single-neuron activity in humans. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.4636-06.2007

Jacobs, J., Miller, J., Lee, S. A., Coffey, T., Watrous, A. J., Sperling, M. R., Sharan, A., Worrell, G., Berry, B., Lega, B., Jobst, B. C., Davis, K., Gross, R. E., Sheth, S. A., Ezzyat, Y., Das, S. R., Stein, J., Gorniak, R., Kahana, M. J., & Rizzuto, D. S. (2016). Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory. *Neuron*. https://doi.org/10.1016/j.neuron.2016.10.062

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). TDCS polarity effects in motor and cognitive domains: A meta-analytical review. In *Experimental Brain Research*. https://doi.org/10.1007/s00221-011-2891-9

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent

validity of the N-back task as a working memory measure. *Memory*. https://doi.org/10.1080/09658211003702171

Jafarpour, A., Fuentemilla, L., Horner, A. J., Penny, W., & Duzel, E. (2014). Replay of very early encoding representations during recollection. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1865-13.2014

Jamadar, S. D. (2020). The CRUNCH model does not account for load-dependent changes in visuospatial working memory in older adults. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2020.107446

James, W. (1891). The Principles of Psychology. *The American Journal of Psychology*. https://doi.org/10.2307/1412102

Jamil, A., Batsikadze, G., Kuo, H. I., Labruna, L., Hasan, A., Paulus, W., & Nitsche, M. A. (2017). Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *Journal of Physiology*. https://doi.org/10.1113/JP272738

Jasper, H. (1958). The ten twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology*.

Jaušovec, N., & Jaušovec, K. (2014). Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). *Biological Psychology*. https://doi.org/10.1016/j.biopsycho.2013.11.006

Jeneson, A., & Squire, L. R. (2012). Working memory, long-term memory, and medial temporal lobe function. In *Learning and Memory*. https://doi.org/10.1101/lm.024018.111

Jenkins, J. G., & Dallenbach, K. M. (1924). Obliviscence during Sleep and Waking. *The American Journal of Psychology*. https://doi.org/10.2307/1414040

Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. E. (2002). Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral Cortex*. https://doi.org/10.1093/cercor/12.8.877

Jensen, O., & Lisman, J. E. (1998). An oscillatory short-term memory buffer model can account for data on the Sternberg task. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.18-24-10688.1998

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

Johnson, E. L., Dewar, C. D., Solbakk, A. K., Endestad, T., Meling, T. R., & Knight, R. T. (2017). Bidirectional Frontoparietal Oscillatory Systems Support Working Memory. *Current Biology*. https://doi.org/10.1016/j.cub.2017.05.046

Johnson, E. L., & Knight, R. T. (2015). Intracranial recordings and human memory. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2014.07.021

Jones, K. T., & Berryhill, M. E. (2012). Parietal contributions to visual working memory depend on task difficulty. *Frontiers in Psychiatry*.

https://doi.org/10.3389/fpsyt.2012.00081

Jones, K. T., Gözenman, F., & Berryhill, M. E. (2015). The strategy and motivational influences on the beneficial effect of neurostimulation: A tDCS and fNIRS study. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.11.012

Jones, K. T., Johnson, E. L., & Berryhill, M. E. (2020). Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2020.116615

Jones, K. T., Peterson, D. J., Blacker, K. J., & Berryhill, M. E. (2017). Frontoparietal neurostimulation modulates working memory training benefits and oscillatory synchronization. *Brain Research*. https://doi.org/10.1016/j.brainres.2017.05.005

Kadosh, R. C., Soskic, S., Iuculano, T., & Kanai, R. (2012). Modulating Neuronal Activity Produces Specific and Long- Lasting Changes in Numerical Competence. *Current Biology : CB*.

Kahana, M. J., Seelig, D., & Madsen, J. R. (2001). Theta returns. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/S0959-4388(01)00278-1

Kalu, U. G., Sexton, C. E., Loo, C. K., & Ebmeier, K. P. (2012). Transcranial direct current stimulation in the treatment of major depression: A meta-analysis. *Psychological Medicine*. https://doi.org/10.1017/S0033291711003059

Kamiński, J., Brzezicka, A., Mamelak, A. N., & Rutishauser, U. (2020). Combined Phase-Rate Coding by Persistently Active Neurons as a Mechanism for Maintaining Multiple Items in Working Memory in Humans. *Neuron*. https://doi.org/10.1016/j.neuron.2020.01.032

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/https://doi.org/10.1016/j.nlm.2010.10.001

Kamondi, A., Acsády, L., Wang, X. J., & Buzsáki, G. (1998). Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: Activity-dependent phase-precession of action potentials. *Hippocampus*. https://doi.org/10.1002/(SICI)1098-1063(1998)8:3<244::AID-HIPO7>3.0.CO;2-J

Kearney, K. (2019). *boundedline.m*. GitHub. https://github.com/kakearney/boundedline-pkg

Kerrén, C., Linde-Domingo, J., Hanslmayr, S., & Wimber, M. (2018). An Optimal Oscillatory Phase for Pattern Reactivation during Memory Retrieval. *Current Biology*. https://doi.org/10.1016/j.cub.2018.08.065

Khadka, N., Borges, H., Paneri, B., Kaufman, T., Nassis, E., Zannou, A. L., Shin, Y., Choi, H., Kim, S., Lee, K., & Bikson, M. (2020). Adaptive current tDCS up to 4 mA. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2019.07.027

Khatoun, A., Asamoah, B., & Laughlin, M. M. (2019). How does transcranial alternating current stimulation entrain single-neuron activity in the primate brain? In *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1912927116

Kim, J., Delcasso, S., & Lee, I. (2011). Neural correlates of object-in-place learning in hippocampus and prefrontal cortex. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2859-11.2011

Kim, J. H., Kim, D. W., Chang, W. H., Kim, Y. H., Kim, K., & Im, C. H. (2014). Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: Electric field simulation using individual MRI data. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2014.01.054

Klein, S. B., Cosmides, L., Tooby, J., & Chance, S. (2002). Decisions and the evolution of memory: Multiple systems, multiple functions. *Psychological Review*. https://doi.org/10.1037/0033-295X.109.2.306

Kleiner, M., Brainard, D. H., Pelli, D. G., Broussard, C., Wolf, T., & Niehorster, D. (2007). What's new in Psychtoolbox-3? *Perception*. https://doi.org/10.1068/v070821

Klimesch, W., Doppelmayr, M., Russegger, H., & Pachinger, T. (1996). Theta band power in the human scalp EEG and the encoding of new information. *NeuroReport*. https://doi.org/10.1097/00001756-199605170-00002

Kloc, M. L., Velasquez, F., Niedecker, R. W., Barry, J. M., & Holmes, G. L. (2020). Disruption of hippocampal rhythms via optogenetic stimulation during the critical period for memory development impairs spatial cognition. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2020.08.011

Knierim, J. J., & Neunuebel, J. P. (2016). Tracking the flow of hippocampal computation: Pattern separation, pattern completion, and attractor dynamics. In *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2015.10.008

Kopell, N., Kramer, A. A., Malerba, P., & Whittington, M. A. (2013). Are different rythms good for different functions? *Neuron*.

Korotkova, T., Ponomarenko, A., Monaghan, C. K., Poulter, S. L., Cacucci, F., Wills, T., Hasselmo, M. E., & Lever, C. (2018). Reconciling the different faces of hippocampal theta: The role of theta oscillations in cognitive, emotional and innate behaviors. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2017.09.004

Köster, M., Finger, H., Graetz, S., Kater, M., & Gruber, T. (2018). Theta-gamma coupling binds visual perceptual features in an associative memory task. *Scientific Reports*. https://doi.org/10.1038/s41598-018-35812-7

Kota, S., Rugg, M. D., & Lega, B. C. (2020). Hippocampal theta oscillations support successful associative memory formation. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.0767-20.2020

Kragel, J. E., Ezzyat, Y., Sperling, M. R., Gorniak, R., Worrell, G. A., Berry, B. M., Inman, C., Lin, J. J., Davis, K. A., Das, S. R., Stein, J. M., Jobst, B. C., Zaghloul, K. A., Sheth, S. A., Rizzuto, D. S., & Kahana, M. J. (2017). Similar patterns of neural activity predict memory function during encoding and retrieval.

NeuroImage. https://doi.org/10.1016/j.neuroimage.2017.03.042

Krause, M. R., Vieira, P. G., Csorba, B. A., Pilly, P. K., & Pack, C. C. (2019). Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1815958116

Krause, M. R., Zanos, T. P., Csorba, B. A., Pilly, P. K., Choe, J., Phillips, M. E., Datta, A., & Pack, C. C. (2017). Transcranial Direct Current Stimulation Facilitates Associative Learning and Alters Functional Connectivity in the Primate Brain. *Current Biology*. https://doi.org/10.1016/j.cub.2017.09.020

Krawczyk, D. C., & D'Esposito, M. (2013). Modulation of working memory function by motivation through loss-aversion. *Human Brain Mapping*. https://doi.org/10.1002/hbm.21472

Krueger, J. M., Nguyen, J. T., Dykstra-Aiello, C. J., & Taishi, P. (2019). Local sleep. In *Sleep Medicine Reviews*. https://doi.org/10.1016/j.smrv.2018.10.001

Kucewicz, M. T., Cimbalnik, J., Matsumoto, J. Y., Brinkmann, B. H., Bower, M. R., Vasoli, V., Sulc, V., Meyer, F., Marsh, W. R., Stead, S. M., & Worrell, G. A. (2014). High frequency oscillations are associated with cognitive processing in human recognition memory. *Brain*. https://doi.org/10.1093/brain/awu149

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: A neurophysiological study. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2012.09.010

Lafon, B., Henin, S., Huang, Y., Friedman, D., Melloni, L., Thesen, T., Doyle, W., Buzsáki, G., Devinsky, O., Parra, L. C., & Liu, A. A. (2017). Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nature Communications*. https://doi.org/10.1038/s41467-017-01045-x

Landfield, P. W., Mcgaugh, J. L., & Tusa, R. J. (1972). Theta rhythm: A temporal correlate of memory storage processes in the rat. *Science*. https://doi.org/10.1126/science.175.4017.87

Lara, A. H., & Wallis, J. D. (2014). Executive control processes underlying multi-item working memory. *Nature Neuroscience*. https://doi.org/10.1038/nn.3702

Lara, A. H., & Wallis, J. D. (2015). The role of prefrontal cortex in working memory: A mini review. In *Frontiers in Systems Neuroscience*. https://doi.org/10.3389/fnsys.2015.00173

Larson, J., Wong, D., & Lynch, G. (1986). Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Research*. https://doi.org/10.1016/0006-8993(86)90579-2

Las, L., & Ulanovsky, N. (2014). Hippocampal neurophysiology across species. In *Space, Time and Memory in the Hippocampal Formation*. https://doi.org/10.1007/978-3-7091-1292-2_16

Latchoumane, C. F. V., Ngo, H. V. V., Born, J., & Shin, H. S. (2017). Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms. *Neuron*. https://doi.org/10.1016/j.neuron.2017.06.025

Laventure, S., Fogel, S., Lungu, O., Albouy, G., Sévigny-Dupont, P., Vien, C., Sayour, C., Carrier, J., Benali, H., & Doyon, J. (2016). NREM2 and Sleep Spindles Are Instrumental to the Consolidation of Motor Sequence Memories. *PLoS Biology*. https://doi.org/10.1371/journal.pbio.1002429

Lee, H., Simpson, G. V., Logothetis, N. K., & Rainer, G. (2005). Phase locking of single neuron activity to theta oscillations during working memory in monkey extrastriate visual cortex. *Neuron*. https://doi.org/10.1016/j.neuron.2004.12.025

Lee, S. H., & Baker, C. I. (2016). Multi-voxel decoding and the topography of maintained information during visual working memory. In *Frontiers in Systems Neuroscience*. https://doi.org/10.3389/fnsys.2016.00002

Lee, S. H., Kravitz, D. J., & Baker, C. I. (2013). Goal-dependent dissociation of visual and prefrontal cortices during working memory. *Nature Neuroscience*. https://doi.org/10.1038/nn.3452

Lega, B., Burke, J., Jacobs, J., & Kahana, M. J. (2016). Slow-Theta-to-Gamma Phase-Amplitude Coupling in Human Hippocampus Supports the Formation of New Episodic Memories. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhu232

Lever, C., Burton, S., Jeewajee, A., Wills, T. J., Cacucci, F., Burgess, N., & O'Keefe, J. (2010). Environmental novelty elicits a later theta phase of firing in CA1 but not subiculum. *Hippocampus*. https://doi.org/10.1002/hipo.20671

Lewis-Peacock, J. A., & Postle, B. R. (2008). Temporary activation of long-term memory supports working memory. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1953-08.2008

Lewis, M. S., & Miller, L. S. (2007). Executive control functioning and functional ability in older adults. *Clinical Neuropsychologist*. https://doi.org/10.1080/13854040500519752

Li, G., Jiang, S., Paraskevopoulou, S. E., Wang, M., Xu, Y., Wu, Z., Chen, L., Zhang, D., & Schalk, G. (2018). Optimal referencing for stereo-electroencephalographic (SEEG) recordings. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.08.020

Lin, J. J., Rugg, M. D., Das, S., Stein, J., Rizzuto, D. S., Kahana, M. J., & Lega, B. C. (2017). Theta band power increases in the posterior hippocampus predict successful episodic memory encoding in humans. *Hippocampus*. https://doi.org/10.1002/hipo.22751

Lisman, J. (2005). The theta/gamma discrete phase code occuring during the hippocampal phase precession may be a more general brain coding scheme. *Hippocampus*. https://doi.org/10.1002/hipo.20121

Lisman, J. E., & Idiart, M. A. P. (1995). Storage of 7 ± 2 short-term memories in

oscillatory subcycles. *Science*. https://doi.org/10.1126/science.7878473

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

Long, N. M., Burke, J. F., & Kahana, M. J. (2014). Subsequent memory effect in intracranial and scalp EEG. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.08.052

Long, N. M., & Kahana, M. J. (2015). Successful memory formation is driven by contextual encoding in the core memory network. *NeuroImage*, *119*, 332–337. https://doi.org/10.1016/j.neuroimage.2015.06.073

Lopes-dos-Santos, V., van de Ven, G. M., Morley, A., Trouche, S., Campo-Urriza, N., & Dupret, D. (2018). Parsing Hippocampal Theta Oscillations by Nested Spectral Components during Spatial Exploration and Memory-Guided Behavior. *Neuron*. https://doi.org/10.1016/j.neuron.2018.09.031

López-Alonso, V., Cheeran, B., Río-Rodríguez, D., & Fernández-Del-Olmo, M. (2014). Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2014.02.004

López-Alonso, V., Fernández-del-Olmo, M., Costantini, A., Gonzalez-Henriquez, J. J., & Cheeran, B. (2015). Intra-individual variability in the response to anodal transcranial direct current stimulation. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2015.03.022

López-Madrona, V. J., Pérez-Montoyo, E., Álvarez-Salvado, E., Moratal, D., Herreras, O., Pereda, E., Mirasso, C. R., & Canals, S. (2020). Different theta frameworks coexist in the rat hippocampus and are coordinated during memory-guided and novelty tasks. *ELife*. https://doi.org/10.7554/eLife.57313

Lorenc, E. S., & Sreenivasan, K. K. (2021). Reframing the debate: The distributed systems view of working memory. *Visual Cognition*. https://doi.org/10.1080/13506285.2021.1899091

Love, J., Selker, R., Marsman, M., Jamil, T., Dropmann, D., Verhagen, J., Ly, A., Gronau, Q. F., Šmíra, M., Epskamp, S., Matzke, D., Wild, A., Knight, P., Rouder, J. N., Morey, R. D., & Wagenmakers, E. J. (2019). JASP: Graphical statistical software for common statistical designs. *Journal of Statistical Software*. https://doi.org/10.18637/jss.v088.i02

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*. https://doi.org/10.1038/36846

Luck, S. J., & Vogel, E. K. (2013). Visual working memory capacity: From psychophysics and neurobiology to individual differences. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.06.006

Lundqvist, M., Herman, P., Warden, M. R., Brincat, S. L., & Miller, E. K. (2018). Gamma and beta bursts during working memory readout suggest roles in its volitional control. *Nature Communications*. https://doi.org/10.1038/s41467-017-02791-8

Lundqvist, M., Rose, J., Herman, P., Brincat, S. L. L., Buschman, T. J. J., & Miller, E. K. K. (2016). Gamma and Beta Bursts Underlie Working Memory. *Neuron*. https://doi.org/10.1016/j.neuron.2016.02.028

Lustenberger, C., Boyle, M. R., Alagapan, S., Mellin, J. M., Vaughn, B. V., & Fröhlich, F. (2016). Feedback-Controlled Transcranial Alternating Current Stimulation Reveals a Functional Role of Sleep Spindles in Motor Memory Consolidation. *Current Biology*. https://doi.org/10.1016/j.cub.2016.06.044

Lustenberger, C., Maric, A., Dürr, R., Achermann, P., & Huber, R. (2012). Triangular Relationship between Sleep Spindle Activity, General Cognitive Ability and the Efficiency of Declarative Learning. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0049561

Lynch, M. A. (2004). Long-Term Potentiation and Memory. In *Physiological Reviews*. https://doi.org/10.1152/physrev.00014.2003

Maillet, D., & Rajah, M. N. (2013). Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: A review. In *Ageing Research Reviews*. https://doi.org/10.1016/j.arr.2012.11.001

Maingret, N., Girardeau, G., Todorova, R., Goutierre, M., & Zugaro, M. (2016). Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nature Neuroscience*. https://doi.org/10.1038/nn.4304

Malenínská, K., Rudolfová, V., Šulcová, K., Koudelka, V., Brunovský, M., Horáček, J., & Nekovářová, T. (2021). Is short-term memory capacity (7±2) really predicted by theta to gamma cycle length ratio? *Behavioural Brain Research*, *414*, 113465. https://doi.org/https://doi.org/10.1016/j.bbr.2021.113465

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. In *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_00956

Manning, J. R., Jacobs, J., Fried, I., & Kahana, M. J. (2009). Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2041-09.2009

Manns, J. R., Zilli, E. A., Ong, K. C., Hasselmo, M. E., & Eichenbaum, H. (2007). Hippocampal CA1 spiking during encoding and retrieval: Relation to theta phase. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2006.05.007

Marcus, D. S., Fotenos, A. F., Csernansky, J. G., Morris, J. C., & Buckner, R. L. (2010). Open access series of imaging studies: Longitudinal MRI data in nondemented and demented older adults. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2009.21407

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2007.03.024

Marshall, L., Cross, N., Binder, S., & Dang-Vu, T. T. (2020). Brain rhythms during sleep and memory consolidation: Neurobiological insights. In *Physiology*. https://doi.org/10.1152/physiol.00004.2019

Martin, D. M., Liu, R., Alonzo, A., Green, M., & Loo, C. K. (2014). Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Experimental Brain Research*. https://doi.org/10.1007/s00221-014-4022-x

Martínez-Cancino, R., Heng, J., Delorme, A., Kreutz-Delgado, K., Sotero, R. C., & Makeig, S. (2019). Measuring transient phase-amplitude coupling using local mutual information. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.10.034

Martorell, A. J., Paulson, A. L., Suk, H. J., Abdurrob, F., Drummond, G. T., Guan, W., Young, J. Z., Kim, D. N. W., Kritskiy, O., Barker, S. J., Mangena, V., Prince, S. M., Brown, E. N., Chung, K., Boyden, E. S., Singer, A. C., & Tsai, L. H. (2019). Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. *Cell*. https://doi.org/10.1016/j.cell.2019.02.014

Mashal, N., & Metzuyanim-Gorelick, S. (2019). New information on the effects of transcranial direct current stimulation on n-back task performance. *Experimental Brain Research*. https://doi.org/10.1007/s00221-019-05500-7

Masse, N. Y., Yang, G. R., Song, H. F., Wang, X. J., & Freedman, D. J. (2019). Circuit mechanisms for the maintenance and manipulation of information in working memory. *Nature Neuroscience*. https://doi.org/10.1038/s41593-019-0414-3

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Berman, K. F., Das, S., Meyer-Lindenberg, A., Goldberg, T. E., Callicott, J. H., & Weinberger, D. R. (2006). Neurophysiological correlates of age-related changes in working memory capacity. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2005.09.025

Maurer, U., Brem, S., Liechti, M., Maurizio, S., Michels, L., & Brandeis, D. (2014). Frontal Midline Theta Reflects Individual Task Performance in a Working Memory Task. *Brain Topography*. https://doi.org/10.1007/s10548-014-0361-y

McCartney, H., Johnson, A. D., Weil, Z. M., & Givens, B. (2004). Theta reset produces optimal conditions for long-term potentiation. *Hippocampus*. https://doi.org/10.1002/hipo.20019

McClelland, J. L., McNaughton, B. L., & Lampinen, A. K. (2020). Integration of new information in memory: New insights from a complementary learning systems perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2019.0637

McGaugh, J. L. (2000). Memory - A century of consolidation. In *Science*. https://doi.org/10.1126/science.287.5451.248

McIntire, L. K., McKinley, R. A., Nelson, J. M., & Goodyear, C. (2017). Transcranial direct current stimulation versus caffeine as a fatigue countermeasure. *Brain*

Stimulation. https://doi.org/10.1016/j.brs.2017.08.005

Medeiros, L. F., de Souza, I. C. C., Vidor, L. P., de Souza, A., Deitos, A., Volz, M. S., Fregni, F., Caumo, W., & Torres, I. L. S. (2012). Neurobiological effects of transcranial direct current stimulation: A review. In *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2012.00110

Medina, J., & Cason, S. (2017). No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. *Cortex*. https://doi.org/10.1016/j.cortex.2017.06.021

Mednick, S. C., McDevitt, E. A., Walsh, J. K., Wamsley, E., Paulus, M., Kanady, J. C., & Drummond, S. P. A. (2013). The critical role of sleep spindles in hippocampal-dependent memory: A pharmacology study. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3127-12.2013

Meltzer, J. A., Zaveri, H. P., Goncharova, I. I., Distasio, M. M., Papademetris, X., Spencer, S. S., Spencer, D. D., & Constable, R. T. (2008). Effects of working memory load on oscillatory power in human intracranial EEG. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhm213

Mendoza-Halliday, D., Torres, S., & Martinez-Trujillo, J. C. (2014). Sharp emergence of feature-selective sustained activity along the dorsal visual pathway. *Nature Neuroscience*. https://doi.org/10.1038/nn.3785

Mercier, M. R., Bickel, S., Megevand, P., Groppe, D. M., Schroeder, C. E., Mehta, A. D., & Lado, F. A. (2017). Evaluation of cortical local field potential diffusion in stereotactic electro-encephalography recordings: A glimpse on white matter signal. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.08.037

Merkow, M. B., Burke, J. F., & Kahana, M. J. (2015). The human hippocampus contributes to both the recollection and familiarity components of recognition memory. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1513145112

Meyer, T., Qi, X. L., Stanford, T. R., & Constantinidis, C. (2011). Stimulus selectivity in dorsal and ventral prefrontal cortex after training in working memory tasks. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.6798-10.2011

Michelmann, S., Treder, M. S., Griffiths, B., Kerrén, C., Roux, F., Wimber, M., Rollings, D., Sawlani, V., Chelvarajah, R., Gollwitzer, S., Kreiselmeyer, G., Hamer, H., Bowman, H., Staresina, B., & Hanslmayr, S. (2018). Data-driven re-referencing of intracranial EEG based on independent component analysis (ICA). *Journal of Neuroscience Methods*, *307*, 125–137. https://doi.org/https://doi.org/10.1016/j.jneumeth.2018.06.021

Michels, L., Bucher, K., Lüchinger, R., Klaver, P., Martin, E., Jeanmonod, D., & Brandeis, D. (2010). Simultaneous EEG-fMRI during a working memory task: Modulations in low and high frequency bands. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0010298

Miller, E. K., Erickson, C. A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *Journal of Neuroscience*.

https://doi.org/10.1523/jneurosci.16-16-05154.1996

Miller, J., Berger, B., & Sauseng, P. (2015). Anodal transcranial direct current stimulation (tDCS) increases frontal-midline theta activity in the human EEG: A preliminary investigation of non-invasive stimulation. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2015.01.014

Miller, J., Watrous, A. J., Tsitsiklis, M., Lee, S. A., Sheth, S. A., Schevon, C. A., Smith, E. H., Sperling, M. R., Sharan, A., Asadi-Pooya, A. A., Worrell, G. A., Meisenhelter, S., Inman, C. S., Davis, K. A., Lega, B., Wanda, P. A., Das, S. R., Stein, J. M., Gorniak, R., & Jacobs, J. (2018). Lateralized hippocampal oscillations underlie distinct aspects of human spatial memory and navigation. *Nature Communications*. https://doi.org/10.1038/s41467-018-04847-9

Miller, K. M., Price, C. C., Okun, M. S., Montijo, H., & Bowers, D. (2009). Is the N-Back Task a Valid Neuropsychological Measure for Assessing Working Memory? *Archives of Clinical Neuropsychology*, *24*(7), 711–717. https://doi.org/10.1093/arclin/acp063

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*. https://doi.org/10.3389/fnhum.2016.00453

Miniussi, C., Harris, J. A., & Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2013.06.014

Missonnier, P., Deiber, M. P., Gold, G., Millet, P., Gex-Fabry Pun, M., Fazio-Costa, L., Giannakopoulos, P., & Ibáñez, V. (2006). Frontal theta event-related synchronization: Comparison of directed attention and working memory load effects. *Journal of Neural Transmission*. https://doi.org/10.1007/s00702-005-0443-9

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

Mölle, M., Eschenko, O., Gais, S., Sara, S. J., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.2009.06654.x

Montaldi, D., & Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus*. https://doi.org/10.1002/hipo.20853

Mormann, F., Fell, J., Axmacher, N., Weber, B., Lehnertz, K., Elger, C. E., & Fernández, G. (2005). Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. *Hippocampus*. https://doi.org/10.1002/hipo.20117

Morris, N., & Jones, D. M. (1990). Memory updating in working memory: The role of the central executive. *British Journal of Psychology*. https://doi.org/10.1111/j.2044-8295.1990.tb02349.x

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic memory and beyond: The hippocampus and neocortex in transformation. *Annual Review of Psychology*. https://doi.org/10.1146/annurev-psych-113011-143733

Murakami, S., & Okada, Y. (2006). Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. *The Journal of Physiology*, *575*(3), 925–936. https://doi.org/https://doi.org/10.1113/jphysiol.2006.105379

Nadel, L., & Hardt, O. (2011). Update on memory systems and processes. In *Neuropsychopharmacology*. https://doi.org/10.1038/npp.2010.169

Nakazono, T., Takahashi, S., & Sakurai, Y. (2019). Enhanced Theta and High-Gamma Coupling during Late Stage of Rule Switching Task in Rat Hippocampus. *Neuroscience*. https://doi.org/10.1016/j.neuroscience.2019.05.053

Nee, D. E., Brown, J. W., Askren, M. K., Berman, M. G., Demiralp, E., Krawitz, A., & Jonides, J. (2013). A meta-Analysis of executive components of working memory. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhs007

Neuling, T., Ruhnau, P., Fuscà, M., Demarchi, G., Herrmann, C. S., & Weisz, N. (2015). Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2015.06.026

Newman, E. L., Gillet, S. N., Climer, J. R., & Hasselmo, M. E. (2013). Cholinergic blockade reduces theta-gamma phase amplitude coupling and speed modulation of theta frequency consistent with behavioral effects on encoding. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2586-13.2013

Nicoll, R. A. (2017). A Brief History of Long-Term Potentiation. In *Neuron*. https://doi.org/10.1016/j.neuron.2016.12.015

Nilsson, J., Lebedev, A. V., Rydström, A., & Lövdén, M. (2017). Direct-Current Stimulation Does Little to Improve the Outcome of Working Memory Training in Older Adults. *Psychological Science*. https://doi.org/10.1177/0956797617698139

Nir, Y., Staba, R. J., Andrillon, T., Vyazovskiy, V. V., Cirelli, C., Fried, I., & Tononi, G. (2011). Regional Slow Waves and Spindles in Human Sleep. *Neuron*. https://doi.org/10.1016/j.neuron.2011.02.043

Nishida, M., & Walker, M. P. (2007). Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0000341

Nissim, N. R., O'Shea, A., Indahlastari, A., Telles, R., Richards, L., Porges, E., Cohen, R., & Woods, A. J. (2019). Effects of in-Scanner Bilateral Frontal tDCS

on Functional Connectivity of the Working Memory Network in Older Adults. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2019.00051

Nissim, N. R., O'Shea, A. M., Bryant, V., Porges, E. C., Cohen, R., & Woods, A. J. (2017). Frontal structural neural correlates of working memory performance in older adults. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2016.00328

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology*. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, Michael A., Bikson, M., & Bestmann, S. (2015). On the use of meta-analysis in neuromodulatory non-invasive brain stimulation. In *Brain Stimulation*. https://doi.org/10.1016/j.brs.2015.03.008

Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: multi-voxel pattern analysis of fMRI data. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2006.07.005

Nozari, N., Woodard, K., & Thompson-Schill, S. L. (2014). Consequences of cathodal stimulation for behavior: When does it help and when does it hurt performance? *PLoS ONE*. https://doi.org/10.1371/journal.pone.0084338

Nyhus, E., & Curran, T. (2010). Functional role of gamma and theta oscillations in episodic memory. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2009.12.014

O'Connell, N. E., Cossar, J., Marston, L., Wand, B. M., Bunce, D., Moseley, G. L., & de Souza, L. H. (2012). Rethinking Clinical Trials of Transcranial Direct Current Stimulation: Participant and Assessor Blinding Is Inadequate at Intensities of 2mA. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0047514

O'Keefe, J. (1976). Place units in the hippocampus of the freely moving rat. *Experimental Neurology*. https://doi.org/10.1016/0014-4886(76)90055-8

O'Keefe, J. (1993). Hippocampus, theta, and spatial memory. *Current Opinion in Neurobiology*. https://doi.org/10.1016/0959-4388(93)90163-S

O'Reilly, R. C., & Norman, K. A. (2002). Hippocampal and neocortical contributions to memory: Advances in the complementary learning systems framework. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/S1364-6613(02)02005-3

Ohn, S. H., Park, C. Il, Yoo, W. K., Ko, M. H., Choi, K. P., Kim, G. M., Lee, Y. T., & Kim, Y. H. (2008). Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *NeuroReport*. https://doi.org/10.1097/WNR.0b013e3282f2adfd

Onton, J., Delorme, A., & Makeig, S. (2005). Frontal midline EEG dynamics during working memory. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2005.04.014

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive

electrophysiological data. *Computational Intelligence and Neuroscience*. https://doi.org/10.1155/2011/156869

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*. https://doi.org/10.1523/JNEUROSCI.1948-06.2006

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20131

Oyanedel, C. N., Durán, E., Niethard, N., Inostroza, M., & Born, J. (2020). Temporal associations between sleep slow oscillations, spindles and ripples. *European Journal of Neuroscience*. https://doi.org/10.1111/ejn.14906

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging*. https://doi.org/10.1037/0882-7974.17.2.299

Park, S. H., Seo, J. H., Kim, Y. H., & Ko, M. H. (2014). Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. *NeuroReport*. https://doi.org/10.1097/WNR.0000000000000080

Parvizi, J., & Kastner, S. (2018). Human Intracranial EEG: Promises and Limitations. *Nature Neuroscience*.

Pashler, H. (1988). Familiarity and visual change detection. *Perception & Psychophysics*. https://doi.org/10.3758/BF03210419

Payne, L., & Kounios, J. (2009). Coherent oscillatory networks supporting short-term memory retention. *Brain Research*. https://doi.org/10.1016/j.brainres.2008.09.095

Persson, J., & Söderlund, H. (2015). Hippocampal hemispheric and long-axis differentiation of stimulus content during episodic memory encoding and retrieval: An activation likelihood estimation meta-analysis. *Hippocampus*. https://doi.org/10.1002/hipo.22482

Piantoni, G., Halgren, E., & Cash, S. S. (2017). Spatiotemporal characteristics of sleep spindles depend on cortical location. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.11.010

Pliatsikas, C., Veríssimo, J., Babcock, L., Pullman, M. Y., Glei, D. A., Weinstein, M., Goldman, N., & Ullman, M. T. (2019). Working memory in older adults declines with age, but is modulated by sex and education. *Quarterly Journal of Experimental Psychology*. https://doi.org/10.1177/1747021818791994

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*. https://doi.org/10.1016/j.cub.2012.05.021

Polyn, S. M., Natu, V. S., Cohen, J. D., & Norman, K. A. (2005). Neuroscience:

Category-specific cortical activity precedes retrieval during memory search. *Science*. https://doi.org/10.1126/science.1117645

Postle, B. R., Berger, J. S., & D'Esposito, M. (1999). Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.96.22.12959

Postle, B. R., Ferrarelli, F., Hamidi, M., Feredoes, E., Massimini, M., Peterson, M., Alexander, A., & Tononi, G. (2006). Repetitive transcranial magnetic stimulation dissociates working memory manipulation from retention functions in the prefrontal, but not posterior parietal, cortex. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2006.18.10.1712

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and metaanalysis. In *Alzheimer's and Dementia*. https://doi.org/10.1016/j.jalz.2012.11.007

Purcell, S. M., Manoach, D. S., Demanuele, C., Cade, B. E., Mariani, S., Cox, R., Panagiotaropoulou, G., Saxena, R., Pan, J. Q., Smoller, J. W., Redline, S., & Stickgold, R. (2017). Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. *Nature Communications*. https://doi.org/10.1038/ncomms15930

R Core Team. (2018). A Language and Environment for Statistical Computing. In *R Foundation for Statistical Computing*.

Rabipour, S., Wu, A. D., Davidson, P. S. R., & Iacoboni, M. (2018). Expectations may influence the effects of transcranial direct current stimulation. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2018.09.005

Raghavachari, S., Lisman, J. E., Tully, M., Madsen, J. R., Bromfield, E. B., & Kahana, M. J. (2006). Theta oscillations in human cortex during a working-memory task: Evidence for local generators. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00409.2005

Raghavachari, S., Kahana, M. J., Rizzuto, D. S., Caplan, J. B., Kirschen, M. P., Bourgeois, B., Madsen, J. R., & Lisman, J. E. (2001). Gating of human theta oscillations by a working memory task. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.21-09-03175.2001

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L. C., & Bikson, M. (2013). Cellular effects of acute direct current stimulation: Somatic and synaptic terminal effects. *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2012.247171

Rajji, T. K., Zomorrodi, R., Barr, M. S., Blumberger, D. M., Mulsant, B. H., & Daskalakis, Z. J. (2017). Ordering Information in Working Memory and Modulation of Gamma by Theta Oscillations in Humans. *Cerebral Cortex (New York, N.Y. : 1991)*, *27*(2), 1482–1490. https://doi.org/10.1093/cercor/bhv326

Ranganath, C. (2010). A unified framework for the functional organization of the

medial temporal lobes and the phenomenology of episodic memory. *Hippocampus*. https://doi.org/10.1002/hipo.20852

Rasch, B., Büchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*. https://doi.org/10.1126/science.1138581

Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: Regional and individual differences. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.03.020

Reddy, L., Self, M. W., Zoefel, B., Poncet, M., Possel, J. K., Peters, J. C., Baayen, J. C., Idema, S., VanRullen, R., & Roelfsema, P. R. (2021). Theta-phase dependent neuronal coding during sequence learning in human single neurons. *Nature Communications*. https://doi.org/10.1038/s41467-021-25150-0

Redick, T. S., & Lindsey, D. R. B. (2013). Complex span and n-back measures of working memory: A meta-analysis. *Psychonomic Bulletin and Review*. https://doi.org/10.3758/s13423-013-0453-9

Reinhart, R. M. G., Cosman, J. D., Fukuda, K., & Woodman, G. F. (2017). Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. In *Attention, Perception, and Psychophysics*. https://doi.org/10.3758/s13414-016-1224-2

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

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., Celnik, P. A., & Krakauer, J. W. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0805413106

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.23-08-03295.2003

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. In *Current Directions in Psychological Science*. https://doi.org/10.1111/j.1467-8721.2008.00570.x

Reuter-Lorenz, P. A., & Lustig, C. (2005). Brain aging: Reorganizing discoveries about the aging mind. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2005.03.016

Reuter-Lorenz, P. A., & Sylvester, C. Y. C. (2009). The Cognitive Neuroscience of Working Memory and Aging. In *Cognitive Neuroscience of Aging: Linking cognitive and cerebral aging*. https://doi.org/10.1093/acprof:oso/9780195156744.003.0008

Ridding, M. C., & Ziemann, U. (2010). Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. In *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2010.190314

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*. https://doi.org/10.1016/j.cub.2020.02.065

Riggall, A. C., & Postle, B. R. (2012). The relationship between working memory storage and elevated activity as measured with functional magnetic resonance imaging. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1892-12.2012

Riley, M. R., & Constantinidis, C. (2016). Role of prefrontal persistent activity in working memory. In *Frontiers in Systems Neuroscience*. https://doi.org/10.3389/fnsys.2015.00181

Ritchey, M., Libby, L. A., & Ranganath, C. (2015). Cortico-hippocampal systems involved in memory and cognition: The PMAT framework. In *Progress in Brain Research*. https://doi.org/10.1016/bs.pbr.2015.04.001

Ritchie, S. J., Dickie, D. A., Cox, S. R., Valdes Hernandez, M. del C., Corley, J., Royle, N. A., Pattie, A., Aribisala, B. S., Redmond, P., Muñoz Maniega, S., Taylor, A. M., Sibbett, R., Gow, A. J., Starr, J. M., Bastin, M. E., Wardlaw, J. M., & Deary, I. J. (2015). Brain volumetric changes and cognitive ageing during the eighth decade of life. *Human Brain Mapping*. https://doi.org/10.1002/hbm.22959

Rizzuto, D. S., Madsen, J. R., Bromfield, E. B., Schulze-Bonhage, A., & Kahana, M. J. (2006). Human neocortical oscillations exhibit theta phase differences between encoding and retrieval. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2006.01.009

Roach, G. D., Dawson, D., & Lamond, N. (2006). Can a shorter psychomotor vigilance task be used as a reasonable substitute for the ten-minute psychomotor vigilance task? *Chronobiology International*. https://doi.org/10.1080/07420520601067931

Robinson, A. K., Grootswagers, T., & Carlson, T. A. (2019). The influence of image masking on object representations during rapid serial visual presentation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2019.04.050

Rosanova, M., & Ulrich, D. (2005). Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2149-05.2005

Rouder, J. N., Morey, R. D., Morey, C. C., & Cowan, N. (2011). How to measure working memory capacity in the change detection paradigm. *Psychonomic Bulletin and Review*. https://doi.org/10.3758/s13423-011-0055-3

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*. https://doi.org/10.1523/JNEUROSCI.0421-12.2012

Rugg, M. D., Vilberg, K. L., Mattson, J. T., Yu, S. S., Johnson, J. D., & Suzuki, M. (2012). Item memory, context memory and the hippocampus: FMRI evidence. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2012.06.004

Rutishauser, U., Ross, I. B., Mamelak, A. N., & Schuman, E. M. (2010). Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature*. https://doi.org/10.1038/nature08860

Ruxton, G. D. (2017). Testing for departure from uniformity and estimating mean direction for circular data. *Biology Letters*, *13*(1), 20160756. https://doi.org/10.1098/rsbl.2016.0756

Ruzich, E., Crespo-García, M., Dalal, S. S., & Schneiderman, J. F. (2019). Characterizing hippocampal dynamics with MEG: A systematic review and evidence-based guidelines. In *Human Brain Mapping*. https://doi.org/10.1002/hbm.24445

Salazar, R. F., Dotson, N. M., Bressler, S. L., & Gray, C. M. (2012). Content-specific fronto-parietal synchronization during visual working memory. *Science*. https://doi.org/10.1126/science.1224000

Samani, M. M., Agboada, D., Jamil, A., Kuo, M. F., & Nitsche, M. A. (2019). Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. *Cortex*. https://doi.org/10.1016/j.cortex.2019.04.016

Sander, M., Oxlund, B., Jespersen, A., Krasnik, A., Mortensen, E. L., Westendorp, R. G. J., & Rasmussen, L. J. (2015). The challenges of human population ageing. *Age and Ageing*. https://doi.org/10.1093/ageing/afu189

Sanfratello, L., Caprihan, A., Stephen, J. M., Knoefel, J. E., Adair, J. C., Qualls, C., Lundy, S. L., & Aine, C. J. (2014). Same task, different strategies: How brain networks can be influenced by memory strategy. *Human Brain Mapping*. https://doi.org/10.1002/hbm.22538

Sauseng, P., Klimesch, W., Gruber, W. R., Hanslmayr, S., Freunberger, R., & Doppelmayr, M. (2007). Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion. *Neuroscience*, *146*(4), 1435–1444. https://doi.org/10.1016/j.neuroscience.2007.03.014

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: A possible function of EEG theta oscillations. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/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? In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2008.03.014

Sauseng, P., Klimesch, W., Doppelmayr, M., Hanslmayr, S., Schabus, M., & Gruber, W. R. (2004). Theta coupling in the human electroencephalogram during a working memory task. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2003.10.002

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*. https://doi.org/10.1111/bjop.12340

Schabus, M., Dang-Vu, T. T., Heib, D. P. J., Boly, M., Desseilles, M., Vandewalle, G., Schmidt, C., Albouy, G., Darsaud, A., Gais, S., Degueldre, C., Balteau, E., Phillips, C., Luxen, A., & Maquet, P. (2012). The fate of incoming stimuli during NREM sleep is determined by spindles and the phase of the slow oscillation. *Frontiers in Neurology*. https://doi.org/10.3389/fneur.2012.00040

Scheeringa, R., Petersson, K. M., Oostenveld, R., Norris, D. G., Hagoort, P., & Bastiaansen, M. C. M. (2009). Trial-by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2008.08.041

Schmidt, C., Peigneux, P., Muto, V., Schenkel, M., Knoblauch, V., Münch, M., De Quervain, D. J. F., Wirz-Justice, A., & Cajochen, C. (2006). Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2464-06.2006

Schneider-Garces, N. J., Gordon, B. A., Brumback-Peltz, C. R., Shin, E., Lee, Y., Sutton, B. P., Maclin, E. L., Gratton, G., & Fabiani, M. (2010). Span, CRUNCH, and beyond: Working memory capacity and the aging brain. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2009.21230

Schomburg, E. W., Fernández-Ruiz, A., Mizuseki, K., Berényi, A., Anastassiou, C. A., Koch, C., & Buzsáki, G. (2014). Theta Phase Segregation of Input-Specific Gamma Patterns in Entorhinal-Hippocampal Networks. *Neuron*. https://doi.org/10.1016/j.neuron.2014.08.051

Schönauer, M., Alizadeh, S., Jamalabadi, H., Abraham, A., Pawlizki, A., & Gais, S. (2017). Decoding material-specific memory reprocessing during sleep in humans. *Nature Communications*. https://doi.org/10.1038/ncomms15404

Schonhaut, D. R., Ramayya, A. G., Solomon, E. A., Herweg, N. A., Fried, I., & Kahana, M. J. (2020). Single neurons throughout human memory regions phase-lock to hippocampal theta. *BioRxiv*. https://doi.org/10.1101/2020.06.30.180174

Schreiner, T., Doeller, C. F., Jensen, O., Rasch, B., & Staudigl, T. (2018). Theta Phase-Coordinated Memory Reactivation Reoccurs in a Slow-Oscillatory Rhythm during NREM Sleep. *Cell Reports*. https://doi.org/10.1016/j.celrep.2018.09.037

Schreiner, T., & Rasch, B. (2017). The beneficial role of memory reactivation for language learning during sleep: A review. In *Brain and Language*. https://doi.org/10.1016/j.bandl.2016.02.005

Scimeca, J. M., Kiyonaga, A., & D'Esposito, M. (2018). Reaffirming the Sensory Recruitment Account of Working Memory. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2017.12.007

Seager, M. A., Johnson, L. D., Chabot, E. S., Asaka, Y., & Berry, S. D. (2002). Oscillatory brain states and learning: Impact of hippocampal theta-contingent training. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.032662099

Sederberg, P. B., Schulze-Bonhage, A., Madsen, J. R., Bromfield, E. B., McCarthy, D. C., Brandt, A., Tully, M. S., & Kahana, M. J. (2007). Hippocampal and neocortical gamma oscillations predict memory formation in humans. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhl030

Sherry, D. F., & Schacter, D. L. (1987). The Evolution of Multiple Memory Systems. *Psychological Review*. https://doi.org/10.1037/0033-295X.94.4.439

Shin, H., Zou, Q., & Ma, W. J. (2017). The effects of delay duration on visual working memory for orientation. *Journal of Vision*. https://doi.org/10.1167/17.14.10

Shinde, A. B., Lerud, K. D., Munsch, F., Alsop, D. C., & Schlaug, G. (2021). Effects of tDCS dose and electrode montage on regional cerebral blood flow and motor behavior. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2021.118144

Siapas, A. G., Lubenov, E. V., & Wilson, M. A. (2005). Prefrontal phase locking to hippocampal theta oscillations. *Neuron*. https://doi.org/10.1016/j.neuron.2005.02.028

Siclari, F., & Tononi, G. (2017). Local aspects of sleep and wakefulness. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2017.05.008

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 of the United States of America*. https://doi.org/10.1073/pnas.0908193106

Siegle, J. H., & Wilson, M. A. (2014). Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. *ELife*. https://doi.org/10.7554/eLife.03061.001

Singh-Manoux, A., Kivimaki, M., Glymour, M. M., Elbaz, A., Berr, C., Ebmeier, K. P., Ferrie, J. E., & Dugravot, A. (2012). Timing of onset of cognitive decline: Results from Whitehall II prospective cohort study. *BMJ (Online)*. https://doi.org/10.1136/bmj.d7622

Snowball, A., Tachtsidis, I., Popescu, T., Thompson, J., Delazer, M., Zamarian, L., Zhu, T., & Cohen Kadosh, R. (2013). Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. *Current Biology*. https://doi.org/10.1016/j.cub.2013.04.045

Solomon, E. A., Stein, J. M., Das, S., Gorniak, R., Sperling, M. R., Worrell, G., Inman, C. S., Tan, R. J., Jobst, B. C., Rizzuto, D. S., & Kahana, M. J. (2019). Dynamic Theta Networks in the Human Medial Temporal Lobe Support Episodic Memory. *Current Biology*. https://doi.org/10.1016/j.cub.2019.02.020

Soutschek, A., Kang, P., Ruff, C. C., Hare, T. A., & Tobler, P. N. (2018). Brain Stimulation Over the Frontopolar Cortex Enhances Motivation to Exert Effort for

Reward. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2017.11.007

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2004.06.005

Squire, L. R. (2009). The Legacy of Patient H.M. for Neuroscience. In *Neuron*. https://doi.org/10.1016/j.neuron.2008.12.023

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. In *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev.neuro.27.070203.144130

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: A new perspective. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn2154

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. In *Science*. https://doi.org/10.1126/science.1896849

Sreenivasan, K. K., Curtis, C. E., & D'Esposito, M. (2014). Revisiting the role of persistent neural activity during working memory. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.12.001

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. In *Neuroscientist*. https://doi.org/10.1177/1073858410386614

Staresina, B. P., Bergmann, T. O., Bonnefond, M., Van Der Meij, R., Jensen, O., Deuker, L., Elger, C. E., Axmacher, N., & Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature Neuroscience*. https://doi.org/10.1038/nn.4119

Staresina, B. P., Michelmann, S., Bonnefond, M., Jensen, O., Axmacher, N., & Fell, J. (2016). Hippocampal pattern completion is linked to gamma power increases and alpha power decreases during recollection. *ELife*. https://doi.org/10.7554/elife.17397

Staudigl, T., & Hanslmayr, S. (2013). Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. *Current Biology*. https://doi.org/10.1016/j.cub.2013.04.074

Stokes, M. G. (2015). "Activity-silent" working memory in prefrontal cortex: A dynamic coding framework. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2015.05.004

Stouffer, S. A., Suchman, E. A., DeVinney, L. C., Star, S. A., & Williams, R. M. J. (1949). Studies in Social Psychology in World War II: The American Soldier. Vol. 1, Adjustment During Army Life. In *Princeton: Princeton University Press*.

Strange, B. A., Witter, M. P., Lein, E. S., & Moser, E. I. (2014). Functional organization of the hippocampal longitudinal axis. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3785

Summers, J. J., Kang, N., & Cauraugh, J. H. (2016). Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta- analysis. In *Ageing Research Reviews*. https://doi.org/10.1016/j.arr.2015.11.004

Tamaki, M., Matsuoka, T., Nittono, H., & Hori, T. (2008). Fast sleep spindle (13-15 Hz) activity correlates with sleep-dependent improvement in visuomotor performance. *Sleep*. https://doi.org/10.1093/sleep/31.2.204

Tamura, M., Spellman, T. J., Rosen, A. M., Gogos, J. A., & Gordon, J. A. (2017). Hippocampal-prefrontal theta-gamma coupling during performance of a spatial working memory task. *Nature Communications*. https://doi.org/10.1038/s41467-017-02108-9

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

ter Wal, M., Linde-Domingo, J., Lifanov, J., Roux, F., Kolibius, L. D., Gollwitzer, S., Lang, J., Hamer, H., Rollings, D., Sawlani, V., Chelvarajah, R., Staresina, B., Hanslmayr, S., & Wimber, M. (2021). Theta rhythmicity governs human behavior and hippocampal signals during memory-dependent tasks. *Nature Communications*, *12*(1), 7048. https://doi.org/10.1038/s41467-021-27323-3

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial direct current stimulation (tDCS): A Beginner's guide for design and implementation. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2017.00641

Thakral, P. P., Madore, K. P., Kalinowski, S. E., & Schacter, D. L. (2020). Modulation of hippocampal brain networks produces changes in episodic simulation and divergent thinking. *Proceedings of the National Academy of Sciences*, *117*(23), 12729 LP – 12740. https://doi.org/10.1073/pnas.2003535117

Thielscher, A., Antunes, A., & Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*. https://doi.org/10.1109/EMBC.2015.7318340

Tort, A. B. L., Brankačk, J., & Draguhn, A. (2018). Respiration-Entrained Brain Rhythms Are Global but Often Overlooked. In *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2018.01.007

Tort, A. B. L., Komorowski, R. W., Manns, J. R., Kopell, N. J., & Eichenbaum, H. (2009). Theta-gamma coupling increases during the learning of item-context associations. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0911331106

Treder, M. S. (2020). MVPA-Light: A Classification and Regression Toolbox for Multi-Dimensional Data. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2020.00289

Truong, D. Q., Guleyupoglu, B., Datta, A., Minhas, P., Magerowski, G., Alonso-

Alonso M, M., Parra, L. C., & Bikson, M. (2014). Inter-Individual Variation during Transcranial Direct Current Simulation and Normaliziation of Dose Using MRI-Derived Computational Models. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2014.01.038

Tseng, M. T., Chiang, M. C., Yazhuo, K., Chao, C. C., Tseng, W. Y. I., & Hsieh, S. T. (2013). Effect of aging on the cerebral processing of thermal pain in the human brain. *Pain*. https://doi.org/10.1016/j.pain.2013.06.041

Tseng, P., Hsu, T. Y., Chang, C. F., Tzeng, O. J. L., Hung, D. L., Muggleton, N. G., Walsh, V., Liang, W. K., Cheng, S. K., & Juan, C. H. (2012). Unleashing potential: Transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.0362-12.2012

Tsujimoto, T., Shimazu, H., & Isomura, Y. (2006). Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00730.2005

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology*. https://doi.org/10.1146/annurev.psych.53.100901.135114

Vallesi, A., McIntosh, A. R., & Stuss, D. T. (2011). Overrecruitment in the aging brain as a function of task demands: Evidence for a compensatory view. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2010.21490

VanRullen, R. (2016). How to evaluate phase differences between trial groups in ongoing electrophysiological signals. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2016.00426

Varela, F., Lachaux, J.-P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: Phase synchronization and large-scale integration. *Nature Reviews Neuroscience*, *2*(4), 229–239. https://doi.org/10.1038/35067550

Vermeij, A., van Beek, A. H. E. A., Olde Rikkert, M. G. M., Claassen, J. A. H. R., & Kessels, R. P. C. (2012). Effects of Aging on Cerebral Oxygenation during Working-Memory Performance: A Functional Near-Infrared Spectroscopy Study. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0046210

Vermeij, A., van Beek, A. H. E. A., Reijs, B. L. R., Claassen, J. A. H. R., & Kessels, R. P. C. (2014). An exploratory st udy of the effects of spatial working-memory load on prefrontal activation in low- and high-performing elderly. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2014.00303

Vertes, R. P. (2005). Hippocampal theta rhythm: A tag for short-term memory. In *Hippocampus*. https://doi.org/10.1002/hipo.20118

Villamar, M. F., Volz, M. S., Bikson, M., Datta, A., Dasilva, A. F., & Fregni, F. (2013). Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation (HD-tDCS). *Journal of Visualized Experiments : JoVE*. https://doi.org/10.3791/50309

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*. https://doi.org/10.7554/eLife.22001

Vivekananda, U., Bush, D., Bisby, J. A., Baxendale, S., Rodionov, R., Diehl, B., Chowdhury, F. A., McEvoy, A. W., Miserocchi, A., Walker, M. C., & Burgess, N. (2021). Theta power and theta-gamma coupling support long-term spatial memory retrieval. *Hippocampus*. https://doi.org/10.1002/hipo.23284

Vogel, E. K., & Machizawa, M. G. (2004). Neural activity predicts individual differences in visual working memory capacity. *Nature*. https://doi.org/10.1038/nature02447

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*. https://doi.org/10.1016/S0167-8760(00)00172-0

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., Kozák, G., Kincses, Z. T., Iványi, B., Buzsáki, G., & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature Communications*. https://doi.org/10.1038/s41467-018-02928-3

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. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2015.00257

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

Wais, P. E. (2008). fMRI signals associated with memory strength in the medial temporal lobes: A meta-analysis. In *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2008.08.025

Walker, M. P., & Stickgold, R. (2006). Sleep, memory, and plasticity. In *Annual Review of Psychology*. https://doi.org/10.1146/annurev.psych.56.091103.070307

Wang, D. X., Schmitt, K., Seger, S., Davila, C. E., & Lega, B. C. (2021). Cross-regional phase amplitude coupling supports the encoding of episodic memories. *Hippocampus*. https://doi.org/10.1002/hipo.23309

Wang, Mengni, Foster, D. J., & Pfeiffer, B. E. (2020). Alternating sequences of future and past behavior encoded within hippocampal theta oscillations. *Science*. https://doi.org/10.1126/science.abb4151

Wang, Min, Gamo, N. J., Yang, Y., Jin, L. E., Wang, X. J., Laubach, M., Mazer, J. A., Lee, D., & Arnsten, A. F. T. (2011). Neuronal basis of age-related working memory decline. In *Nature*. https://doi.org/10.1038/nature10243

Warden, M. R., & Miller, E. K. (2010). Task-dependent changes in short-term

memory in the prefrontal cortex. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1569-10.2010

Watrous, A. J., Tandon, N., Conner, C. R., Pieters, T., & Ekstrom, A. D. (2013). Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. *Nature Neuroscience*. https://doi.org/10.1038/nn.3315

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*. https://doi.org/10.1037//0022-3514.54.6.1063

Wen, H., & Liu, Z. (2016). Separating Fractal and Oscillatory Components in the Power Spectrum of Neurophysiological Signal. *Brain Topography*. https://doi.org/10.1007/s10548-015-0448-0

White, T. P., Jansen, M., Doege, K., Mullinger, K. J., Park, S. B., Liddle, E. B., Gowland, P. A., Francis, S. T., Bowtell, R., & Liddle, P. F. (2013). Theta power during encoding predicts subsequent-memory performance and default mode network deactivation. *Human Brain Mapping*. https://doi.org/10.1002/hbm.22114

Wiethoff, S., Hamada, M., & Rothwell, J. C. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimulation*. https://doi.org/10.1016/j.brs.2014.02.003

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*. https://doi.org/10.1126/science.8036517

Winson, J. (1972). Interspecies differences in the occurrence of theta. *Behavioral Biology*. https://doi.org/10.1016/S0091-6773(72)80210-4

Winson, J. (1978). Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. *Science*. https://doi.org/10.1126/science.663646

Wixted, J. T., & Mickes, L. (2010). A Continuous Dual-Process Model of Remember/Know Judgments. *Psychological Review*. https://doi.org/10.1037/a0020874

Wixted, J. T., & Squire, L. R. (2010). The role of the human hippocampus in familiarity-based and recollection-based recognition memory. In *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2010.04.020

Wolff, M. J., Ding, J., Myers, N. E., & Stokes, M. G. (2015). Revealing hidden states in visual working memory using electroencephalography. *Frontiers in Systems Neuroscience*. https://doi.org/10.3389/fnsys.2015.00123

Wolff, M. J., Jochim, J., Akyürek, E. G., & Stokes, M. G. (2017). Dynamic hidden states underlying working-memory-guided behavior. *Nature Neuroscience*. https://doi.org/10.1038/nn.4546

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

Wolpert, N., & Tallon-Baudry, C. (2021). Coupling between the phase of a neural oscillation or bodily rhythm with behavior: Evaluation of different statistical procedures. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2021.118050

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., Cohen, L. G., Fregni, F., Herrmann, C. S., Kappenman, E. S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P. C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., & Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. In *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2015.11.012

Xiao, J., Hays, J., Ehinger, K. A., Oliva, A., & Torralba, A. (2010). SUN database: Large-scale scene recognition from abbey to zoo. *Proceedings of the IEEE Computer Society Conference on Computer Vision and Pattern Recognition*. https://doi.org/10.1109/CVPR.2010.5539970

Xu, M., Jia, Y., Qi, H., Hu, Y., He, F., Zhao, X., Zhou, P., Zhang, L., Wan, B., Gao, W., & Ming, D. (2016). Use of a steady-state baseline to address evoked vs. oscillation models of visual evoked potential origin. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.03.073

Yamamoto, J., Suh, J., Takeuchi, D., & Tonegawa, S. (2014). Successful execution of working memory linked to synchronized high-frequency gamma oscillations. *Cell*. https://doi.org/10.1016/j.cell.2014.04.009

Yoo, H. Bin, Umbach, G., & Lega, B. (2021). Neurons in the human medial temporal lobe track multiple temporal contexts during episodic memory processing. *NeuroImage*, *245*, 118689. https://doi.org/https://doi.org/10.1016/j.neuroimage.2021.118689

Young, C. K., & McNaughton, N. (2009). Coupling of theta oscillations between anterior and posterior midline cortex and with the hippocampus in freely behaving rats. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhn055

Zaehle, T., Sandmann, P., Thorne, J. D., Jäncke, L., & Herrmann, C. S. (2011). Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: Combined behavioural and electrophysiological evidence. *BMC Neuroscience*. https://doi.org/10.1186/1471-2202-12-2

Zakrzewska, M. Z., & Brzezicka, A. (2014). Working memory capacity as a moderator of load-related frontal midline theta variability in Sternberg task. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2014.00399

Zaksas, D., & Pasternak, T. (2006). Directional signals in the prefrontal cortex and in area MT during a working memory for visual motion task. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3420-06.2006

Zanto, T. P., Rubens, M. T., Thangavel, A., & Gazzaley, A. (2011). Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. *Nature Neuroscience*. https://doi.org/10.1038/nn.2773

Zhang, L., Lee, J., Rozell, C., & Singer, A. C. (2019). Sub-second dynamics of theta-gamma coupling in hippocampal CA1. *ELife*. https://doi.org/10.7554/eLife.44320

Zhang, W., & Luck, S. J. (2009). Sudden Death and Gradual Decay in Visual Working Memory: Research Report. *Psychological Science*. https://doi.org/10.1111/j.1467-9280.2009.02322.x

Zhang, X., Zhong, W., Brankačk, J., Weyer, S. W., Müller, U. C., Tort, A. B. L., & Draguhn, A. (2016). Impaired theta-gamma coupling in APP-deficient mice. *Scientific Reports*. https://doi.org/10.1038/srep21948

Zheng, L., Yu, M., Lin, R., Wang, Y., Zhuo, Z., Cheng, N., Wang, M., Tang, Y., Wang, L., & Hou, S. T. (2020). Rhythmic light flicker rescues hippocampal low gamma and protects ischemic neurons by enhancing presynaptic plasticity. *Nature Communications*. https://doi.org/10.1038/s41467-020-16826-0

Zimerman, M., Nitsch, M., Giraux, P., Gerloff, C., Cohen, L. G., & Hummel, F. C. (2013). Neuroenhancement of the aging brain: Restoring skill acquisition in old subjects. *Annals of Neurology*. https://doi.org/10.1002/ana.23761

Zucker, R. S., & Regehr, W. G. (2002). Short-term synaptic plasticity. In *Annual Review of Physiology*. https://doi.org/10.1146/annurev.physiol.64.092501.114547

Zuure, M. B., Hinkley, L. B. N., Tiesinga, P. H. E., Nagarajan, S. S., & Cohen, M. X. (2020). Multiple midfrontal thetas revealed by source separation of simultaneous MEG and EEG. *BioRxiv*. https://doi.org/10.1101/2020.03.11.987040

Appendices:

Appendix 1: Supplementary Information for Chapter 2

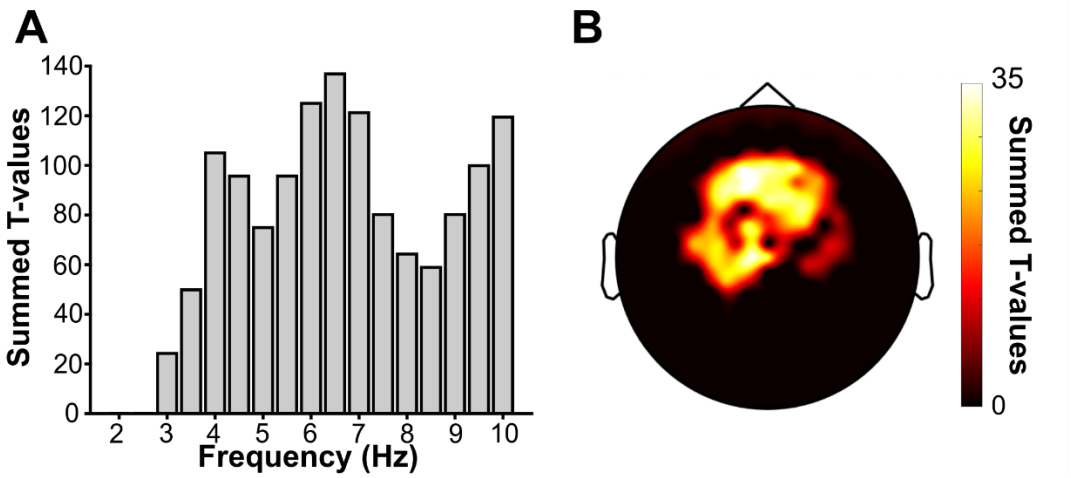

Figure A1.1. WM-induced fronto-medial theta (FMT) power with an alternative baseline comparison. Cluster-corrected comparison of oscillatory power in the delay period of the 1-back task relative to an inter-block baseline period, revealing a significant increase in theta power (4-8 Hz; **A**, summed across significant channels) at fronto-medial channels (**B**, summed across significant frequencies from 4-8 Hz).

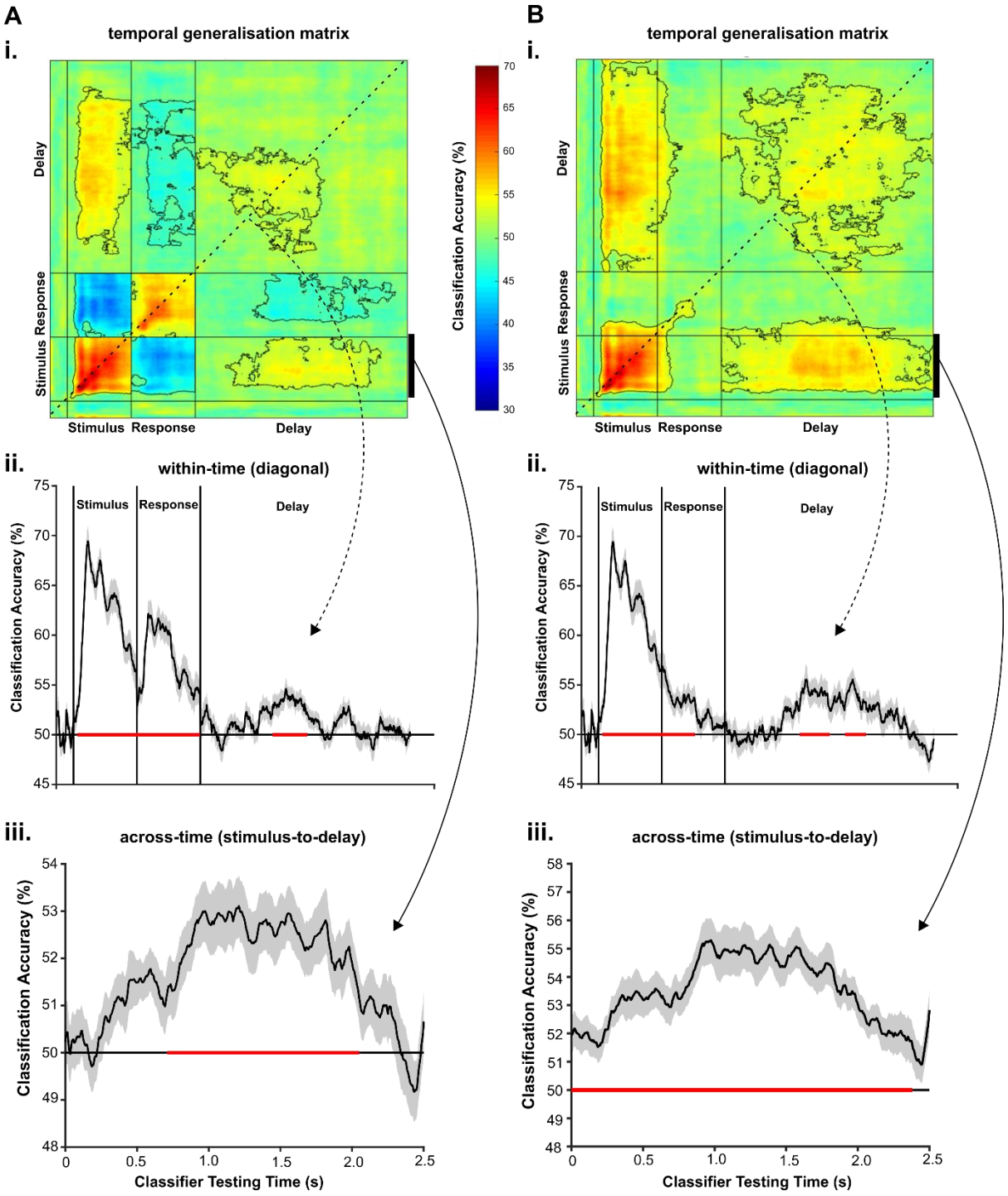

Figure A1.2. Classification across the full period of the 1-back task. A.i. Classifiers trained and tested on every time point of each period of 1-back trials revealed generalisation between the stimulus and delay periods. Black outlines indicate cluster-corrected significance ($p < 0.05$). **A.ii.** Training and testing on the same time periods reveals significant decoding above chance in the stimulus, response, and delay periods. Note that these data reflect the diagonal of A.i. **A.iii.** Classifier accuracy was averaged across the training dimension during the period when the stimulus was on the screen (0-750 ms), revealing significant generalisation (as shown by above-chance accuracy) during the delay period. **B.** same as A., but conducting baseline correction using only the pre-stimulus period.

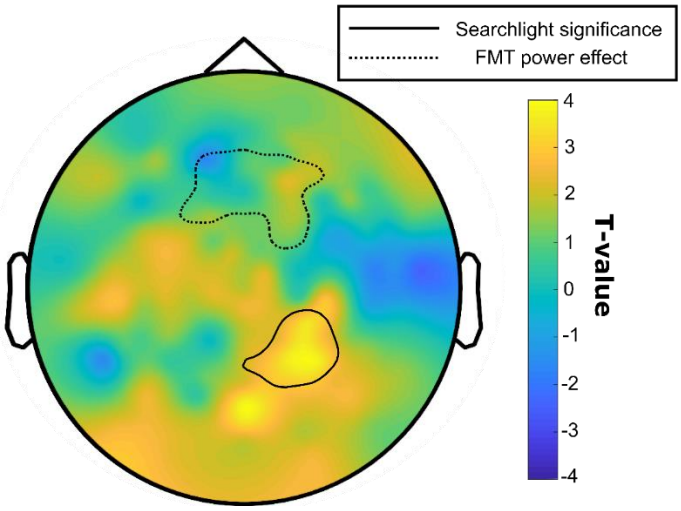

Figure A1.3. Un-thresholded searchlight decoding topography. Topography of testing searchlight decoding accuracy against chance (cluster-corrected t-test); as in Figure 3B but plotting all channels (rather than only the significant cluster). Searchlight decoding was performed by using taking each channel and its immediate neighbours and decoding during the previously defined temporal window of interest (860-1275 ms). The value for each channel indicates the t-value (comparing the decoding performance relative to chance) when this channel was used as the centre of the decoding searchlight. The solid outline indicates cluster-corrected significance. To contrast, the dotted black line indicates channels showing the WM-induced FMT power difference (as in Figure 2B).

Table A1.1. Decoding across the full delay period. Table displaying t-values, p values, and effect sizes averaging classifier accuracies (columns 2-4) and the time course of cluster-corrected periods of above-chance accuracy (column 5) across the full delay period (t-tests against chance). Asterisk indicates statistical significance ($p < 0.05$).

Comparison	t-value	p-value	Cohen's d	Cluster-corrected time (ms)
Stimulus-to-delay generalisation	4.40	<0.001*	0.83	710-2050
Decoding with channels showing coherence with FMT activity	2.46	0.02*	0.46	700-970

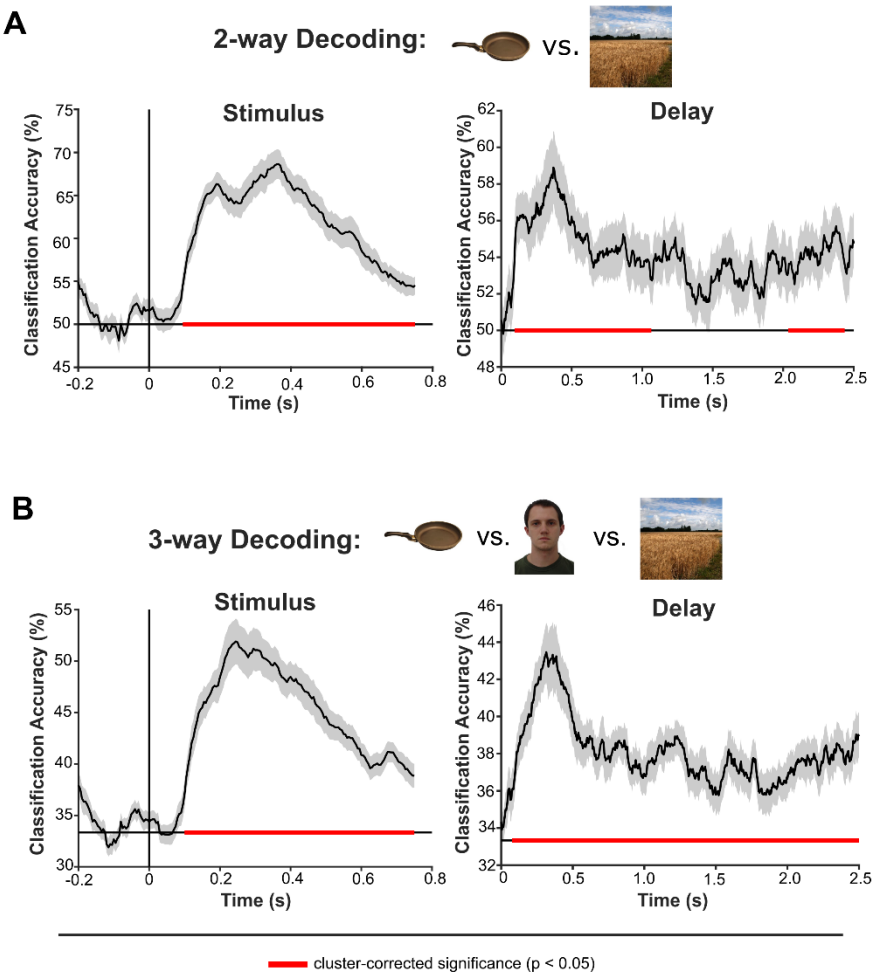

Figure A1.4. Decoding category of maintained content in the DMS task. In order to test generalisability of 1-back maintenance decoding of WM representations to a similar task, we trained and tested classifiers on the stimulus and delay periods of the DMS task (main text Figure 1). **A.** Binary decoding accuracy (classifying between object and scene trials) was significantly above chance during the stimulus and delay period intervals, as well as when averaging accuracy over the full time in each period [stimulus, $t_{(27)}$ = 11.46, $p < 0.001$, Cohen's d = 2.17; delay, $t_{(27)}$ = 5.07, $p < 0.001$, Cohen's d = 0.96]. **B.** Decoding between the three categories present in the DMS task (object/scene/face) was also above-chance during the stimulus and delay periods both when examining accuracy across-time and when averaging over the time dimension [$t_{(27)}$ = 10.87, $p < 0.001$, Cohen's d = 2.05; delay, $t_{(27)}$ = 6.97, $p < 0.001$, Cohen's d = 1.32].

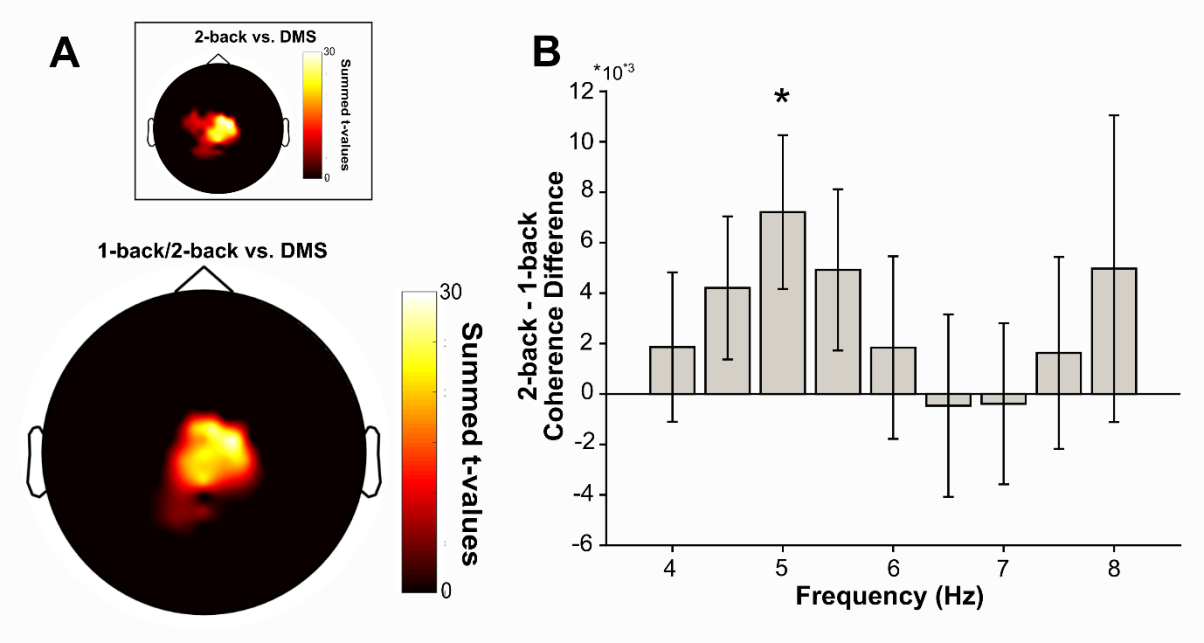

Figure A1.5. Theta coherence with increasing WM load. A. Cluster-corrected comparison revealed an extended cluster showing increased coherence during the delay period of both the 2-back and 1-back tasks relative to the DMS task. T-values were summed across significant frequencies for each comparison and then averaged over the 1-back and 2-back tasks. **Inset.** Cluster showing significantly increased coherence in the delay period of the 2-back task relative to the DMS task. **B.** Averaging across the full delay period and significant channels, subtracting coherence values in the 1-back task from the 2-back task revealed a shift to the lower end of the theta band. This was evidenced by coherence at 5 Hz being significantly greater in the 2-back task relative to the 1-back task. Error bars indicate the standard error of the mean and the asterisk indicates statistical significance at alpha = 0.05.

Appendix 2: Supplementary Information for Chapter 4

Table A2.1. Hippocampal electrode contacts by participant. Electrode contacts for analysis were first defined as hippocampal based on visual inspection of a post-operative anatomical MRI scan and the variance in the signal. Contacts were further pruned by visual inspection of signal quality and removed if excessive artifactual/epileptic activity was observed. Finally, contacts were reduced to those showing the most robust gamma power increase (either showing a significant increase or showing the closest to significance) following stimulus onset compared to pre-stimulus.

Participant #	Hippocampal contacts identified	Removed following visual inspection	Removed following power criterion selection	Final electrode count
1	10	2	4	4
2	14	2	10	2
3	6	0	1	5
4	10	5	2	3
5	0	0	0	0
6	0	0	0	0
7	11	1	6	4
8	2	0	0	2
9	2	0	1	1
10	3	1	0	2
11	2	0	0	1

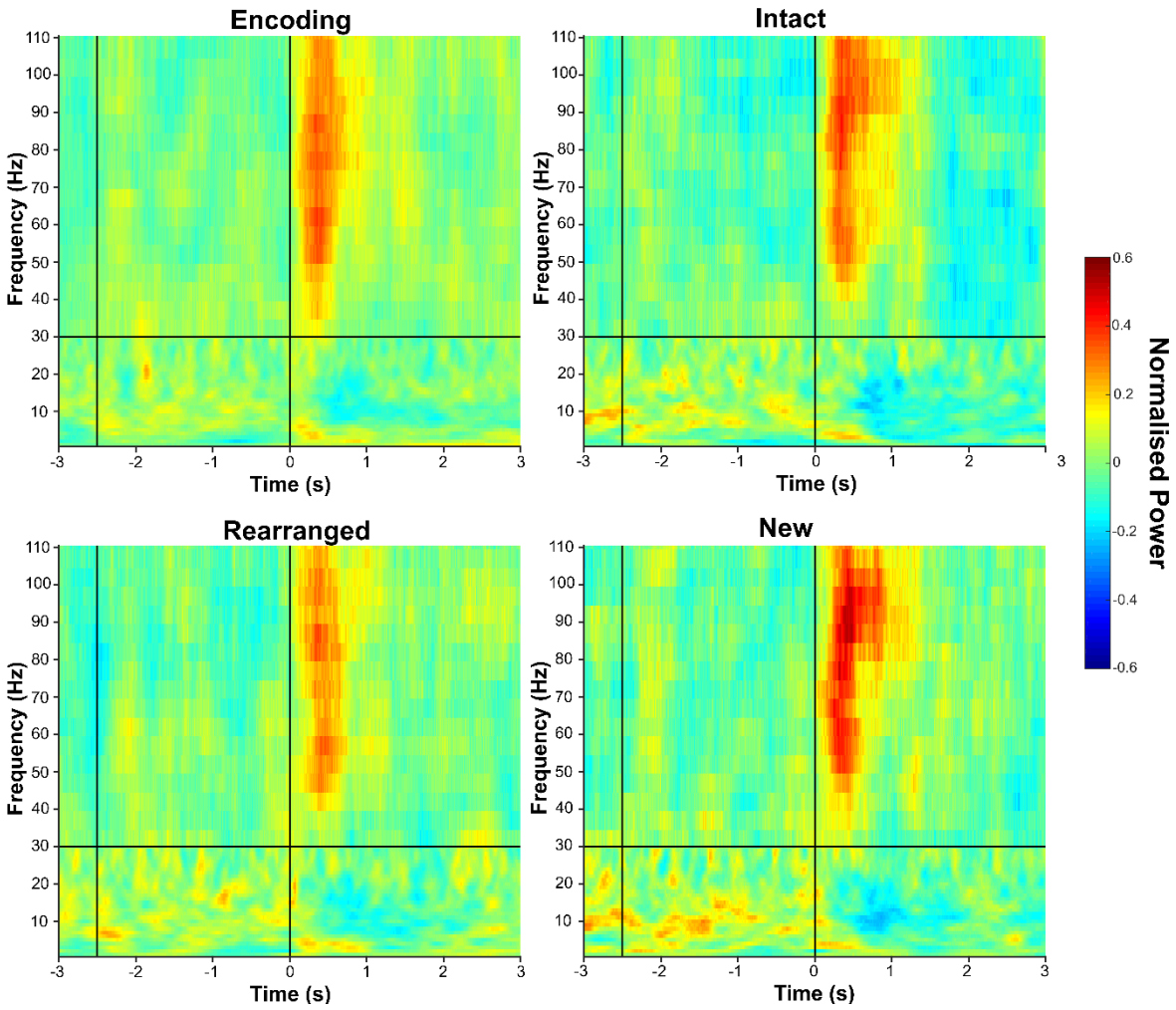

Figure A2.1. Stimulus-locked power by memory condition. All four memory conditions showed clear increases in the gamma range and decreases in the alpha/beta range in response to stimulus onset. Solid vertical lines indicate cue onset (at -2.5 seconds) and stimulus onset (at 0 seconds). The solid horizontal line at 30 Hz indicates where the frequency at which smoothing parameters were adjusted (from a Hanning taper to multiple Slepian tapers).

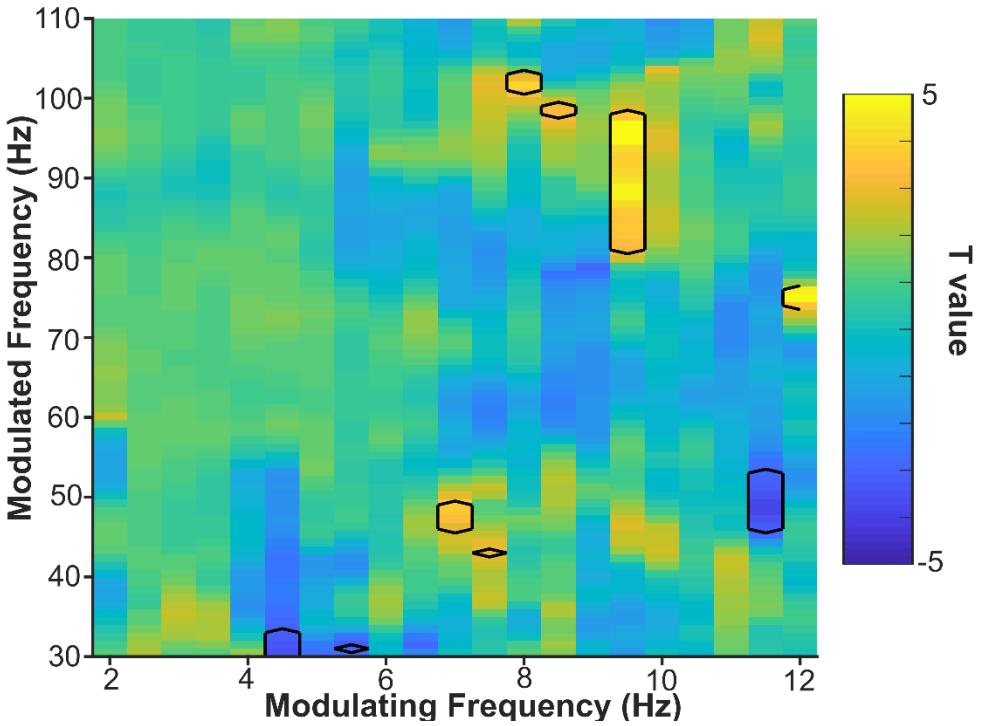

Figure A2.2. Uncorrected t values comparing MI values between encoding and retrieval. Subtracting retrieval PAC values from those for encoding for each participant revealed that phase-amplitude modulation was greater in encoding than retrieval trials, specifically for the phase of modulating activity at 8-10 Hz and at high frequency amplitude activity at 80-105 Hz. Outlines indicate uncorrected statistical significance as determined by one-sample t-test. Note that no clusters survived correction for multiple comparisons.

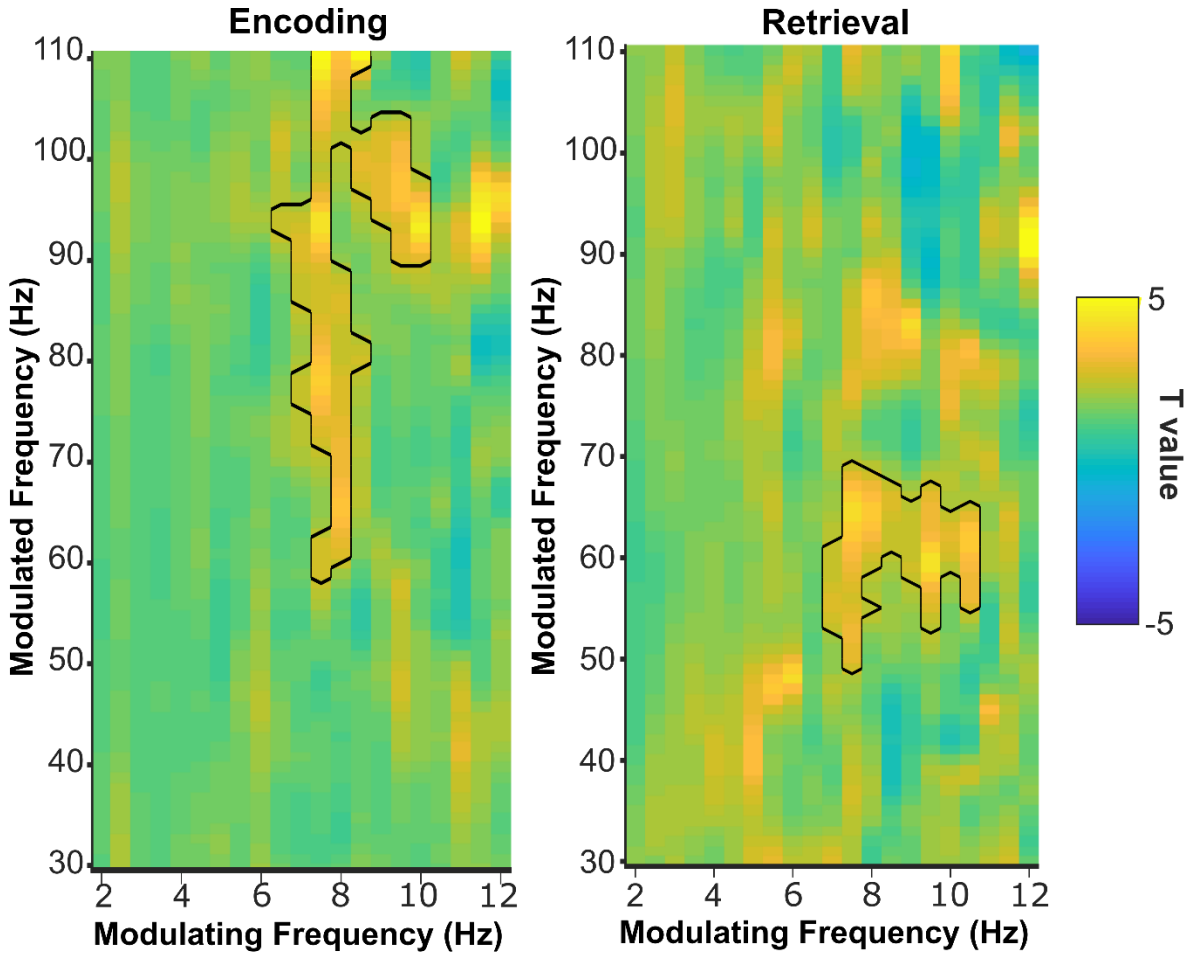

Figure A2.3. Calculating PAC via the Canolty method. Calculating theta-gamma PAC via the Canolty method (Canolty et al., 2006) corroborated the frequency difference between phase-coupled gamma oscillations. Specifically, the amplitude of activity in a higher gamma range (especially ~85-100 Hz) was phase-modulated by activity in the theta range (5-8 Hz) following the encoding cue. Although retrieval trials showed a similar effect, the theta-gamma effect was present at a lower gamma frequency (~60 Hz).

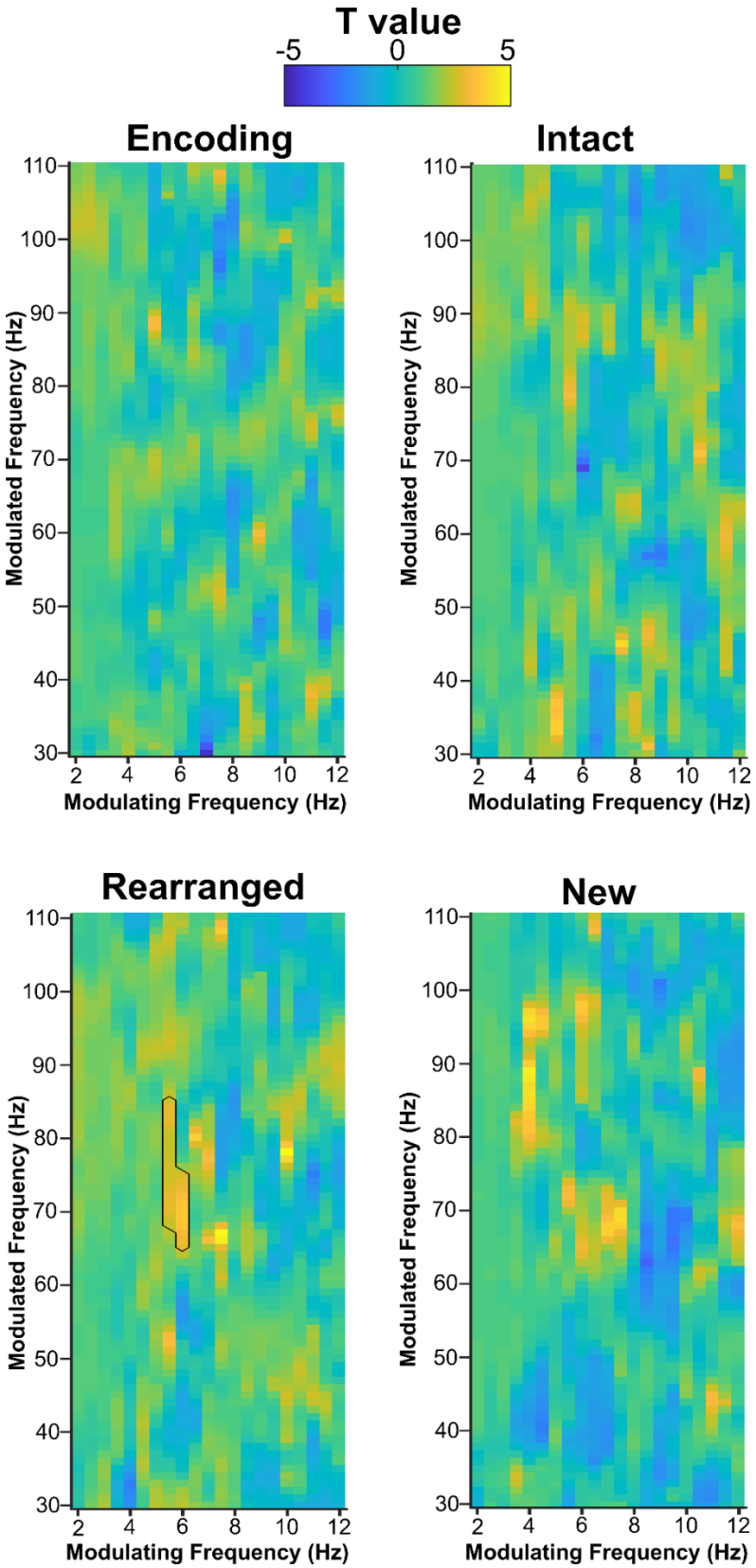

Figure A2.4. Theta-Gamma PAC following stimulus onset comparing all conditions. Examining MI values in the time window after stimulus onset against those generated under shuffled trials, no significant clusters emerged in except for a small cluster in rearranged trials.

Appendix 3: Planned Sleep Stimulation Experiment

A3.1 Preface

Although data for this experiment were ultimately not collected due to disruption to participant testing caused by the Covid-19 pandemic, the method section is reported in the past tense as if the data had been collected.

A3.2 Abstract

Rhythmic sleep spindles occurring during NREM sleep are implicated in sleep-dependent memory consolidation. Sleep spindles, in coordination with other rhythmic components of sleep, may facilitate the reactivation of previously encoded stimuli. It is unclear the extent to which spindles are a regionally restricted or brain-wide phenomenon and whether localised spindle activity provides the temporal reference frame for local reactivation of previously activated cortical circuits.

In the present study, the modality of material was manipulated to promote hemisphere-selective processing in an associative memory task. In a within-subjects counter-balanced design, high-definition transcranial direct current stimulation (HD-tDCS) was applied to either the left or the right hemisphere or to neither (sham condition).

It was expected that stimulation should modulate measures of sleep spindle activity in a hemispheric-specific fashion. Additionally, material more likely to be processed in the stimulated hemisphere should show greater sleep-related consolidation. Spindle density and amplitude were measured and related to retrieval performance.

A3.3 Introduction

A3.3.1 Sleep-dependent Memory Consolidation

Years of research have revealed a beneficial effect of sleep on the consolidation of memory, during which labile memories are transformed into longer-lasting representations (Diekelmann & Born, 2010; Jenkins & Dallenbach, 1924; McGaugh, 2000; Walker & Stickgold, 2006). Sleep itself can be subdivided into different sleep stages (NREM-1, NREM-2, REM, and slow wave sleep). These stages are partially characterised by the presence or absence of synchronised rhythmic activity at a number of distinct frequency bands (Marshall et al., 2020). Slow wave sleep in particular shows pronounced rhythmic activity at several canonical frequency bands: slow oscillations (0.5-1 Hz), sleep spindles (10-15 Hz), ripples (>100 Hz). Notably these appear to be tightly coordinated, with ripples preferentially occurring during spindle troughs and spindles occurring during the slow oscillation up-state (Latchoumane et al., 2017; Maingret et al., 2016; Oyanedel et al., 2020; Staresina et al., 2015).

A3.3.2 Sleep Spindles and Memory

Sleep spindles in particular are a key marker of successful memory consolidation. Empirically, the density of spindle occurrences has been shown to increase following periods of learning both declarative (Clemens et al., 2005; Clemens et al., 2006; Gais et al., 2002; Schmidt et al., 2006) and procedural (Barakat et al., 2011) information, and to correlate with subsequent memory recall (Mölle et al., 2009; Nishida & Walker, 2007; Tamaki et al., 2008). Although it is important to distinguish between trait-like spindle characteristics (Cox et al., 2017; Finelli et al., 2001; Purcell et al., 2017) which correlate with IQ-related measures (Bódizs et al., 2005; Fogel & Smith, 2011; Lustenberger et al., 2012; Schabus et al., 2012), the occurrence of spindles linked to specific instances of memory consolidation. Spindle activity

increases following learning relative to the same individual's non-learning baseline (Fogel & Smith, 2006), pharmacologically increasing spindle density promotes better consolidation of previously encoded verbal material (Mednick et al., 2013), and spindles selectively increase following a more difficult associative task (Schmidt et al., 2006). The development of targeted memory reactivation (Astori et al., 2013; Rasch et al., 2007), whereby previous learning-associated cues are presented during sleep, has further corroborated the role of sleep spindles in memory re-processing during sleep. Specifically, cue onset during sleep which leads to improved consolidation also elicits spindle activity (Laventure et al., 2016).

A3.3.3 The Function of Sleep Spindles

Given their relationship to subsequent memory retention, spindles may play a key mechanistic role in memory consolidation. Notably, spindle activity may be crucial to facilitating the necessary synaptic plasticity. Stimulation at a spindle frequency facilitates the induction of long-term potentiation (Rosanova & Ulrich, 2005). Specific neuronal networks that were active during encoding become reactivated during sleep. Neurons firing in synchrony during learning to fire in the same manner during a subsequent sleep period (Foster, 2017; Wilson & McNaughton, 1994). The observed rhythms of sleep, including spindles, may serve to provide temporal frameworks in which such activity can be highly coordinated (Buzsáki & Draguhn, 2004).

In support of their co-occurrence, Cairney et al. (2018) demonstrated that cueing via TMR prompted both an increase in fast spindle activity and an increase in the ability to decode the category of previously learned content. Compellingly, Schönauer et al. (2017) showed that such reactivation occurs spontaneously in the absence of cues. Furthermore, particularly informative to the decoding was activity in the spindle

range. As this decoding was based on the topography of power, this finding implicates local content-related spindles.

A3.3.4 Spindle Locality

If spindles gate local reactivation in this manner, one would anticipate spindle occurrence to be a regional phenomenon. Generally, there has been an increasing focus on conceptualising processes involved in sleep-dependent memory consolidation as local phenomena (Krueger et al., 2019; Siclari & Tononi, 2017). Whilst sleep spindles have historically been differentiated by frequency into slow (<13 Hz) and fast (>13 Hz) spindles and by their topography into centroparietal or frontal spindles (Anderer et al., 2001; De Gennaro & Ferrara, 2003), more recent evidence points towards spindles as a local phenomenon. Combining intracranial recordings with those made at the scalp level in the same participants, the spatial distribution of sleep spindles has been further characterised (Nir et al., 2011). Notably, the authors reported a high proportion (75%) of local spindles (as defined by </> 50% of recording sites showing spindle activity), although spindles did become less local over the course of the night. Additionally, approximately 40% of spindles were detected in one hemisphere exclusively. Several other intracranial studies have corroborated the presence of frequent, local spindle activity (Andrillon et al., 2011; Frauscher et al., 2015; Piantoni et al., 2017).

A3.3.5 Probing Spindle Locality

Manipulating the hemisphere in which a memory is consolidated has been attempted by presenting verbal stimuli in either the left or the right hemi-field exclusively (Cox et al., 2014). Importantly, unilaterally presented words were paired with one of two odours. During a subsequent nap, one of the two odours was presented. Posterior fast spindles showed greater amplitude and density in a hemispheric-specific

fashion. Similarly, in Bar et al. (2020), TMR was used to selectively target one hemisphere. Participants learned to associate words with locations on the screen in the presence of a rose-like odour. During a subsequent nap, when these associations were presumably being consolidated, participants were stimulated with the previously associated scent via only one nostril. Use of a control experiment where odour stimulation was applied (but not associated with memory encoding) facilitated. Behaviourally, cued items were better maintained whereas non-cued items showed a significant accuracy decline suggesting a hemispherically-constrained TMR effect. Neurophysiologically, slow wave activity increased in response to odour stimulation (regardless of previous odour-encoding association). Notably however, spindle power was increased only when the odour had relevance to prior learning. Despite this, neither the number/density nor the power of sleep spindles was correlated with memory improvement. Additionally, there was a change in slow oscillation-spindle phase amplitude coupling (PAC) in which spindles occurred at a later phase, closer to the peak.

Although these two studies in particular are suggestive of a functional local role of spindles in memory reactivation, both experiments employed TMR and it is unclear the extent to which TMR-induced reactivation resembles spontaneous reactivation. Given that the timing of spindles relative to ongoing slow oscillations may be critical (Latchoumane et al., 2017), artificially prompting memory reactivation via TMR might occur at an inopportune time relative to the brain's own timing (Batterink et al., 2016). Thus we aimed to boost endogenous spindle activity but to do so selectively in regions which had been engaged in prior processing of a sub-selection of material.

A3.3.6 Hypotheses and Predictions

This experiment was designed to examine the locality of sleep spindles by modulating spontaneously occurring spindle activity. In the present study, we designed a paradigm in which encoded information would be selectively consolidated according to the type of material presented, in either the left (verbal encoding trials) or the right hemisphere (visual encoding trials).

During the subsequent sleep period when previously associated materials were being consolidated, we selectively stimulated one hemisphere over another via HD-tDCS. Firstly, we hoped to be able to selectively stimulate one hemisphere and observe whether this had a detectable difference in spindle characteristics of interest, i.e. whether tDCS could selectively modulate spindle density or amplitude over one hemisphere (compared to both the opposing, unstimulated hemisphere and compared to the sham session). Secondly, if spindles do indeed reflect local reprocessing of stimuli, only information previously encoded in the stimulated hemisphere should benefit from this stimulation of spindles. Finally, this behavioural improvement should correlate with the increased spindle activity. In addition to these primary hypotheses, the paradigm may assist in resolving the occurrence of spindle-accompanied theta activity. Changes in theta power has been shown to accompany memory content reactivation but this varies between paradigms (Antony et al., 2019; Schreiner et al., 2018; Schreiner & Rasch, 2017). This discrepancy may be a result of the variability in use of verbal learning material, but a direct comparison within the same paradigm of different material types has not yet been performed.

A3.4 Methods

A3.4.1 Participants

Data from 24 participants were collected. This sample size is consistent with previous sleep studies (e.g., Lustenberger et al., 2016). Participants were right-

handed self-reported good sleepers, reporting typical sleep durations of 6-9 hours. Participants were excluded if they had any neuropsychological disorder or sleep disorder. Participants were also required not to have participated in night-shift work or to have changed time zones in the month prior to the experiment. On experimental days, participants were instructed not to drink any coffee or alcohol. In keeping with contemporary guidelines regarding transcranial current stimulation, participants were excluded if they had any electrical pacemaker or metal implant and if they had participated in a tCS/TMS experiment in the preceding 6 months.

A3.4.2 Design

Participants completed three separate sessions of the experiment experiencing either left-only, right-only, or sham stimulation. The order of these conditions was randomised and counter-balanced across participants. These three sessions were conducted a minimum of one week apart to allow for an adequate washout period for stimulation. Prior to the three experimental sessions, participants slept in the sleep lab with the EEG and stimulation electrodes attached but switched off. This session served as an adaptation night to avoid the first night effect whereby participants exhibit reduced sleep quality when sleeping in a novel environment for the first time (Agnew et al., 1966; Curcio et al., 2004).

A3.4.3 Procedure

Participants arrived at the sleep laboratory at approximately 19:30 for the experiment (See Figure A3.1 for procedure). Stimulation and EEG electrodes were attached to their scalp ensuring that impedances remained below 10kΩ. As described in the stimulation setup, stimulation electrodes were attached at Fpz, Oz, CP6, and FC5 according to the 10/20 system. Impedances for stimulation were kept under 15kΩ and stimulation automatically terminated if this was not the case. The stimulation

electrode setup remained the same regardless of which stimulation condition a participant was in to ensure that the participant was unaware of which hemisphere was being stimulated.

Participants then performed the training section of the task. As described in the task section, participants performed the encoding portion of the task until they had achieved 60% accuracy in both the verbal and the visual trials. Given that participants were likely to perform better on verbal trials and to avoid over-training of participants, once a participant had achieved the criterion accuracy in either category, those trials were removed from the training rotation.

After performing the encoding portion of this task, participants performed a brief psychomotor vigilance task (Roach et al., 2006) and filled out the Stanford Sleepiness Scale. Participants were then tested on their ability to recall cued visual and verbal material. This test resembled the retrieval portion of the training task except that there were also new stimuli presented. Participants therefore first had to make an old/new judgement as to whether they had previously seen that stimulus paired with another. In the case that they reported having seen a stimulus, they then reported which of the four stimuli it had been paired with.

Importantly, only 50% of stimuli were presented (resulting in 60 ‘old’ trials) together with 15 new stimuli previously not presented. In the post-sleep test, the remaining half of trials were presented along with an additional 15 new stimuli. This splitting of the encoded trials was to preclude alternative explanations of any sleep-based improvement in retention, given that recall is known to promote consolidation (Antony et al., 2017). Thus, if all trials were presented before and after sleep, any

post-sleep improvement could be attributed to both retrieval-related and sleep-related consolidation.

Immediately after this, participants slept overnight. Once participants had entered slow-wave sleep (as judged via visual inspection of the EEG signal by the experimenter), the stimulation protocol began. Stimulation ramped up for 30 seconds before remaining on at 2 mA for 5 minutes. Stimulation then remained off for 10 minutes. Periods of stimulation-on and stimulation-off recording ensured both concurrent and immediately post-stimulation recording periods. When removing the stimulation artifact, this facilitated comparison between artifact-removed and artifact-free periods. Additionally, in the event that the stimulation artifact were not able to be removed, artifact-free periods remained. This pattern of 5 minutes on/10 minutes off proceeded throughout the night. If participants left slow-wave sleep, stimulation was switched off (with 30 seconds of ramping down to minimise sensation and the risk of sleep disruption/waking).

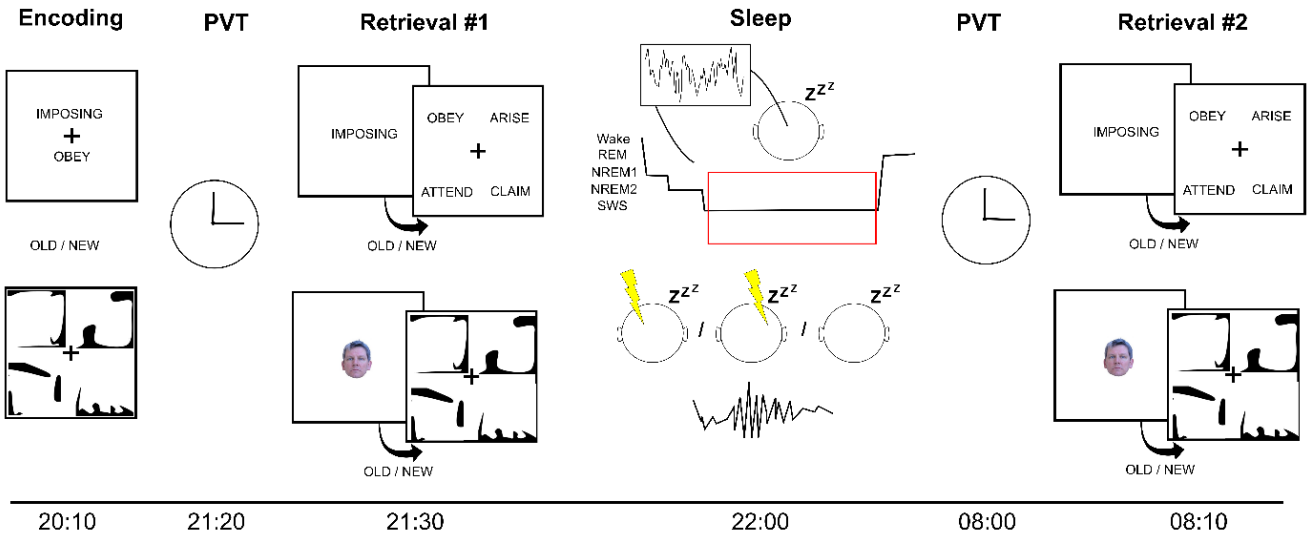

Figure A3.1. Timeline of the experiment. EEG and stimulation electrodes were attached to participants and EEG recording began. Participants then performed the training portion of the task with corrective feedback until they reached the criterion performance (60 % accuracy in both tasks). Prior to the night's sleep, participants performed a PVT task to assess general arousal and the first retrieval test (pre-sleep test). Whilst participants slept, EEG was recorded and tDCS applied in an on-off protocol. Depending on the session, a given participant received left-only, right-only, or sham

stimulation. Spindle metrics were later determined offline. After sleep, participants performed the PVT and the second retrieval task (post-sleep test). Stimulation conditions were counterbalanced within participants with a minimum washout period of one week.

A3.4.4 Memory Task

Participants were trained on the memory task to criterion performance. The training task alternated between an encoding portion, in which participants were required to associate a cue and a stimulus, and a retrieval portion, in which participants were tested on their retention of stimuli associations (See Figure A3.2). Verbal and visual trials were randomly interleaved in both the encoding and retrieval portions of the task. Participants were required to encode 120 stimuli in each category (240 total stimuli pairs). Stimuli were shuffled from the set for each participant and thus randomly presented across the three sessions.

In the encoding portion of the task, participants were first presented with a pre-stimulus fixation period. The duration of this was temporally jittered (by 0/50/100 ms) but lasted at least 1000 ms. In a verbal trial, participants were then presented with two words above and below the fixation cross. The word in the upper position was always an adjective. The word below the fixation cross was one of four verbs: ‘obey’, ‘attend’, ‘arise’, or ‘claim’. The verbal stimuli remained on the screen for a jittered period of > 3000 ms. The participant was required to judge whether the pairing of the two words was unusual or not. The participant registered this judgement by pressing either the left or the right arrow key on the subsequent screen. In a visual trial, after the fixation cross participants were instead presented with a face in one of four quadrants of the screen. In each of these quadrants, an abstract environment was presented. The location of these environments varied across participants but remained the same within participants. The participant’s task in a visual trial was to judge whether the face was suited to the environment it had been placed in relative

to the other environment options. The participant registered this response, as in the verbal trial, by pressing the left or right arrow key on the subsequent screen.

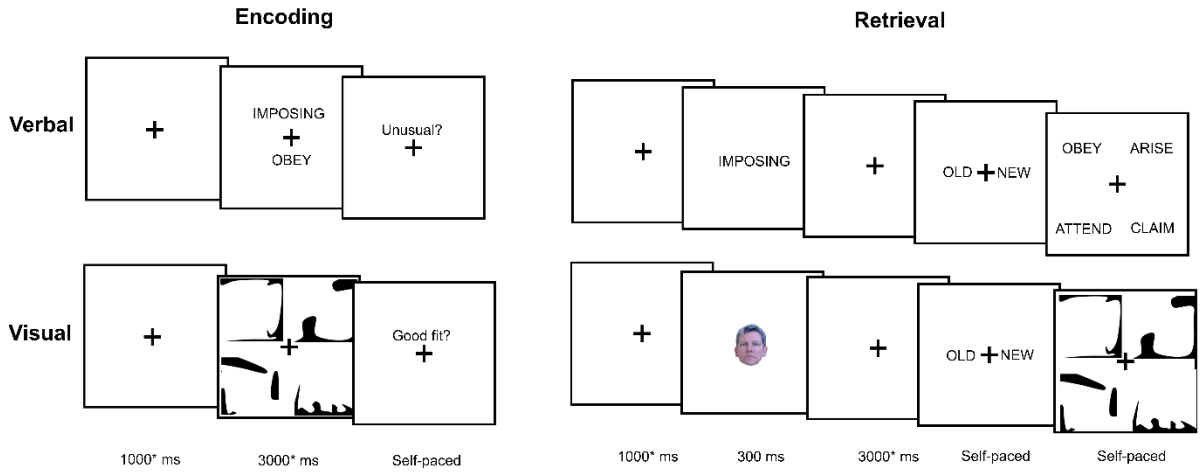

Figure A3.2. Memory Task. An exemplar of a trial featuring either verbal or visual material. During the training procedure, participants performed a round of encoding (**left**) followed by a retrieval test (**right**) with feedback. Participants were trained in this manner until they had achieved 60% accuracy in both categories. Retrieval tests were conducted pre-sleep and post-sleep without feedback.

A3.4.5 Statistical Analysis

As participants were trained according to a criterion performance, successful recall rate should be approximately 60% at retrieval 1 (pre-sleep test). Consolidation was quantified as the percentage recalled at retrieval 2 (post-sleep test) relative to retrieval 1 (pre-sleep test).

A3.4.6 EEG

EEG signal was recorded using a 64 channel Brain Products system, although the sensors at the stimulation sites were removed resulting in a reduced channel array. Data were sampled at 1000 Hz. Electromyographic (EMG) and electrocardiographic (ECG) recordings were acquired simultaneously to facilitate accurate analysis of sleep architecture.

A3.4.7 Transcranial Current Stimulation

Electrodes were arranged in a custom high-definition 2x1 setup consisting of one central anode and two cathodes (Kuo et al., 2013; Villamar et al., 2013) using a

Neuroelectrics StarStim device. The stimulation protocol was manually triggered to begin once the participant had entered slow-wave sleep (as judged by the experimenter). Sleep architecture and stages were determined offline by two independent examiners to quantify the degree to which stimulation was correctly applied only during slow-wave sleep. If the participant began to leave slow-wave sleep or approach wakefulness, stimulation was manually terminated (with a ramping down period to avoid sensation). Stimulation ramped up and down over 30 seconds to reduce skin sensation.

Stimulation was conducted in an on-off protocol. Stimulation ramped up and remained active for 5 minutes. After these 5 minutes, stimulation ramped down for an additional 30 seconds. It remains contested the degree to which tDCS-induced artifacts can be removed from the EEG signal (Gebodh et al., 2019) so this approach ensured that there the presence of artifact-free periods of analysis. This on-off procedure continued throughout the night until the total on/off time of stimulation reached 120 minutes or until it was judged that the participant was spending too little time in SWS to reliably stimulate.

A3.5 Results

A3.5.1 Current Flow Modelling

Current flow was estimated using SimNIBS 2.0 (Thielscher et al., 2015). The standard head model was employed to assess Conductivities assigned were the standard values, as determined by ex vivo studies: white matter 0.126 S/m; grey matter 0.275 S/m; CSF 1.654 S/m; bone 0.010 S/m; scalp 0.564 S/m; spongy bone 0.025 S/m; compact bone 0.008 S/m; eye balls 0.500 S/m; eye region 0.250 S/m; electrode rubber 0.100 S/m; and saline 1.000 S/m. PiStim electrodes (NeuroElectrics, Barcelona, Spain) were represented in the model as

2cmx2cmx1mm with 2mm of conductive gel. Stimulation modelling indicated selective stimulation of each hemisphere (See Figure A3.3).

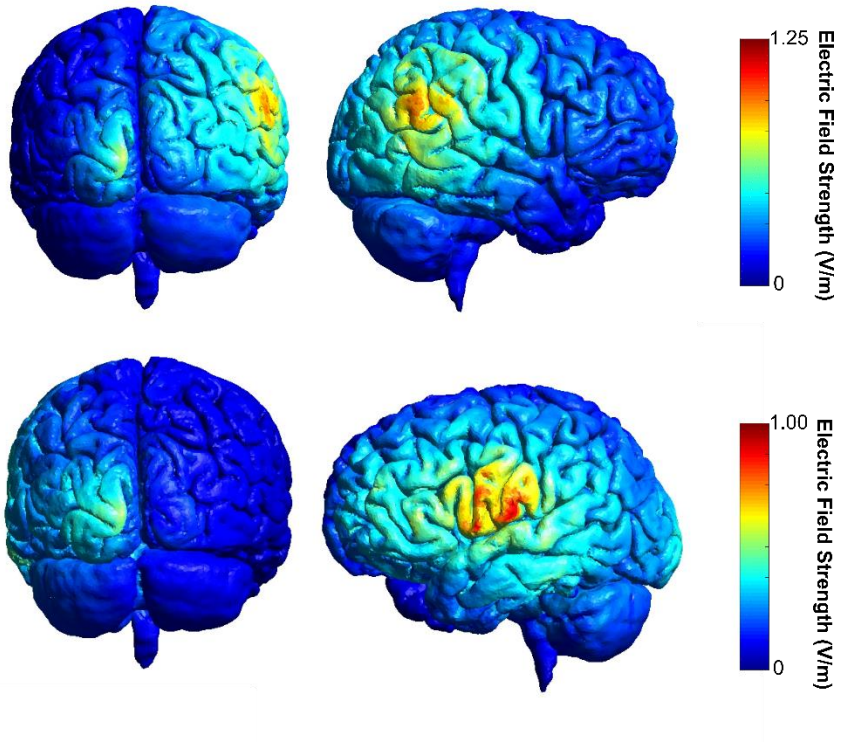

Figure A3.3. Modelling current flow of sleep stimulation setups. Finite element models (FEM) modelling the current flow of right-lateralised **(A)** and left-lateralised **(B)** transcranial current stimulation montages. Estimates of the electric field strength indicated constrained current flow with minimal cross-hemispheric overlap.