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VLOGA MOŽGANSKIH OSCILACIJ V DELOVNEM SPOMINU

(THE ROLE OF BRAIN OSCILLATIONS IN WORKING MEMORY)

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Table of contents

Abstract

Working memory is important for a number of higher cognitive functions such as problem solving, reasoning, reading and language comprehension. Moreover, working memory measures are significantly correlated with measures of intellectual abilities. Investigating the neural basis of working memory provides the opportunity to gain a deeper understanding of individual differences in general cognitive ability. This thesis aimed to elucidate the roles of brain oscillations in working memory, with a particular focus on theta and gamma frequency bands. Two techniques were employed that are best suited for the non-invasive study of brain oscillations: scalp recorded EEG and transcranial alternating current stimulation (tACS). In the first step, correlational studies were conducted followed by neuromodulatory studies in the next step. The results showed that individuals with high working memory capacity, contrasted against individuals with low working memory capacity, display stronger alpha and gamma band desynchronisation and increased coherence in the theta frequency band between fronto-parietal areas during maintenance and between frontal brain areas during retrieval. The results further demonstrated that interactions between theta and gamma frequency bands are related to individual differences in working memory capacity. The neuromodulatory studies showed that theta tACS applied over parietal brain areas can be used to enhance performance on working memory tasks, thereby providing support for the causal role of theta band oscillations in working memory.

Povzetek

Delovni spomin je pomemben za višje kognitivne funkcije, kot so reševanje problemov, sklepanje, jezik ter bralno razumevanje. Mere delovnega spomina in mere fluidne inteligentnosti so statistično značilno povezane. Proučevanje nevrobiološke osnove delovnega spomina omogoča boljše razmevanje individualnih razlik v kognitivnih sposobnostih. V disertaciji se osredotočam na vlogo možganskih oscilacij v delovnem spominu, predvsem v theta in gama ritmih. Uporabljeni sta bili tehniki, ki omogočata neinvazivno proučevanje možganskih oscilacij: elektroencefalografija (EEG) in transkranialna stimulacija z izmenjujočim električnim tokom (angleško: transcranial alternating current stimulation; v nadaljevanju tACS). V prvem delu so predstavljene korelacijske študije, v drugem pa študije, v katerih je bil uporabljen tACS za vplivanje na možganske oscilacije. Prvi del študij je pokazal, da imajo osebe z visoko kapaciteto delovnega spomina v primerjavi z osebami z nizko kapaciteto delovnega spomina močnejšo desinhronizacijo v alfa in gama frekvencah ter povečano koherenco v theta frekvenci med frontalnimi in posteriornimi predeli možganov med ohranjanjem informacij ter med frontalnimi predeli med priklicom informacij. Rezultati so nadalje pokazali, da so interakcije med theta in gama frekvencami povezane z individualnimi razlikami v kapaciteti delovnega spomina. Drugi del študij je pokazal, da theta tACS izboljša reševanje nalog delovnega spomina, če je stimulacija usmerjena na parietalne predele možganov, s čimer se je potrdila vzročna povezava med možganskimi oscilacijami v theta frekvenci in delovnim spominom.

1. Introduction

1.1 Working memory

Baddeley (2003) views working memory as “an integrated system for temporarily storing and manipulating information” (p. 837). Patricia Goldman-Rakic, whose seminal work on the cellular correlate of working memory in the monkey’s dorsolateral prefrontal cortex (Funahashi, Bruce, & Goldman-Rakic, 1989; Goldman-Rakic, 1995) represents one of the milestones in working memory research, has defined working memory as “the blackboard of the mind” (Goldman-Rakic, 1992). Indeed, working memory is viewed as a core cognitive process that underlies many different behaviours, from perception to problem solving, reading, and action control (Ma, Husain, & Bays, 2014). Moreover, research indicates that measures of working memory capacity are strongly linked to measures of fluid intelligence (Ackerman, Beier, & Boyle, 2005; Burgess, Gray, Conway, & Braver, 2011; Harrison, Shipstead, & Engle, 2015; Unsworth & Engle, 2005; Wiley, Jarosz, Cushen, & Colflesh, 2011). Some even claimed that working memory and fluid intelligence are identical constructs (Kyllonen & Christal, 1990), however, a meta-analysis by Ackerman et al. (2005) did not support this: the average correlation between the two measures was less than unity (0.479, 95% CI 0.44 - 0.52). Since the capacity of working memory is limited it can be used to measure individual differences in cognitive ability.

The ability to manipulate items in working memory improves throughout childhood and adolescence, which is important for academic performance (Dumontheil & Klingberg, 2012). Developmental changes in this ability correspond to the time courses of development of different brain regions (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). In individuals aged 6-25 years, a cross-sectional analysis showed that working memory performance is related to (1) cortical activity in frontal and parietal cortices, (2) cortical thickness in the parietal cortex, and (3) white matter structure of fronto-parietal and fronto-striatal tracts. A longitudinal analysis of the same dataset demonstrated that subcortical white matter tracts and activity in the caudate predict future working memory capacity (Darki & Klingberg, 2015). This is in line with Jung and Haier's (2007) parieto-frontal theory of intelligence, which proposes that intelligent behaviour is related to the fidelity of underlying white matter structures necessary to facilitate rapid and error-free transmission between brain areas.

On the other side of the coin, failure to maintain and manipulate items in working memory can hinder the ability to carry out many day-to-day activities. Given that working memory declines with age (Grady & Craik, 2000) and that working memory dysfunction has been associated with traumatic brain injury (McAllister, Flashman, McDonald, & Saykin, 2006), schizophrenia (Lee & Park, 2005), attention-deficit/hyperactivity disorder (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), fragile-x syndrome (Munir, Cornish, & Wilding, 2000), and dyslexia (Smith-Spark & Fisk, 2007), studying the neural basis of working memory can improve our understanding of this core cognitive function both in healthy and clinical populations.

1.1.1 Models

Early models of memory provided the distinction between short term memory (STM) and long term memory (LTM) (Atkinson & Shiffrin, 1968; Broadbent, 1958; Waugh & Norman, 1965). Broadbent's selective filter theory of attention (1958) proposed a stage model in which the basic physical properties of all stimuli are processed and representations of these features are temporarily stored. A selective filter is applied to determine which stimuli should be processed further. After the semantic features of these stimuli are processed, the information is stored in long-term memory. Even though this model was criticized for the relative lack of parallel processing of information and for the notion that semantic information processing only occurs after the processing of physical features, the core features of Broadbent's model held up well even after 50 years (Lachter, Forster, & Ruthruff, 2004).

Atkinson and Shiffrin (1968) kept certain mechanisms described in Broadbent's (1958) selective filter theory and Waugh and Norman's (1965) theory of primary and secondary memory, such as rehearsal and decay, but modified the model in certain ways. The authors defined the memory system along two dimensions: (1) permanent, structural features as opposed to modifiable control processes and (2) a dimension that is divided into three components – the sensory register, the short-term store, and the long-term store. In their model, information first enters the sensory register, where it stays briefly while being initially processed and transferred to the short-term store. The short-term store receives information both from the sensory register and from the long-term store. The information is rapidly lost if it is not attended to, on the other hand, control processes such as rehearsal can maintain the information in short term store as long as necessary. Portions of information are transferred to the long-term store only after they had been stored in short-term memory. They assumed that the store of information in long term memory is permanent (Shiffrin & Atkinson, 1969).

The term working memory (WM) was coined by Miller, Galanter and Pribram (1986) as an analogy to a computer function and was later adopted by Baddeley and Hitch (1974). The phrases short term memory and working memory are sometimes used interchangeably, however, Baddeley (2012) uses the phrase short term memory to describe temporary *storage* of information, yet uses the phrase working memory to refer to a combination of *storage and manipulation*. Throughout this thesis, I will adhere to these explanations of STM and WM.

Atkinson and Shiffrin's (1968) model was widely popular until Baddeley and Hitch (1974) introduced the concept of a multi-component system that replaced the idea of a unitary store. Their model also differed from earlier models by stressing the role of this system in complex cognition over and beyond memory. The three-component model of working memory consisted of an attentional control system, called the central executive, which is supported by two slave systems, the phonological loop and the visuospatial sketchpad. The former temporarily holds verbal and acoustic information and an articulatory rehearsal system, whereas the latter holds visuospatial information. The central executive is responsible both for storage and retrieval of information in the form of conscious awareness, and can manipulate and modify information (Baddeley, 2000). The phonological loop has been associated with processing in the left hemisphere in Broadmann areas (BA) 40, 44, and 6, and visuospatial information is thought to be processed mainly in the right hemisphere in BAs 47, 19, 40, and 6. In contrast, the central executive has been linked to activity in the dorsolateral prefrontal cortex (BAs 9, 10, 44, 45, 46) (Gathercole, Pickering, Roy, & Gathercole, 1999). A systematic review by Kane and Engle (2002) confirmed that the dorsolateral prefrontal cortex (PFC) is critical to executive-attention functions. Evidence related to the neurobiological basis of working memory has expanded since then, and will be discussed in Chapter 1.1.3.

The concept of working memory as defined by Baddeley and Hitch (1974) proved to be durable over the years, nevertheless, a theoretical reformulation was required in light of certain limitations of the model. For example, the model struggled to explain evidence from patients with short-term memory deficits, which suggested that there is a system responsible for integrating storage of information from different modalities and systems (Baddeley, 2000). In 2000, Alan Baddeley published a paper titled "The episodic buffer – a new component of working memory?" in which the episodic buffer was introduced as the fourth component of the working memory model. The fourth component was defined as "a limited-capacity temporary storage system that is capable of integrating information from a variety of sources" (Baddeley, 2000, p. 421). The episodic buffer represents a temporary interface between the two slave systems and long term memory, and it is controlled by the central executive.

These models of working memory (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974; Broadbent, 1958; Waugh & Norman, 1965) have been termed *system-based models* (LaRocque, Lewis-Peacock, & Postle, 2014) or *multistore models* (Jonides et al., 2008), since they assume a division between primary and secondary memory (i.e. a distinction between short and long term memory). The most important evidence in favour of this distinction comes from neuropsychology (Jonides et al., 2008): cases have been reported in which patients show a deficit in long term memory but have an apparently normal short term memory (e.g., Scoville & Milner, 1957) and vice versa, patients with deficits in short term memory but not in long term memory (e.g., Shallice & Warrington, 1970). However, a review of empirical studies revealed that evidence for a dissociation between short term and long term memory is not well supported (Ranganath & Blumenfeld, 2005).

Despite the fact that the multicomponent model (Baddeley, 2000; Baddeley & Hitch, 1974) is the most enduring conceptualization of working memory, the construct itself is subject to an ongoing revision of models (D'Esposito & Postle, 2015). It has even been proposed that working memory is separable from short term memory and represents a domain-free limitation in the ability to control attention (Randall W. Engle, 2002). Functional overlap between the mechanisms of spatial working memory and spatial selective attention was also reported by Awh and Jonides (2001). Specifically, the authors proposed that mechanisms of spatial attention are needed to maintain information active in working memory in a rehearsal-like manner. On the other hand, a structural equation modeling study by Buehner, Krumm and Pick (2005) did not confirm the relation between working memory and concepts of attention, but demonstrated that working memory components explain a great amount of variance in reasoning. The two working memory components that served as the best predictors of reasoning were *storage in the context of processing* and *coordination*[1].

More recently, *state-based models* of working memory have gained in popularity (D'Esposito & Postle, 2015). In contrast to the *system-based/multistore models* described above (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974; Broadbent, 1958; Waugh & Norman, 1965)*, state-based models* assume a common store for STM and LTM (Anderson et al., 2004; Cowan, 1999; McElree, 2001; Oberauer, 2002); for a review see LaRocque et al. (2014). Broadly speaking, information being held in working memory is thought to exist in one of several states of activation, depending on the allocation of attention. *State-based models* can be further categorized into *activated LTM models* and *sensorimotor recruitment models*. These models differ on the basis of the type of stimuli they were designed for and tested with: the former focus on semantic/symbolic stimuli whereas the latter specialize in perceptual stimuli – visual, auditory and tactile characteristics of stimuli (D'Esposito & Postle, 2015). Nevertheless, both categories of models assume that allocation of attention to different representations in long term memory (either semantic, sensory or motor) governs temporary retention in working memory.

One of the most well-known state-based models was proposed by Cowan (1995), in which two states of short term memory are described: (1) focus of attention – a small,

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[1] Coordination was measured with tasks that required monitoring of changing relations between independently changing objects (Buehner et al., 2005).

capacity-limited state and (2) activated LTM – a more extensive state reflecting the activated portion of long term memory. The focus of attention is limited by approximately four chunks of information that can be temporarily retained with the help of top-down attentional control. In Baddeley's (2000) model, this information is thought to be held (and integrated) in the episodic buffer. In Cowan's (1995) model, a shift in attention towards other information incites the items that were previously in the focus of attention to move into activated long term memory, which in itself has no capacity limit, but is prone to decay over time and interference (Cowan, 1995; D'Esposito & Postle, 2015). The initial two-level model was later upgraded to an embedded processes model of working memory. Cowan (1999) suggested that there are embedded processes in the information processing system: the memory system represents one of these embedded processes, and within this system, a part of it is in a heightened state of activation. Finally, within the heightened state of activation there is a part of the system that is currently in the focus of attention. The model posits that the focus of attention is capacity limited, whereas activation is time limited. Both voluntary processes (a central executive system) and involuntary processes (the attentional orienting system) control the focus of attention. The most readily accessible information is the one that is in current focus. However, information that is activated but not within conscious awareness can also be retrieved, although with a larger delay (Cowan, 1999). Cowan (2001) famously proposed the magical number 4 - stating that the capacity limit of short term memory corresponds to 3 to 5 chunks of information. Cowan et al. (2005) also suggested that there are at least two dimensions of attention: control of attention and its scope. A successful measure of the scope of attention must prevent rehearsal and grouping processes, allowing a clearer estimate of how many separate chunks of information the focus of attention circumscribes at once.

While Cowan's embedded processes model of working memory (1995, 1999) seems quite different from Baddeley's multicomponent model (2000), Baddeley (2012) actually views it as consistent with his own theoretical framework, and views the differences in terms of different emphasis on terminology. For instance, Baddeley (2012) agrees that working memory involves the activation of many areas of the brain that involve LTM.

Oberauer's (2002, 2009) three-embedded-components theory is a variant of Cowan's (1995) model. Working memory is conceptualized as a concentric structure of representations with three functionally distinct regions (Oberauer, 2002):

> 1. The activated part of long-term memory can serve, among other things, to memorize information over brief periods for later recall.
>
> 2. The region of direct access holds a limited number of chunks available to be used in ongoing cognitive processes.
>
> 3. The focus of attention holds at any time the one chunk that is actually selected as the object of the next cognitive operation. (p. 412)

The number of independent items that can be held in the region of direct access at the same time represents the limit of working memory capacity, and is similar to Cowan's (1995) focus of attention (Oberauer, 2002). Oberauer (2009) distinguishes between declarative and procedural working memory. Declarative WM makes representations available for processing, whereas procedural WM does the processing – these systems can also be seen as the memory part and the working part of WM. This distinction somewhat resembles the distinction between the central executive and the slave systems (Baddeley and Hitch, 1974). However, Oberauer's (2009) model views these two systems as equal, i.e. one is not subordinate to the other. Essentially, Oberauer (2009) views working memory as an attentional system that in equal measures interacts with perception and long term memory. However, even the authors himself acknowledges that there is little evidence for independence of declarative and procedural working memory, and uses this distinction because it makes sense on theoretical grounds. Specifically, his model proposes six requirements for a WM system (Oberauer, 2009, p. 45): "(1) maintaining structural representations by dynamic bindings, (2) manipulating structural representations, (3) flexible reconfiguration, (4) partial decoupling from long-term memory, (5) controlled retrieval from long-term memory, and (6) encoding of new structures into long-term memory." As Baddeley (2012) pointed out, while the model is promising, its complexity may make it difficult to evaluate experimentally.

Another example of a state-based model is McElree's (2001) model of working memory, which is based on empirical studies involving the n-back task. These studies revealed that attention can be concurrently directed only to a small number of memory representations, perhaps just 1. It was proposed that only the last item is maintained in the focus of attention, while the rest are held in long term memory with varying levels of memory strength.

In sum, there is no shortage of models of working memory, some of which use different terms to describe the same processes. System-based models assume distinct stores for STM and LTM, whereas state-based models assume that temporary holding and manipulating information is achieved by activating long term memory representations and that focus of attention keeps the information active. The most prominent difference between various state-based models is the amount of information that can be held in the focus of attention (1 or multiple) (D'Esposito & Postle, 2015). The mechanisms underlying the capacity limit of working memory sparked another debate that will be discussed in the next section.

1.1.2 Capacity

While most would agree that working memory capacity is limited, there are different opinions why this is the case. Some claim that it would be biologically expensive for the brain to have a larger WM capacity, and that the representation of large numbers of items would be prone to interference, whereas others view this capacity limit as a strength. Certain mathematical simulations have suggested that searching through information is most efficient when the to-be-searched groups contain 3.5 items on average (Cowan, 2010). Another important question is how does this limit occur? Researches focusing on visual working memory have debated whether its capacity is constrained by a limited number of discrete representations or by an infinitely divisible resource.

The original slot model was proposed by Luck and Vogel (1997), who conducted a series of experiments in which it was demonstrated that integrated rather than individual features of items are stored in visual working memory. The results showed that at least four features (e.g. colour, orientation, size) can be integrated in this manner without cost to storage capacity. *Slot-based models* therefore assume that a limited number of items can be stored in visual working memory, regardless of the complexity of any single item. This limit has been labelled K_{max}. If the number of items in the sensory register exceeds K_{max}, then one or more items will not be stored (Luck & Vogel, 2013). These theories predict that errors in report of a given item will consist of a mixture of high-precision responses (items that were allocated a slot) and random guesses (items that did not receive a slot) (Ma et al., 2014).

On the other hand, *resource-based models* (Bays & Husain, 2008; Franconeri, Alvarez, & Cavanagh, 2013; Wilken & Ma, 2004) assume that "visual WM capacity is a flexibly divisible resource that can be spread among all the items in the display, but with fewer resources per item and therefore reduced precision as the set size increases" *(*Luck & Vogel, 2013, p. 394). For example, a series of visual short term memory experiments revealed that the assumption of neuronal noise, with a simple decision rule, provides a better account of visual short term memory than the slot model (Wilken & Ma, 2004). Similarly, modeling visual working memory performance led Bays and Husain (2008) to suggest that visual WM capacity is not limited by a fixed number of items, but by a limited resource that is shared flexibly between items in the visual scene. The results further suggested that making an eye movement to an item, or directing covert attention to it, results in a greater amount of memory resources allocated to it.

The study of the neural basis of working memory capacity has provided support both for slot-based and resource-based theories. Event related potential (ERP) studies have demonstrated that there is sustained change in voltage during the delay part of a change detection task and that this neural activity predicts individual differences in visual working memory capacity (Vogel & Machizawa, 2004; Vogel, McCollough, & Machizawa, 2005). A change detection task typically consists of an array of items that is briefly presented, followed by a delay period in which no stimuli are presented, and the presentation of a target array. The participants are asked to indicate whether they detected a change in the target array (in comparison to the first array). ERP studies lend support to slot-based theories of working memory capacity. For instance, Vogel and Machizawa (2004) reported that the magnitude of the amplitude increase correlated with individual visual working memory capacity, but reached an asymptote when the individual's storage capacity was exceeded. Activity from individuals with low visual working memory capacity reached a plateau sooner than the activity from high-capacity individuals. A similar effect was reported in a functional magnetic resonance imaging study (fMRI): blood oxygen dependent (BOLD) activity in the posterior parietal cortex predicted individual differences in visual working memory capacity (Todd & Marois, 2005). However, identifying a plateau in the presence of noise presents is not an easy task – it is possible that neural signals do not reach a maximum and then plateau, but increase continuously toward an asymptotic limit (Ma et al., 2014). Slot-based theories have also been questioned with respect to the idea that an item is present or not, without internal noise, which does not seem to be in line with models of perceptual encoding (Wilken & Ma, 2004).

Zhang and Luck (2008) tested the predictions of the two classes of models in a series of experiments and determined that the model in which there is a small set of discrete, fixed-resolution representations provides the best account of memory performance. The individuals stored a few items with high resolution, but did not retain information about the other items. The authors proposed a new model (termed slots + averaging) in which slots act as a shared resource that is distributed between items, however, no more items can be stored than there are slots. Since the model combines features of slot and resource models, it was classified as a *discrete-representation model* (Ma et al., 2014). The results reported by Zhang and Luck (2008) were supported in a more recent study by the same authors (Zhang & Luck, 2011). Finally, a fourth class of models, termed *variable-precision models* (Fougnie, Suchow, & Alvarez, 2012; van den Berg, Shin, Chou, George, & Ma, 2012), states that working memory precision varies around a mean that decreases with a growing number of items as a result of limited resources (Ma et al., 2014). According to van den Berg et al. (2012), variability in gain across items and trials is consistent with neurophysiological evidence of single-neuron firing rate variability and with attentional fluctuations. Fougnie et al. (2012) also reported that the quality of visual working memory varies independently across trials and items. The authors proposed a framework for visual working memory capacity in which the quality of a memory representation is not deterministic and based exclusively on the amount of resources allocated to it. Instead, they propose that there is independent, stochastic[2] variation in memory quality, thereby taking a step towards defining a biologically plausible neural model of working memory.

Bays (2015) also views the inherently stochastic nature of neural activity as incompatible with a deterministic limit on number of item stores (slots). He agrees that capacity limits result from flexible allocation of a limited amount of neural signal between memorized stimuli. Bays (2014) proposed a population coding model in which the limited resource is the number of action potentials generated in a neural population. As the neural signal decreases, the internal representations of external stimuli become increasingly dominated by noise, until they cannot be distinguished from random noise. Bays (2015) argues that the mechanisms proposed in his model are in line with the established neurophysiological principles of population coding, normalization, diffusion, and accumulation-to-bound.

Animal studies may help clarify the mechanisms underlying working memory capacity. For example, Buschman, Siegel, Roy and Miller (2011) conducted a study in which two adult rhesus monkeys were trained to perform a change localization task. Simultaneous recordings made from single neurons in prefrontal and parietal cortices revealed that (1) capacity limits depended on initial sensory encoding and not on memory failure, (2) the left and right halves of the visual space had independent capacities, and (3) the two hemifields acted as discrete resources (supporting slot-based models), however, within each hemifield neural information was divided among objects in a graded fashion (supporting resource-based models). These results suggest that visual capacity limits stem from competition for encoding within independent, but limited pools of neural information that can each be divided among multiple items.

Another approach would be to conduct factorial comparisons of models with the goal of combining ingredients from existing models in new ways. This was done by van den Berg, Awh and Ma (2014), who also warned that this process could lead to extreme proliferation of models, some of which may be indistinguishable. In their study, all possible combinations of 5 models of working memory capacity (Bays, Catalao, &

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[2] Partly or wholly unpredictable (Bays, 2015).

Husain, 2009; Cowan, 2001; van den Berg et al., 2012; Wilken & Ma, 2004; Zhang & Luck, 2008) were entered in a three-dimensional model space. The results showed that (1) mnemonic precision is continuous and variable across items and trials (van den Berg et al., 2012) rather than quantitized (Zhang & Luck, 2008), (2) the number of items remembered is probably variable across trials, with a median value of 6.4 in the best model, and (3) there are non-target reports in working memory, which may reflect spatial binding errors - but only in a small fraction of responses (Bays et al., 2009).

According to Ma et al. (2014), there is accumulating evidence in favour of resource-based models (e.g., Marshall & Bays, 2013; Schneegans & Bays, 2016), which can be extended to other sensory domains (Kumar et al., 2013). Hybrid models such as the discrete-representation model (Zhang & Luck, 2008) and models that assume variability in the allocation of resources have also been supported by a number of studies, however, further research is needed to determine which class of models can best explain working memory capacity limits. As stated by Luck and Vogel (2013), if variations in working memory capacity cause variations in general cognitive ability, one could investigate whether improving working memory capacity can also improve general cognitive ability – a question that is related to the topic of this thesis.

1.1.3 Neural basis

Electrophysiological and lesion studies in animals have provided insight into the mechanisms underlying working memory at neuronal, synaptic, and receptor levels (Hasselmo & Stern, 2006). In humans, the neural correlates of working memory have been investigated in studies involving electroencephalography (EEG), functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), transcranial magnetic stimulation (TMS), and more recently transcranial electrical stimulation (TES). I will first provide a brief description of evidence obtained from animal studies and computational models of memory, followed by empirical studies of working memory using the techniques mentioned above, and the theories based on these studies.

1.1.3.1 Animal research and computational models

Electrophysiological studies in animals demonstrated that neurons in the prefrontal cortex show persistent activity during the delay in working memory tasks. Disrupting persistent activity either by electrical stimulation or by the presentation of highly distracting stimuli during the delay period increases the chances that the animal will make an error (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 1973). Memory-related persistent activity has also been reported for other brain areas, such as the parietal cortex (Gnadt & Andersen, 1988; Qi et al., 2010; Quintana & Fuster, 1992) and the entorhinal-hippocampal system (Egorov, Hamam, Fransén, Hasselmo, & Alonso, 2002; Hahn, McFarland, Berberich, Sakmann, & Mehta, 2012; Watanabe & Niki, 1985), but it appears to be strongest in the prefrontal cortex (Durstewitz, Seamans, & Sejnowski, 2000; Qi et al., 2010). The substrate of long term memory is thought to be lasting synaptic change (Bliss & Lomo, 1973) and memory acquisition is impaired if long term plasticity is blocked (Takeuchi, Duszkiewicz, & Morris, 2013).

One of the central challenges for computational models of memory is the issue of time (Chaudhuri & Fiete, 2016): membrane time constants are on the order of milliseconds to tens of milliseconds, postsynaptic potentials last for tens to hundreds of milliseconds and certain facilitation processes persist for several hundred milliseconds. On the other hand, behavioural timescales for short term memory are on the order of tens of seconds to minutes. Another challenge is the presence of noise in the brain, which was discussed in the section 1.1.2. Recently, scientists have stopped seeing this as a problem, in fact, noise is seen as a resource for computation and learning in networks of spiking neurons (Maass, 2014).

Early firing-rate and spiking-neurons models of working memory differ based on how they assume that persistent activity is generated. One hypothesis is that activity persists through strong recurrent excitatory connections in a *cell assembly* (Hebb, 1949). Another hypothesis is that activity circulates in *loops* (synfire chains), which consist of feedforward-connected subgroups of neurons, with no feedback links between successive groups (Abeles, 1991; Aertsen, Diesmann, & Gewaltig, 1999). The latter hypothesis assumes that activity is propagated from one subgroup of neurons to the other through asymmetric connections as opposed to the dense reciprocal connectivity that is thought to sustain activity within cell assemblies (Durstewitz et al., 2000). Hebb's (1949) theory of cell assemblies presents one of the earliest theories of cortical associative memory. Lansner (2009) provided the following summary of the dynamic of cell assemblies:

> Excitatory synapses strengthened by coincident pre- and postsynaptic activity will connect neurons co-activated by the same stimulus. Cell assemblies so formed will subsequently serve as mental representations of their respective generating object. If a stimulus similar to one of those memorized later appears, perhaps in a fragmentary or otherwise somewhat distorted form, pattern completion will activate the entire cell assembly, which then reverberates in the cortex for a fraction of a second (p. 178).

Hebb’s (1949) work inspired more recent attractor-memory models of cortex (Lansner, 2009). An attractor network is a “neural circuit in which some patterns of activity are stable and self-sustaining” (Bays, 2015, p. 435). Discrete attractor-memory models assume that strong feedback through excitatory connection supports multiple discrete stable states (Hopfield & Tank, 1986) and each of these states has a different distributed pattern of activation across the neurons (Chaudhuri & Fiete, 2016). The idea that attractors are discrete has been questioned as they struggle to explain how variables that are valued as continuous, such as spatial position, can be maintained in memory (Durstewitz et al., 2000). This led to the development of continuous attractor-memory models, which are based on networks with a continuum of attractor states. For instance, memory for a continuous variable such as spatial position can be stored in a “ring attractor” network, where every possible spatial position corresponds to a different point on the ring of stable states (Bays, 2015).

Computational models of working memory continue to develop rapidly, propelled by the availability of supercomputers to simulate millions of neurons and synapses, and even networks the size of the mouse cortex (Lansner, 2009). However, these models should be extended to provide answers about the dynamics of higher order functions of the prefrontal cortex, such as planning and problem solving, in order to fully explain the mechanisms of working memory in terms of goal-directed behaviour (Durstewitz et al., 2000).

1.1.3.2 Human research

Integrating data from neuroscience, computational brain modelling, and psychology can help determine the biological basis of working memory (D'Esposito, 2007). For instance, the finding from animal studies that neurons in the prefrontal cortex (PFC) show persistent activity during the delay in working memory tasks has been supported by functional neuroimaging studies in humans, specifically for the dorsolateral prefrontal cortex (Curtis & D'Esposito, 2003). In addition, research on patients with focal lesions involving the dorsolateral prefrontal cortex suggested that this region supports manipulation of verbal and spatial representations in working memory (Barbey, Koenigs, & Grafman, 2013). It should be noted that active maintenance of information is a complex process that cannot be reduced to individual brain areas (Baddeley, 2012). Functional imaging of the human brain has shown that maintaining information in working memory is specifically associated with activity in prefrontal (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; D'Esposito, Postle, Ballard, & Lease, 1999; Haxby, Petit, Ungerleider, & Courtney, 2000; Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002) and posterior parietal cortices (Honey, Bullmore, & Sharma, 2000; Mitchell & Cusack, 2008; Pessoa et al., 2002; Todd & Marois, 2004). Presumably, the prefrontal cortex contributes to working memory by exerting top down control on posterior cortical areas, which strengthens the internal representations of sensory information stored in these areas (Curtis & D'Esposito, 2003; Feredoes, Heinen, Weiskopf, Ruff, & Driver, 2011; Postle et al., 2006). Medial temporal lobe regions also contribute to retention and manipulation of information over brief periods of time (Axmacher et al., 2007; Libby, Hannula, & Ranganath, 2014; Olson, Moore, Stark, & Chatterjee, 2006).

The fronto–parietal network has been consistently associated with performance on working memory tasks (Chein & Fiez, 2010; Jonides et al., 2008; Palva, Monto, Kulashekhar, & Palva, 2010; Posner & Petersen, 1990; Schumacher et al., 1996). It has been further suggested that the central executive function of working memory is linked to the frontal lobes, whereas the working memory storage component is associated with parietal areas (Champod & Petrides, 2010; Collette & Van der Linden, 2002; Olson & Berryhill, 2009; Sauseng et al., 2009; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005; Sreenivasan, Gratton, Vytlacil, & D'Esposito, 2014). Based on evidence from several brain imaging studies, the left intraparietal sulcus has been identified as a unique area responsible for amodal or multimodal storage of information (Cowan et al., 2011; Majerus et al., 2006; Majerus et al., 2010; Xu & Chun, 2006). Support for a fronto–parietal distinction related to processing and storing of information in working memory comes also from EEG research (Klimesch, 1999; Klimesch, Freunberger, Sauseng, & Gruber, 2008; Sauseng, Griesmayr, Freunberger, et al., 2010).

A meta-analysis of functional neuroimaging studies examining performance on one of the most widely used working memory tasks, the *n*-back, revealed that six regions were consistently activated across studies: (1) bilateral and medial posterior parietal cortex, including precuneus and inferior parietal lobules; (2) bilateral premotor cortex; (3) dorsal cingulate/medial premotor cortex, including supplementary motor area; (4) bilateral rostral prefrontal cortex or frontal pole; (5) bilateral dorsolateral prefrontal cortex and (6) bilateral mid-ventrolateral prefrontal cortex or frontal operculum (Owen, McMillan, Laird, & Bullmore, 2005). It should be noted that these results cannot be extended to performance on other working memory tasks (e.g. change detection or span tasks), nevertheless, one would expect a similar pattern of activation, particularly in relation to task control systems: the cingulo-opercular system and the fronto-parietal system (Power & Petersen, 2013).

1.1.3.3 Neural oscillations

Research suggests that neural oscillations play an important role in a range of cognitive functions, including working memory. Changes in voltage over time generated by neurons can be recorded at different spatial scales. Extracellular recordings measure the activity of nearby cells, whereas scalp-recorded EEG and MEG signals reflect the summed activity of millions of neurons in regions of the cortex (Kahana, 2006). Increased amplitude and synchrony of brain oscillatory activity has been linked to working memory maintenance, moreover, modulation at different frequencies in relation to working memory load has also been reported. The most often reported frequency bands in EEG, MEG and intracranial EEG studies of working memory maintenance are theta (4-7 Hz), alpha (8-13 Hz) and gamma (30-200 Hz) (for a review see Roux & Uhlhaas, 2014).

Several EEG and MEG studies have reported working memory-related increases in oscillations in the theta frequency band (Gevins, Smith, McEvoy, & Yu, 1997; Jensen & Tesche, 2002; Khader, Jost, Ranganath, & Rösler, 2010; Maurer et al., 2015; Onton, Delorme, & Makeig, 2005). For example, Jensen and Tesche (2002) reported that frontal midline theta[3] activity increases parametrically with the number of items retained in working memory. There is evidence to suggest that theta synchronises during working memory processes and serves as a gating mechanism, providing optimal neural conditions for specific processing (Sauseng, Griesmayr, & Freunberger, 2010). Further evidence for gating comes from an intracranial EEG study by Raghavachari et al. (2001), who showed that the power of theta oscillations recorded from the middle frontal gyrus significantly increased at the start of a trial in a working memory task, remained elevated throughout all the phases of the trial, and decreased sharply at the end. Power and phase synchronisation in the theta frequency band between frontal and parietal areas are thought to play a role in binding different types of information into coherent representations (Wu, Chen, Li, Han, & Zhang, 2007).

Klimesch et al. (2008) further suggested that upper alpha (10-13.5 Hz) is related to long-term memory processes. Scalp alpha rhythms result from sequences of inhibitory and excitatory post-synaptic potentials at the dendrites of cortical pyramidal neurons. These potentials depend mainly on the influence of near and distant cortical modules (Nunez, Wingeier, & Silberstein, 2001), as well as on the interactions of excitatory cortico-thalamo-cortical relay fibers and inhibitory thalamic reticular fibers (Lopes da Silva, Vos, Mooibroek, & Van Rotterdam, 1980). Alpha power reflects the number of neurons that discharge synchronously in these integrated cortico-cortical and cortico-thalamo-cortical

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[3] Frontal midline theta is a term that refers to scalp-recorded theta oscillations around the Fz electrode site (Hsieh & Ranganath, 2014)

systems (Hindriks & van Putten, 2013; Klimesch, 1999). Its activity desynchronises in relation to task performance (Pfurtscheller & Aranibar, 1977). Until recently alpha synchronisation was considered a cortical idling phenomenon (Pfurtscheller, 1999). However, recent evidence suggests that synchronisation of alpha activity does not merely indicate cortical deactivation, but reflects internal top-down processes and selective inhibition of brain regions (Fink et al., 2009; Jensen & Mazaheri, 2010; Klimesch, 2012; Klimesch, Sauseng, & Hanslmayr, 2007). On the other hand, peak alpha frequency, or individual alpha frequency (IAF) is assumed to mainly reflect a delay in the intra-cortical circuit at alpha baseline frequency (Hindriks & van Putten, 2013). It has been further suggested that each of these measures, IAF and alpha power, may capture different neural processes (Moretti et al., 2004). Several recent studies lend support to the suggestion that IAF is related to characteristics of the white matter structure like fiber density, axonal diameter, and myelination (Jann, Koenig, Dierks, Boesch, & Federspiel, 2010; Valdés-Hernández et al., 2010). Alpha frequency has been seen as: (1) an individual neurophysiological trait marker that is stable over time, but shows age-related slowing (Grandy et al., 2013) – inter-subject variability in "trait" alpha frequency could explain differences in overall cognitive performance and (2) a "state" variable - intra-subject variability may reflect fluctuations in moment-to-moment performance (Haegens, Cousijn, Wallis, Harrison, & Nobre, 2014).

Another brain oscillation that has been associated with working memory performance is gamma (Honkanen, Rouhinen, Wang, Palva, & Palva, 2015; Howard et al., 2003; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012; Van Vugt, Chakravarthi, & Lachaux, 2014). Howard (2003) conducted an intracranial EEG study and demonstrated that gamma oscillations correlate with working memory load. Roux et al. (2012) demonstrated that gamma-band activity in the left prefrontal cortex predicts the number of items maintained in working memory. Spectral changes were also observed in alpha and gamma band frequencies in parietal and premotor cortices, however, delay activity in these brain regions did not predict WM maintenance of items. In a more recent study by Honkanen et al. (2015), concurrent MEG and EEG was used to show that gamma oscillations support (1) the maintenance of feature-specific information and (2) directly reflect the maintenance of visual representations. The results also suggested that gamma oscillations contribute to feature binding in the formation of memory representations.

As mentioned previously, it is clear that both the prefrontal cortex and sensory areas contribute to working memory maintenance, however, their exact roles in this process remain a topic of debate. Van Vugt et al. (2014) attempted to address this issue by proposing a reactivation model in which gamma oscillations underlie the representation of items in high-level visual areas. The model assumes that memory traces of sensory stimuli are stored in sensory areas. Once the stimulus is no longer physically present, the activity of its neural representations decays progressively over time. As long as gamma band activity is above baseline level in its neural assembly, the neural representation of a stimulus remains active. Top-down attention can reactivate these decaying gamma-band representations in a rhythmic manner at around 6-10 Hz. The authors propose that this reactivation originates from the lateral prefrontal cortex. Distinct neural assemblies cannot be reactivated simultaneously as there is a minimum shift-time between two assemblies. Hence the number of items that can be kept active at the same time is determined by a rhythmically sampling attentional spotlight given the known decay rate.

Evidence suggests that low frequencies are responsible for long-range cortico-cortical interactions (e.g. between prefrontal and posterior cortices) over long temporal windows, whereas high frequencies regulate activity over small spatial regions (local sensory integration) on a shorter time-scale (von Stein & Sarnthein, 2000). It has been proposed that distinct frequency bands parse ongoing neuronal activity into discrete packets that have unique spatial and temporal scales (Canolty & Knight, 2010). Recently there has been a surge of interest in investigating synchronic interactions between groups of neurons in the prefrontal and parietal lobes (Yates, 2012). For example, Palva et al. (2010) used EEG and MEG to measure synchronised oscillatory activity of groups of neurons in frontal, parietal and occipital cortices during working memory maintenance. Maintenance of information was associated with phase synchronisation between fronto-parietal and occipital areas in alpha, beta and gamma frequency bands. The results further showed that synchronisation increased as working memory load increased. The participants' individual working memory capacity was predicted by synchrony in a network in which the intraparietal sulcus represented the central hub. These results suggest that synchronisation of electric activity between distal neural networks underlies the process of maintaining information in working memory.

Interactions between distinct frequency bands, termed cross-frequency coupling, can use the discrete packets mentioned earlier to transfer information between large scale networks (slower processing) and local neuronal populations (faster processing), thereby integrating activity across different spatial and temporal scales (Canolty & Knight, 2010). This type of integration is thought to be subserved by synchronisation of oscillatory phases between different brain regions. The oscillatory phase determines the degree of excitability of the neurons and the discharge times of these neurons, thereby affecting the relative timing of action potentials. This process is thought to promote neural communication and facilitate neural plasticity (Fell & Axmacher, 2011). One of the most studied phase-based mechanisms is phase-amplitude cross-frequency coupling, which refers to a statistical dependence between the phase of a low frequency band and the amplitude of a high frequency band (Canolty & Knight, 2010). Phase-phase cross-frequency coupling has also been studied in relation to working memory and long term memory (Fell & Axmacher, 2011).

There is evidence to suggest that cross-frequency coupling plays an important role in working memory (Axmacher et al., 2010; Friese et al., 2013; Holz, Glennon, Prendergast, & Sauseng, 2010; Rajji et al., 2016; Schack, Vath, Petsche, Geissler, & Möller, 2002). For example, Holz et al. (2010) conducted a study in which participants solved a visuospatial delayed match to sample task while their EEG was recorded. The results showed that comparing new with old information is associated with cross-frequency theta–gamma phase synchronisation in parieto-occipital brain areas in an early time window (150–200 ms after stimulus presentation). Matching items was linked to enhanced theta-gamma phase coupling in the right hemisphere, whereas non-matching items led to stronger theta-gamma phase coupling in the left hemisphere (posterior areas). Coupling between frontal theta and posterior gamma has also been observed during encoding of visual stimuli as demonstrated by Friese et al. (2013). In this study, theta-gamma phase-amplitude coupling was larger for subsequently remembered items than for forgotten items. The authors suggested that the coupling reflected interactions between a frontal control system and cortical representations that are activated and held in posterior brain regions (Friese et al., 2013).

1.1.3.3.1 Theta-phase coding models

There has been growing interest in the neurophysiological mechanisms associated with processing of multiple items in working memory (Fallon, Zokaei, & Husain, 2016). Recurrent feedback loops can explain how a single item is maintained, but have problems explaining why representations of multiple different items do not collapse into a single representation (Luck & Vogel, 2013). To avoid this, models have been proposed in which an item is represented by all the neurons that are in a synchronously firing cell assembly, and only one cell assembly fires at a given time point (see section 1.1.3.1). According to Luck and Vogel (2013), these types of models are consistent with slot-based models of working memory and present a solution to the problem of items collapsing into single representations: synchrony within a cell assembly helps maintain recurrent activation, whereas asynchrony between different cell assemblies prevents interference between the items' representations (Luck & Vogel, 2013). Research involving rats supports the idea of population coding by cell assemblies during memory processing - particularly in the hippocampal formation (Sakurai, 1996). Hippocampal pyramidal neurons are organized into assemblies whose activity synchronises transiently at a temporal resolution of about 25 ms – this matches the period of the hippocampal gamma oscillation. Organization into cell assemblies is thought to enable propagation and storing of information in neuronal circuits (Harris, Csicsvari, Hirase, Dragoi, & Buzsáki, 2003).

Lisman and Idiart (1995) proposed that each memory is stored in a different high-frequency subcycle (~40 Hz) of a low-frequency oscillation (5-12 Hz). Firing is sustained by an increase in membrane excitability, which is refreshed on each cycle of a network oscillation. This cycle is sometimes referred to as a cell assembly or an ensemble. One of the suggested mechanisms for the maintenance of firing is the presence of acetylcholine and serotonin. The authors suggested that this type of network can store multiple short-term memories in oscillatory subcycles. Lisman and Jensen (2013) extended this work to propose a *theta-gamma neural code* of working memory. Their theory assumes that there are largely non-overlapping assemblies active in different gamma cycles (at different theta phases), and because 4-8 gamma cycles can fit into a theta cycle, multiple items can be represented in a defined order. In other words, the maximal number of stored items is limited by the maximal number of gamma cycles that can fit into a theta cycle. The theta-gamma neural code has received widespread support from rodent studies (Belluscio, Mizuseki, Schmidt, Kempter, & Buzsaki, 2012; Bragin et al., 1995; Brown, Liu-Ambrose, Tate, & Lord, 2009; Colgin et al., 2009; Fuchs et al., 2007; Senior, Huxter, Allen, O'Neill, & Csicsvari, 2008) and some support from human studies (Axmacher et al., 2010; Kamiński, Brzezicka, & Wróbel, 2011).

Axmacher and colleagues (2010) used intracranial EEG recordings in human epilepsy patients to show that working memory maintenance of multiple items is associated with theta–gamma cross-frequency coupling in the hippocampus. Specifically, cross-frequency coupling of beta/gamma amplitude to theta phase was increased during working memory maintenance compared to baseline and a control condition. Increased working memory load was associated with a decrease in theta frequency band, which is line with the idea that longer cycles (e.g., 4 Hz instead of 5 Hz) are needed to accommodate more gamma cycles – more representations of items. Furthermore, Kamiński et al. (2011) demonstrated that verbal short term memory capacity can be predicted by theta-to-gamma cycle length ratio; however, a significant relationship was found only at the Fz site. The authors also reported that individual theta and gamma cycle lengths predicted verbal STM. Further support for these findings comes from a recent modelling study of brain oscillatory activity and its relationship with WM capacity and reasoning abilities (Chuderski & Andrelczyk, 2015). The model predicted individual differences in reasoning ability, the success of which depended on its theta-to-gamma cycle length ratio in the same way that the performance of participants depended on their WM capacity.

Since there are only a limited number of studies that directly test whether human working memory capacity can be explained by theta-phase coding models, further research is needed to determine whether consecutive items in a sequence are represented by locking of gamma cycles to consecutive phases of theta oscillations (Axmacher, 2016). A promising step in this direction is the recent study by Heusser, Poeppel, Ezzyat, and Davachi (2016), in which it was demonstrated that theta-gamma phase-amplitude coupling supports item sequence memory (i.e. temporal aspects of memory formation).

Based on evidence linking maintenance of information in working memory with (1) theta, alpha, and gamma-band activity, and (2) cross-frequency coupling between these frequency bands, Roux and Uhlhaas (2014) proposed a framework aiming to integrate disparate findings on the roles of neuronal oscillations in working memory maintenance. The authors proposed that gamma band oscillations play a general role in active maintenance of information, whereas theta band oscillations play a more specific role in the temporal organization of items. On the other hand, alpha band oscillations are not involved in maintenance as such, but are important for active inhibition of information that is not relevant to the task. Cross-frequency coupling between low (theta, alpha) and high (beta, gamma) frequencies enable processing of distinct WM information. Specifically, an alpha-gamma code is involved in maintenance of sensory-spatial working memory items whereas a theta-gamma code is involved in sequential working memory information (Roux & Uhlhaas, 2014). Presently, the framework provided by Roux and Uhlhaas (2014) presents one of the most prominent models of the oscillatory basis of working memory.

1.1.3.3.2 Individual differences

Few studies have focused on the neural underpinning of individual differences in working memory performance. Studies based on the neuro-electric approach have revealed mixed results (Angelakis, Lubar, Stathopoulou, & Kounios, 2004; Bashivan, Bidelman, & Yeasin, 2014; del Río et al., 2012; Dong, Reder, Yao, Liu, & Chen, 2015; Gulbinaite, Johnson, de Jong, Morey, & van Rijn, 2014; Klimesch, Schimke, & Pfurtscheller, 1993; Lebedev, 1994; Pahor & Jaušovec, 2017; Clark et al., 2004; Stam, 2000; Vogel & Machizawa, 2004; Wiegand et al., 2016). This diversity is further enlarged by the variety of methodological approaches used, which were based on resting state eyes closed/open EEG recordings (Angelakis, Lubar, & Stathopoulou, 2004; Angelakis, Lubar, Stathopoulou, & Kounios, 2004; del Río et al., 2012), data obtained under cognitive load

(Gulbinaite et al., 2014), or a combination of both (Klimesch et al., 1993; Pahor & Jaušovec, 2017). An additional source for conflicting results are the different computational algorithms used for the derivation of brain activity measures and biomarkers, ranging from linear (Bashivan et al., 2014; Vogel & Machizawa, 2004) to nonlinear (del Río et al., 2012; Stam, 2000), analysed in time (Gulbinaite et al., 2014; Wiegand et al., 2016) or frequency domains (Stam, 2000), or in a combination of both (Dong et al., 2015).

In general, increased ERP amplitudes were observed in individuals with high visual WM capacity as compared to low ones (Dong et al., 2015; Vogel & Machizawa, 2004; Wiegand et al., 2016). ERP responses capture the time-locked activity of the brain and therefore fail to detect induced brain activity, which is not directly phase-locked. This activity is best analysed with event-related synchronisation/desynchronisation (ERD/ERS) as demonstrated by Pfurtscheller (1999). Bashivan et al. (2014) applied this methodology to the same tasks as used by Vogel and Machizawa (2004), yet did not replicate their findings.

Given the strong relationship between intelligence and working memory (Buehner et al., 2005; Colom, Abad, Quiroga, Shih, & Flores-Mendoza, 2008; Deary, 2012; Engle, Tuholski, Laughlin, & Conway, 1999; Unsworth & Engle, 2007), some authors (del Río et al., 2012; Nussbaumer, Grabner, & Stern, 2015) have also explored the possibility of neural efficiency in working memory, similar to the one observed for intelligence demonstrating a negative correlation between brain activity under cognitive load and intelligence (for a review see Neubauer & Fink, 2009). These studies further found that neural efficiency was corroborated mainly when participants work on tasks of low to medium complexity and is particularly prominent in frontal brain regions (Doppelmayr, Klimesch, Hödlmoser, Sauseng, & Gruber, 2005). Although two studies (del Río et al., 2012; Nussbaumer et al., 2015) found some confirmation for neural efficiency in working memory performance, it is difficult to link the findings directly to working memory, or to neural efficiency. The study by Nussbaumer et al. (2015) employed the n-back task with increasing complexity (n-back level) as a measure of task difficulty. As stressed by Kane, Conway, Miura, and Colflesh (2007), the cognitive mechanisms involved in performance on the n-back task are not well understood, and its relationship to other complex working memory tasks is also unclear (Shipstead, Hicks, & Engle, 2012). On the other hand, the study by del Río et al. (2012) based the neural efficiency claims on MEG resting state connectivity related to individual differences on a verbal memory span task. However, neural efficiency is usually determined in relation to differences between resting and cognitive load conditions, hence further research is needed to clarify this relation.

1.2 Transcranial electrical stimulation

Transcranial electrical stimulation (TES) is a form of non-invasive brain stimulation that involves the application of weak electrical currents directly to the head. It is an umbrella term for at least three techniques: (1) direct current, (2) alternating current, and (3) random noise stimulation (Herrmann, Rach, Neuling, & Strüber, 2013). The applied currents can be constant over a time (transcranial direct current stimulation - tDCS), or they can alternate at a specific frequency (transcranial alternating current stimulation - tACS), or in a random frequency window (transcranial random noise stimulation - tRNS). The oscillations and frequencies can be also combined into oscillatory tDCS (otDCS). In tACS, the waveform of the alternating current is usually sinusoidal, but it can also be rectangular or have a more complex shape (Herrmann et al., 2013). Some authors also categorize TES techniques with respect to the number and shape of stimulation electrodes used, distinguishing between approaches with two big sponge electrodes (tDCS; anode/cathode, 25 cm^2) and high-definition transcranial direct current stimulation HD-tDCS. In HD-tDCS, smaller electrodes are used (e.g., Pi electrodes, 3.1 cm^2) that are optimized for a specific target brain area to be stimulated. For example, a 4 x 1 ring montage with a central electrode (anode/cathode) and four return electrodes can be used in HD-tDCS (Dmochowski, Datta, Bikson, Su, & Parra, 2011). A review of 693 different TES sessions confirmed that it is a painless and safe technique. Importantly, no adverse events were reported. The review also demonstrated that alternating currents appear to be less perceivable than tDCS (Fertonani, Ferrari, & Miniussi, 2015). For a detailed description of different non-invasive brain stimulation techniques see Jaušovec & Pahor (2017).

These transcranial electrical stimulation techniques do not induce activity in resting neuronal networks, but influence or alternate spontaneous nerve activity. The amount and the direction of effects depend on the previous physiological state of the stimulated neural structures. The stimulation intensities of TES are not high enough to trigger discharge in resting neurons or axons and do not cause massive synchronised discharge of action potentials as transcranial magnetic stimulation (TMS) does (Paulus, 2011; Woods et al., 2016). Furthermore, these methods share basic electrode montage and low-intensity stimulation features (1 – 2 μA) and their application is generally regarded as safe. The electrodes do not directly contact the skin: an electrolyte is used as a buffer between the electrode and the skin. The experimental procedures require blinding of participants (single-blind) and blinding of experimenters (double-blind) is even more desirable. This can be achieved with active and sham experimental conditions, either performed on the same individuals or on matched samples. The sham condition, which resembles a placebo condition, involves the application of the same current as in the active condition, except that the stimulation only lasts a few seconds. The participants feel the initial itching sensation, but the stimulation duration is too short to induce after effects (Cohen Kadosh, 2015; Paulus, 2011; Wagner, Valero-Cabre, & Pascual-Leone, 2007; Woods et al., 2016). Setting up the sham condition is straightforward since TES does not make any noise. This represents another advantage over TMS, which is characterized by a loud clicking sound that is difficult to reproduce in sham conditions (Sommer et al., 2006).

Transcranial alternating current stimulation (tACS) is a relatively new stimulation technique in which weak oscillating electrical currents are applied to the head (Thut & Miniussi, 2009). In this technique one electrode serves as an anode and the other as a cathode during one half cycle of a tACS oscillation, whereas in the next half cycle the pattern reverses – the former anode is now the cathode and vice versa. Because the current strength increases and decreases following a half sine wave, the membrane potential is not affected (Woods et al., 2016). Instead, the goal of tACS is to modulate brain oscillations in a frequency-specific manner (Herrmann et al., 2013). This is thought to occur via entrainment of endogenous oscillations at the frequency of stimulation (Ali, Sellers, Frohlich, & Fröhlich, 2013; Herrmann et al., 2013).

There is evidence to suggest that tACS leads to frequency-specific power enhancement of EEG oscillations (Helfrich et al., 2014; Kasten, Dowsett, & Herrmann, 2016; Neuling, Rach, & Herrmann, 2013; Vossen, Gross, & Thut, 2015; Witkowski et al., 2016; Zaehle, Rach, & Herrmann, 2010). This was first shown in an EEG study in which tACS applied at individual alpha frequency (IAF) increased individual alpha power, but did not affect lower and upper alpha power (Zaehle et al., 2010). Neuling and colleagues (2013) reported that the induced alpha power enhancement remained present up to 30 minutes after stimulation onset, however, this effect depended on endogenous IAF power: tACS-induced aftereffects were present in the low IAF power condition (eyes open) whereas in the high IAF power condition (eyes closed) no aftereffects were observed. Similar findings were reported by a modeling study in which EEG scalp activity was simulated under tACS (4 – 16 Hz) and under no stimulation (Merlet et al., 2013). The authors reported that only tACS frequencies ranging from 8 to 12 Hz affected alpha power.

A review of 22 tACS and otDSC studies by Veniero, Vossen, Gross, and Thut (2015) showed that aftereffects were reported in all but three studies (Antal et al., 2008; Krause et al., 2014; Strüber, Rach, Neuling, & Herrmann, 2015). The null effects reported in these three studies could be explained by insufficient stimulation intensity and duration and by the mental characteristics of subjects. While all other studies showed some aftereffects, they did not reveal a consistent pattern in aftereffects in relation to the stimulation frequency, especially when the frequency was not in the alpha band range. The authors suggested that entrainment or resonance of cortical networks cannot explain all aftereffects on brain oscillations. The results of a recent study by Vossen et al. (2015) also point in this direction. IAF tACS resulted in expected alpha power enhancements, however, the comparison between intermittent tACS protocols with a sham condition suggested that spike-timing dependent plasticity rather than entrainment is the main mechanism for the observed tACS aftereffects. It is assumed that tACS entrainment (periodic hyper- and depolarization of neural membranes) induces longer-lasting synaptic plasticity that results in frequency-specific changes in oscillatory activity. The model suggests that when neurons are stimulated at a frequency slightly slower than the dominant frequency (tACS < IAF), the synapse is strengthened and it is weakened when pre-synaptic events follow post-synaptic events of the next cycle (tACS > IAF). It was further suggested that tACS-entrainment effects may not be strong enough to outlast the stimulation period, hence spike-timing dependent plasticity is the mechanism that underlies offline enhancement of oscillatory brain activity (Vossen et al., 2015). This is of particular relevance to the present research, as tACS was applied offline in all of the studies.

Another key characteristic in alternating current stimulation is that the phase of the EEG can become phase-locked to the alternating current of tACS. It should be noted that in the studies presented in this thesis, tACS was applied via two electrodes, which does not allow for manipulation of the phase of stimulation. At least three electrodes are needed to enable anti-phase or in-phase stimulation (Antal, Alekseichuk, & Paulus, 2016). It has been suggested that if phase synchronisation reflects information transfer between two brain areas, oscillations in the two areas would show a phase lag corresponding to the conduction delay between these regions (Fell & Axmacher, 2011). The idea that regions with direct transmission have a phase lag above 0° was supported in a tACS study by Tseng, Chang, Chang, Liang, and Juan (2016). On the other hand, this may not always be the case; there is evidence to suggest that communication between certain brain regions may be supported by zero-lag phase synchronisation in the theta frequency band (Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012). Specifically, Polanía et al. (2012) demonstrated that frontoparietal theta tACS delivered in-phase (0° phase difference) significantly improved reaction times of a delayed letter discrimination task as compared to placebo stimulation. In contrast, frontoparietal theta tACS delivered out-of-phase (180° phase difference) deteriorated performance. These findings are in line with contemporary theta-phase coding models.

The growing number of tACS studies promises to bring a better understanding of the mechanisms of action through which tACS interacts with endogenous oscillations. Presently, it is believed that these mechanisms include entrainment of oscillations and spike-timing dependent plasticity (Zaehle, Rach, Herrmann, & Paulus, 2010). For example, a novel approach in which tACS was combined with whole-head MEG enabled the reconstruction and mapping of entrained brain oscillations underneath the stimulator electrodes (Witkowski et al., 2016). The results confirmed that amplitude-modulated tACS has electrode site-specific effects that can be used for frequency-specific entrainment of brain oscillations. Moreover, the authors demonstrated that the entrained brain oscillations underneath and in proximity of stimulation electrodes, measured by phase-locked activity, can be mapped (Witkowski et al., 2016). A five year view of promising approaches in this field involve individualized targeting of tACS, feedback stimulation, and spatial targeting, all of which could contribute to the development of novel tACS-based treatments for neurological and psychiatric disorders (Fröhlich, Sellers, & Cordle, 2015).

There are five methods available in neuroscience to modulate EEG oscillations (Herrmann, Strüber, Helfrich, & Engel, 2016, p. 14): "1) Neuromodulation via pharmacology, 2) Rhythmic sensory stimulation/steady-state-evoked potentials, 3) EEG-neurofeedback, 4) Repetitive transcranial magnetic stimulation (rTMS), and 5) transcranial alternating current stimulation (tACS)." In the present research, tACS was chosen for neuromodulation because it provides the unique opportunity to directly modulate the ongoing rhythmic brain activity at the frequency of the applied current (Herrmann, 2016) without the presentation of sensory stimuli. It should be noted that stimulation effects can also be expected at harmonics and sub-harmonics of the stimulation frequency (Ali et al., 2013; Helfrich et al., 2014). Given that coupling of cortical oscillations between discrete brain regions triggers changes within the whole functional network, it is assumed that the effects of tACS on oscillatory brain activity are not linear nor are they limited to the area of stimulation (Antal et al., 2016).

2. Research problem and hypotheses

Neurophysiological studies on humans that show increased activity of certain brain oscillations during working memory maintenance show mainly correlational results, thereby not excluding the possibility that these brain oscillations are merely epiphenomenal. In order to gain a better understanding of the neural basis of working memory, one must establish causal relations between specific brain oscillations and the processes of encoding, temporary storage, and retrieval of information. It is also imperative to define the brain regions that are involved in these processes.

The research problem was tackled with a two-step approach that involved a series of empirical studies involving healthy human participants:

1. A *correlative approach* was used to examine the brain oscillatory substrates of working memory performance. EEG oscillations represented the dependent variables and experimental manipulations related to cognitive processes represented the independent variables. Specifically, two studies were conducted with the goal of examining: (1) the relation between working memory capacity and neuro-electric patterns of brain activity in selected frequency bands and (2) the relation between working memory capacity and theta-gamma coding.
2. *A neuromodulatory approach* was employed using non-invasive transcranial alternating current stimulation. In this technique, an exogenous oscillation is applied to the scalp with the goal of modulating endogenous oscillations. In this approach, the oscillations represented the independent variables and the performance on the task represented the dependent variable. The advantage of this method is that it has the potential to demonstrate the causal role of EEG oscillations in working memory (Herrmann et al., 2016).

The main research question was: What are the roles of brain oscillations, particularly in theta and gamma frequency bands, in working memory? Specifically, the aim was to:

1. Compare brain oscillatory activity in individuals with low and high working memory capacity (Study 1).
2. Determine whether resting-state theta and gamma frequency bands, and the interaction between these frequency bands, are related to verbal and spatial working memory capacities (Studies 1 and 2).
3. Use tACS to investigate whether theta and gamma frequency bands are causally related to working memory. Determine which parameters of tACS are most appropriate for brain stimulation with the goal of increasing working memory capacity (Studies 3-5).

With respect to the goals mentioned above, the following hypotheses were set:

1. Individuals with higher working memory capacity will display neural efficiency, similar to the one observed for the intelligence construct (Study 1).
2. Resting-state theta and gamma frequency bands and particularly the interaction between these bands will correlate with verbal and spatial WM capacities. This hypothesis is based on the theta-gamma neural code (Lisman in Jensen, 2013) (Studies 1 and 2).
3. tACS in theta and gamma frequency bands will improve performance on working memory tasks compared to sham stimulation. These results will causally link theta and gamma oscillations with working memory processes (Studies 3-5).

3. Method

The materials and methods used in the studies are discussed in detail in Chapters 4-8. Here I present only the methods that were applied in the same way across the studies. The experiments were conducted in line with the recommendations of the ethics committee of the Slovene Psychological Association and in accordance with the Declaration of Helsinki.

EEG data acquisition: EEG activity was monitored over 19 scalp locations based on the 10-20 Electrode Placement System using a Quick-Cap with sintered (Silver/Silver Chloride; 8mm diameter) electrodes. All leads were referenced to linked mastoids (A1 and A2) and a ground electrode was applied to the forehead. Vertical eye movements were recorded via electrodes placed above and below the left eye. Electrode impedance was maintained below 5 kΩ. The digital EEG data acquisition and analysis system (SynAmps RT) had a band-pass of 0.15 - 100.0 Hz. The 19 EEG traces were digitized online at 1000 Hz with a gain of 10x and stored on a hard disk.

Transcranial alternating current stimulation: tACS was applied offline via two electrodes (7×5 cm) that were placed in saline-soaked sponges (DC-stimulator plus, Neuroconn, Ilmenau, Germany). It has been demonstrated that the aftereffects of tACS persist for at least 30 minutes (Neuling et al., 2013). In the present studies, behavioural and EEG measures were collected within 25 minutes after the end of the stimulation period. Recent research suggest that the aftereffects of tACS may last up to 70 minutes (Kasten et al., 2016). The waveform of the stimulation was sinusoidal without DC offset and a 0^{o} relative phase. The impedance was kept below 10 k*Ω*. The magnitude of the current was individually determined on the first session based on thresholds for skin sensations (Zaehle, Rach, & Herrmann, 2010). The amplitude was increased stepwise by 250 μA (duration per step = 30 s) starting with 1250 μA until a maximum of 2000 μA was reached. After each increase in amplitude, the participants were asked to report the presence of a skin sensation. For based on thresholds for skin sensations the remaining experiment, stimulation intensity was kept 250 μA below the lower threshold for skin sensations. In the sham session, tACS was applied for 30-60 seconds. In the active session, tACS was applied for 15 minutes – less than the recommended time limit for TES, which is 20 minutes (Bikson, Datta, & Elwassif, 2009). These parameters of tACS were selected based on established and safe protocols reported in the literature (Zaehle, Rach, & Herrmann, 2010).

According to dynamic systems theory, entrainment is strongest when the stimulation frequency is at (or close to) the brain network's preferred frequency (Ali et al., 2013; Vossen et al., 2015). The stimulation frequency should therefore be matched to the frequency of the endogenous oscillatory state, which presents a challenge for tACS research since most EEG frequency bands, with the exception of alpha, do not show preferred resonance or peak frequency (Ali et al., 2013). In an attempt to match the stimulation frequency to the endogenous oscillatory state, oscillating theta currents were adjusted to the individual alpha peak frequency (IAF) of each participant in the studies presented in Chapters 6 and 7, whereas in the study presented in Chapter 8, a method proposed by Kamiński et al. (2011) was used to determine the stimulation frequency on an individual basis.

4. Individual differences in working memory capacity

4.1 Introduction

The objective of this study was to elucidate the relationship between individual differences in visual working memory capacity and neuro-electric patterns of brain activity. For that purpose we adopted the event-related desynchronisation and event-related synchronisation (ERD/ERS) methodology that detects induced brain activity, which is not directly phase-locked (Pfurtscheller, 1999). The analysis was performed in three individually determined narrow frequency bands (theta, alpha and gamma) for which there is robust evidence that they are related to cognitive processes contained in the WM construct (Gevins et al., 1997; Huang et al., 2013; Klimesch, 2012; Roux & Uhlhaas, 2014; Sauseng et al., 2009; Sauseng, Klimesch, Doppelmayr, et al., 2005; Sauseng, Griesmayr, Freunberger, et al., 2010). Resting eyes-closed EEG data was used to determine individual alpha, theta, and gamma frequency bands. To determine the individual theta and gamma bands, a novel approach was introduced based on the method proposed by Kamiński, Brzezicka, and Wróbel (2011). In this procedure, the characteristic theta and gamma frequency is determined at the highest coupling level between these frequencies in each channel. This approach is grounded on recent theoretical assumptions in which theta-gamma frequency coupling is seen as a key component of WM capacity (Sauseng et al., 2009; Van Vugt et al., 2014). It is assumed that recurrent feedback loops between sets of neurons maintain single bits of information in an active state. When there are more elements in the sensory input, synchronous oscillations of a cell assembly prevent these elements from collapsing into a single representation. In that way synchrony *within* a cell assembly keeps the element available in WM representations, whereas asynchrony *between* cell assemblies enables more elements to be stored in a WM representation. Multiple firing makes the cell assembly decay and the elements to vanish from the WM representations. This represents the capacity constraint of working memory (Lisman & Idiart, 1995; Raffone & Wolters, 2001). In this model, gamma band activity, which is characteristic for representations of items in visual areas, is reactivated by top-down attention in the theta to alpha range (Van Vugt et al., 2014). It is further assumed that these top-down processes are mediated by long-range synchronisation between different neuronal assemblies. Inter-regional synchronisation during WM tasks has been reported for alpha, theta, and gamma frequencies (Crespo-Garcia et al., 2013; Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser, 2002; Palva et al., 2010; Payne & Kounios, 2009; Sarnthein, Petsche, Rappelsberger, Shaw, & von Stein, 1998; Sauseng et al., 2004; Sauseng, Klimesch, Doppelmayr, et al., 2005; Sauseng, Griesmayr, Freunberger, et al., 2010). Therefore, in the present study not only power analysis but also the connectivity between different brain areas was analysed with induced event-related coherence (ErCoh).

Since the main objective of the study was to characterize specific dimensions of individual differences in WM capacity rather than to estimate the exact effect size, an extreme-groups design was used (Yarkoni & Braver, 2010). Because group assignment was based on performance on the visual-array comparison task (Luck & Vogel, 1997), we decided to control for possible sex differences. Recent research has shown that correlations between task performance and IAF measures showed a sex specific pattern – in males the relation tended to be stronger for the amount of correct answers, whereas in females it was stronger for processing speed (Pahor & Jaušovec, 2017). Sex differences in cognitive performance and sensory processing could explain these results. For instance, Irwing (2012) reported that females outperformed males on tasks of processing speed. It has been further shown that females have larger visual fields than males (Burg, 1968) and they are also better at visual scanning of objects (Kimura, 1999).

Most of the studies on individual differences in WM performance focused on oscillatory EEG or MEG correlates in specific WM processes, or examined the responses throughout the entire trial, making no distinction between specific processes (e.g., Bonnefond & Jensen, 2012; Dong, Reder, Yao, Liu, & Chen, 2015; Stam, 2000; Zhang, Zhao, Bai, & Tian, 2016). In the present study, the relation between WM capacity and brain oscillatory activity was investigated during each of the three processes (encoding, maintenance, and retrieval) associated with the WM task. Even though the study was to some extent exploratory, certain predictions were made:

1. Neural efficiency would predict more theta ERD, gamma ERD, and alpha ERS in individuals with superior WM capacity (Neubauer & Fink, 2009). It was further

expected that this relation would be moderated by the number of items in the visual array, similar to the findings reported by Doppelmayr, Klimesch, Hödlmoser, Sauseng, & Gruber (2005) for complex Raven's matrices. A relation between brain activity and set size would also be predicted by the model of discrete slots, suggesting that working memory capacity is limited by a maximal number of slots, each storing an object representation (for a review see Luck & Vogel, 2013). In contrast, the continuous single resource model assumes that working memory capacity is a flexible resource that can be spread among all elements in the sensory input (for a review see Ma, Husain, & Bays, 2014). From a neurocognitive perspective, slot models would predict that an increase in the number of sensory input elements would result in increased brain activity reaching a plateau when the maximal capacity is attained. In contrast, for continuous resource models the number of elements in sensory input has no influence on engaged brain resources. The same amount of resources are engaged in one element or divided among several input elements (Luck & Vogel, 2013; Ma et al., 2014). Brain imaging studies employing ERP or fMRI have shown that brain activity is sensitive to the number of elements in sensory input reaching an abrupt plateau when memory load exceeds the maximal capacity thus supporting the discrete slots model (Todd & Marois, 2004; Vogel & Machizawa, 2004; Xu & Chun, 2006).

2. With respect to connectivity measures (ErCoh), main differences in frontoparietal networks in the theta and gamma frequency bands were expected. This hypothesis is grounded on robust findings relating WM to gamma and theta brain oscillations in fronto-parietal brain areas (Lisman & Jensen, 2013; Sauseng et al., 2009; Sauseng, Griesmayr, & Freunberger, 2010; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005; Sreenivasan, Curtis, & D'Esposito, 2014; for a review see D'Esposito & Postle, 2015).

3. No sex-related differences in relation to WM capacity were expected. This hypothesis was based on the findings by Luck and Vogel (1997), who demonstrated that storage capacity is not influenced by processes related to perceiving and encoding of visual stimuli or limited by decision factors for which sex differences have been reported (Burg, 1968; Jaušovec & Jaušovec, 2009; Kimura, 1999).

4. Based on recent research (Kamiński et al., 2011), it was predicted that average

theta/gamma cycle length ratios would be positively related to WM capacity.

4.2. Method

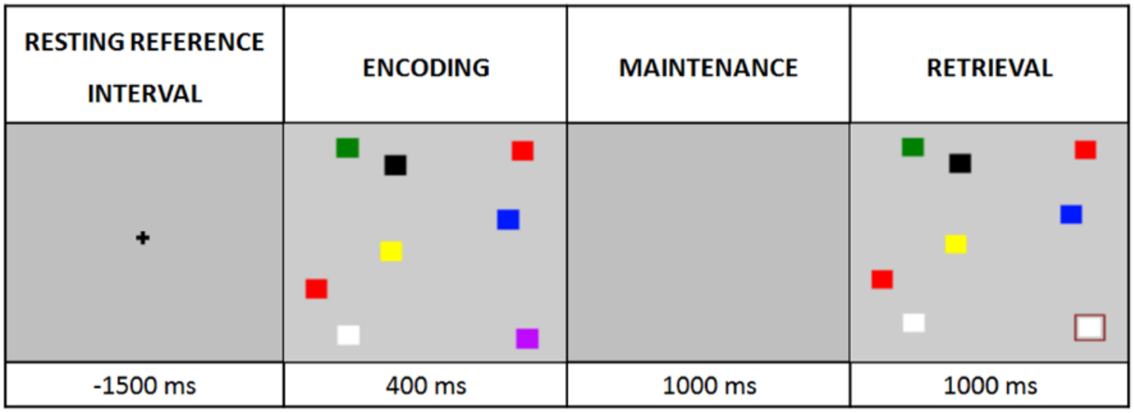
4.2.1. Participants

Sixty students were selected from a pool of participants (*N* = 125) that had been tested on a visual-array comparison task during which their EEG was recorded. The task provided an estimation of individual visual working memory capacity (Luck & Vogel, 1997). The experiment was undertaken with the understanding and written consent of each participant. The students represented two extreme groups: the lowest (N = 30; 11 males and 19 females) and highest (N = 30; 12 males and 18 females) performers, which were determined by taking 1 standard deviation above and below the mean. The average age of the low performers was 21 years and 11 months (SD = 3.89 months), while for the high performers it was 21 years and 5 months (SD = 4.53 months). Average performances on the visual array comparison task in the low and high visual WM capacity groups are presented in Table 1.

4.2.2. Procedure

The participants performed on a change detection task termed the visual-array comparison task (Luck & Vogel, 1997) while their EEG was recorded (see Figure 1). After 20 practice trials the participants completed the experimental trials. The visual-array comparison task is supposed to measure the scope of attention, i.e. the capacity of the focus of attention (Cowan et al., 2005). On each trial, an array of coloured squares was presented for 400 ms, followed by an inter-stimulus interval of 1000 ms, after which a second array similar to the first one was presented for 1000 ms. One square in the second array was encircled and the participant had to press “2” on the response pad if the square differed in colour from the square in the previously presented array, or press “1” if it did not differ in colour. Three series with 4, 6, and 8 simultaneously presented coloured squares were used. Each series consisted of 16 trials. The number of correct and incorrect responses for each set size were used to compute the WM capacity score for each participant (i.e., the number of items successfully held in memory). WM capacity was also calculated for each set size and participant using the WM capacity index, K, defined as $K = S(H-F)$, where S is the number of items in the memory array, H is the hit rate and F is the false alarm rate (Cowan, 2001; Pashler, 1988). Also determined were the reaction times for each response averaged for each K and across set size. The STIM^2 stimulator (Compumedics Neuroscan Systems, Charlotte, NC, USA) was used to generate all task items.

Figure 1: *Example of the time sequence of task presentation on one trial (set size 8) for the visual-array comparison task (Luck & Vogel, 1997).*



4.2.3. EEG recording and quantification

The participants were asked to relax with their eyes closed for 5 minutes during which their EEG was recorded. EEG data was also collected during performance on the visual-array task. Resting EEG data was used to determine individual alpha, theta, and gamma frequencies. For each subject, IAF was calculated by averaging peak alpha frequencies of all 19 electrodes (Angelakis, Lubar, Stathopoulou, et al., 2004). First, power spectra were calculated over the entire epoch length of 11s and automatically screened for artifacts. Second, an automatic peak detection procedure found the highest peak (maximum alpha power) in a 7 to 14 Hz window (frequency steps of 0.09 Hz) separately for each lead. This method was used because it is more adequate for studying endophenotypic qualities during resting eyes-closed EEG sessions (Hooper, 2005; Klimesch, Schimke, & Pfurtscheller, 1993) than the peak frequency centre of gravity method proposed by Klimesch et al. (1993), which is used for eyes-open conditions.

Individual theta and gamma frequencies were determined based on the method proposed by Kamiński et al. (2011). EEGLAB toolbox (freely available from HYPERLINK http://www.sccn.ucsd.edu/eeglab/) for MATLAB (The MathWorks, Natick, MA, USA) was used to filter the signal forward and backward in time in sequential bands for theta (4–5 Hz, 5–6 Hz, …, 8–9 Hz) and gamma (25–26 Hz, 26–27 Hz, ..., 47–48 Hz) oscillations. The envelope of each theta band was correlated with the envelope of each gamma band using Pearson's *r* correlations. The two frequency bands that had the highest positive correlation between the envelopes were defined as characteristic theta and gamma frequency bands in a given channel (Kamiński et al., 2011). Individual theta and gamma frequencies were determined by taking the average of the characteristic values across 19 electrodes. These individual frequencies were then used to calculate average theta/gamma cycle length ratios for each individual (Bekisz & Wróbel, 1999; Kamiński et al., 2011; Wrobel, Ghazaryan, Bekisz, Bogdan, & Kaminski, 2007).

Neuroscan software Version 4.5 (Compumedics, El Paso, TX, USA) was used to remove ocular artifacts from continuous EEG recordings obtained during task performance. In the next step, epochs were extracted ranging from -1500 ms to 3400 ms. Sweeps were automatically rejected if the voltage in the VEOG channel exceeded ± 100 µV. In total, less than 1.0 % of the epochs were excluded from further analysis. Induced ERD/ERS and event-related coherence (ErCoh) measures were used to investigate differences in neuro-electric brain activity in individuals with low and high working memory capacity. Complex demodulation with a simultaneous signal envelope computation was used to quantify the induced ERD/ERS values (Pfurtscheller, 1999). The raw data for each channel was multiplied point by point by a pure cosine based on the centre frequency (individual alpha, theta, and gamma frequencies) and by a pure sine with the same centre frequency. The time series (multiplied by a pure sine and cosine) were then low-pass filtered by the half-bandwidth (1 Hz). The quantification of induced ERD was done using the intertrial variance method, which gives a measure of induced, non-phase-locked activity. The formulas used were as follows (Pfurtscheller, 1999):

$$\mathrm{IV}_{(j)} = \frac{1}{N-1}\sum_{i=1}^{N}\left\{y_{f(i,j)} - \bar{y}_{f(j)}\right\}^2 \qquad (1)$$

In equation (1) N is the total number of trials, yf (i, j) is the j-th sample of i-th trial data, and $\bar{y}_{i,n}$ is the mean of the j-th sample over all trials. The ERD (IV) data were used to calculate the ERD/ERS values which were defined as the percentage change of the power at each sample point (Aj) relative to the average power in the resting reference interval (R) preceding the stimulus onset (–800 ms to –300 ms):

$$\mathrm{ERD}_j = \frac{R - A_j}{R} \times 100\% \tag{2}$$

A positive ERD in formula (2) indicates the percentage of power decrease (in relation to the average power during resting) or desynchronisation and a negative ERD indicates the percentage of power increase or synchronisation – ERS (Pfurtscheller, 1999). The ERD/ERS values for each frequency (alpha, theta, and gamma) and WM process (encoding, maintenance and retrieval) were determined for each electrode and collapsed over different electrode locations, distinguishing the hemispheres as well as frontal, central and parieto-occipital brain areas. The electrode positions were aggregated as follows: frontal left (Fp1, F3, F7), frontal right (Fp2, F4, F8), central left (T3, C3), central right (T4, C4), parieto-occipital left (P3, T5, O1), and parieto-occipital right (P4, T6, O2).

The induced ErCoh was determined from the same time series: $y_{i,n}^{(j)}$. The time-dependent complex correlation between each pairwise combination of channels, i and k, was then computed as:

$$\hat{\rho} = \frac{\sum_{j=1}^{J}\left[y_{i,n}^{(j)} - \bar{y}_{i,n}\right]\left[y_{k,n}^{(j)} - \bar{y}_{k,n}\right]^{*}}{\sqrt{\sum_{j=1}^{J}[y_{i,n}^{(j)} - \bar{y}_{i,n}]^{2}\sum_{j=1}^{j}[y_{k,n}^{(j)} - \bar{y}_{k,n}]^{2}}} \tag{3}$$

In equation (3) '*' denotes complex conjugation and $\bar{y}_{i,n}$ are the complex average potentials calculated by averaging the complex time series for channel i across all trials.

$$\bar{y}_{i,n} = \frac{1}{R}\sum_{r=1}^{R} y_{i,n}^{(r)};\ n = 0,1,\ldots,N-1 \tag{4}$$

In this way, the coherence time course is computed at discrete steps of time equal to the sampling interval of the EEG trials.

Because of the potential for spurious coherence due to volume conduction effects, surface Laplacian EEG methods are usually used to minimize these effects (Srinivasan, Winter, Ding, & Nunez, 2007). It has been shown that volume conduction is most pronounced for EEG recordings with densely spaced electrodes (< 7 cm) in the high frequency range (40-50 Hz) (Nunez & Westdorp, 1994). On the other hand, Thatcher (2012) reported that Laplacian transforms distort physiologically generated phase differences and invalidate the use of these transforms in the computation of coherence and phase differences. In the present study, we were mainly interested in ErCoh differences between groups and not in the absolute values of coherence, therefore no Laplacian transform was applied.

Coherence values were estimated for all electrode pairs. In that way, 171 coherence measures were computed for each process, giving a total of 513 coherence measures. Subsequently, the Fisher Z-transform was applied to the coherence values. This serves not only to normalize the distributions of values, but also to reduce the difference in confidence intervals between greater and smaller values.

4.2.4. Statistical analysis

SPSS version 23 (IBM Corp, 2015) was used for the statistical analysis. Behavioural (WM capacity, K and Reaction Time – RT) as well as neuropsychological measures (frequency and ERD/ERS) were analysed with a General Linear Model (GLM – univariate, or for repeated measures as required) including the between group variables of group (high/low performers) and sex (male/female) and the within group variables of hemisphere (left/right), location (frontal, central and parieto-occipital); K (set size: 4, 6, 8). A separate GLM analysis was conducted to determine the temporal dynamic of ERD/ERS between-group differences in each WM process (encoding, maintenance and retrieval). For that purpose, the ERD/ERS measures were collapsed into 100 ms time intervals from stimulus onset till 2400 ms.

ErCoh differences between the low and high WM capacity groups were directly compared with independent sample t-tests. The resulting *p* values were corrected using false discovery rate (FDR) with $p < 0.05$ (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001). In contrast to familywise error rate corrections such as Bonferroni, which controls for the probability of single errors in rejection of null hypotheses, FDR works by controlling the proportion of the rejected null hypotheses and is therefore less conservative than Bonferroni.

4.3. Results

4.3.1 Behavioural results

The univariate analysis of variance for WM capacity showed a significant main effect of group ($F(1,56) = 275.36$; $p < .001$; $\eta^2 = .83$) with no significant sex-related differences. Also significant was the GLM conducted for K for each set (4, 6, and 8). Besides showing a significant main effect of group ($F(1,56) = 275.45$; $p < .001$; $\eta^2 = .83$), the interaction effect between set size and group was significant ($F(2,112) = 24.18$; $p < .001$; $\eta^2 = .30$). No significant sex-related differences were observed. The subsequent t-tests are summarized in Table 1. These results are expected given the selection criteria for group recruitment.

***Table 1**: Means, standard deviations, and independent sample t-tests with Cohen's d, for the high and low working memory group for WM capacity and K for each set size (4, 6, 8).*

Measure	**High WM capacity**		**Low WM capacity**		***t- test df* (58)**
	M	***SD***	***M***	***SD***	
Capacity	5.09	0.25	2.63	0.71	$t = 16.93$; $p < .001$; $d = 4.45$
K = 4	3.65	0.34	2.39	0.73	$t = 8.56$; $p < .001$; $d = 2.25$
K = 6	5.40	0.57	2.75	1.36	$t = 9.83$; $p < .001$; $d = 2.58$
K = 8	6.22	0.25	2.75	0.71	$t = 13.07$; $p < .001$; $d = 3.43$

Reaction time (RT) analyses showed no significant differences in relation to group or sex, neither for the averaged RT, nor for the separate RTs for each K.

4.3.2 EEG results

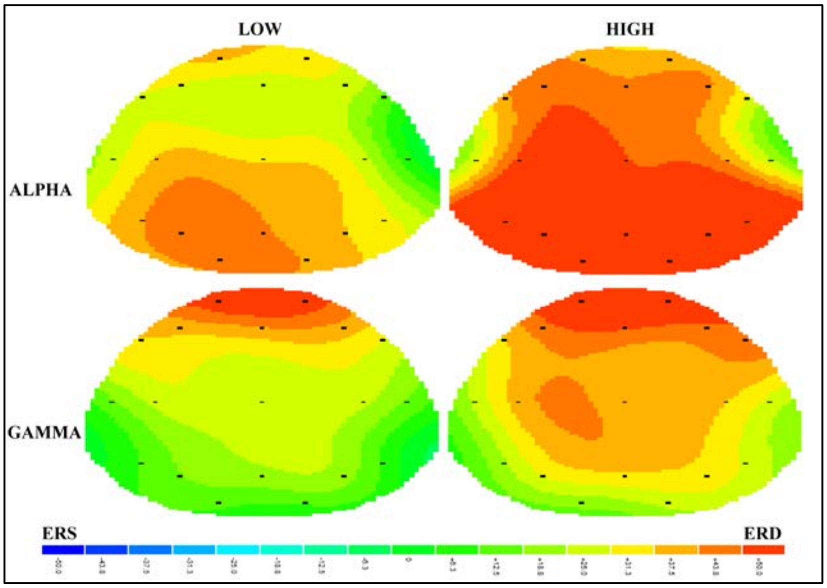
None of the GLM analyses in relation to frequency (individual alpha, theta, and gamma) showed significant between group or sex differences. The univariate analysis of variance conducted for the average theta/gamma cycle length ratios were not significant ($F(1,56) = 2.56$; $p = .12$; $\eta^2 = .04$), however, the high WM group tended to have higher theta/gamma cycle length values than the low WM group.

4.3.2.1 EEG synchronisation

In the theta band (individual theta ± 1 Hz) no significant differences in ERD/ERS measures related to the between group variables of group (low/high), sex or the within group variables K (set size), hemisphere (left/right) and location (frontal, central, parieto-occipital) were observed.

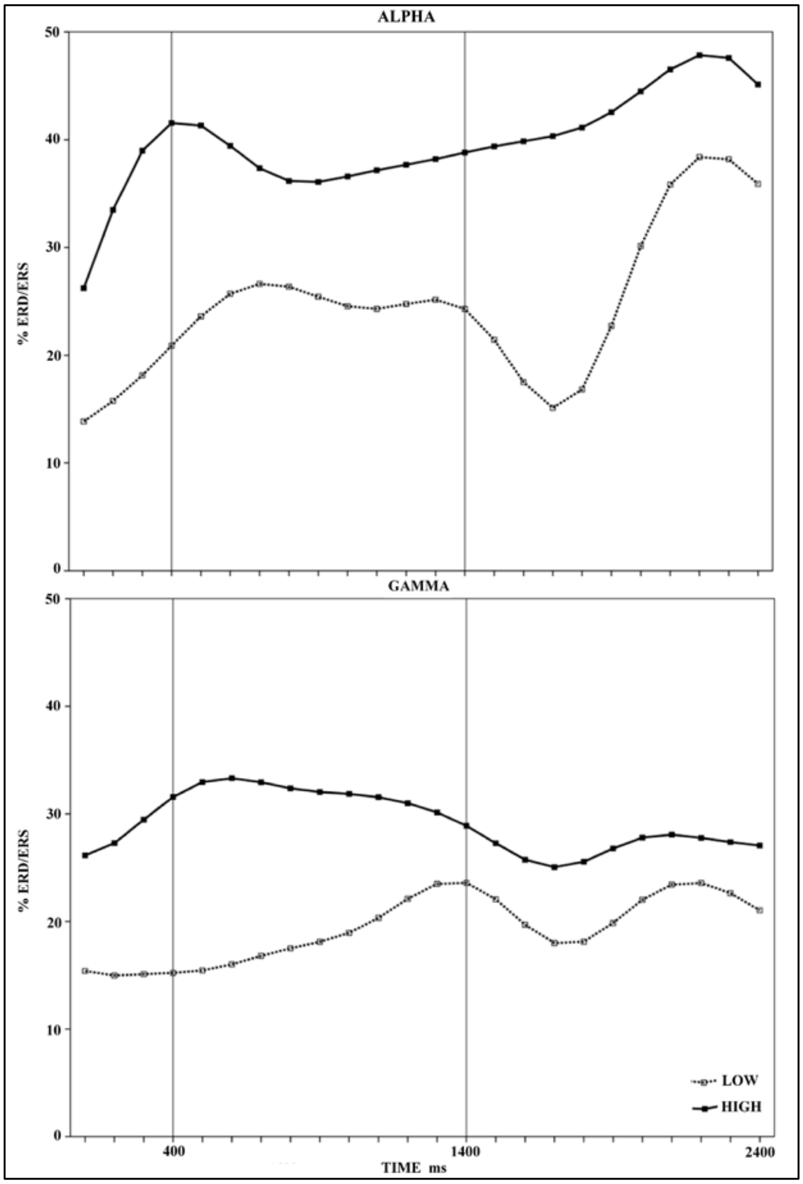
In the alpha band (IAF ± 1 Hz) a significant main effect of the variable group ($F(1,56) = 8.56$; $p = .006$; $\eta^2 = .12$), and an interaction effect between the variables group and location ($F(2,112) = 3.62$; $p = .03$; $\eta^2 = .06$) emerged. As can be seen in the upper part of Figure 2, high performers displayed higher ERD than low performers, which was slightly more prominent in parieto-occipital brain areas. No sex- or set size-related differences were observed.

Figure 2: *ERD/ERS in individual alpha and gamma frequency bands averaged over the entire task in the low and high working memory capacity groups.*



The GLM conducted to capture time-related alpha band ERD/ERS between group differences showed a significant group by time interaction effect for the encoding process ($F(3,58) = 4.36$; $p = .04$; $\eta^2 = .07$), also significant was the main effect for group ($F(1,58) = 10.89$; $p = .002$; $\eta^2 = .16$). As revealed in the upper part for Figure 3, high performers showed increased alpha ERD throughout the encoding phase. Furthermore, this pattern was characterized by an escalated ERD rise starting 100 ms after stimulus onset and peaking at 400 ms when the stimulus was replaced by a grey display containing no stimulus (maintenance – see Figure 3). In contrast, the low performers' alpha ERD peak occurred 700 ms after stimulus onset (during maintenance).

Figure 3: *Temporal distribution of ERD/ERS in individual alpha and gamma frequency bands averaged over 100 ms time intervals displayed by high and low WM capacity groups.*



A similar time-related difference in alpha ERD was observed in the retrieval phase, showing just a time by group interaction (*F*(3,58) = 4.00; *p* = .02; η^2 = .07). This difference was mainly due to a drop in alpha ERD observed in the low performing group. On the other hand, during maintenance no time-related between group alpha ERD/ERS differences were observed.

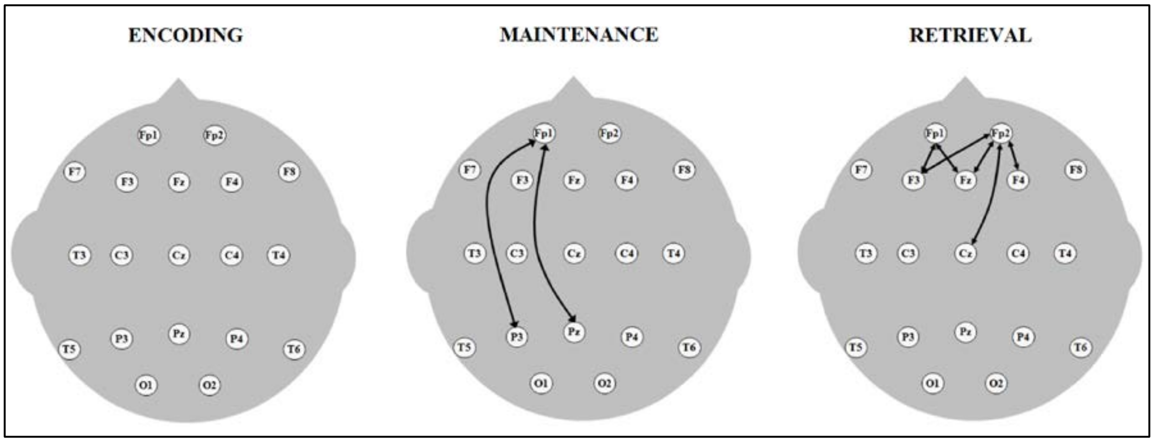
In the gamma band (individual gamma ± 1 Hz) the GLM revealed a main effect for the variables group ($F(1,56) = 9.19$; $p = .004$; $\eta^2 = .14$) and sex ($F(1,56) = 12.55$; $p = .001$; $\eta^2 = .18$). High performers displayed increased gamma ERD as compared to low performers (see lower part of Figure 2). Further, females with no regard to their level of WM capacity displayed less gamma ERD than males. No interaction effects for the variable K were observed.

The GLM analysing differences between high and low performers with respect to the temporal distribution of gamma ERD/ERS revealed a significant main effect for the variable group during encoding ($F(1,58) = 11.94$; $p = .001$; $\eta^2 = .17$) and maintenance ($F(1,58) = 9.47$; $p = .003$; $\eta^2 = .14$). The interaction between the variables group and time during encoding was also significant ($F(3,58) = 3.85$; $p = .04$; $\eta^2 = .06$). The major between group difference in gamma ERD/ERS during encoding was that almost no change in gamma ERD was observed in the low performers. In contrast, high performers displayed an increase in gamma ERD peaking about 600 ms after stimulus onset. In fact, low performers showed a gamma ERD peak about 1300 ms after stimulus onset, almost at the end of the no-stimulus display (maintenance – see lower part of Figure 3). No time-related between group differences in gamma band ERD/ERS were observed during retrieval.

4.3.2.2 Coherence

The ErCoh analysis based on FDR-corrected independent sample t-tests showed significant between group differences only in the individually determined theta band. As revealed in Figure 4, differences in induced ErCoh values were observed only during maintenance and retrieval. High performers displayed stronger connectivity between left frontal and parietal areas (maintenance) and between prefrontal brain areas (retrieval).

***Figure 4:** Differences in ErCoh in the individual theta frequency band between the low and high working memory capacity groups during encoding, maintenance and retrieval.*



4.4. Discussion

The main objective of the study was to characterize specific neuro-electric patterns of brain activity related to the level of visual WM capacity. It was hypothesized that individuals with higher WM capacity would display neural efficiency, similar to the one observed for the intelligence construct, demonstrating a negative correlation between brain activity under cognitive load and intelligence (Neubauer & Fink, 2009). The predicted ERD/ERS pattern within this theoretical framework was that there would be more alpha ERS, theta ERD and gamma ERD in individuals with superior WM capacity, which would be especially pronounced during performance on WM tasks of moderate complexity (e.g., set size of 4 squares). At first glance, the results obtained only partly confirmed this assumption, showing more ERD merely in the gamma band in high WM performers as compared to low performers. In contrast, a pattern opposite to our expectations was observed in alpha band ERD/ERS: high performers showed more alpha ERD than low performers, while no difference in ERD/ERS was observed in the theta band.

However, as stressed by several authors (Başar, 1998; Başar, 1999; Buzsáki, 2006; Buzsaki & Draguhn, 2004), neuronal networks in the brain show several oscillatory bands covering frequencies from approximately 0.02 Hz to 600 Hz. Furthermore, the brain does not operate continuously but discontinuously, using temporal packages as information carriers which enlarges capability. Hence, it can be assumed that the relation between cognitive functions and brain oscillations is not related just to the amplitude in one frequency band but to several other parameters like phase and coherence, and to where in the brain and when these oscillations occur (Herrmann et al., 2016). In light of this theoretical background the results obtained in the study point to a multifaceted pattern of neural efficiency in visual WM capacity, which will be explained in more detail in the following paragraphs.

Gamma band activity (>30 Hz) accompanies almost all brain processing ranging from sensory (Gray & Singer, 1989), motor (Van Der Werf, Jensen, Fries, & Medendorp, 2008) to higher cognitive functions like working memory (Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). As emphasized by Merker (2013), a "master-key" that would account for the variety of gamma band activity in relation to cognition has not been discovered. It has been suggested that gamma synchrony provides a mechanism for perceptual grouping of elements into a whole, which has become known as "binding-by-synchrony" (Gray & Singer, 1989; Merker, 2013). However, recent research revealed that gamma oscillations do not provide enough accuracy for a precise timing mechanism (Burns, Xing, & Shapley, 2011; Xing et al., 2012) and thus make the binding hypothesis controversial (Nikolić, Fries, & Singer, 2013; Uhlhaas et al., 2009). Therefore, an even more general function was recently assigned to gamma oscillations: infrastructural neural control similar to the hemodynamic BOLD response (Merker, 2013). This assumption is supported by robust correlations between gamma oscillations and the BOLD signal (Jerbi et al., 2010; Lachaux et al., 2007; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Niessing et al., 2005; Zaehle et al., 2009).

According to these findings, increased gamma band ERD displayed by high WM performers would indicate a reduction in basic neural control needed to cope with the task at hand. An explanation that is the essence of neural efficiency – "[…] the disuse of many brain areas irrelevant for good task performance, […]" (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992, p. 415). But even when adopting the narrower "binding-by-synchrony" explanation of gamma band oscillations, the gamma band ERD pattern would point to less stimulus directed activity, or bottom-up processing in high performers as compared to low ones. Furthermore, the timing of gamma ERD increases was in high WM performers most pronounced during encoding and maintenance, whereas no differences were observed during retrieval, which would suggest more involvement with stimulus characteristics in low performers during encoding and maintenance compared to high performers.

Alpha band oscillations are dominant in the human brain and play an active role in information processing. They are thought to be closely linked to the fundamental functions of attention: suppression of irrelevant or conflicting information characterized by alpha band ERS and the focused attention and selection of relevant information reflected in alpha band ERD (Klimesch, 2012). Hence, the enlarged alpha ERD observed in high performers would indicate increased focus of attention in all stages of WM processing. The topographic pattern of this top-down processing was more parietal, which would further suggest that more attention was devoted to spatial characteristics of the visual array task. This makes sense given the requirements of the task asking subjects to make judgments about the colour and location of squares. Similar parietal activity during visual WM processing was also observed in studies employing fMRI (Todd & Marois, 2004; Xu & Chun, 2006). Furthermore, this intense and fast (100 – 400 ms) boost in neural resources focusing on the spatial locations of stimuli was mainly pronounced during encoding, which was revealed by the time-related ERD/ERS analysis. In comparison, low performers displayed much slower information processing that was delayed for about 300 ms, a finding that is in line with research into the brain-intelligence relationship. For instance P3 latency, which has been related to the closure of a perceptual process and to an update of information in working memory (Donchin & Coles, 1988; Polich, 2007; Verleger, 1988), showed a consistent association with intelligence (Vernon, Wickett, Bazana, & Stelmack, 2000). Research relating intelligence and ERPs has indicated that peak latencies correlate with IQ (Amin, Malik, Kamel, Chooi, & Hussain, 2015; Barrett & Eysenck, 1994; Caryl, 1994; Chalke & Ertl, 1965; De Pascalis, Varriale, & Matteoli, 2008; Jausovec & Jausovec, 2000; Shucard & Horn, 1972; Troche & Rammsayer, 2009). The average correlation found across these studies was about -0.30, inferring a positive relationship between intelligence and the speed of information processing.

In summary, the obtained ERD/ERS findings suggest faster information processing in high WM performers characterized by intensified top-down processing as compared to slower bottom-up processing observed in low performers.

Contrary to expectations, no between group differences in ERD/ERS brain activation patterns in relation to set size (K) were observed. This finding is surprising given the immense between group difference in WM capacity of almost 3 units. As revealed in Table 1, the WM capacity of high performers was estimated to be 5 units, whereas the capacity of low performers was about 3 units. The model of discrete slots would predict that low performers' brain activity would reach a plateau at set size 4 and for high performers set size 6 would show a plateau. Hence, at least at set size 4 less brain activity in high performers compared to low ones would be expected. However, this was not the case. The same pattern of between group differences in ERD/ERS, with no relation to set size (effect size η^2 between 0.002 and 0.004) was observed in all three frequency bands. This finding lends support to the continuous single resource model assuming that working memory capacity is a flexible resource that can be spread among all elements in the sensory input (Ma et al., 2014). However, this inference must be taken with some caution because several other factors might have biased the outcome. A methodological shortcoming of the present study was the number of trials per set size, which is low even for an ERD/ERS analysis (Pfurtscheller, 1999). However, given the extremely stable pattern of between group differences, this shortcoming represents a less likely source of bias. This also probably holds true for the rather long (400 ms) encoding time. As repeatedly shown in studies using encoding times between 100 ms to 500 ms, this had no influence on working memory capacity and brain activity observed (Luck & Vogel, 1997; Todd & Marois, 2004; Xu & Chun, 2006). The most probable source of bias represents the lowest set size of 4 elements used in the present study, which exceeded the WM capacity of low performers by one unit. Therefore, one cannot exclude that beside WM capacity other factors like motivation could have influenced the observed outcomes. Research exploring the brain-intelligence relation also points in this direction. In a study by Doppelmayr et al. (2005), the expected findings of a negative relation between brain activation and intelligence emerged solely for the easier items of the Raven's matrices test, whereas a tendency in the opposite direction was observed for the difficult ones. The authors further showed that less intelligent individuals displayed a decrease in activation from easy to difficult tasks, whereas the opposite was true for brighter participants. It is likely that individuals with low IQs did not even attempt to solve harder problems, which could explain their lower activation levels compared to those with high IQs. Likewise, in our study low performers showed a sudden decrease in alpha ERD in the first 300 ms during retrieval, which could point to a decline in attention due to the complexity of the stimuli and to more bottom-up processing as indicated by decreased gamma band ERD.

On the other hand, in support of our suggestion that the results represent a tentative proof for the continuous single resource model is the novelty of the research approach employed in the present study using ERD/ERS methodology with individually determined alpha, theta and gamma frequency bands. Previous studies have based their claims mainly on ERP analyses (Vogel & Machizawa, 2004) or on indirect methods of brain imaging with a lower temporal resolution such as fMRI (Todd & Marois, 2004; Xu & Chun, 2006). When ERD/ERS methodology was applied, previous findings were not replicated (Bashivan et al., 2014). Further research is needed to overcome the mentioned methodological shortcomings of the present study.

Another finding contrary to our prediction was that no between-group difference in theta band ERD/ERS was observed, which is unexpected given the number of studies pointing to a robust relationship between theta band frequency and WM (Jaušovec & Jaušovec, 2014; Jaušovec, Jaušovec, & Pahor, 2014; Kamiński et al., 2011; Klimesch, 1999; Klimesch et al., 2008; Pahor & Jaušovec, 2014; Sauseng, Griesmayr, & Freunberger, 2010; Tseng, Chang, Chang, Liang, & Juan, 2016). It is possible that the method used for determining individual theta affected the outcome. Individual theta was determined in relation to the highest level of between-frequency coupling (with gamma frequency), whereas all other studies either used a fixed 4-8 Hz frequency band, or theta was determined in relation to IAF. In the theta band, between group differences were only observed in ErCoh values during maintenance and retrieval. High performers during maintenance showed more connectivity in fronto-parietal networks, while during retrieval higher coherence values were observed in prefrontal brain areas. As already mentioned theta oscillations have been linked to memory processes reflecting communication with the hippocampus – between hippocampal interneurons and pyramidal cells (Klimesch, 1999). Further, mainly in the prefrontal cortex, theta oscillations were observed in relation to executive functions (Colgin, 2013; Enriquez-Geppert, Huster, & Herrmann, 2013). It is assumed that theta cycles act as information carriers packing data into discrete processing entities and in that way linking information from different modalities and brain areas (Gupta, van der Meer, Touretzky, & Redish, 2012; Jezek, Henriksen, Treves, Moser, & Moser, 2011). Overall the ErCoh patterns observed in high performers suggest an intensified information flow between frontal and parietal brain areas, probably in the function of keeping the encoded visuo-spatial information in an active and accessible state for retrieval when a shift to enhanced theta connectivity in the prefrontal area related to executive function was observed. This fits well with the proposed efficiency model of enhanced top-down processing of high performers based on gamma and alpha band ERD/ERS measures and is in line with contemporary neuroscience research (Champod & Petrides, 2010; Collette & Van der Linden, 2002; D'Esposito & Postle, 2015; Olson & Berryhill, 2009; Sauseng et al., 2009; Sauseng, Griesmayr, & Freunberger, 2010; Sauseng, Klimesch, Schabus, et al., 2005; Sreenivasan, Curtis, et al., 2014).

As hypothesized, no sex differences in relation to WM capacity were observed. Females with no regard to their WM capacity displayed less gamma ERD, a finding that is in correspondence with reported sex differences in brain activity in the gamma band (Jaušovec & Jaušovec, 2009, 2010).

The results of the present study did not confirm a relation between average theta/gamma cycle length ratios and WM capacity as demonstrated by Kamiński et al. (2011). One possibility could be that in the present study a visual WM task was used, whereas the studies showing weak relations between theta/gamma cycle length ratios and WM capacity used different memory span tasks that to some extent allow rehearsal and chunking.

5. The relation between theta-nested gamma oscillations and working memory capacity

5.1 Introduction

In the next study (Pahor & Jaušovec, 2016), the relation between theta/gamma cycle length ratio and working memory capacity was investigated in further detail (Kamiński et al., 2011). Kamiński and colleagues (2011) reported that verbal short-term memory capacity, measured via a forward digit span task, shows a positive correlation with theta/gamma cycle length ratio. These results supported Lisman and Idiart's (1995) model in which STM capacity is limited by the number of gamma cycles that can be nested in a theta cycle. The goal of the present study was to investigate whether the results reported by Kamiński et al. (2011) can be replicated with the task that was used in the original paper (digit span) and whether they can be extended to a visuospatial version of the task. It was predicted that theta/gamma cycle length ratio would correlate both with verbal and spatial STM. Given that Kane et al. (2004) reported that verbal and spatial STM share only 40% of their variance, the same patterns of correlations for the two types of STM tasks were not expected (the nature of this part of the study was exploratory). The relationships between individually determined theta and gamma frequencies and STM capacity were also investigated.

5.2 Method

Eighty students (40 males and 40 females; average age= 21 years and 3 months) participated in the study. The participants were briefed about the experiment and completed informed consents. None of the participants reported health problems or use of medication. Resting (eyes-closed) EEG was recorded for 3 minutes using a Quick-Cap with sintered electrodes. After the EEG recording session, the participants solved first the forward and then the backward versions of a Digit span test and a Corsi block tapping test (the order of the two tests was counterbalanced across subjects) via PEBL (Mueller & Piper, 2014). The Digit span test measures verbal WM capacity (Wechsler, 1981), whereas the Corsi block test provides a measure of spatial WM capacity (Corsi, 1972). Both tasks were presented on a computer screen; they were self-paced and adaptive. The tasks started with a low number of items to-be-remembered (i.e. list length), which gradually increased. Prior to performance on the task, the participants completed short practice sessions. In the forward Digit span task, the participants were presented with a stream of numbers (1000 ms presentation time and 1500 ms inter-trial interval) and were asked to repeat them by typing on a keyboard in the order of presentation. In the backward version of the task, the participants were asked to repeat the numbers in reverse order. In the Corsi block tapping test, the participants were presented with blue squares (1000 ms presentation time and 1000 ms inter-trial interval) against a black background, some of which turned white in a particular sequence. Their task was to repeat the sequence by clicking on the squares in the same (forward version) or reverse order (backward version). In both tasks, two trials were used per list length; if at least one of them was recalled correctly, the next list length appeared. For digit span, the shortest list length was 3, whereas for the Corsi block test the shortest list length was 2. For each task, the longest sequence that was correctly recalled before missing two successive lists of the same length was used as a measure of STM capacity. As can be seen in Table 2, there were no significant gender differences in performance on the four tests, hence the whole sample was used for subsequent analyses.

Table 2: *Average performance, standard deviation, and t-test results on four working memory tests for males and females: DIGf= forward digit span test, DIGb= backward digit span test, CORf= forward corsi block test, CORb= backward corsi block test.*

	Males		**Females**		**t- test *df* (78)**
	M	**SD**	**M**	**SD**	
DIGf	6.75	1.08	6.95	1.15	*t* = .80; *p* = .43; *d* = .18
DIGb	6.58	1.71	6.93	1.47	*t* = .98; *p* = .33; *d* = .22
CORf	6.06	0.96	5.93	0.96	*t* = .64; *p* = .52; *d* = .14
CORb	5.66	1.09	5.65	0.96	*t* = .05; *p* = .96; *d* = .01

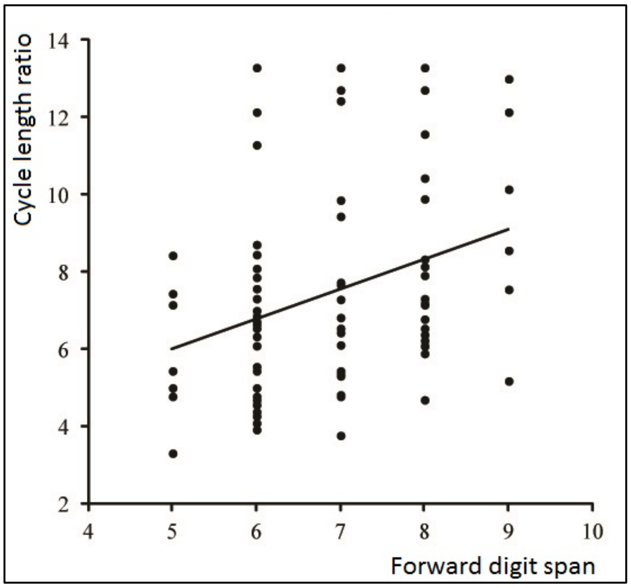
5.2.1 Data analysis

Individual theta and gamma frequencies, and the cycle length ratio between these frequencies, were determined for each EEG channel as proposed by Kamiński et al. (2011) – see section 4.2.3 for a detailed description. EEG data was processed using EEGLAB toolbox (freely available from http://www.sccn.ucsd.edu/eeglab/) for MATLAB (The MathWorks, Natick, MA, USA). SPSS version 23 (IBM Corp, 2015) was used for the statistical analysis. Average theta/gamma cycle length ratios in 19 EEG channels were correlated with performance on working memory tests (Pearson's r). In the next step, individual theta and gamma frequencies in 19 EEG channels were correlated with performance on the STM tests.

5.3 Results and discussion

Performance on the forward digit span significantly correlated with theta/gamma cycle length ratio at electrode F8 ($r = .33$, $p = .003$) while performance on the backward digit span correlated with theta/gamma cycle length ratios at electrodes F8 ($r = .26$, $p = .02$), C3 ($r = .22$, $p = .047$), and O1 ($r = .27$, $p = .02$) (see Table 3). Figure 5 shows theta/gamma cycle length ratios at electrode F8 and forward digit spans of 80 participants. Similarly, Kamiński et al. (2011) reported that theta/gamma cycle length ratio positively correlated with performance on a forward digit span task at the Fz electrode.

Figure 5: *Scatter plot of verbal STM capacity (performance on the forward digit span task) and theta/gamma cycle length ratio in all subjects.*



Performance on the forward Corsi block test significantly correlated with theta/gamma cycle length ratio at electrode P4 (*r* = .27, *p* = .02) whereas performance on the backward Corsi block test showed significant correlations at electrodes F3 (*r* = -.26, *p* = .02) and C3 (*r* = -.28, *p* = .01). These results suggest that at certain electrode locations, theta-gamma cycle length ratio positively predicts performance on verbal STM tests and on the forward spatial STM test. However, the effect sizes are small to moderate (Cohen, 1987). The results also demonstrated that theta/gamma cycle length ratio at electrodes F3 and C3 negatively correlated with performance on the backward spatial STM test. The different correlations observed on the four STM tests support the view that verbal and spatial STM represent domain-specific storage mechanisms. Alternatively, it is possible that the method proposed by Kamiński et al. (2011) does not represent an optimal way of calculating how many gamma cycles fit into a theta cycle, and that some of the observed effects can be explained by chance alone.

Table 3: *Correlation (Pearson's r) between STM tests and theta/gamma cycle length ratio. DIGf= forward digit span test, DIGb= backward digit span test, CORf= forward corsi block test, CORb= backward corsi block test.*

Electrode	**DIGf**	**DIGb**	**CORf**	**CORb**
FP1	-.003	.003	.176	.002
FP2	.109	.053	.078	.160
F3	.083	.009	-.192	**-.263***
F4	.045	.001	-.065	-.038
C3	.174	**.223***	-.126	**-.276***
C4	.086	.018	.127	-.215
P3	.045	.118	-.011	-.081
P4	-.068	.085	**.267***	.030
O1	.164	**.267***	.010	.123
O2	.104	.107	-.041	-.068
F7	-.079	-.069	-.172	.019
F8	**.326****	**.261***	.138	.074
T3	.018	.086	.060	.172
T4	.141	.152	.138	-.116
T5	-.019	-.094	-.076	-.086
T6	.030	.007	.191	.012
CZ	.086	.065	.085	-.131
FZ	.004	-.113	-.108	-.041
PZ	.037	.023	.123	.077

* $p < .05$, ** $p < .01$

We were also interested in examining whether individual theta and gamma frequencies in 19 EEG channels correlate with performance on the STM tests. For the theta frequency band, significant correlations were found only for forward (FP1: $r = -0.25$, $p = 0.02$) and backward Corsi block tests (F3: $r = 0.26$, $p = 0.02$; C3: $r = 0.22$, $p = 0.05$). In contrast, averaged gamma band frequencies showed significant correlations with performance in three tests: forward corsi block (P4: $r = .23$, $p = .04$; F8: $r = .30$, $p = .01$); forward digit span (FP2: $r = .26$, $p = .02$; C3: $r = .31$, $p = .01$; O1: $r = .24$, $p = .03$; F8: $r = .37$, $p = .001$), and backward digit span (C3: $r = .23$, $p = .04$; O1: $r = .40$, $p = .001$; F8: $r = .30$, $p = .01$; Fz: $r = -.23$, $p = .04$). In short, theta correlated with performance on spatial STM tests in left frontal areas: it negatively correlated with the forward Corsi block test and positively correlated with the backward Corsi block test. In contrast, gamma correlated with performance on verbal and spatial STM tests, showing positive correlations across the whole head (with the exception of electrode Fz). Thus, individual gamma frequency may serve as a stronger predictor of STM capacity than individual theta frequency.

To conclude, individual theta/gamma cycle length ratio positively correlated with verbal STM capacity at electrodes F8, C3, and O1, which is line with the findings reported by Kamiński et al. (2011). In order to extend these findings, theta/gamma cycle length ratios were also correlated with performance on tests of spatial STM capacity. As expected, a different pattern of results was observed: the ratio positively correlated with the forward version of the task (electrode P4) and negatively correlated with the backward version of the task (electrodes F3 and C3). It should be noted that the obtained significant correlations had small to moderate effect sizes and were not uniformly present across the electrodes, thereby casting doubt on the reliability of this method to predict verbal and spatial STM capacities. Given the complex pattern of neural efficiency in relation to WM capacity observed in the previous study (see Chapter 4), it is likely that the cycle length ratio idea is too simplistic and even if some relations exists, it is probably difficult to capture them with such noisy data as EEG obtained from scalp electrodes. In the next step, STM capacity was correlated with individual theta and gamma frequencies. While theta frequency only correlated with spatial STM capacity (in left frontal areas), gamma frequency positively correlated with verbal and spatial STM capacity across the whole head. These results suggest that individually determined theta and gamma frequencies, measured during a resting period, may be related to subsequent performance on tests of STM. Future studies should examine whether a different method for determining individual theta and gamma frequencies, such as the mean peak frequency method, would yield similar results.

6. The effects of theta tACS on working memory storage and processing functions

6.1 Introduction

This study was conducted in order to examine the conflicting viewpoints regarding the role of theta band oscillations in frontal and parietal brain areas in working memory. Up to that point, most of the transcranial electric stimulation studies that focused on working memory targeted the dorsolateral prefrontal cortex (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Boggio et al., 2006; Fregni et al., 2005; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011) – for a review see Brunoni and Vanderhasselt (2014). In contrast, the parietal brain areas had been somewhat neglected in TES research targeting working memory. For this reason, a single-blind sham controlled approach was adopted in which we applied tACS offline in the theta frequency band to left and right parietal areas and to a left frontal area. If theta band oscillations are causally involved in working memory processing, tACS applied in this frequency band should affect performance on working memory tasks. Specifically, the aim was to examine the effects of sham and active theta tACS applied to frontal and parietal brain areas on working memory functions: storage capacity and executive processes. In light of the results reported by Jaušovec and Jaušovec (2014), it was predicted that active tACS would enhance performance on working memory compared to sham stimulation. The results of this study were published by Jaušovec, Jaušovec and Pahor (2014).

6.2 Method

Thirty-six right-handed students (27 females; average age = 20 years and 5 months; SD = 4.25 months) participated in the study. The participants were briefed about the experiment and completed informed consents. None of the participants reported health problems or use of medication. The participants were divided into three groups, left frontal, left parietal and right parietal, which corresponded to the placement of tACS electrodes (see Figure 6). The three groups of participants were equalized with respect to sex and performance on a digit span task (Wechsler, 1981) administered prior to the experiment (left parietal group: *M* = 7.00; *SD* = 1.00; right parietal group: *M* = 6.88; *SD* = 0.93; left frontal group: *M* = 6.96; *SD* = 1.32).

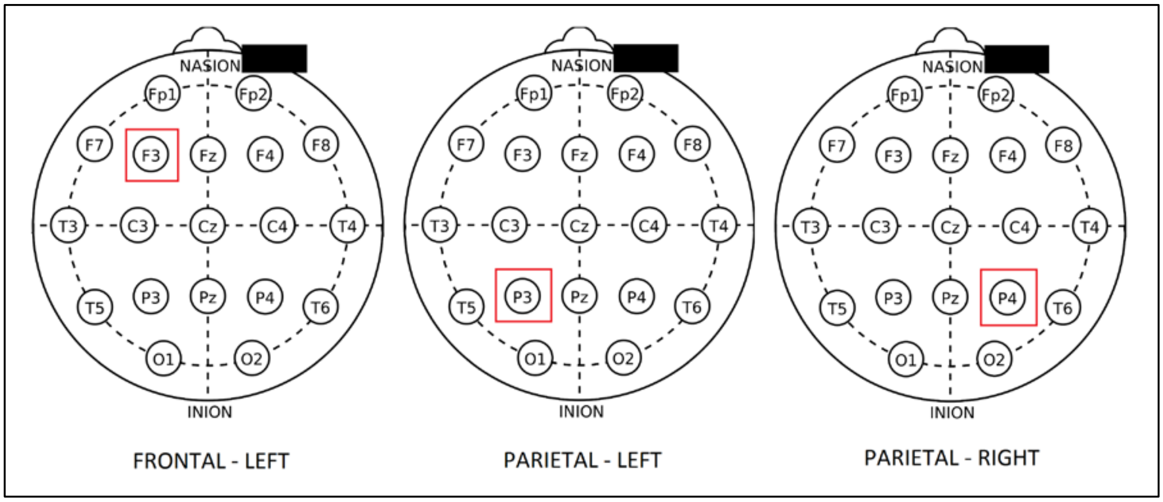
The participants completed two sessions, sham and active tACS, which were counterbalanced across subjects. The sham and active settings were separated by 28 days because we wanted to ensure that females on sham and active settings were tested on the same day of their menstrual cycle. It has been reported that the relative release of sexual hormones in different phases of the menstrual cycle can affect cognitive responses of females (e.g., Amin, Epperson, Constable, & Canli, 2006; Berman et al., 1997). The duration of the menstrual cycle was determined with a questionnaire administered after the first tACS session. Most of the female participants had a regular 28 days menstrual cycle (*M* = 28.42 days; *SD* = 0.73 days).

In each session, the participants were exposed to sham/active tACS for 15 minutes, after which they solved a short questionnaire about their sensations during stimulation, followed by performance on the WM tasks. Like in the previous study, forward and backward versions of Digit span and Corsi block tapping test were used (Mueller & Piper, 2014). In addition, the n-back tasks used by Jaeggi, Buschkuehl, Jonides, and Perrig (2008) were employed in this study and presented via STIM2 (Compumedics Neuroscan Systems, Charlotte, NC, USA). The order of task presentation was rotated between the participants, but was the same for each participant in the sham and active setting. All of the tasks were presented on a computer monitor. For a detailed description of Digit span and Corsi block tapping tests see section 5.2. In the n-back tasks, two series of stimuli were presented simultaneously at a rate of 2000 ms per stimulus – one in the auditory domain and the other in the visual domain. One string of stimuli consisted of single letters (presented via headphones), whereas the other involved the presentation of blue squares in different spatial locations on a computer screen. The participants were asked to decide whether the current stimulus matched the one that was presented *n* items back in the series. We used 5 strings with 1-back, 2-back, and 3-back series consisting of 20 items per string. For each WM storage task (1-2), a WM memory span score was determined. For each series of the n-back tasks the number of correct responses (corrected for wrong responses) was determined. The time needed by participants to complete the session was on average 30– 40 minutes.

Dependent variables were the aggregated outcome measures from the different memory tasks used and were based on the multi-component WM model proposed by Baddeley, Allen, and Hitch (2011), which represents a broad theoretical framework allowing for experimental testing. SPSS version 23 (IBM Corp, 2015) was used for the statistical analysis. The analysis of data was hierarchical: it started by testing the influence of the three tACS stimulation sites on storage and executive processes represented in the multi-component model as the episodic buffer and central executive. In the next step, we separately analysed the storage and executive control functions: (1) the influence of tACS protocols on spatial/verbal, and forward/backward storage capacity, and (2) the influence of tACS protocols on executive control.

tACS was applied using a battery-operated stimulator system (DC-stimulator plus, Neuroconn, Ilmenau, Germany) via two electrodes enveloped in sponges that were placed on the head underneath an EEG recording cap (see Figure 6 and Chapter 3). The target electrode was placed over the left parietal location (P3), the left frontal location (F3), or the right parietal location (P4), and the return electrode was placed above the right eyebrow. These brain areas were stimulated because research has shown that they play a key role in different WM processes (Andrews et al., 2011; Fregni et al., 2005; Polanía et al., 2012; Postle et al., 2006). We applied oscillating theta currents adjusted to the individual alpha peak frequency (IAF) of each participant. IAF was determined by averaging peak alpha frequencies of all 19 electrodes during eyes closed resting EEG recording (left parietal group: theta = IAF – 5Hz; *M* = 5.07; *SD* = 1.25; right parietal group: theta = IAF – 5Hz; *M* = 5.68; *SD* = .87; left frontal group: IAF – 5Hz; *M* = 4.69; *SD* = 0.69). The magnitude of the current was determined based on individual thresholds for skin sensations (see Chapter 3). Left and right parietal group: Modus = 1750 μA peak-to-peak; Range = 1000 μA to 2000 μA; left frontal Group: Modus = 1750 μA peak-to-peak; Range = 1000 μA to 2250 μA. In the active condition tACS was applied for 15 minutes; the current was ramped up and down over the first and last 15 s of stimulation. In the sham condition, the procedure, current magnitude, and current frequency were the same as in the active condition, except for the duration of stimulation, which was applied for just 30 seconds and then turned off automatically. Because most subjects feel an itching sensation only initially during tACS, this procedure prevents awareness of the stimulation conditions (Gandiga, Hummel, & Cohen, 2006; Nitsche et al., 2008).

Figure 6: *Position of target electrodes (red square) and return electrode (black rectangle) for the three tACS protocols.*



6.3 Results and discussion

The questionnaire data about participants' sensations during tACS was analysed with a Wilcoxon Signed Ranks Test. The test showed no significant difference between the participants' sensations during sham and active tACS settings ($Z(35) = .31$; $p = .77$).

Storage versus processing

Differences between the three tACS protocols in relation to storage and executive processes were analysed with a GLM for repeated measures with tACS (sham/active) and WM function (storage/process) as within-subjects factors, and group (left parietal/right parietal/left frontal) as a between-subjects factor. The analysis was performed on aggregated measures of the WM span tasks (forward/backward Digit span and Corsi block), and the n-back tasks (1-back/2-back/3-back). The main effect of tACS was significant ($F(1,33) = 21.56$; $p < .001$; $\eta^2 = .40$), as were the interaction effects between tACS and group ($F(1,33) = 3.76$; $p = .03$; $\eta^2 = .19$), and between tACS, group and WM function (*F*(2,33) = 3.79; *p* = .03; η^2 = .19). After active tACS, the participants' WM storage capacity and executive processes significantly increased compared to sham stimulation.

To gain a deeper insight into between-group differences of the effect of tACS on WM storage and executive processes, a GLM for repeated measures with tACS (sham/active) as a within-subjects factor and group (left parietal, right parietal and left frontal) as a between-subjects factor was performed separately for each WM function. The GLM for WM storage capacity showed a significant main effect of tACS (*F*(1,33) = 8.74; *p* = .006; η^2 = .21). On the other hand, the interaction effect between tACS and group was not significant (*F*(2,33) = 0.75; *p* = .48; η^2 = .04). In the next step, paired-sample t-tests between sham/active tACS were computed for each group separately (not Bonferroni corrected). As can be seen in Table 4, more pronounced influences of active tACS were observed when the target electrodes were placed over parietal areas. In contrast, the influence was minimal when the target electrode was placed over the left frontal area. The GLM for WM executive processes showed a significant main effect of tACS (*F*(1,33) = 20.42; *p* < .001; η^2 = .38) and a significant interaction effect between tACS and group (*F*(2,33) = 3.78; *p* = .03; η^2 = .19). As can be seen in Table 4, subsequent paired-sample t-tests (Bonferroni corrected) between sham/active tACS computed for each group separately showed that the influence of active tACS was most pronounced when the target electrode was placed over the right parietal brain area.

Table 4: *Means and standard deviations (in brackets) and paired-sample t-tests for sham/active differences between aggregated scores for tests measuring working memory capacity and executive processing for the three tACS groups.*

Group	**WM Capacity**			**WM executive processing**		
	Sham	**Active**	***df* (11)**	**Sham**	**Active**	***df* (11)**
Frontal left	6.54 (1.04)	6.68 (0.84)	$t = 0.74$ $p = .48$ $d = .20$	51.94 (11.71)	56.18 (8.72)	$t = 1.17$ $p = .27$ $d = .34$
Parietal left	6.52 (0.79)	6.95 (0.81)	$t = 2.39$ $\mathbf{p = .03}$ $d = .69$	49.79 (9.53)	53.49 (13.28)	$t = 2.07$ $p = .06$ $d = .60$
Parietal right	6.33 (0.58)	6.64 (0.76)	$t = 2.14$ $\mathbf{p = .05}$ $d = .66$	47.53 (9.35)	60.48 (4.56)	$t = 5.80$ $\mathbf{p < .001}$ $d = 1.68$

Storage capacity

Differences between the three tACS protocols in relation to storage capacity were analysed with a GLM for repeated measures with tACS (sham/active), direction (forward/backward) and content (verbal/figural), as within-subjects factors, and group (left parietal/right parietal/left frontal) as a between-subjects factor.

The GLM not only showed a significant effect of tACS on WM storage capacity ($F(1,33) = 8.74$; $p = .006$; $\eta^2 = .21$), but also a significant interaction effect among the factors tACS, direction and group ($F(2,33) = 3.94$; $p = .03$; $\eta^2 = .19$). On the other hand, there was no significant interaction effect between the factors tACS, content and group ($F(2,33) = 1.15$; $p = .34$; $\eta^2 = .07$). Subsequent paired-sample t-tests (not Bonferroni corrected) between sham/active tACS computed for each group separately showed that the influence of active tACS on backward memory span was most pronounced when the target electrode was placed over the left parietal area (see Table 5). Also observed was a positive influence of active tACS on forward memory span in the right parietal group (significant paired-sample t-test, not Bonferroni corrected).

***Table 5**: Means and standard deviations (in brackets) and paired-sample t-tests for sham/active differences between aggregated scores for forward/backward memory span for the three tACS groups.*

Group	**Forward**			**Backward**		
	Sham	**Active**	***df* (11)**	**Sham**	**Active**	***df* (11)**
Frontal left	6.54 (1.09)	6.60 (0.72)	$t = 0.26$ $p = .80$ $d = .07$	6.54 (1.04)	6.75 (1.22)	$t = 9.99$ $p = .34$ $d = .27$
Parietal left	6.73 (0.72)	6.79 (0.78)	$t = 0.26$ $p = .80$ $d = .07$	6.31 (0.91)	7.10 (0.97)	$t = 4.18$ $\boldsymbol{p = .002}$ $d = 1.20$
Parietal right	6.29 (0 .66)	6.77 (0.76)	$t = 2.26$ $\boldsymbol{p = .04}$ $d = .64$	6.38 (0.97)	6.50 (0.93)	$t = 0.63$ $p = .54$ $d = .17$

Executive processes

Differences between the three tACS protocols in relation to executive process were analysed with a GLM for repeated measures with tACS (sham/active) and n-back (1-back/2-back/3-back) as within-subjects factors, and group (left parietal/right parietal/left frontal) as a between-subjects factor. The GLM showed a significant main effect of tACS ($F(1,33) = 20.41$; $p < .001$; $\eta^2 = 9.38$), a significant interaction effect between the factors tACS and group ($F(2,33) = 3.74$; $p = .03$; $\eta^2 = .19$), and a significant interaction effect among tACS, n-BACK and group ($F(4,66) = 3.86$; $p = .007$; $\eta^2 = 0.19$). As can be seen in Table 6, active tACS had the most pronounced influence on n-back performance when the target electrode was placed over the right parietal site. This influence was also dependent on the difficulty of the task and the placement of the target electrode as indicated by subsequent paired-sample t-tests, which were FDR corrected with the classical one-stage method (Benjamini & Hochberg, 1995). These tests suggested that when the target electrode was placed over (1) the left parietal site, the highest performance increases were observed for the 2-back tasks, (3) the right parietal area, the increases were most pronounced for the 1-back and 2-back tasks, and (3) the left frontal area, a moderate increase for the 1-back was observed.

Table 6*: Means and standard deviations (in brackets) and paired-sample t-tests for sham/active differences between performance on n-back tasks for the three tACS groups. Paired-sample t-tests were FDR corrected with the classical one-stage method (Benjamini, & Hochberg, 1995).*

Group	**1-back**			**2-back**			**3-back**		
	Sham	**Active**	***df*** **(11)**	**Sham**	**Active**	***df*** **(11)**	**Sham**	**Active**	***df*** **(11)**
Frontal left	81.08 (18.64)	87.83 (14.14)	*t* = 2.31 ***p* = .04** *d* = .67	42.27 (17.16)	45.27 (13.37)	*t* = 0.46 *p* = .66 *d* = .13	32.03 (13.05)	35.44 (10.67)	*t* = 0.62 *p* = .55 *d* = .18
Parietal left	83.72 (16.41)	80.89 (21.50)	*t* = 0.81 *p* = .44 *d* = .23	39.42 (16.54)	48.69 (21.50)	*t* = 2.84 ***p* = .01** *d* = .82	26.22 (3.73)	30.89 (7.47)	*t* = 1.59 *p* = .14 *d* = .46
Parietal right	82.17 (16.89)	95.58 (3.34)	*t* = 2.65 ***p* = .02** *d* = .77	35.61 (14.88)	59.17 (12.62)	*t* = 8.00 ***p* <.001** *d* = 2.31	25.08 (7.89)	26.69 (6.92)	*t* = 0.54 *p* = .60 *d* = .15

In sum, this study showed that stimulation of parietal areas in the theta frequency band (target electrodes positioned at P3 or P4) had a positive effect on WM storage capacity, whereas no such influence was observed for the stimulation of the left frontal area. This is line with previous neuroimaging research suggesting that parietal brain areas play a central role for WM storage capacity (Champod & Petrides, 2010; Collette & Van der Linden, 2002; Cowan, 2011; Cowan et al., 2011; Olson & Berryhill, 2009; Sauseng, Griesmayr, Freunberger, et al., 2010), research involving rTMS (Postle et al., 2006), tDCS (Jacobson, Goren, Lavidor, & Levy, 2012), and tACS (Jaušovec & Jaušovec, 2014). The study further demonstrated that left parietal theta tACS had a more pronounced influence on backward recall than on forward recall, which was not related to task content (spatial or verbal). A neuroimaging study by Gerton et al. (2004) demonstrated that both forward and backward digit span tasks are associated with activations in the right dorsolateral prefrontal cortex, the bilateral inferior lobule, and the anterior cingulate cortex. The backward digit span task recruited these regions above and beyond the levels seen during performance on the forward digit span task. In particular, Broca's area and the left inferior parietal lobe were more active during performance on backward compared to forward span tasks, suggesting that the former places greater demands on phonological processing. This may explain why theta tACS applied to the left parietal area affected backward but not forward recall. In contrast, right parietal tACS improved forward but not backward recall, which is difficult to explain in the context of the Gerton et al. (2004) study.

Another objective of the study was to explore the effects of theta tACS on processing components of WM: inhibition of irrelevant items, monitoring of ongoing performance, updating representations in memory, and binding processes between spatial positions and temporal context. This was investigated by examining the effects of the three tACS protocols on performance on n-back tasks, which are not as prone to chunking strategies as the memory span tasks. The most pronounced influence on *n*-back performance was observed after right parietal tACS; the influence was stronger on the 2-back task than on the 1-back task. Stimulation of the left parietal area improved performance on the 2-back tasks. These results are in line with neuropsychological evidence suggesting that patients with superior parietal lesions show deficits on demanding n-back tasks compared to controls (Koenigs, Barbey, Postle, & Grafman, 2009).

The n-back tasks not only required executive processes of inhibition, monitoring, and updating, but also required binding between spatial positions and temporal context. This function is assigned to the episodic buffer in Baddeley's multicomponent model of WM (Baddeley et al., 2011). One could say that the episodic buffer temporarily stored and bounded information streaming from the phonological loop (the aurally presented single letters) and the visuo-spatial sketchpad (blue squares in different spatial locations) into unitized episodes or chunks. On the other hand, if it is assumed that storage capacity is essential for task solution in more complex tasks, whereas attentional control is important in less complex tasks, it would be expected that parietal stimulation (especially left parietal) would affect performance on the 3-back tasks. However, as can be seen in Table

6, only a trend indicating the expected increase was observed. Compared to the other tACS protocols, left parietal tACS had the greatest impact on performance on the 3-back tasks, although this was not statistically significant.

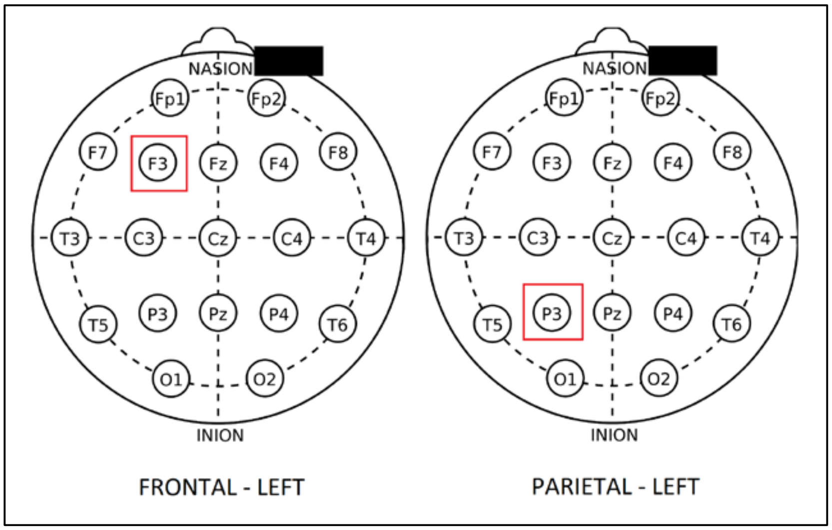
Stimulation of the left frontal area had a minor positive influence on n-back performance – improvements were only observed on the 1-back task. This finding is not in line with experimental evidence employing tDCS, in which WM improvements were reported for stimulation that targeted frontal areas (Andrews et al., 2011; Fregni et al., 2005; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Zaehle et al., 2011). It is possible that for more complex tasks (higher level of n), WM storage capacity and manipulation of information are crucial for task performance, whereas for easier tasks (lower level of n) attentional control is dominant. Indeed, patients with superior parietal lesions do not differ from controls in terms of their performance on tests that require sustained attention but present minimal demands on manipulation of information in working memory (i.e. 0-back and 1-back tests) (Koenigs et al., 2009). Hence the frontal tACS improvement might have stemmed from improvements in sustained attention. According to Klimesch (2012), alpha-band oscillations have inhibitional and timing roles that are related to attentional functions of suppression and selection of information. Monitoring new information, for instance, elicits an increase in the theta frequency band accompanied by alpha synchronisation. On the other hand, alpha-band activity can also act as an inhibitory filter that keeps target information activated (Klimesch, 2012). One could speculate that stimulating the frontal areas in one of the alpha bands would have a more pronounced influence, affecting the attentional buffer that keeps target information activated, which would lead to a more prominent effect on n-back performance.

In conclusion, the study confirmed the central role of parietal brain areas in working memory storage capacity. On the other hand, the study also opened several questions (e.g., the relation between backward recall, attentional control and storage capacity; the role of theta and alpha band oscillations in WM executive control), some of which are addressed in subsequent studies.

7. The effects of theta tACS on fluid intelligence

The results of the present study were published by Pahor and Jaušovec (2014) and will only be briefly discussed in relation to the research described in the previous sections. Like the study described in Chapter 6, this was a single-blind, sham-controlled, offline tACS study. As described in the introduction, working memory and fluid intelligence are highly related constructs (Ackerman, Beier, & Boyle, 2005; Burgess, Gray, Conway, & Braver, 2011; Harrison, Shipstead, & Engle, 2015; Unsworth & Engle, 2005; Wiley, Jarosz, Cushen, & Colflesh, 2011). Assuming that theta tACS affects performance on working memory tests, it can be predicted that similar findings would be observed in relation to performance on tests of fluid intelligence. Based on (1) the results of the study described in Chapter 6 and (2) prominent neurobiological models of intelligence - the Parieto-Frontal Integration model by Jung and Haier (2007) and Duncan's adaptive coding model (Duncan, 2001, 2003), it was decided that left frontal and left parietal brain areas would be targeted with tACS (the return electrode was positioned above the right eyebrow). The sample included 28 right-handed individuals (average age = 20 years and 8 months; SD = 4.35 months) that were assigned to two groups and equalized with respect to IQ (WAIS IV): Frontal group (N = 14; M_{IQ} = 105.45; SD = 8.93) and Parietal group (n = 14; M_{IQ} = 105.38, *SD* = 9.25) – see Figure 7. The general procedure including the characteristics of tACS were the same as in the study described in Chapter 6. There were two sessions, during which the participants were exposed to 15 minutes of tACS (in the sham setting only for 1 minute), after which they rested with their eyes closed for 5 minutes while their EEG was recorded. Afterwards the participants solved two tests of fluid intelligence: Raven's Advanced Progressive Matrices (Raven, 1990) and the Paper Folding and Cutting (PF&C) subtest of the Stanford-Binet IQ test as described by Rideout and Laubach (1996).

Figure 7: *Position of target electrodes (red square) and return electrode (black rectangle) for the two tACS protocols.*



The effects theta tACS on resting EEG data were more prominent when stimulation was applied to the left parietal site compared to the left frontal site. In both groups, theta decreased lower alpha power (IAF-4 Hz to IAF) in brain areas located close to the site of stimulation. However, theta tACS applied to the left parietal area (but not the left frontal area) significantly increased theta power in frontal brain areas. Furthermore, active theta tACS improved performance on Raven's Advanced Progressive Matrices (RAPM) and on the Paper Fold & Cut test (PF&C) compared to sham tACS (significant main effect of tACS: $F(1,26) = 27.19$; $p < .001$; $\eta^2 = .51$; significant interaction between tACS and group: $F(1,26) = 6.19$; $p = .02$; $\eta^2 = .19$). The improvement was more pronounced in the group of participants that received stimulation to the left parietal area, which is line with the results of the study described in Chapter 6. Within the left parietal group, tACS had a more pronounced influence on difficult test items. In fact, the only significant difference between sham/active sessions in the frontal group was on the easy RAPM test items (see Table 7). Yet again, this mirrors the finding reported in the previous study, in which theta tACS applied to a left frontal area only affected performance on easy 1-back tasks that required sustained attention.

Table 7: *Means and standard deviations (in brackets) for RAPM and PF&C tests (separately for total scores and scores on easy/difficult items) in sham and active tACS settings for the Parietal and Frontal groups (* – FDR adjusted significance).*

	Sham setting	**Active setting**	**t-test**
FRONTAL	***M (SD)***	***M (SD)***	***df (13)***
RAPM-total	14.00 (2.72)	14.86 (3.13)	*t* = 1.06; *p* = .18; *d* = 0.28
RAPM-easy	8.71 (1.44)	9.72 (1.33)	*t* = 2.39; **p = .03***; *d* = 0.64
RAPM-difficult	5.29 (1.68)	5.14 (2.63)	*t* = 0.22; *p* = .83; *d* = 0.06
PF&C-total	11.71 (2.27)	12.50 (3.16)	*t* = 1.01; *p* = .31; *d* = 0.27
PF&C-easy	5.86 (1.17)	5.36 (1.15)	*t* = 1.29; *p* = .22; *d* = 0.34
PF&C-difficult	5.85 (1.56)	7.14 (2.88)	*t* = 1.66; *p* = .12; *d* = 0.44
PARIETAL	***M (SD)***	***M (SD)***	***df(13)***
RAPM-total	13.50 (3.35)	15.79 (2.01)	*t = 2.88;* **p = .01***; *d = 0.77*
RAPM-easy	8.86 (1.70)	9.64 (0.63)	*t = 1.76; p = .10; d = 0.47*
RAPM-difficult	4.64 (2.27)	6.14 (1.92)	*t = 3.07;* **p = .009***; *d = 0.82*
PF&C-total	10.29 (2.13)	12.64 (3.43)	*t = 3.16;* **p = .008***; *d = 0.77*
PF&C-easy	4.93 (1.27)	5.57 (1.79)	*t = 1.04; p = .41; d = .28*
PF&C-difficult	5.36 (1.87)	7.07 (1.92)	*t = 3.97;* **p = .002***; *d = 1.06*

Altogether, these findings suggest that theta tACS increases resting theta power and, contrary to previous research (Merlet et al., 2013; Zaehle, Rach, & Herrmann, 2010), also affects power in frequencies other than the stimulating frequency, such as the alpha band. Theta tACS applied to the left parietal brain area moderately increased performance on tests of fluid intelligence, which is in line with the results reported in Chapter 6. Theta tACS appears to have a greater positive influence on performance on working memory and fluid intelligences tests if one of the electrodes is placed over the posterior parietal cortex compared to the frontal cortex. These results support the P-FIT model proposed by Jung and Haier (2007), suggesting that a network of brain regions play a role in general intelligence, with an emphasis on the parietal cortex and do not lend support to Duncan's (2003) idea that psychometric *g* is bound to processing networks of the prefrontal cortex.

8. The effects of theta and gamma tACS on working memory

8.1 Introduction

According to Roux & Uhlhaas (2014), (1) theta-band oscillations are involved in the organization of sequentially ordered WM items, (2) gamma-band oscillations play a general role in maintenance of WM information, and (3) alpha-band oscillations represent active inhibition of task-irrelevant information. In addition, the authors propose that cross-frequency coupling between low (theta, alpha) and high (beta, gamma) frequencies enable processing of distinct working memory information. It has been proposed that working memory and selective attention are subserved by a common neural mechanism: activity in prefrontal and parietal regions that provide top-down control over sensory cortices (Gazzaley & Nobre, 2012) either to bias sensory processing in a preparatory phase or to reactivate a sensory representation during memory retrieval (Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015). In the studies described in the previous chapters, theta tACS was applied to frontal and parietal areas prior to performance on working memory tasks – a decision motivated by neurobiological models of working memory (Gazzaley & Nobre, 2012; Frédéric Roux & Uhlhaas, 2014; Sreenivasan, Curtis, et al., 2014). A logical next step was to apply tACS also in the gamma frequency band.

One of the goals of this study was to provide causal evidence for the roles of theta and gamma-band oscillations in frontal and parietal areas in working memory. The other goal was related to the fact that there is a lack of consensus concerning the optimal parameters of transcranial alternating current stimulation (tACS) for reliable physiological and behavioural changes. Beneficial effects on memory performance have been reported for different electrode montages: *frontal* (Alekseichuk, Turi, Antal, & Paulus, 2016a; Alekseichuk, Turi, de Lara, Antal, & Paulus, 2016b; Hoy et al., 2015; Meiron & Lavidor, 2014; Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012; Santarnecchi et al., 2016), *parietal* (Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Polanía et al., 2012; Tseng et al., 2016), *temporal* (Tseng et al., 2016), and *midline* (Vosskuhl, Huster, & Herrmann, 2015). Different stimulation frequency bands have been used: *theta* (Alekseichuk et al., 2016a,b; Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Meiron & Lavidor, 2014;

Polanía et al., 2012; Santarnecchi et al., 2016; Tseng et al., 2016; Vosskuhl et al., 2015), *beta* (Braun, Sokoliuk, & Hanslmayr, 2016), *gamma* (Hoy et al., 2015; Santarnecchi et al., 2016; Tseng et al., 2016), and *theta and gamma co-stimulation* (Alekseichuk et al., 2016b). In addition, various memory tasks have been employed: *n-back* (Alekseichuk et al., 2016a,b; Hoy et al., 2015; Jaušovec et al., 2014; Meiron & Lavidor, 2014), *memory span* (Jaušovec et al., 2014; Vosskuhl et al., 2015), *episodic memory task* (Braun et al., 2016), *change detection* (Jaušovec & Jaušovec, 2014; Santarnecchi et al., 2016; Tseng et al., 2016) and *delayed discrimination* (Polanía et al., 2012).

In order to systematically investigate how specific parameters of tACS affect working memory, the frequency of stimulation (theta vs. gamma frequency bands), the type of WM task (n-back vs. change detection) and the content of the tasks (verbal vs. figural stimuli) were manipulated. In addition, EEG data was recorded before and after stimulation, and during performance on the WM tasks. In total, 4 experiments were conducted which differed only with respect to placement of tACS electrodes (bilateral frontal, bilateral parietal, left fronto-parietal, and right fronto-parietal). Thus it was possible to investigate which electrode montage and which frequency of stimulation produced the strongest behavioural and electrophysiological aftereffects in relation to sham stimulation.

As explained in the introduction (section 1.2), the mechanisms through which tACS produces its effects are thought to be (1) direct entrainment of endogenous oscillations at the frequency of stimulation (Ali et al., 2013; Herrmann et al., 2013) and/or (2) induction of synaptic changes via spike-timing dependent plasticity (Vossen et al., 2015; Zaehle, Rach, & Herrmann, 2010). Specifically, spike timing-dependent plasticity may underlie offline effects of tACS on brain oscillatory activity (Vossen et al., 2015). There is evidence to suggest that tACS leads to frequency-specific power enhancement (Helfrich et al., 2014; Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015; Witkowski et al., 2016; Zaehle, Rach, & Herrmann, 2010), although not all studies support this finding (Antal et al., 2008; Chander et al., 2016). In the present study, it was predicted that active tACS would affect spectral power in a frequency-specific manner. This would be evident in terms of changes in resting EEG data from pre- to post-stimulation in active tACS sessions. Moreover, task-based electrophysiological data would differ on sham and active tACS sessions.

Based on the theta tACS studies conducted in our lab (Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Pahor & Jaušovec, 2014) and based on correlational studies that showed that theta band oscillations are involved in working memory processing (e.g., Bastiaansen, Posthuma, Groot, & de Geus, 2002; Jensen & Tesche, 2002; Lisman, 2010; Onton, Delorme, & Makeig, 2005; Raghavachari et al., 2006; Sauseng et al., 2004, 2010; for a review see D'Esposito & Postle, 2015); it was hypothesized that theta tACS would positively affect performance on WM tasks compared to sham stimulation. In particular, it was predicted that stimulation involving at least one target electrode placed over posterior parietal areas would elicit the greatest behavioural effects.

There is very little research on the effects of gamma tACS on WM performance. A recent study by Hoy and colleagues (2015) demonstrated that gamma tACS improved performance on a 3-back task compared to tDCS or sham stimulation. In this study, anodal/active electrode was placed over F3 (left DLPFC) and the cathodal/reference electrode was placed over the right supraorbital area. Therefore, it was predicted that gamma tACS would positively affect performance on WM tasks in the groups in which at least one target electrode was placed over prefrontal areas. However, Santarnecchi et al. (2016) reported that 40 Hz tACS did not affect performance on a visuospatial change localization task. The electrodes were placed over the left middle frontal gyrus and over Cz (vertex). This paper was published after the present study had been completed, thus the results were not taken into account during hypothesis formation.

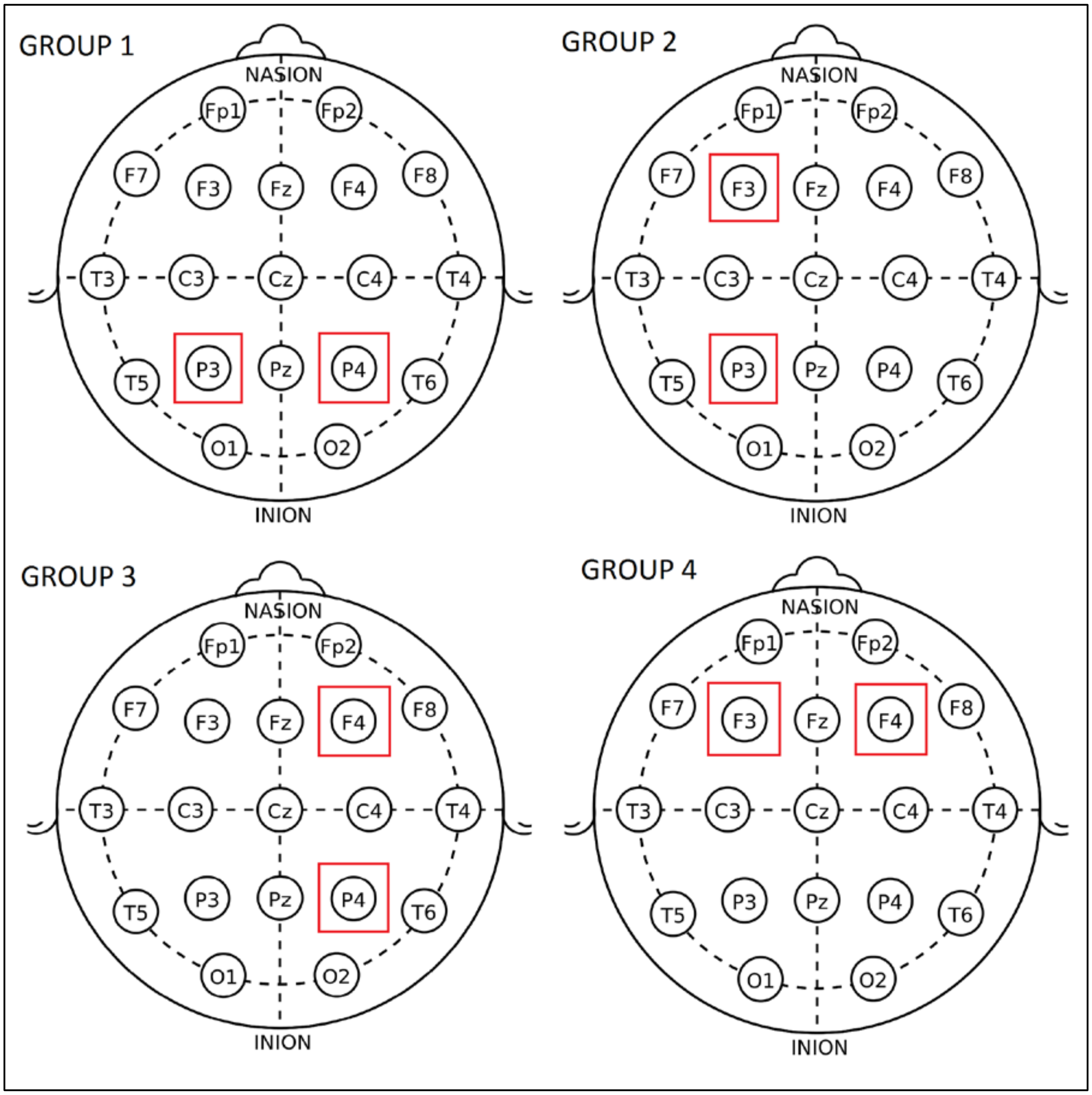
8.2. Method

8.2.1 Participants

Seventy-two healthy female students (mean age = 20.38, *SD* = 1.48) participated in the study. The experiment was undertaken with the understanding and informed consent of each subject and was conducted according to the declaration of Helsinki. The participants were randomly assigned to 4 groups based on the site of stimulation they would receive: group 1 = P3-P4, group 2 = F3-P3, group 3 = F4-P4, and group 4 = F3-F4 (see Figure 8).

Cortical localization of scalp electrodes suggested that F3 (F4) scalp electrodes correspond to the left (right) middle frontal gyrus, and that P3 (P4) scalp electrodes correspond mainly to the angular gyrus of left (right) inferior parietal lobule just below the intraparietal sulcus (Kim et al., 2007).

Figure 8: *Position of tACS electrodes in the four groups.*



In order to verify that the four groups of participants did not differ with respect to baseline short term memory capacity, computerized versions of the Digit span task and of the Corsi block tapping test were administered. As expected, there were no significant differences in performance on these tests among the four groups (see Table 8).

***Table 8**: Kruskal-Wallis test statistics. Average scores and standard deviation (in brackets) are presented for the entire sample of participants.*

	Forward Digit	**Backward Digit**	**Forward Corsi**	**Backward Corsi**
Kruskal-Wallis H test	$\chi2(3) = 0.85$ $p = .84$	$\chi2(3) = 3.85$ $p = .28$	$\chi2(3) = 2.59$ $p = .46$	$\chi2(3) = 6.42$ $p = .09$
Mean (SD) N = 72	6.33 (1.09)	5.83 (1.49)	5.77 (0.95)	5.43 (1.01)

8.2.2 Procedure

A single blind, sham-controlled approach was adopted in order to minimise potential differences between experimental conditions and groups. Except for the placement of the tACS electrodes, the 4 groups of participants were treated the same throughout the experiment. The participants completed 3 sessions over 3 consecutive days (active theta tACS, active gamma tACS, and sham tACS), the order of which was counterbalanced across individuals. Each experimental session started with 2.5 min of pre-stimulation resting (eyes closed) EEG recording, followed by 15 minutes of sham or active tACS, 2.5 min of post-stimulation resting (eyes closed) EEG recording and ended with performance on behavioural tasks during which EEG data was recorded. The participants also answered a 5-point likert scale questionnaire about the intensity of skin sensations during stimulation.

8.2.3 Working memory tasks

The participants solved four n-back tasks (figural and verbal variants of 2- and 3-back tests) and two change detection tasks (figural and verbal) while their EEG was recorded. Half of the participants solved the change detection tasks first whereas the other half solved the n-back tasks first. At the start of each experiment, they were given a few practice sessions in order to get acquainted with the tasks and with the response pad. In the n-back tasks, the participants viewed a stream of stimuli and were asked to compare the current item with an item they saw N items previously (Figure 9: $N = 2$, Figure 10: $N = 3$). The order of the tests remained fixed, starting with the easier 2-back tests and ending with the more difficult 3-back tests. The task items, which consisted of coloured squares and two-letter syllables, were generated on STIM2 (Compumedics Neuroscan Systems, Charlotte, NC, USA) and appeared on the screen for 400 ms with an inter-stimulus interval of 2000 ms. A two-alternative forced choice design was used: the participants were asked to press *1* on a response pad if the current stimulus matched the stimulus presented *N* items previously, or press *2* if the stimuli didn't match. For each participant, target accuracy and reaction time for correct responses were determined on the four n-back tests.

Figure 9: *2-back task – an example for figural stimuli.*

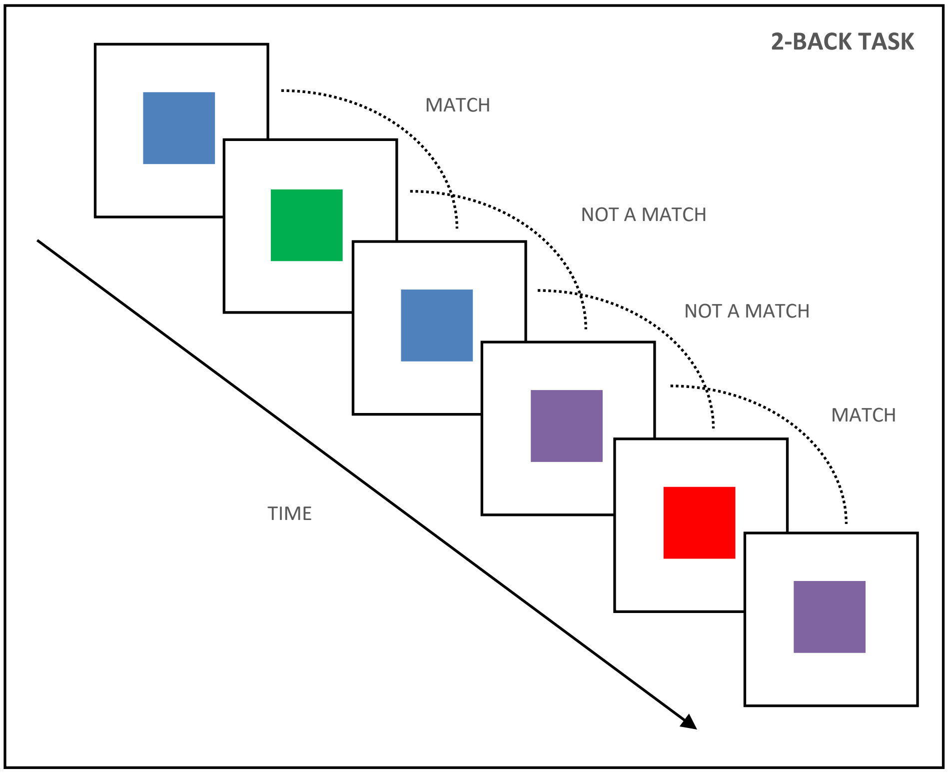
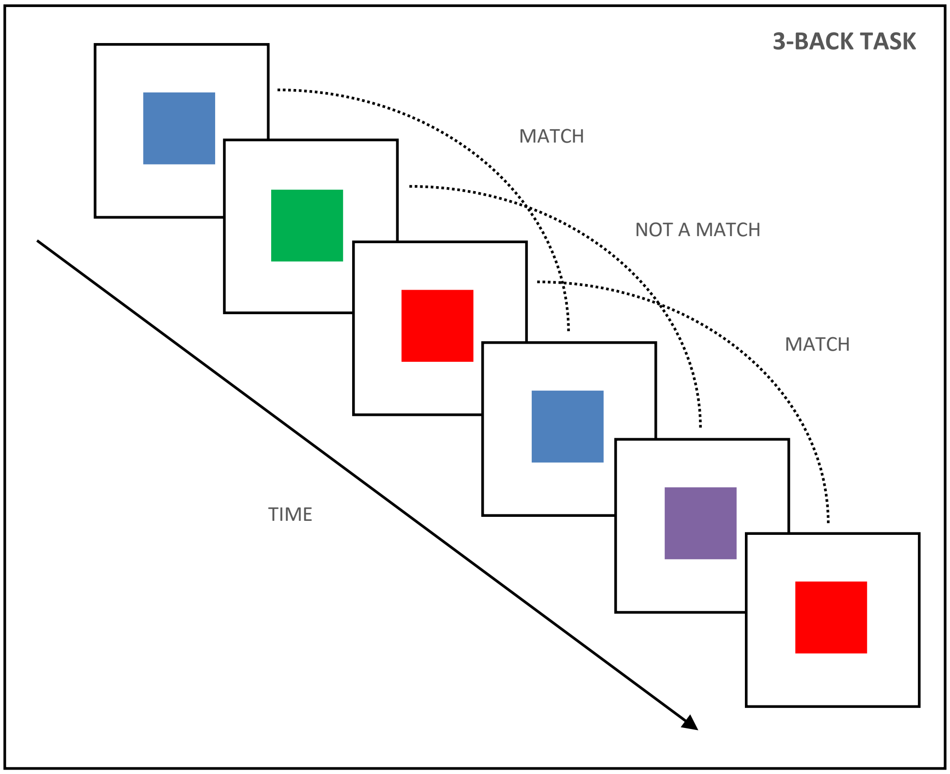


Figure 10: *3-back task – an example for figural stimuli.*



The change detection task involved presenting an array of objects (coloured squares or two-letter syllables) on a computer screen and, after a period of delay, presenting a second array that was identical to the first but could differ in one object (Luck & Vogel, 1997). The participants were asked to compare the two arrays and decide whether the cued object had changed. In these types of tasks, the first array needs to be stored in short term memory, maintained for a short period, and then compared to the second array (Saults & Cowan, 2007). The stimuli (1.5 x 1.5 cm) consisted of squares of different colours or two-letter syllables arranged at random locations in a grey rectangular display area (see Figure 11). The items initially appeared for 400 ms, disappeared during the delay period of 1000 ms, and then reappeared in the same spatial positions for 2000 ms. The inter-trial interval was 1000 ms. When the second array was presented, one of the stimuli was cued by a rectangle and the participants were asked to indicate their answer via the response pad (*1* = same, *2* = different*)*. The set size of the visual array consisted of 4, 6, and 8 objects thus the difficulty increased as the task progressed. Each set size was presented for 16 trials, giving a total of 48 trials. In the EEG analysis, the data was pooled across the whole task (i.e. the three set sizes). Likewise, reaction time and memory span scores were determined for the entire task. Memory span was calculated according to the formula k= N*(H-FA)/(1-FA), where N = the number of items in the array, H = the proportion of hits and FA = the proportion of false alarms (Pashler, 1988; Saults & Cowan, 2007).

Figure 11: *Change detection task – an example trial from the figural version of the task.*

8.2.4 Transcranial alternating current stimulation

Transcranial alternating current stimulation was applied via two electrodes that were placed in saline-soaked sponges (DC-stimulator plus, Neuroconn, Ilmenau, Germany) – for more information, see Chapter 3. The electrodes were positioned under an EEG cap according to the 10-20 system: P3 and P4 (Group 1), F3 and P3 (Group 2), F4 and P4 (Group 3), or F3 and F4 (Group 4). The participants were instructed to keep their eyes closed during the tACS sessions, which lasted 15 minutes. In the sham condition, active tACS was applied at 10 Hz for 1 minute after which it ended unbeknownst to the participant. This procedure was employed in order to ensure that the participants would not differentiate between active and sham sessions. The participants later reported that the skin sensations were only present in the first 30-60 seconds of the experiment. The questionnaire data about the participants' sensations during tACS was analysed with a Wilcoxon Signed Ranks Test (sham/active). The test showed no significant differences between the reported sensations during sham and theta tACS sessions (*Z* = -0.34; *p* = .73) or between sham and gamma tACS sessions (*Z* = -0.18; p = .99), suggesting that the participants did not distinguish between sham and active sessions.

Individual theta and gamma stimulation frequencies were determined based on pre-stimulation resting EEG data (see Table 9 for descriptive statistics).

Table 9: *Means and standard deviations (in brackets) of tACS parameters used during active sessions. The same intensity was used in theta and gamma tACS sessions.*

	Group 1	**Group 2**	**Group 3**	**Group 4**
Theta (Hz)	4.94 (0.87)	4.89 (0.95)	5.08 (0.86)	5.28 (1.02)
Gamma (Hz)	31.81 (5.03)	33.22 (6.33)	32.60 (5.69)	32.53 (5.77)
Intensity (μA)	1763.89 (104.04)	1750 (100.00)	1602.78 (199.61)	1452.78 (183.49)

8.2.5 EEG recording

EEG was recorded over 19 scalp locations using a Quik-Cap (Quik-Cap Compumedics Neuromedical supplies, Charlotte, NC, USA) with sintered electrodes (see Chapter 3).

8.2.5.1 Pre-stimulation resting EEG data analysis for tACS

Prior to the start of active tACS, one minute of artifact-free resting EEG data was manually selected and exported to EEGLAB toolbox (freely available from http://sccn.ucsd.edu/eeglab/) for MATLAB (The MathWorks, Natick, MA, USA). Given that there are no typical peaks in the power spectra for the gamma frequency band, we decided to use the method proposed by Kamiński et al. (2011) to determine individual theta and gamma frequency bands. For a detailed description of this method, see section 4.2.3. The calculations were based on the two EEG channels that marked the location for the upcoming tACS (P3-P4, F3-P3, F4-P4, F3-F4). The individual stimulation frequencies were determined by taking the average of the two channels. Average stimulation frequencies are presented in Table 9. One-way ANOVAs showed that there were no significant differences in average theta (*F*(3,71) = 0.63, *p* = .60) and gamma (*F*(3,71) = 0.19, *p* = .91) stimulation frequencies between the four groups of participants.

8.2.5.2 Task-related EEG analysis

Neuroscan software Version 4.5. (Compumedics, El Paso, TX, USA) was used to remove ocular artifacts from continuous files. The common average reference was used to perform the ERP analysis on the EEG data. For both tasks, epochs were extracted ranging from 200 ms before stimulus onset to 1000 ms after its presentation and were rejected if the amplitudes exceeded ± 100 μV. The average voltage in the 200 ms that preceded stimulus onset was used for baseline correction. Peak-to-baseline amplitudes and latencies were determined using the following time windows: P1 (40–120 ms), N1 (120–220 ms), P3 (250–600 ms). These values were imported into SPSS Version 24.0 (IBM Corp, 2016) for statistical analysis.

8.2.5.3 Pre- and post-stimulation resting EEG analysis

For each person, 6 resting EEG data files were obtained: pre- and post-measurements collected during sham, theta tACS and gamma tACS sessions. A 1 minute-long artifact-free section of the resting EEG data was manually selected for further analysis. The data was filtered with a band pass of 0.15–70.0 Hz (roll-off 24 dB per octave). On average, 29 epochs were extracted (2 s per epoch) from each section and were rejected if amplitudes exceeded ± 100 μV. A Fast Fourier Transformation was performed using a cosine window on the obtained epochs in order to derive estimates of power amplitude (μV)[4] in delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-14 Hz), beta (14-30 Hz), low gamma (30-45 Hz) and high gamma (45-70 Hz) frequency bands (separately for each condition). The obtained values were imported into IBM SPSS Version 24.0 for statistical analysis.

8.2.6 Statistical analyses

Performance on the visual array comparison tasks (memory span and reaction time) and the n-back tasks (target accuracy and reaction time) was analysed with mixed ANOVAs

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[4] The square root of the power spectrum was calculated and expressed in microvolts. Amplitude is an approximate measurement of the baseline to peak amplitude (not peak-to-peak).

with the following within-subjects factors: tACS (sham/theta/gamma tACS), type (figural/verbal) and for n-back tasks only, load (2-back/3-back), whereas the between-subjects factor was group (1-4). Based on the results of these analyses, further ANOVAs were conducted in order to investigate the effects of tACS on task performance separately in each group. In all cases, Greenhouse-Geisser values are reported.

In order to investigate the effects of theta tACS on ERP characteristics (compared to sham tACS) at the sites of stimulation, a region of interest approach was adopted in which the amplitude and latency of P1, N1 and P3 components were analysed at electrodes F3, F4, P3 and P4 (separately for each group). Namely, repeated measures ANOVAs with the factors tACS (sham/active), type (figural/verbal), load (2-back/3-back), and electrode (F3/F4/P3/P4) were conducted on each ERP component. In the next step, the same analyses were conducted on ERP components during performance on the visual array tasks (without the fact load), despite the lack of behavioural effects.

The effects of tACS on resting EEG activity were examined in delta, theta, alpha, beta, low gamma, and high gamma frequency bands. The goal was to investigate whether the mean change in amplitude in the EEG spectra from pre- to post-stimulation differed between sham and active conditions and between the four groups. The focus was on the areas in which stimulation was delivered: bilateral frontal and posterior parietal areas. For each frequency band, a mixed ANOVA was conducted with the following within-subjects factors: tACS (sham/active), time (pre/post), and electrode (F3, F4, P3, P4), whereas the between-subjects factor was group (1-4).

8.3 Results

8.3.1 Behavioural results

The mixed ANOVA on performance on visual array comparisons tasks (i.e. memory span) showed that the interactions between tACS and group were not significant (tACS×group: $F(6,136) = .50$, $p = .801$, $\eta^2 = .02$; tACS×type×group: $F(6,136) = .69$, $p = .657$, $\eta^2 = .03$), nor were the main effects for tACS or group significant, or any of the other interactions of interest. Similar results were obtained for reaction time: the interactions between the factors involving tACS and group were not significant (tACS×group: *F*(6,136) = .50, *p* = .803, η^2 = .02; tACS×type×group: *F*(6,136) = .93, *p* = .474, η^2 = .01), nor were the main effects for tACS and group significant. Since there was no evidence that performance on these tasks differed with respect to the tACS condition or as a function of group, further analyses were not conducted. Descriptive statistics for these tasks are presented in Table 10.

Table 10: *Average scores (memory span) and reaction times (in ms) on the visual array comparison tasks in sham, theta and gamma tACS sessions for each group. G = group.*

G	**tACS**	**Figural array (span)**		**Verbal array (span)**		**Figural array (RT)**		**Verbal array (RT)**	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	sham	4.30	1.30	2.94	0.80	698.41	171.61	850.03	206.96
	theta	4.14	1.21	3.12	0.59	666.80	130.89	817.19	191.49
	gamma	4.15	1.19	3.29	0.75	684.32	167.98	829.06	195.29
2	sham	4.48	0.96	3.21	0.82	720.41	145.01	818.78	147.26
	theta	4.09	0.61	3.20	0.82	687.31	133.65	819.78	141.99
	gamma	4.48	0.54	3.37	0.72	740.17	190.93	862.32	170.06
3	sham	3.97	0.99	3.06	0.87	780.12	100.47	875.97	127.81
	theta	3.85	0.90	3.07	0.74	778.17	161.15	914.80	165.16
	gamma	3.97	0.76	3.02	0.81	781.91	165.80	895.10	166.00
4	sham	3.91	0.91	2.70	1.08	691.31	153.89	817.41	212.81
	theta	3.86	0.95	2.97	0.80	696.68	177.23	799.09	240.85
	gamma	4.01	0.99	2.65	0.73	709.29	164.32	788.34	214.92

The same analyses were conducted on n-back accuracy and reaction time, except that the factor load (2-back/3-back) was added. For n-back accuracy, the interaction between tACS and group was not significant (*F*(6,136) = .62, *p* = .703, η^2 = .03), however, a trend towards significance emerged between the factors tACS, type, load and group (*F*(6,136) = 1.93, *p* = .080, η^2 = .08), suggesting that the effects of tACS not only depended on electrode placement, but also on the content of the tasks and their difficulty level. For n-back reaction time, the interactions that involved the factors tACS and group were not significant (e.g., tACS×group: *F*(6,136) = .30, p = .936, η^2 =.01), nor were the main effects for tACS or group significant. In order to determine which type of active tACS, theta or gamma tACS, drove the changes in n-back accuracy, each of these conditions were separately compared to the sham condition. The sham-theta tACS analysis showed a significant interaction between tACS, type, load and group (*F*(3,68) = 4.16, *p* = .009, η^2 = .16), whereas in the sham-gamma tACS analysis, this interaction was not significant (*F*(3,68) = .80, *p* = .496, η^2 = .03), nor were the main effects for tACS or group significant. Given that theta but not gamma tACS seemed to affect n-back accuracy in comparison to sham stimulation, and that this interacted with the factor group, subsequent analyses focused on sham – theta tACS comparisons separately in each group. Descriptive statistics for target accuracy and reaction time are presented in Tables 11 and 12, respectively.

Table 11: *Average scores (target accuracy) and standard deviation (SD) on the n-back tasks in sham, theta and gamma tACS sessions for each group. G = group.*

G	**tACS**	**Figural 2-back**		**Figural 3-back**		**Verbal 2-back**		**Verbal 3-back**	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	sham	43.72	9.02	38.50	6.90	41.67	9.15	39.56	8.56
	theta	42.44	6.95	40.94	4.72	43.89	5.14	40.33	6.60
	gamma	42.83	6.87	39.28	9.11	41.17	9.87	36.83	8.51
2	sham	42.72	6.91	39.00	8.02	42.83	5.84	38.94	7.20
	theta	44.33	4.74	38.11	8.16	43.61	4.68	39.56	6.41
	gamma	43.67	6.40	39.33	6.31	44.72	5.87	39.28	8.03
3	sham	42.06	8.36	37.72	6.58	43.00	6.35	37.50	6.54
	theta	45.06	3.06	38.78	6.84	43.44	4.68	40.22	6.26
	gamma	43.78	4.91	40.22	5.82	44.56	5.26	40.17	5.14
4	sham	44.22	5.88	38.39	7.13	44.94	4.58	40.39	5.68
	theta	44.28	3.46	38.00	6.53	43.56	4.82	39.72	5.88
	gamma	45.39	3.81	39.17	6.31	45.17	3.91	40.28	5.56

Table 12: *Average reaction time (in ms) and standard deviation (SD) on the n-back tasks in sham, theta and gamma tACS sessions for each group. G = group.*

G	**tACS**	**Figural 2-back**		**Figural 3-back**		**Verbal 2-back**		**Verbal 3-back**	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1	sham	512.26	179.22	534.35	197.87	573.84	213.66	553.24	173.24
	theta	508.94	195.28	507.46	181.76	530.77	158.74	501.22	162.45
	gamma	535.12	200.82	539.00	192.49	541.31	178.13	566.07	163.83
2	sham	616.70	213.73	627.22	190.59	598.82	195.97	630.08	175.05
	theta	594.22	221.34	598.75	190.60	604.06	203.97	616.87	179.16
	gamma	568.31	186.07	585.50	181.22	560.48	160.70	595.73	164.13
3	sham	536.55	155.41	602.38	177.44	570.32	150.57	600.37	156.72
	theta	523.63	180.32	560.78	185.15	535.46	174.45	554.74	179.85
	gamma	559.29	152.75	586.60	184.88	554.88	161.70	583.82	153.98
4	sham	536.55	155.41	602.38	177.44	570.32	150.57	600.37	156.72
	theta	523.63	180.32	560.78	185.15	535.46	174.45	554.74	179.85
	gamma	559.29	152.75	586.60	184.88	554.88	161.70	583.82	153.98

Group 1: bilateral parietal stimulation

The results of the ANOVA in which n-back task accuracy was examined on sham and theta tACS sessions showed a trend towards significance for the main effect of tACS ($F(1,17) = 0.45$, $p = .051$), suggesting a beneficial effect of theta tACS on working memory performance. A significant interaction between tACS, load, and type ($F(1,17) = 6.36$, $p = .022$, $\eta^2 = .27$) indicated that theta tACS mainly improved performance on the verbal 2-back task and on the figural 3-back task (see Figure 12). Post-hoc t-tests in which we compared performance on the figural and verbal 2- and 3-back tests on sham and theta tACS sessions were not significant at $p < .05$.

Group 2: left frontoparietal stimulation

There is no evidence that theta tACS significantly affected performance on n-back tasks compared to sham stimulation: there were no significant main effects of tACS for average scores ($F(1,17) = .14$, $p = .72$) or for reaction time ($F(1,17) = .15$, $p = .70$), nor were there any significant interactions that included the factor tACS.

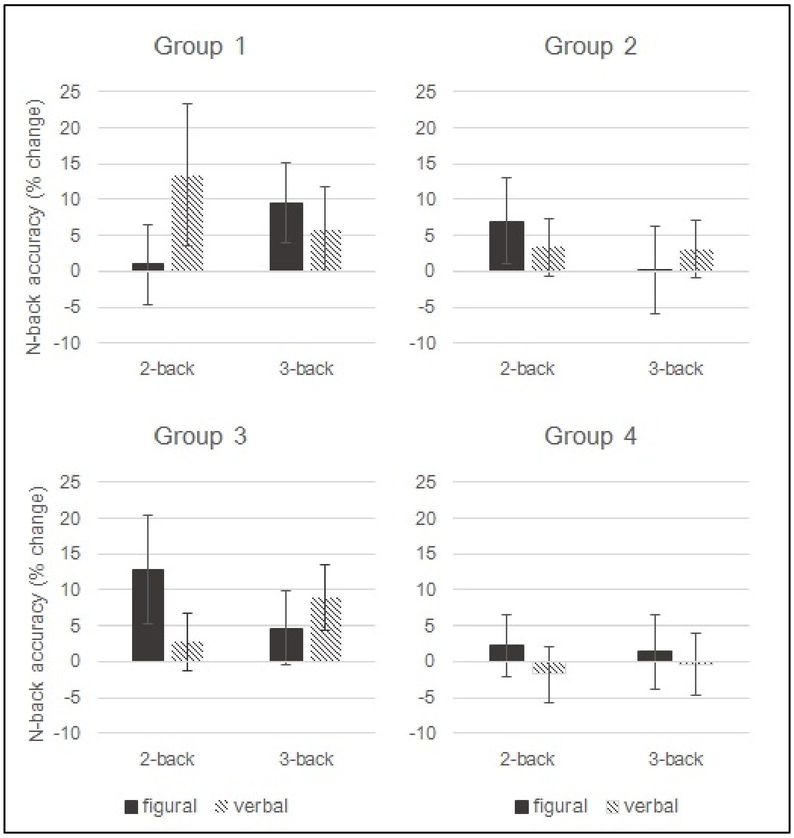
Group 3: right frontoparietal stimulation

The ANOVA showed a significant interaction between the factors tACS, load, and type ($F(1,17) = 4.41$, $p = .05$, $\eta^2 = .21$). As can be seen in Figure 12, theta tACS was associated with increased scores on both tasks, particularly on the figural 2-back task and the verbal 3-back task. Interestingly, the opposite behavioural patterns were observed in Group 1. One of the post-hoc t-tests showed a trend toward significance (uncorrected $t(17) = -1.92$, $p = .07$): after theta tACS, the average score on the 3-back verbal test was higher than after sham tACS ($M_{sham}= 37.5$, $SD_{sham}= 1.54$; $M_{theta}= 40.22$, $SD_{theta}= 1.48$).

Group 4: bilateral frontal stimulation

There is no evidence that theta tACS significantly affected performance on n-back tasks compared to sham stimulation: there were no main effects of tACS for average scores scores ($F(1,17) = .18$, $p = .676$) or for reaction time ($F(1,17) = .65$, $p = .431$), nor were there any significant interactions of interest.

***Figure 12**: Percent change in n-back target accuracy (theta tACS sessions compared to sham sessions) in the four groups.*



In sum, these findings suggest that theta but not gamma tACS affected performance on the working memory tasks compared to sham stimulation. In particular, theta tACS improved n-back accuracy in two out of four groups: the bilateral parietal and the right fronto-parietal group. However, task content and difficulty affected the results. In group 1, an improvement in target accuracy was observed on the verbal 2-back task, whereas in group 3, an improvement was observed on the figural 2-back task. An opposite, albeit less pronounced pattern was observed for 3-back tasks.

8.3.2 Task-based EEG results

Figures 13-16 show grand-average ERP plots at midline electrodes during performance on the n-back tasks in sham and active tACS conditions, separately for each group.

***Figure 13**: Grand-average ERPs at midline electrodes during performance on n-back tasks in Group 1 (bilateral parietal stimulation). Blue = sham tACS session, red = theta tACS session, green = gamma tACS session.*

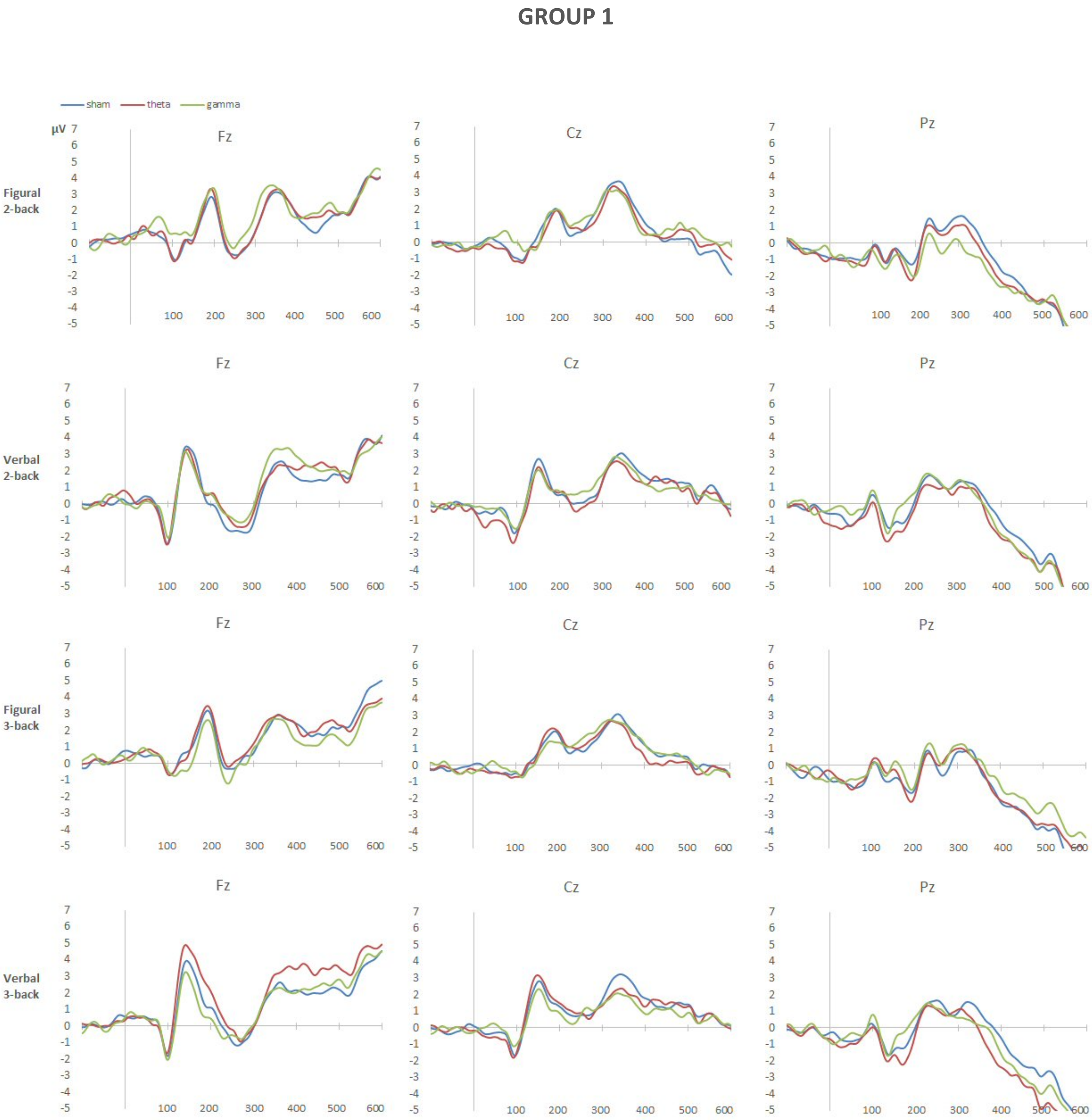


***Figure 14**: Grand-average ERPs at midline electrodes during performance on n-back tasks in Group 2 (left frontoparietal stimulation). Blue = sham tACS session, red = theta tACS session, green = gamma tACS session.*

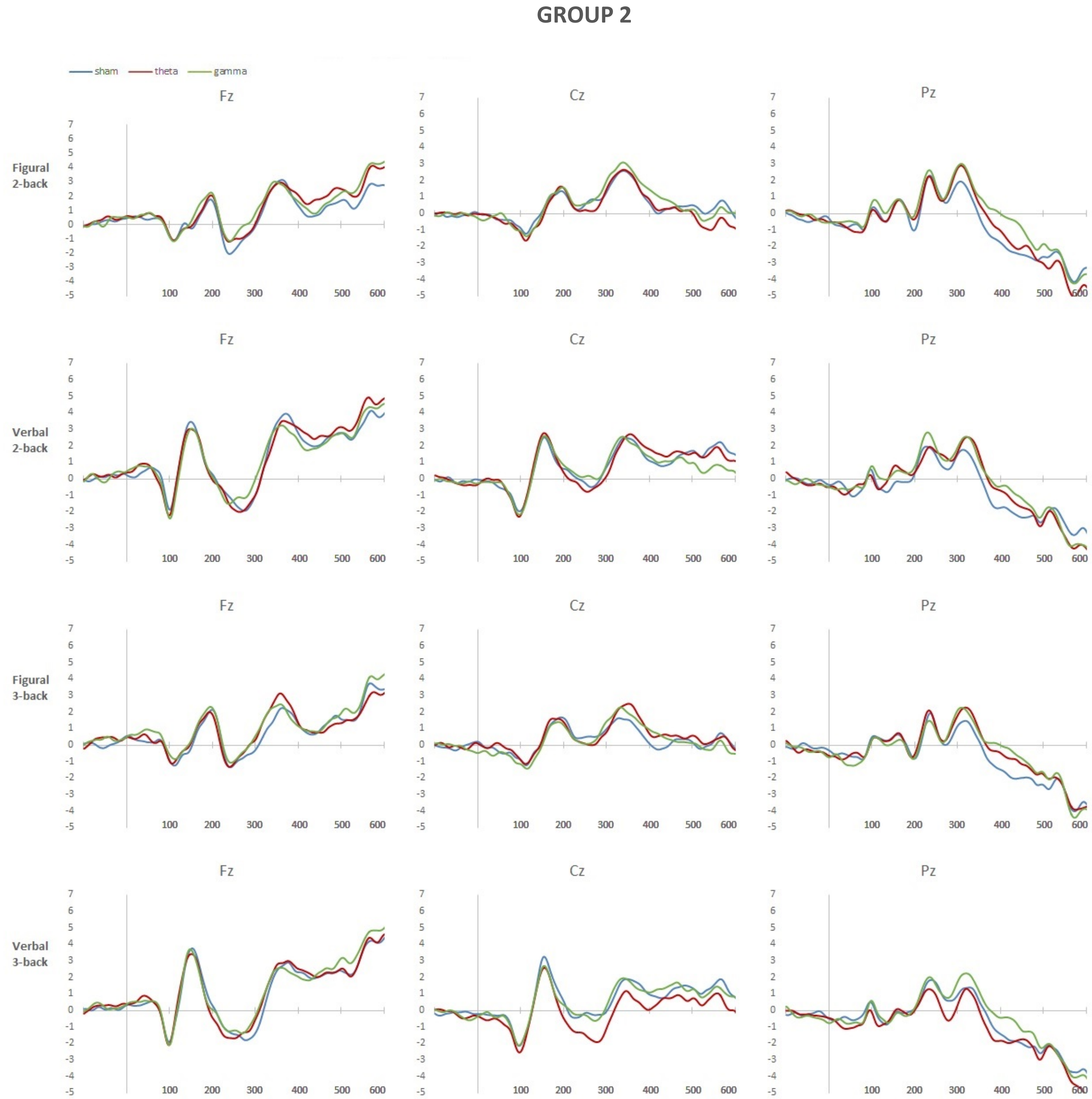


***Figure 15**: Grand-average ERPs at midline electrodes during performance on n-back tasks in Group 3 (right frontoparietal stimulation). Blue = sham tACS session, red = theta tACS session, green = gamma tACS session.*

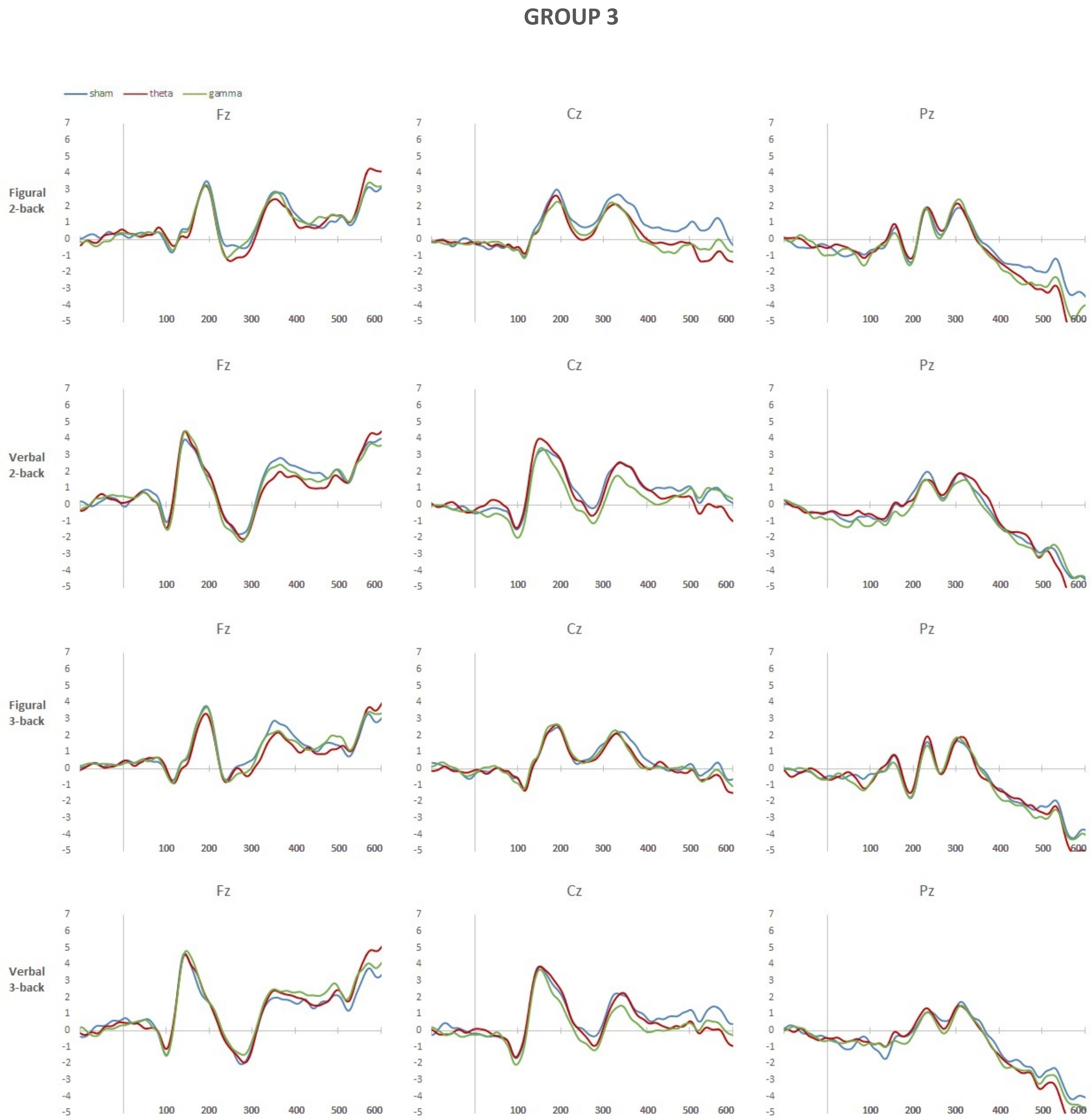
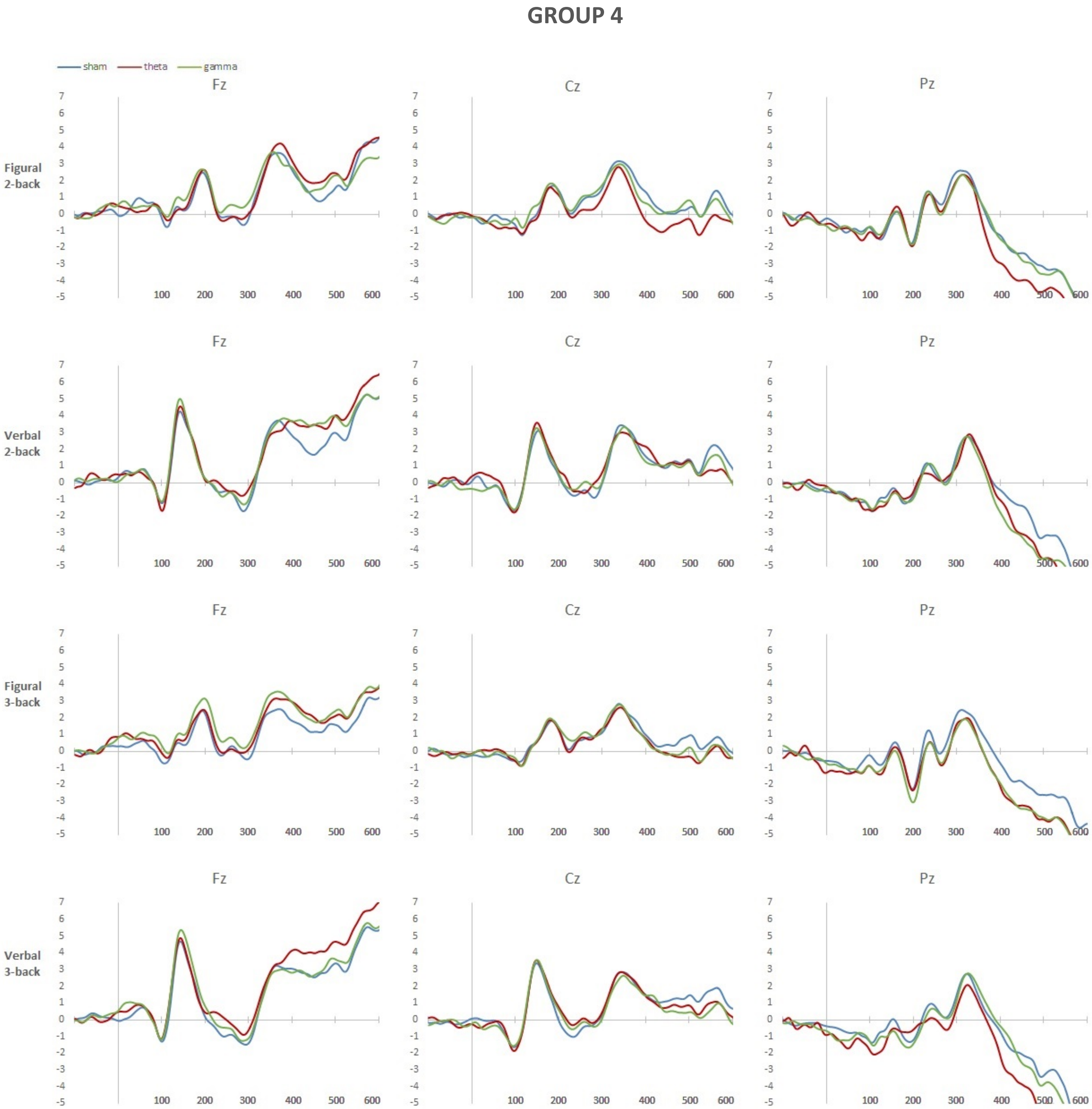


***Figure 16**: Grand-average ERPs at midline electrodes during performance on n-back tasks in Group 4 (bilateral frontal stimulation). Blue = sham tACS session, red = theta tACS session, green = gamma tACS session.*



8.3.2.1 Event-related potentials during performance on n-back tasks

Group 1: bilateral parietal stimulation

Theta tACS increased P1 amplitude in 3-back tasks compared to the sham stimulation session, particularly over frontal (F3, F4) areas (tACS×N: $F(1,17) = 7.60$, $p = .013$, $\eta^2 = .31$; tACS×electrode: $F(1,17) = 3.45$, $p = .050$, $\eta^2 = .17$). Theta tACS also decreased P3 latency in comparison to sham tACS, particularly during two tasks: the verbal 2-back task and the figural 3-back task ($F(1,17) = 5.06$, $p = .038$, $\eta^2 = .23$). This pattern corresponds to the behavioural results: the greatest increases in n-back accuracy in theta tACS compared to sham sessions were observed in these two tests (see Figure 12). Since P3 latency is thought to be proportional to stimulus evaluation timing (Polich, 2007), decreased P3 latency in the theta tACS sessions might reflect quicker matching of items.

Gamma tACS increased P1 amplitude on n-back tasks compared to sham tACS (3-back > 2-back), particularly over the left parietal electrode (tACS×N×electrode: $F(3,51) = 4.40$, $p = .025$, $\eta^2 = .21$). In addition, gamma tACS increased P1 latency on the figural 3-back task and on the verbal 2-back task in comparison to sham stimulation sessions (tACS×N×type: $F(1,17) = 6.32$, $p = .022$, $\eta^2 = .27$). Gamma tACS also decreased N1 amplitude on 2-back tasks, especially over the right parietal area (tACS×N×electrode: $F(3,51) = 3.62$, $p = .036$, $\eta^2 = .18$). For figural n-back tasks, gamma tACS decreased P3 amplitude on the 2-back tasks and increased it on the 3-back tasks, whereas for verbal n-back tasks, increased P3 amplitude was observed both in 2-back and 3-back tasks (tACS×N×type: $F(1,17) = 5.43$, $p = .032$, $\eta^2 = .24$).

Group 2: left frontoparietal stimulation

There were no significant main effects or interactions of interest for any of the ERP components (amplitude/latency) for theta-sham comparisons. Gamma tACS increased P1 amplitude in n-back tasks compared to sham tACS (3-back > 2-back), particularly over bilateral parietal areas (P3 and P4) (tACS×N×electrode: $F(3,51) = 5.49$, $p = .009$, $\eta^2 = .24$). Gamma tACS also increased N1 amplitude during performance on the n-back tasks, especially during the 2-back tasks (tACS×N: $F(3,51) = 4.74$, $p = .044$, $\eta^2 = .22$).

Group 3: right frontoparietal stimulation

Theta tACS increased P3 amplitude mainly on the figural 2-back task and on the verbal 3-back task with respect to sham tACS (tACS×N×type: $F(1,17) = 4.77$, $p = .043$, $\eta^2 = .22$). Like in Group 1, this finding is line with the behavioural results. Increased P3 amplitude has been linked to greater memory and attention loading (Chen, Mitra, & Schlaghecken, 2008). There were no significant main effects or interactions of interest for any of the ERP components (amplitude/latency) for gamma-sham comparisons.

Group 4: bilateral frontal stimulation

There was a significant main effect of tACS; the amplitude of P1 was larger during performance on n-back tasks in the theta tACS condition compared to sham tACS ($F(1,17) = 6.56$, $p = .020$, $\eta^2 = .28$). There were no significant main effects or interactions of interest for any of the ERP components (amplitude/latency) for gamma-sham comparisons.

8.3.2.2 Correlation of P3 amplitude with n-back performance

Since Keeser et al. (2011) reported significant correlations between P3-amplitude at electrode Pz and working memory performance after tDCS, we decided to verify whether a similar relation could be observed after tACS. Only Group 1 showed significant Pearson linear correlations between the two measures (see Table 13). During the theta tACS session, P3-amplitude at electrode Pz positively correlated with n-back accuracy on two tests: the verbal 2-back ($r = .47$) and the figural 3-back ($r = .68$). During the sham session, a negative correlation between P3 amplitude and n-back accuracy was observed on the figural 2-back test ($r = -.63$).

Table 13: *Relation between P3 Voltage (µV) and behavioural n-back results for the electrode Pz.*

tACS	Task	Group 1	Group 2	Group 3	Group 4
Sham	Fig. 2-back	**r = -.63**	r = .44	r = -.21	r = .01
		p = .005	p = .067	p = .407	p = .947
	Verb. 2-back	r = -.34	r = .27	r = .01	r = .01
		p = .167	p = .282	p = .965	p = .972
	Fig. 3-back	r = -.37	r = .21	r = -.39	r = -.10
		p = .131	p = .400	p = .107	p = .696
	Verb. 3-back	r = -.32	r = .15	r = -.20	r = -.31
		p = .194	p = .548	p = .437	p = .216
Theta	Fig. 2-back	r = -.07	r = .34	r = -.12	r = .46
		p = .775	p = .172	p = .637	p = .057
	Verb. 2-back	**r = .47**	r = .33	r = -.28	r = -.23
		p = .048	p = .189	p = .263	p = .351
	Fig. 3-back	**r = .68**	r = .45	r = -.08	r = .09
		p = .002	p = .060	p = .745	p = .724
	Verb. 3-back	r = .30	r = .21	r = .05	r = .12
		p = .232	p= .400	p = .848	p = .634

8.3.2.3 Event-related potentials during performance on visual array comparison tasks

The same analyses were also conducted on ERP components during performance on the visual array tasks (only the significant effects of interest are reported). The effects of theta tACS compared to sham stimulation on ERP amplitude during performance on visual array comparisons tasks were consistent across the groups: tACS×electrode interactions suggested increased amplitude over the two frontal electrodes yet decreased amplitude over the two parietal electrodes in the following ERP components: P1 (Group 1: *F*(3,51) = 5.33, *p* = .014, η^2 = .24; Group 3: *F*(3,51) = 5.91, *p* = .011, η^2 = .26), N1 (Group 3: *F*(3,51) = 7.97, *p* = .003, η^2 = .32) and P3 (Group 3: *F*(3,51) = 4.53, *p* = .018, η^2 = .21). The effects of gamma tACS compared to sham stimulation showed the same pattern: increased amplitude over frontal electrodes and decreased amplitude over parietal regions in the following ERP components: P1 (Group 2: (*F*(3,51) = 4.58, *p* = .026, η^2 =

.21, Group 3: $F(3,51) = 4.92$, $p = .020$, $\eta^2 = .22$) and P3 (Group 3: $F(3,51) = 4.43$, $p = .034$, $\eta^2 = .21$). In addition, sham-gamma tACS comparisons revealed a significant main effect of tACS in Group 2 for N1 amplitude ($F(1,17) = 7.57$, $p = .014$, $\eta^2 = .31$); gamma tACS increased N1 amplitude compared to sham.

The analysis on ERP latency showed the following significant effects for theta tACS compared to sham: P1 latency in group 3 (tACS×type×electrode: $F(3,51) = 4.11$, $p = .023$, $\eta^2 = .19$) – for figural stimuli, theta tACS increased P1 latency mainly over a left frontal area, whereas for verbal stimuli, theta tACS increased P1 latency mainly over the right frontal area; N1 latency in group 2 (tACS×type): $F(3,51) = 4.41$, $p = .029$, $\eta^2 = .21$) – theta tACS increased N1 latency on verbal tasks more than on figural tasks; and P3 latency in group 3 (tACS×type×electrode: $F(3,51) = 3.98$, $p = .028$, $\eta^2 = .19$) – for figural stimuli, theta tACS decreased P3 latency over frontal areas, whereas for verbal stimuli, theta tACS increased P3 latency over the right frontal area.

The analysis on ERP latency showed the following significant effects for gamma tACS compared to sham: P1 latency in group 3 (tACS×type×electrode: $F(3,51) = 3.83$, $p = .039$, $\eta^2 = .18$) – for figural stimuli, gamma tACS increased P1 latency over a left frontal area (electrode F3) but somewhat decreased it over parietal areas, whereas for verbal stimuli, gamma tACS increased P1 latency over a right frontal area (electrode F4), but decreased it over the parietal electrodes; and P3 latency in group 4 (tACS×electrode): $F(3,51) = 5.06$, $p = .017$, $\eta^2 = .23$) – gamma tACS increased P3 latency over a left frontal area (electrode F3).

8.3.3 Resting EEG results

The effects of tACS on resting EEG activity were examined in delta, theta, alpha, beta, low gamma, and high gamma frequency bands. Figures 17-24 show pre- and post-stimulation amplitude-frequency plots in theta and gamma tACS sessions (at electrode Pz). Since the participants rested with their eyes closed while EEG data was collected, high alpha band power was expected. Indeed, this can be observed in Figures 17-24. In addition, minor differences between pre- and post-stimulation data can be observed in the low frequency bands, which were explored in statistical analyses. The goal was to investigate whether the mean change in amplitude in the EEG spectra from pre- to post-stimulation differed between sham and active conditions and between the four groups. For each frequency band a mixed ANOVA was conducted, in which the tACS-by-time interaction was of particular interest. The only mixed ANOVA that showed a significant interaction involving these factors was the one conducted on theta amplitude for the comparison between sham tACS and theta tACS sessions. Specifically, significant interactions between tACS and time ($F(3,68) = 8.46$, $p = .005$, $\eta^2 = .11$), tACS and electrode ($F(3,204) = 3.64$, $p = .025$, $\eta^2 = .05$), and between tACS, time, electrode, and group ($F(9,204) = 2.22$, $p = .045$, $\eta^2 = .09$) were observed. During the sham session, theta amplitude increased after tACS, whereas during the theta tACS session, theta amplitude decreased after stimulation; these effects depended on the location of the recorded EEG data and on the site of stimulation (i.e. group). In contrast, the mixed ANOVA in which the effects of gamma and sham tACS were examined in relation to theta amplitude did not show any significant interaction effects that involved the factors tACS and time, or any main effects of interest. The effects of theta tACS and gamma tACS (contrasted against sham) on EEG amplitudes were also examined in delta, alpha, beta, low gamma, and high gamma frequency bands with mixed ANOVAs, however, the analyses did not show any significant interaction effects that involved the factors tACS and time, suggesting that mean change in EEG amplitude from pre- to post-stimulation did not differ between sham and active conditions or between the four groups hence further analyses were not conducted.

In order to further explore the effects of sham and theta tACS on theta amplitude, within-subjects ANOVAs were conducted separately in each group.

Group 1

The mean change in theta amplitude from pre- to post-stimulation did not appear to differ between sham and active conditions. However, a significant interaction between time and electrode ($F(3,51) = 11.54$, $p < .001$, $\eta^2 = .41$) suggested that tACS decreased theta amplitude over parietal but not frontal brain areas.

Group 2

Significant interactions (tACS×time: $F(1,17) = 8.49$, $p = .01$, $\eta^2 = .33$; tACS×electrode: $F(3,51) = 4.34$, $p = .016$, $\eta^2 = .21$; time×electrode: $F(3,51) = 5.16$, $p = .012$, $\eta^2 = .23$) indicate that sham tACS increased theta amplitude whereas theta tACS decreased it. During the sham session, an increase in theta amplitude was observed at all locations, whereas during the theta tACS sessions, theta amplitude decreased over left frontal (F3) and left parietal (P3) areas, which corresponds to the placement of electrodes in this group.

Group 3

The mean change in theta amplitude from pre- to post-stimulation did not appear to differ between sham and active conditions. A significant interaction between time and electrode ($F(3,51) = 3.94$, $p = .026$, $\eta^2 = .19$) suggested that tACS decreased theta amplitude over electrode F4 yet increased it over electrodes F3, P3 and P4.

Group 4

There is no evidence to suggest that the mean change in theta amplitude from pre- to post-stimulation significantly differed or that it depended on sham and active conditions.

Post-hoc t-tests were conducted for groups 1-3 in order to compare pre-stimulation theta amplitude with post-stimulation theta amplitude (measured at four locations) in the active theta tACS session. Only groups 1 and 2 displayed significant differences in theta amplitude. In group 1, theta tACS significantly reduced theta amplitude at bilateral parietal areas compared to baseline (P3: $t(1,17) = 2.63$, $p = .017$; P4: $t(1,17) = 2.82$, $p = .012$); the t-test for the P4 area was still significant after Bonferroni correction ($p < .0125$). The reduction in theta amplitude corresponds to the placement of tACS electrodes in this group. In group 2, theta tACS significantly reduced theta amplitude at a left parietal area compared to baseline (P3: $t(1,17) = 3.32$, $p = .004$), which remained significant after Bonferroni correction ($p < .0125$). No significant t-tests were obtained in group 3. For comparison, the same post-hoc t-tests were conducted on theta amplitude during the sham sessions. In group 1, sham tACS decreased theta amplitude at electrode P4 compared to baseline ($t(1,17) = 2.23$, $p = .04$), but this difference was no longer significant after Bonferroni correction ($p > .0125$). In group 2, theta amplitude increased after sham tACS at electrode F4 ($t(1,17) = -3.70$, $p = .002$), which remained significant after Bonferroni correction ($p < .0125$). No significant t-tests were obtained in group 3.

For comparison, the same post-hoc t-tests were conducted on theta amplitude during the sham sessions. In group 1, sham tACS decreased theta amplitude at electrode P4 compared to baseline ($t(1,17) = 2.23$, $p = .04$), but this difference was no longer significant after Bonferroni correction ($p > .0125$). In group 2, theta amplitude increased after sham tACS at electrode F4 ($t(1,17) = -3.70$, $p = .002$), which remained significant after Bonferroni correction ($p < 0.0125$). No significant t-tests were obtained in group 3.

Figure 17: *Theta tACS session - Group 1*

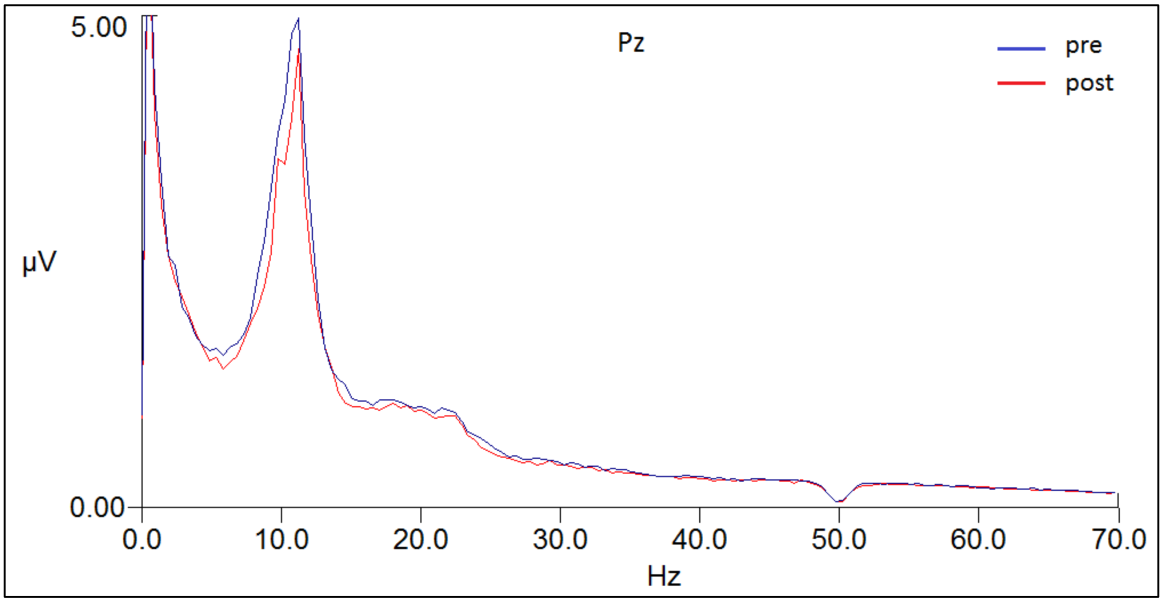


Figure 18: *Gamma tACS session - Group 1*

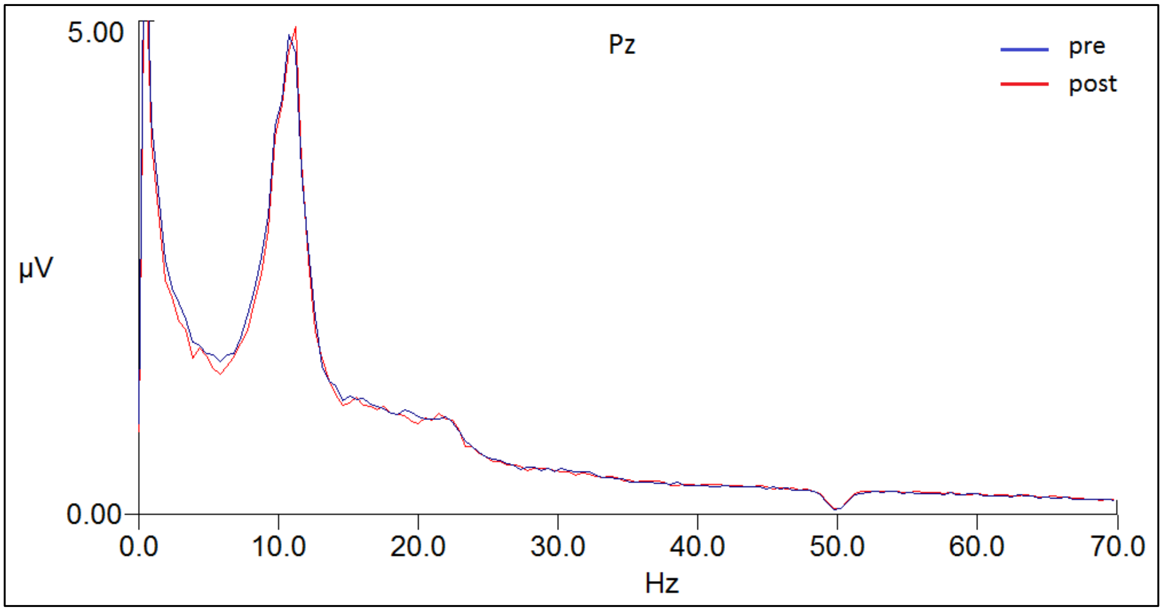


Figure 19: *Theta tACS session - Group 2*

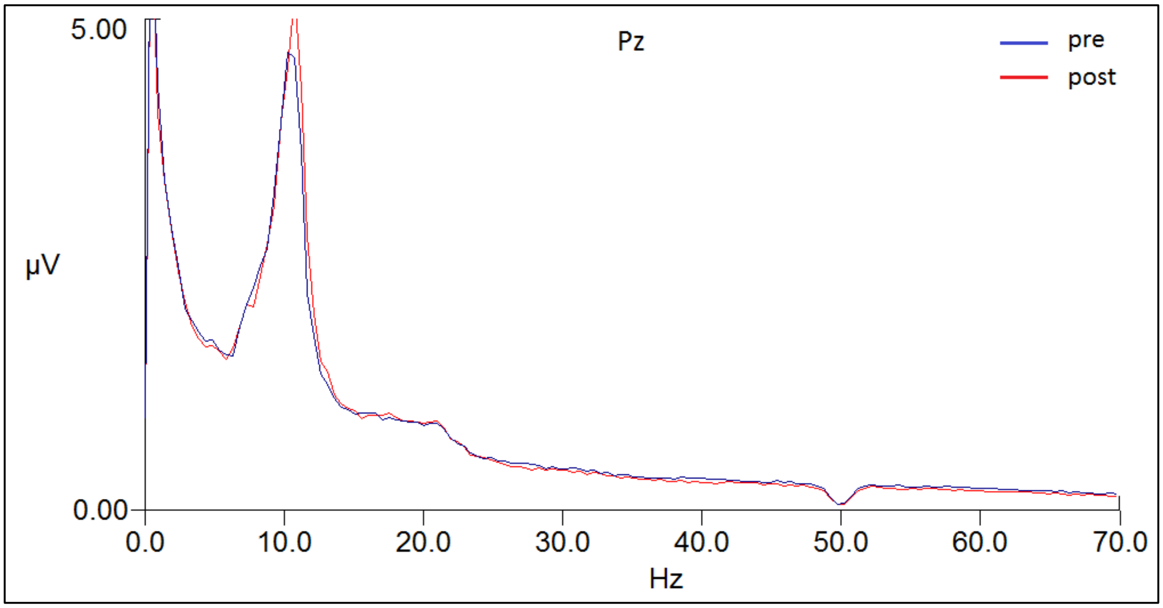


Figure 20: *Gamma tACS session - Group 2*

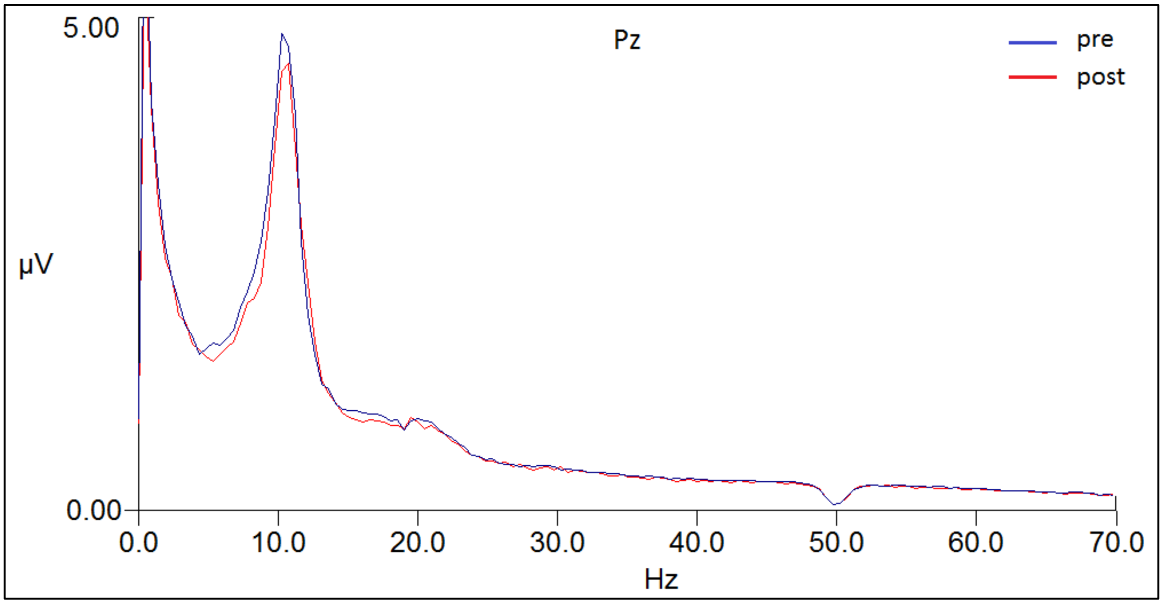


Figure 21: *Theta tACS session - Group 3*

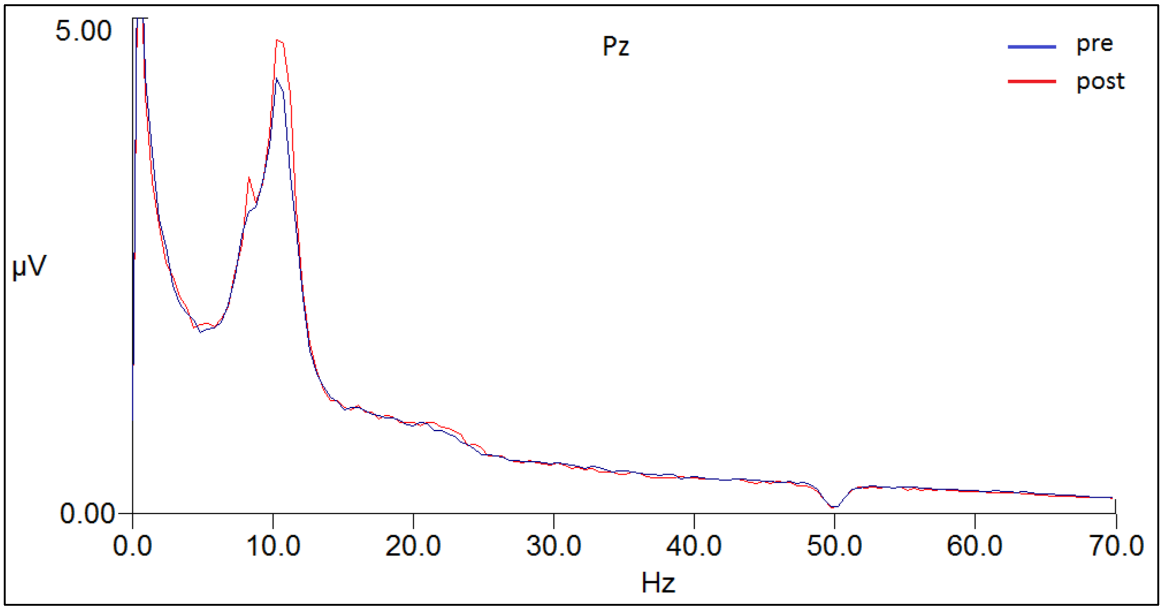


Figure 22: *Gamma tACS session - Group 3*

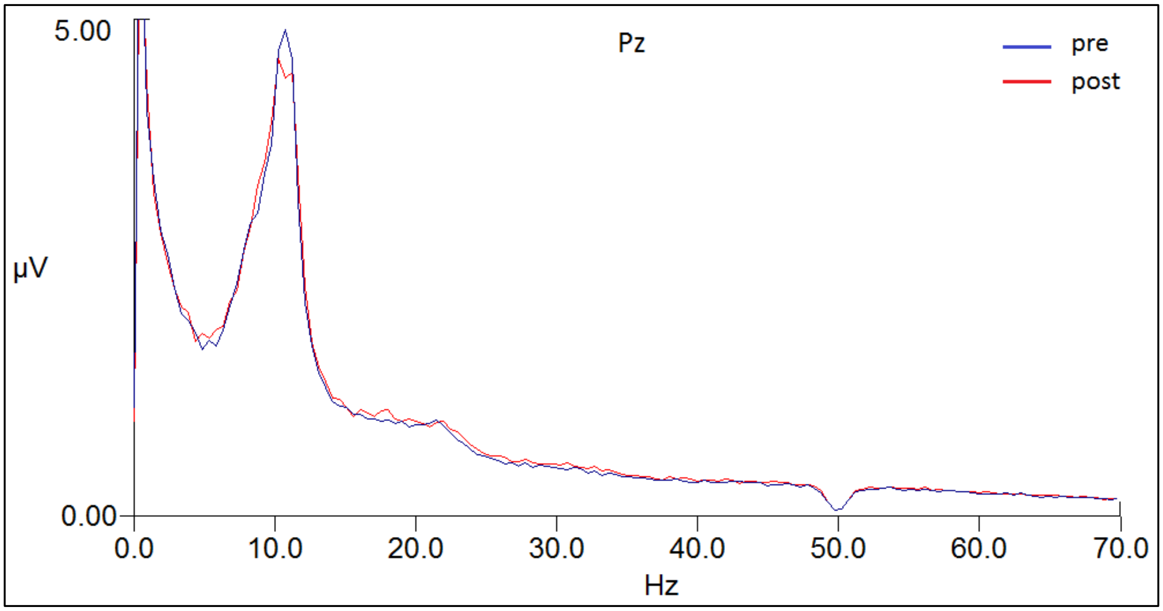


Figure 23: *Theta tACS session - Group 4*

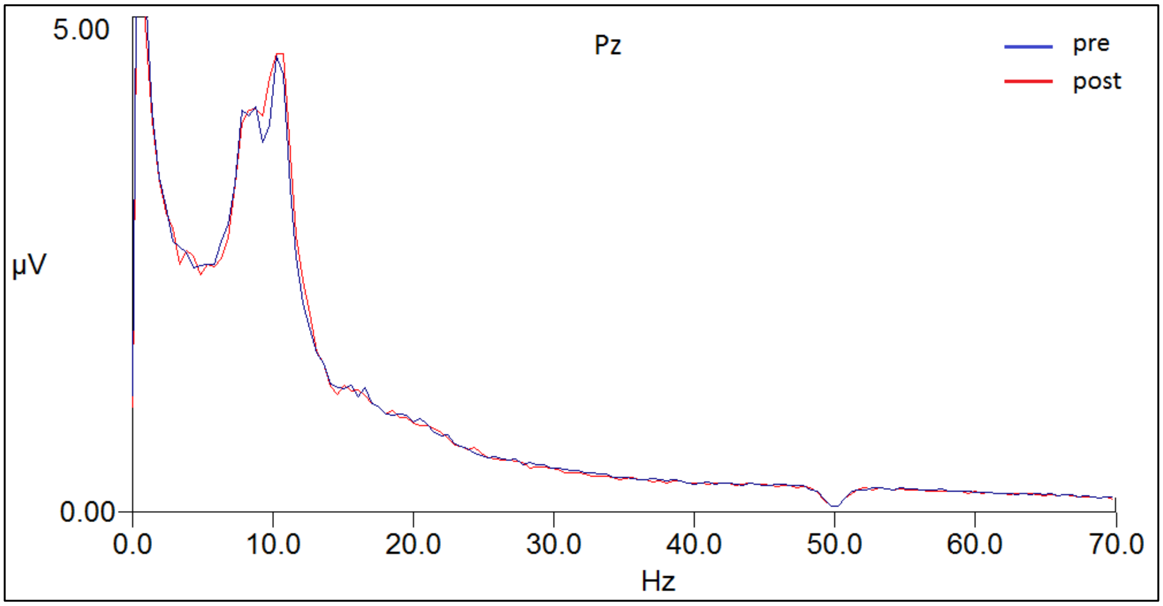
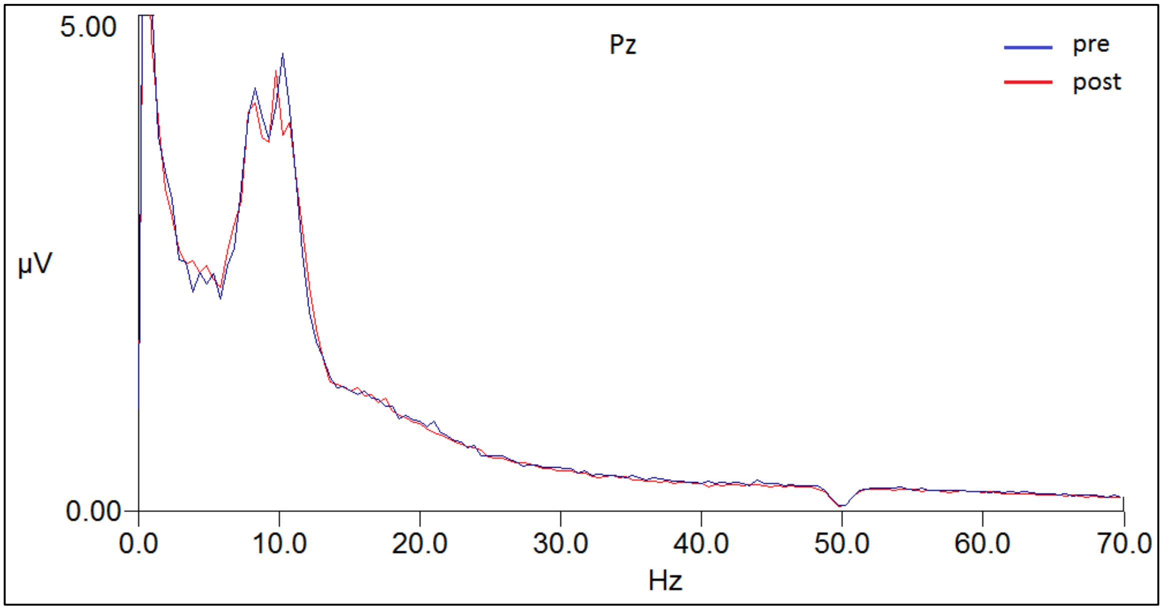


Figure 24: *Gamma tACS session - Group 4*



8.4 Discussion

Behavioural results

The results showed that the effects of tACS on working memory performance are frequency-, task-, location-, and content-specific. Each of these points will be discussed separately. Afterwards, the effects of tACS on neuro-electric patterns of activity will be discussed.

First, significant changes in performance on working memory tasks were observed only after theta tACS compared to sham. This finding is in line with previous theta tACS studies (Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Pahor & Jaušovec, 2014; Polanía et al., 2012; Vosskuhl et al., 2015) and supports correlational research showing that theta band oscillations are involved in working memory processing (e.g., Bastiaansen, Posthuma, Groot, & de Geus, 2002; Jensen & Tesche, 2002; Lisman, 2010; Onton, Delorme, & Makeig, 2005; Raghavachari et al., 2006; Sauseng et al., 2004, 2010). Since tACS was applied offline, it is assumed that the observed behavioural changes reflect short-term neural plasticity (Vossen et al., 2015), however, this was not directly tested in the present study.

In contrast, there is no evidence to suggest that gamma tACS affected working memory performance. As discussed earlier, one study demonstrated that gamma tACS improved performance on a 3-back task compared to sham (Hoy et al., 2015), whereas another reported that performance on a change localization working memory task was not affected by gamma tACS (Santarnecchi et al., 2016). Interestingly, the study by Santarnecchi and colleagues (2016) showed gamma tACS-induced enhancement of fluid intelligence, yet no effect on working memory performance. These results can be explained by the following methodological differences: (1) *stimulation frequency*; 32.5 Hz (present study) versus 40 Hz (Hoy et al., 2015; Santarnecchi et al., 2016), (2) *target areas for stimulation*; different combinations of F3, F4, P3, and P4 electrodes (present study), F3-right supraorbital area (Hoy et al., 2015), and left middle frontal gyrus-Cz (Santarnecchi et al., 2016), (3) *average intensity*; 1642 µA (present study), between −750 µA and +750 µA (Hoy et al., 2015), and 750 µA (Santarnecchi et al., 2016), and (4) *tACS procedure*; offline (present study and Hoy et al., 2015) versus online (Santarnecchi et al., 2016), to name a few. Any one of these methodological differences could explain the disparate findings.

For instance, deciding which stimulation frequency to use within the gamma range (40-200 Hz) plays an important role in tACS research. It is possible that for working memory performance, optimal gamma stimulation frequencies are not 30-40 Hz, but should be higher. In a recent study, standard continuous theta tACS as well as a novel paradigm, theta-gamma cross-frequency alternating current stimulation, were applied to the left prefrontal cortex while participants solved a spatial working memory task (Alekseichuk et al., 2016). Cross-frequency stimulation involved repetitive bursts of fast alternating current (40 – 200 Hz) superimposed on either the peaks or troughs of the continuous current (6 Hz). The results showed that both continuous theta tACS and cross-frequency tACS affected EEG characteristics and improved spatial working memory performance. Specifically, high gamma power (80-100 Hz) superimposed over the peaks, but not over the troughs, enhanced working memory performance. In contrast, low gamma frequency protocols and superimposition on the trough of the theta wave did not significantly affect working memory performance. These findings provide a causal role for phase-amplitude coupling in the prefrontal cortex in relation to working memory.

Another important factor is the site of stimulation: modulating endogenous gamma oscillations in the left prefrontal cortex (Alekseichuk et al., 2016; Hoy et al., 2015) may provide a unique setting which allows for more efficient working memory processing. It also supports previous research suggesting that the relationship between gamma activity and the number of items retained in working memory is specific to this area (Roux et al., 2012). Since the electrode F3 in the 10-20 EEG system is thought to target the left dorsolateral prefrontal cortex, one would expect that at least Groups 2 (F3-P3) and 4 (F3-F4) would show a beneficial effect on performance after gamma tACS. This was not the case, suggesting that the placement of the "return" electrode is crucial. Modeling current flow during tACS showed that there are two modes of stimulation. When the electrodes are placed on homologous areas (Group 4 in the present study), the two hemispheres are stimulated at 180° phase shift. In absence of stimulation, the two homologous areas typically oscillate without a significant phase shift. Hence, if working memory processes require the bilateral prefrontal areas to operate without a phase shift, applying tACS to homologous areas could potentially disrupt these processes. On the other hand, if one of the electrodes is placed along the midline, which was the case in Santarnecchi et al.'s study (2016), the generator of an oscillation would be stimulated without a phase shift (Neuling, Wagner, Wolters, Zaehle, & Herrmann, 2012). However, in the Santarnecchi et al. study (2016) improved performance was observed on measures of fluid intelligence, but not on measures of working memory – this may also depend on the fact that the stimulation was online rather than offline, and that low gamma was used for stimulation.

These findings help explain why no effects were observed for gamma tACS applied over homologous frontal areas (F3-F4) and may even be used to explain the lack of effects for homologous parietal areas (P3-P4). What about the left fronto-parietal site of stimulation (F3-P3)? The study by Polanía et al. (2012) may provide a clue why this was the case. Two experiments were conducted: in the first experiment, the authors found an increase in phase synchronisation between the left dorsolateral prefrontal cortex and the posterior parietal cortex at 4-7 Hz during performance on a delayed letter discrimination task. In the second experiment, theta tACS was applied to these areas either with a relative 0° ("synchronised" condition) or 180° ("desynchronised" condition) phase difference. As a control frequency, tACS was applied in the gamma frequency band (35 Hz) using the same procedure as in the theta tACS sessions. As predicted, theta tACS decreased reaction times during synchronisation of fronto-parietal regions at 0° phase difference yet increased reaction times in the desynchronised condition. In contrast, 35 Hz tACS applied with or without a phase difference did not significantly affect any of the behavioural measures. Since the gamma frequency range has been associated with (1) local synchronisation during visual processing (von Stein & Sarnthein, 2000) and (2) matching of bottom-up signals with memory contents – a process that occurs rapidly and is well localized (Herrmann, Munk, & Engel, 2004), it is possible that "long-range" gamma tACS involving frontal and parietal brain areas does not affect endogenous oscillatory activity in a beneficial manner. To my knowledge, the only study that reported low gamma tACS enhancement of working memory performance (Hoy et al., 2015) restricted stimulation to the frontal lobes. Conversely, long-range fronto-parietal interactions during working memory maintenance have been associated with oscillatory activity in theta and alpha frequency ranges (von Stein & Sarnthein, 2000). In the present study, right fronto-parietal theta tACS benefited n-back accuracy, which may reflect improvements in top-down processing necessary for successful performance on the task.

Finally, it has also been suggested that an individualized tACS approach might be crucial for behavioural changes rather than stimulating all participants with the same frequency band. In fact, one of the main reasons why there is substantial variability in tACS research is presumably the dependence of tACS on the interactions with endogenous oscillatory activity (Santarnecchi et al., 2016). In the present study, an individualized approach was adopted, however, significant changes in working memory performance were only observed in theta tACS compared to sham sessions. Future research should directly compare the effectiveness of individualized and non-individualized tACS paradigms.

This brings us the second point: task-specific effects of tACS. Theta tACS improved n-back accuracy compared to sham stimulation, but there is no evidence to suggest that it affected performance on the change detection task. This might stem from the fact that these tasks measure different working memory processes. Change detection tasks were developed according to the discrete-slots model of working memory; assuming that capacity remains constant across changes in set size (4, 6, or 8 items) (Rouder, Morey, Morey, & Cowan, 2011). This task, along with its variations, is one of the most often used paradigms for measuring visual working memory capacity. It is especially useful for studying the processes of encoding, maintenance, and retrieval in a separate manner. The n-back task is also one of the most popular measures of working memory, particularly in neuroimaging research as it is easy to manipulate its presentation and response requirements (Conway, Kane, & Engle, 2003). Performance on the n-back task requires encoding of stimuli, monitoring, maintenance and updating of the incoming stimuli, along with matching of the current stimulus to the one that was presented *n* positions back in the sequence (Jaeggi, Buschkuehl, Perrig, & Meier, 2010). Jaeggi and colleagues (2010) argue that the *n*-back task involves processes that go beyond the processes that are traditionally associated with working memory, such as inhibition and interference resolution (Kane et al., 2007) and binding (Oberauer, 2005). From a psychometric perspective, the n-back is not a useful measure of individual differences in working memory capacity because it shows low reliability. Nevertheless, it can still be used for working memory research and performance on the n-back can be used to predict other higher cognitive functions like fluid intelligence (Jaeggi et al., 2010). In the present study, theta tACS may have tapped into some of the processes involved in the more complex task of the two – the n-back. In that case the improved target accuracy may not reflect an increase in capacity, but improvements in executive functions such as updating, inhibitory control and shifting of attention. The results of a recent study point in this direction (Vosskuhl et al., 2015); instead of applying tACS in an individually determined theta frequency band, the authors decided to downregulate it by delivering tACS in 1 frequency below the individual frequency. Theoretically, this would increase the theta-to-gamma cycle length ratio, thereby allowing more items to be stored in short term memory. Indeed, the results showed that downregulating tACS increased individual short term memory capacity as measured by a forward digit span task, but did not affect performance on the backward version of this task or on a 3-back task, suggesting an increase in capacity and not in manipulation of information stored in working memory.

The results of the present tACS study were location-specific. Theta tACS only improved n-back accuracy when the electrodes were placed over bilateral parietal areas and over right fronto-parietal areas, thereby partially supporting the hypothesis that stimulation involving at least one target electrode placed over posterior parietal areas would elicit the greatest behavioural effects. In order to avoid excessive application of tACS, the participants were randomly assigned to four groups with different target stimulation areas. Thus, it is possible that some of the observed effects stem from between-group differences. Nevertheless, this seems unlikely since the four groups of participants did not significantly differ on independent measures of working memory capacity. These findings are in line with the studies reported in Chapters 6 and 7, in which theta tACS applied to posterior parietal areas was more effective in enhancing working memory/reasoning ability performance compared to theta tACS applied to prefrontal areas (Jaušovec et al., 2014; Pahor & Jaušovec, 2014).

The last point refers to content-specificity. The present results demonstrate that the effects of theta tACS depend both on the type of stimuli (figural versus verbal; both presented in the visual domain) and on the difficulty of the task (2-back versus 3-back). The group that received bilateral parietal stimulation showed an improvement in n-back accuracy (theta tACS > sham) in the verbal 2-back task and in the figural 3-back task. In the group that received right fronto-parietal stimulation, an improvement in n-back accuracy (theta tACS > sham) was observed on the figural 2-back task and on the verbal 3-back task. In both groups the greatest change was observed on the 2-back tasks.

Why would bilateral parietal theta tACS affect verbal 2-back performance and right frontoparietal theta tACS affect figural 2-back performance? According to the model by Baddeley and Hitch (1974), verbal information is maintained in a store and regularly refreshed by articulatory rehearsal to avoid decay. It is likely that the participants subvocally rehearsed the verbal material, but it is also possible that they rehearsed the names of the colours throughout the task. A recent fMRI study (Langel, Hakun, Zhu, & Ravizza, 2014) reported dissociable patterns of activity in the left and right ventral parietal cortex (VPC). The anterior VPC, bilaterally, was active during an oddball task and a working memory task, suggesting that it plays a role in non-mnemonic processes such as stimulus-driven attention. In contrast, the left anterior VPC seemed to uniquely support verbal working memory storage, with maintenance involving areas linked to speech perception. These findings are in line with research suggesting that the left VPC is important for working memory processes involved in storing verbal information (Gruber & von Cramon, 2001; Paulesu, Frith, & Frackowiak, 1993; Salmon et al., 1996). The reason why bilateral parietal theta tACS enhanced verbal 2-back performance may be the site of stimulation, which included the electrode P3, presumably targeting the left inferior parietal lobule (Kim et al., 2007). Thus, both the store of verbal information along with other non-mnemonic processes may have been affected in this group. Conversely, right-frontoparietal theta tACS may have contributed to non-verbal working memory via enhanced stimulus-driven attention. The differences observed in performance in relation to type of information and load may also reflect the placement of stimulation electrodes: unilateral long-range versus contralateral short-range.

Task-based electrophysiological results

The group that received bilateral parietal theta tACS stimulation showed increased P1 amplitude during performance on the 3-back tasks compared to sham. The P1 component is generated in the extrastriate cortex (Natale, Marzi, Girelli, Pavone, & Pollmann, 2006), and is modulated by attention (Finnigan, O'Connell, Cummins, Broughton, & Robertson, 2011). This group also showed decreased P3 latency in comparison to sham tACS, particularly during two tasks: the verbal 2-back task and the figural 3-back task, which corresponds to the behavioural results. P3 latency reflects matching of items on the n-back task – the quicker the better (Chen et al., 2008). These results suggest that the improved accuracy observed on verbal 2-back and figural 3-back tasks stems from faster matching of the current item to the item presented 2 or 3 trials back. Moreover, P3 amplitude at electrode Pz positively correlated with n-back accuracy on two tests: the verbal 2-back and the figural 3-back, thereby supporting the findings reported by Keeser et al. (2011). These correlations were not significant in the sham condition. Significant correlations were not observed on any of the other tests, or in any of the other groups. Collectively, these findings suggest that faster matching of items and larger attention and memory loading (Chen et al., 2008) contributed to the improvement in accuracy on verbal 2-back and figural 3-back tasks after bilateral parietal theta tACS.

The group that received left fronto-parietal stimulation did not show any significant effects for ERP amplitude or latency in theta tACS sessions compared to sham. This may also help explain why this group did not show significant changes in working memory performance. In contrast, the group that received right fronto-parietal stimulation showed increased P3 amplitude mainly on the figural 2-back task and on the verbal 3-back task with respect to sham tACS, which is yet again in line with the behavioural results. This corresponds with the results of a study in which more efficient performance on n-back tasks correlated with a larger P3 amplitude at parietal sites in young adults (Saliasi, Geerligs, Lorist, Maurits, & Lee, 2013). Finally, the group that received theta tACS to bilateral frontal areas showed increased P1 amplitude compared to sham, but no significant effects for P3 amplitude or latency.

Even though theta tACS did not produce statistically meaningful changes in performance on the change detection task compared to sham, the results suggest that it induced changes in EEG activity during performance on this task. A consistent pattern emerged across the groups: theta tACS increased amplitude over the two frontal electrodes of interest (F3, F4) yet decreased amplitude over the two parietal electrodes of interest (P3, P4) in the following ERP components: P1 (groups 1 and 3), N1 (group 3), and P3 (group 3). Note that groups 2 and 4 did not show any significant effects pertaining to ERP amplitude. These results suggest that even bilateral parietal stimulation can affect ERP amplitude in frontal areas – stimulating one area can affect other areas that are structurally and/or functionally connected to it, which opens up the possibility of combining noninvasive brain stimulation with neuroimaging and graph theory (Luft, Pereda, Banissy, & Bhattacharya, 2014); this would enable the study of the effects of TES on brain connectivity. The analysis of ERP latency showed significant changes in the following ERP components after theta tACS: P1 (group 3), N1 (group 2), and P3 (group 3). These results further suggest that group 3 (right frontoparietal stimulation) showed the most prominent task-based changes in ERP components following theta tACS.

Despite the fact that gamma tACS did not produce statistically meaningful changes in performance on the change detection or n-back tasks, the present results suggest that it produced significant changes in EEG activity compared to sham during performance on both tasks. During performance on *n-back tasks*, significant changes in ERP amplitude and latency were observed in two groups: group 1 (bilateral parietal) and group 2 (left frontoparietal). Gamma tACS increased P1 amplitude in both groups, and increased P1 latency in the first group. The results for N1 and P3 amplitude are more variable: group 1 showed a decrease in N1 amplitude and task-dependent changes in P3 amplitude (both increases and decreases), whereas group 2 showed an increase in N1 amplitude. During performance on *change detection tasks*, a similar pattern of changes in ERP amplitude was observed after gamma tACS compared to sham as it was for theta tACS compared to sham. Increased amplitude over frontal electrodes and decreased amplitude over parietal regions was observed in two ERP components: P1 (groups 2 and 3) and P3 (group 3). Gamma tACS also increased N1 amplitude in group 2 compared to sham. The analysis of

ERP latency during these tasks showed significant changes in the following ERP components after gamma tACS: P1 (group 3; increases and decreases) and P3 latency (group 4; increase). Collectively, the task-based ERP results are variable and are difficult to explain in the absence of significant behavioural results. Suffice to say that even if changes in performance are not observed, this does not mean that offline EEG activity is not affected.

One observation is that performance on the tasks that did not differ between active and sham conditions was in some groups associated with significant changes in the amplitude of N1 (40-120 ms), which is thought to reflect orienting of attention (Natale et al., 2006). It seems as though the component P3, which peaks later (250-600 ms post stimulus presentation), is related to tACS-induced behavioural changes when the frequency of stimulation is in the theta range (groups 1 and 3).

Resting electrophysiological results

Resting EEG data was examined in order to determine whether the average change in amplitude in the EEG spectra from pre- to post-stimulation differed between sham and active conditions and between the four groups. Collectively, there is no evidence that gamma tACS significantly affected EEG amplitude in comparison to pre-stimulation EEG data or in relation to sham stimulation. This may explain why no significant behavioural effects were observed following gamma tACS. The only frequency band in which significant changes in EEG amplitude were observed in relation to baseline was the theta frequency band, showing a complex interaction between condition (theta tACS/sham), location, and group. There is no evidence that active tACS affected EEG amplitudes in other frequency bands: delta, alpha, beta and gamma, providing further support for frequency-specific modulation of EEG amplitudes, at least for theta tACS.

Subsequent analyses showed that only group 2 (left frontoparietal stimulation) showed the predicted interaction effect between stimulation and time, suggesting that after theta tACS, theta amplitude decreased whereas after sham tACS, theta amplitude increased. Groups 1 and 3 also showed pre-to-post changes in EEG amplitude, yet this did not seem to depend on the condition (active versus theta tACS). On the other hand, post-hoc t-tests corrected for multiple comparisons revealed that in groups 1 and 2, theta tACS decreased theta amplitude at the locations corresponding to the sites of stimulation. While a decrease in theta activity immediately after theta tACS might seem counterintuitive, there is evidence to suggest that individuals with small resting theta power show a larger percent increase in evoked power during task performance than subjects with large resting theta power (Klimesch et al., 2004). Sham tACS also seemed to affect theta amplitude in group 2, but in a different direction: sham tACS increased theta amplitude in a right frontal area. It is possible that the 1-minute long stimulation period in the alpha frequency band within the sham session was long enough to produce aftereffects in EEG spectra. Even though these findings are not straightforward, they lend support for findings suggesting that theta tACS affects resting EEG amplitude in the frequency band that matches the stimulation frequency (Helfrich et al., 2014; Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015; Witkowski et al., 2016; Zaehle, Rach, & Herrmann, 2010).

The limitations of this study include a relatively low sample size per group (18), and the fact that the sample was restricted to female university students hence the findings cannot be extended to the general population. One of the strengths of this study, using an individualized approach for determining the frequency and intensity of stimulation, may also represent a weakness, as it is possible that variations in these parameters led to variations in performance on the tasks and systematic changes in EEG activity. The average stimulation frequency was similar across the groups (no significant differences were observed) therefore this explanation seems unlikely. On the other hand, the average stimulation intensity did differ substantially between the groups – particularly group 4 (bilateral frontal stimulation) had a lower average intensity value compared to the other groups. Nevertheless, even in group 4 the stimulation intensity was much higher than in other studies that produced significant effects (e.g. Hoy et al., 2015; Santarnecchi et al., 2016), therefore it can be assumed that it was high enough.

To conclude, this study provides one of the first direct comparisons of the effects of theta and gamma tACS on behavioural and electrophysiological data in different brain areas associated with working memory performance. The results demonstrated that the effects of tACS are (1) frequency-specific: theta but not gamma tACS resulted in significant changes both in working memory performance and in pre/post-stimulation resting EEG data, (2) location-specific: bilateral parietal and right frontoparietal theta tACS had a beneficial effect on working memory performance (i.e. n-back accuracy), whereas this was not observed after bilateral frontal and left frontoparietal theta tACS. The finding that theta tACS involving posterior parietal areas is more effective than frontal theta tACS is line with the studies described in the previous chapters (Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014; Pahor and Jaušovec, 2014), (3) task-specific: theta tACS led to improvements in performance on the n-back tasks but not in performance on change detection tasks, however, tACS-related changes in EEG activity were observed on both tasks, and (4) content-specific: the effects of theta tACS on n-back performance depended both on the type of stimuli (verbal, nonverbal) and load. Even though the behavioural effects were small and restricted to the n-back task, these results provide further support for the causal role of theta oscillations in the regulatory component of working memory and point towards their integrative role in organization of brain activity across frontal and parietal areas. Moreover, these findings provide support for studies showing that theta tACS represent a valuable tool for the study of the neural basis of working memory (Alekseichuk et al., 2016; Jaušovec et al., 2014; Pahor & Jaušovec, 2014; Polanía et al., 2012; Vosskuhl et al., 2015).

9. General discussion

This thesis aimed to elucidate the roles of brain oscillations in working memory. The two techniques that are best suited for the non-invasive study of brain oscillations, scalp recorded EEG and transcranial alternating current stimulation, were used in this process. In the first step, correlational studies were conducted followed by neuromodulatory studies in the next step. In the first study, EEG was used to examine the relationship between individual differences in visual working memory capacity and neuro-electric patterns of brain activity. In the second study, the interactions between theta and gamma oscillations were examined in more detail. The last three studies presented in this thesis involved the application of tACS, which enables the study of the causal role of oscillations in cognition (Schmidt, Iyengar, Foulser, Boyle, & Fröhlich, 2014).

The study by Jaušovec and Jaušovec (2010) provided the first evidence that tACS applied in the theta frequency band over a left posterior parietal area increases working memory capacity. Previous tACS studies were largely focused on the alpha frequency band and examined other cognitive or motor functions. The studies presented in Chapters 6, 7 (Jaušovec et al., 2014; Pahor & Jaušovec, 2014), and 8 (manuscript in preparation) provide support for the findings reported by Jaušovec and Jaušovec (2010). While these studies only scratch the surface of the emerging field of using tACS to enhance intrinsic network dynamics, they provide insight into the optimal parameters of offline tACS for enhancing performance on measures of working memory and fluid intelligence. Importantly, none of the studies demonstrated a significant negative effect of tACS on performance on cognitive tasks. Since the results of these studies were discussed in the previous chapters, a detailed discussion of the findings will not be presented again. Instead, a synopsis of findings and their interpretations will be presented in relation to the general hypotheses set in Chapter 2.

Hypothesis 1: Individuals with higher working memory capacity will display neural efficiency, similar to the one observed for the intelligence construct.

This hypothesis was tested in the study titled "Individual differences in working memory capacity". Research on human intelligence provides support for neural efficiency, which assumes less (or more focused) activation in more intelligent individuals (Neubauer & Fink, 2009). Previous studies provided only indirect support for the neural efficiency hypothesis in working memory (del Río et al., 2012; Nussbaumer et al., 2015). An extreme-groups design was used to investigate synchronous oscillatory activity within and between brains areas during performance on a change detection task. The analysis focused on three processes: encoding, maintenance, and retrieval. According to the neural efficiency hypothesis, it was predicted that individuals with superior working memory capacity would display more theta ERD, gamma ERD, and alpha ERS during performance on the task. Differences in connectivity in frontoparietal networks in theta and gamma frequency bands were also expected in the two groups. Finally, it was predicted that average theta/gamma cycle length ratios determined during rest would be positively related to working memory capacity, a hypothesis that was not confirmed.

The results obtained partly confirmed the neural efficiency hypothesis – only for gamma ERD, which was observed in individuals with high working memory capacity compared to individuals with low working memory capacity, particularly during encoding. This corresponds with the finding that gamma ERD in the inferior frontal cortex appeared simultaneously with frontal midline theta during a task that required focusing attention in mental calculation tasks (Ishii et al., 2014). The authors interpreted frontal gamma ERD as a mechanism for temporary disruption of local neural communication in cortical areas that are not relevant to the current task – in other words, neural efficiency. A pattern opposite to the hypothesis was observed in the alpha band: high performers showed more alpha ERD than low performers, while no difference in ERD/ERS was observed in the theta band.

According to Klimesch (2012), alpha synchronisation (ERS) reflects inhibition of task-irrelevant memory items, which is followed by alpha desynchronisation (ERD) approximately 250-400 ms post stimulus presentation. Alpha ERD therefore reflects a release from inhibition. Indeed, both groups of participants showed an increase in alpha ERD in this time period. The high capacity group showed significantly stronger alpha ERD than the low capacity group, particularly over parieto-occipital areas. These group differences were observed mainly during encoding thereby supporting the idea that alpha band activity is not directly involved in working memory maintenance (Frédéric Roux & Uhlhaas, 2014). Alpha ERD was interpreted as increased focus of attention in individuals with high working memory capacity, as opposed to the function of suppression of irrelevant information typically associated with alpha ERS.

Even though no significant between-group differences were observed in theta ERD/ERS, the results suggested that high performers displayed stronger event related coherence in the theta band (1) between left frontal and parietal areas during maintenance and (2) between prefrontal brain areas during retrieval. Theta frontoparietal connectivity has been linked with proactive and reactive cognitive control processes (Cooper et al., 2015) and short-term memory retention (Payne & Kounios, 2009). The increased theta-band coherence between left frontal and parietal areas in individuals with high working memory capacity may reflect enhanced top-down processing that is required to strengthen the activation of memory representations. In contrast, increased theta-band coherence between prefrontal brain areas probably reflects the activity of the frontal-midline theta network, which has been linked working memory processes in a large body of studies (for a review see Hsieh & Ranganath, 2014).

Overall, these results provided tentative evidence for neural efficiency in the gamma frequency band during performance on a working memory task, suggesting that individuals with high working memory capacity utilize gamma desynchronisation to prevent or interrupt activity in task-irrelevant areas. Even though the hypothesis regarding alpha ERS was not supported, the obtained results are in line with research suggesting that alpha ERD plays an active role in information processing (Klimesch, 2012). Finally, the results support the idea that working memory maintenance is associated with an intensified information flow between frontal and parietal brain areas (Sauseng, Klimesch, Schabus, et al., 2005), probably in the function of keeping the encoded visuo-spatial information in an active and accessible state for retrieval. During retrieval, there is a shift to enhanced theta connectivity in the prefrontal area, which can be attributed to increased need for cognitive control. These findings also indirectly support the continuous single resource model assuming that working memory capacity is a flexible resource that can be spread among all elements in the sensory input (Ma et al., 2014). The fact that there were significant between-group differences in oscillatory brain activity provided further incentive for the application of tACS in subsequent studies.

As mentioned earlier, a relationship between theta-gamma cycle length ratio and working memory capacity, as proposed by Kamiński et al. (2011), was not confirmed in this study. Since the results may have been affected by methodological differences, a second study was conducted in which the same verbal memory span task was used as in the original study, along with a visuospatial version of the task. The participants solved four tasks: forward and backward versions of Digit span and Corsi block tapping tests. In this study, the following hypothesis was tested:

Hypothesis 2: Resting-state theta and gamma frequency bands and particularly the interaction between these bands will correlate with verbal and spatial WM capacities.

Individually determined resting-state theta and gamma frequency bands correlated with memory span, however, the relationship was not clear: theta frequency only correlated with visuospatial span (both positively and negatively), whereas gamma frequency showed positive correlations with performance on both tasks. It was concluded that the method used for determining individual theta and gamma frequencies bands does not reliably predict memory span. Nevertheless, the results supported the finding that theta/gamma cycle length ratio positively correlates with verbal memory span reported by Kamiński et al. (2011), thereby providing support for the theta-gamma neural code of working memory by Lisman and Jensen (2013). In this theory, the number of gamma cycles that can fit into a theta cycle determines the number of items that can be held in working memory. For example, the ratio between 40 Hz gamma and 5 Hz theta is 8, whereas the ratio between 40 Hz gamma and 4 Hz theta is 10. The higher the ratio, the higher the short-term memory capacity, indicated by verbal memory span measures in this study. However, for visuospatial short term memory, a different pattern of correlations was observed: the ratio positively correlated with the forward version of the task and negatively correlated with the backward version of the task. Two explanations come to mind: either verbal and visuospatial short term memory capacities are characterized by different storage mechanisms, and this may also be the case for forward and backward versions of the tasks, or this method does not represent an optimal way of calculating how many gamma cycles fit into a theta cycle, which may certainly be the case in noisy EEG data, and that some of the observed effects can be explained by chance alone.

Neuromodulation may present a more effective way of investigating the role of brain oscillations in working memory. This approach was adopted in the studies presented in Chapters 6-8, in relation to which the following hypothesis was set:

Hypothesis 3: tACS in theta and gamma frequency bands will improve performance on working memory tasks compared to sham stimulation.

In the first two tACS studies, only theta tACS was compared to sham tACS, whereas in the last study, tACS was also applied in the gamma frequency band. The first two studies shared a similar placement of tACS electrodes, which was based on the 10-20 EEG system: the "return" electrode was placed over the right orbitofrontal area, whereas the other electrode was placed either over electrode F3 (presumably targeting the left dorsolateral prefrontal cortex), electrode P3 (presumably targeting the left inferior parietal lobule) or electrode P4 (presumably targeting the right inferior parietal lobule) in the first tACS study and the same areas, but without targeting P4, in the second tACS study. In the third tACS study, the pairs of electrodes were placed at the following electrode positions: F3-F4, P3-P4, F3-P3, and F4-P4. Different tasks were used in the studies: forward and backward memory span (first tACS study), n-back (first and third tACS study), change detection task (third tACS study), and tests of fluid intelligence (second tACS study). Due to these methodological differences, the results of the three studies cannot be directly compared, nevertheless, certain general conclusions can be drawn.

A common finding across the studies is that theta tACS positively affected performance on cognitive tasks compared to sham stimulation, however, this depended on the site of stimulation, the task used, and cognitive load.

Broadly speaking, theta tACS applied to at least one parietal brain area, either in the left hemisphere or in the right hemisphere, was more effective in eliciting behavioural changes than theta tACS applied to frontal areas (e.g. F3-F4 or F3-contralateral orbitofrontal area). Stimulation involving the left inferior parietal lobe area (P3) tended to show significant improvements in performance on working memory and fluid intelligence tasks. The only exception was the left frontoparietal target site used in the last study – it differed from the other target sites involving P3 with respect to the placement of the "return" electrode, which was in the left hemisphere rather than in the right hemisphere. This observation could be related to fMRI and ERP research suggesting that retrieval-related activity in the parietal cortex is more frequently observed in the left than in the right hemisphere (Vilberg & Rugg, 2008). Moreover, the present findings are in line with the study of neuropsychological patients and neuroimaging research suggesting that the left inferior parietal area plays an important role in verbal short term memory (Majerus et al., 2006). Neuroimaging studies revealed two sites of activation within this area: a dorsal region involving the intraparietal sulcus and a more inferior and ventral region. The former has been associated with the phonological store proposed by Baddeley and Hitch (1974), but keep in mind that there is evidence that this region is also active during non-verbal working memory tasks (e.g., Ravizza et al., 2004), whereas the latter does not seem to be associated with temporary storage and maintenance of verbal information, but with processing of verbal information in general (Majerus et al., 2006). Since there is a lot of heterogeneity in neuroimaging research of working memory, Majerus and colleagues (2006) suggested that the left inferior parietal area is not specific to verbal short term memory, but acts as an attentional modulator of distant neural networks that are responsible for processing serial order and language representations. Another explanation for the variety of neuroimaging findings in this domain was provided by Cowan et al. (2011), who proposed that the left intraparietal sulcus represents a neural region for abstract working memory. The experiments designed to test this hypothesis provided evidence for the involvement of this region in working memory maintenance regardless of the modality of stimuli (Cowan et al., 2011). On the other hand, the fact that theta tACS improved working memory performance in configurations involving the P4 electrode (P4-ipsilateral supraorbital area, F4-P4, and P3-P4) should not be neglected. In the first and the third tACS study, stimulation in the theta frequency band directed towards this area resulted in improved accuracy on n-back tasks compared to sham. In addition, tACS applied to the P4-ipsilateral supraorbital area also improved forward memory span. In the second study, P4 was not targeted. Collectively, these findings indicate that the parietal areas are causally involved in factors that determine performance on a variety of working memory tasks, thereby supporting previous neuroimaging (Honey, Bullmore, & Sharma, 2000; Mitchell & Cusack, 2008; Pessoa et al., 2002; Todd & Marois, 2004) and tACS (Jaušovec & Jaušovec, 2014; Polanía et al., 2012; Vosskuhl et al., 2015) research.

Conversely, applying theta tACS to the left dorsolateral prefrontal cortex resulted in relatively weak effects on the 1-back task (Jaušovec et al., 2014) and on the easy test items of Raven's advanced progressive matrices (Pahor & Jaušovec, 2014) and had no significant effect on performance on n-back tasks or change detection tasks in the last tACS study. It should be noted that in the last study, easy test items such as the 1-back were not used. This may seem strange given the vast amount of literature demonstrating a link between the prefrontal cortex and working memory maintenance (e.g., Barbey et al., 2013; Courtney et al., 1998; D'Esposito et al., 1999; Haxby et al., 2000; Kane & Engle, 2002; McNab & Klingberg, 2008; Pessoa et al., 2002; Stokes, 2015); for a recent review see Lara and Wallis (2015). It is likely that theta tACS applied to this area merely affected sustained attention, but did not modulate the top down signal that influences posterior sensory areas - areas in which working memory representations are thought to be stored. The dorsolateral prefrontal cortex seems to be more responsive to transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). A systematic review and meta-analysis of 12 studies (33 experiments) showed that both forms of non-invasive brain stimulation significantly improved all measures of working memory performance, with tDCS improving reaction time rather than accuracy (Brunoni & Vanderhasselt, 2014).

Since tACS-related improvement in performance was observed on a variety of working memory tasks (forward and backward simple memory span tasks and updating tasks), which tap into different components of the working memory system (Jaeggi et al., 2010; Redick & Lindsey, 2013), it can be concluded that the effects of theta tACS are not limited to a specific task, but have a more general effect on the working memory system. Even the tACS-induced enhancement of performance on measures of fluid intelligence can be explained in terms of more efficient updating of information in working memory (Belacchi, Carretti, & Cornoldi, 2010), however, this was not directly tested in the study. The study presented in Chapter 8 suggested that theta tACS affects working memory manipulation and updating rather than storage capacity, yet these findings do not correspond with the increases observed in forward memory span tasks obtained in the first tACS study (see Chapter 6). This may be in part explained by the methodological differences between the two studies. Even though storage and processing components of working memory are very difficult to tease apart, future research should investigate which of these components (or what combination of these components) are affected in response to exogenous application of oscillations in the theta frequency band. Further research is also needed to explore the effects of task content and working memory load on tACS-induced changes in working memory performance.

Altogether, these findings support the hypothesis that tACS in the theta frequency band will improve performance on working memory tasks compared to sham stimulation. There is no evidence to suggest that gamma tACS significantly affects working memory performance, therefore only theta oscillations can be causally linked to working memory. For a detailed discussion about gamma tACS see section 8.4. A recent study by Tseng et al. (2016) may be able to shed light on this issue. The authors applied tACS over the left temporal and parietal cortex in gamma and theta frequency, with a phase difference of either 0° (in-phase) or 180° (anti-phase). Thus, they were able to test whether synchronisation in the temporoparietal network supports binding features into objects in visual working memory. Brain oscillations represent an ideal mechanism for binding, since information about features that are processed in different parts of the brain can be communicated and linked into a coherent form via coordinated oscillatory activity. In particular, it was speculated that synchronisation in the gamma range would depend on the optimal phase difference between the left temporal and parietal areas: in-phase synchronisation (0°) would imply indirect neural transmission, whereas anti-phase (180°) synchronisation-lag would imply direct neural transmission. The results supported the latter: anti-phase 40 Hz tACS improved low-performers' binding visual working memory performance, an affect that was observed both online and offline (up to 20 minutes post-stimulation). These findings provide an important step towards understanding the role of gamma oscillations in binding, which in this study depended on a direct sender-and-receiver relationship between left temporal and parietal areas (Tseng et al., 2016).

The effects of tACS on EEG activity were examined in the studies presented in Chapters 7 and 8. In the tACS-fluid intelligence study (Pahor & Jaušovec, 2014), EEG was measured for 5 minutes immediately after tACS (resting; eyes closed) and for 20 minutes during problem solving. Resting and task-based EEG data obtained in active tACS sessions were compared to EEG data measured during sham sessions. The resting EEG analysis in the tACS-fluid intelligence study showed that theta tACS increased theta power and decreased alpha power in the parietal group - the group that showed the strongest tACS-induced behavioural effects, whereas the frontal group only showed a decrease in alpha power. The finding for the parietal group is in line with tACS studies demonstrating an increase in oscillatory activity in the frequency band that matches the stimulation frequency (Helfrich et al., 2014; Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015; Witkowski et al., 2016; Zaehle, Rach, & Herrmann, 2010). While it is unclear why the same effect was not observed in the group that received tACS applied to frontal areas, it can help explain why no significant effects were observed for the total scores on the tests of fluid intelligence in this group. If tACS does not induce changes in resting EEG data in the targeted frequency band, behavioural effects are unlikely to occur. One of the major limitations of this study was that prestimulation resting EEG data was not recorded. Even though the two sessions were counterbalanced, it is possible that the obtained effects were confounded by the natural variability in EEG activity over days. The tasked-based EEG analysis revealed a decrease in lower alpha power in the parietal group, whereas the frontal group showed a decrease in theta power. The former was thought to reflect attentional processes and corresponds to the finding that task-related alpha power desynchronisation, along with the theta power synchronisation (not observed here), reflects good cognitive performance (Klimesch, 1999). Based on this assumption, the decrease in theta power observed during task performance in the frontal group does not present an advantage in terms of cognitive performance.

More conclusive findings were obtained in the tACS-working memory study presented in Chapter 8. EEG was measured before and after tACS (resting; eyes closed) and also during problem solving. In that way, it was possible to compare poststimulation resting EEG data relative to prestimulation EEG data, contrasted against sham stimulation. The pre-post resting EEG analysis (contrasted against sham) showed that gamma tACS did not significantly affect EEG amplitude in any of the frequency bands, which corroborates the idea that significant changes in behavioural measures are not typically observed in the absence of changes in endogenous oscillatory activity. In contrast, theta tACS significantly decreased theta amplitude, but did not affect other frequency bands. These results suggest that theta tACS desynchronised neuronal networks in a frequency-dependent manner. Small theta power during rest has been associated with good memory performance (Klimesch, 1999) and may even help enhance evoked theta (Klimesch et al., 2004). However, this may be driven by the fact that during sham sessions, theta amplitude increased, implying synchronisation of neuronal networks. As discussed in section 8.4, it is possible that the 1-minute long stimulation period in the sham session was long enough to produce aftereffects in EEG spectra. Since these effects depended on the site of stimulation, further analyses were conducted to examine changes in theta amplitude in each group of participants. Most of these findings seem to be driven by groups 1 and 2 (bilateral parietal and left frontoparietal tACS), in which a decrease in theta amplitude was observed at the locations corresponding to the sites of stimulation.

The analysis of task-based EEG data was focused on event-related potentials (ERPs), which can be used to detect changes in the strength and latency of brain responses to an event (Murray, Brunet, & Michel, 2008). For an in-depth discussion of the results, see section 8.4. Here I will highlight a few interesting findings pertaining to the two groups that showed significant improvements in n-back performance after theta tACS. The bilateral parietal group showed significantly decreased P3 latency in comparison to sham tACS on the two tasks that showed the greatest improvements in accuracy: the verbal 2-back task and the figural 3-back task. This is in line with the finding reported by Jaušovec & Jaušovec (2014): theta tACS applied to the left parietal area improved working memory capacity, which was accompanied by a decrease in P3 latency. The P3 component represents the last phase in the identification of a relevant stimulus according to the demands of the task (Hillyard & Münte, 1984). Both studies suggest that tACS-induced improvements in working memory performance (at least in part) reflect faster classification speed. In the same group of individuals, P3 amplitude at electrode Pz measured in the theta tACS session positively correlated with n-back accuracy on the two tests that showed the greatest improvements in accuracy, a finding that was not observed in the sham session. P3 amplitude has been associated with attentional processing of target stimulus events (Polich, 2007). The group that received right frontoparietal theta tACS showed a significant increase in P3 amplitude during performance on the two n-back tests in which the greatest improvements in terms of accuracy were observed, however, this did not significantly correlate with performance. The other two groups, left frontoparietal and bilateral frontal groups, did not show any significant effects for P3 amplitude or latency, nor did they show significant changes in n-back accuracy.

The only tACS protocol that showed consistent changes in (1) resting EEG data (frequency-dependent modulation of EEG oscillations), (2) task-based EEG data (decreased P3 latency, correlations between P3 amplitude and n-back accuracy), and (3) behavioural measures (n-back accuracy) is bilateral parietal stimulation in the theta frequency band. Given that performance on the n-back but not on the change detection tasks was affected in this protocol, it is likely that theta tACS enhanced working memory processes such as updating, inhibitory control and shifting of attention. Further research is needed to verify whether this configuration of tACS electrodes affects performance on other measures of working memory. Altogether, these findings provide support for the causal role of theta oscillations in working memory.

Conclusions

Since almost every cognitive process has been associated with at least one of the five prominent EEG frequency bands (delta, theta, alpha, beta, and gamma), it is clear that a direct (1:1) relationship does not exist. Brain oscillations support cognitive functions depending on the brain structures that participate in certain oscillations, which is further modulated by phase, amplitude, and coherence features of oscillatory activity (Herrmann et al., 2016). The studies presented here focused on theta and gamma EEG frequency bands, and to a lesser extent on the alpha EEG frequency band.

The present results suggest that desynchronisation in the alpha frequency band in parieto-occipital areas represents one of the factors that contributes to successful performance on working memory tasks (Chapter 4). Parieto-occipital alpha band activity is involved in regulating the incoming information flow at early processing stages (Romei, Gross, & Thut, 2010). Roux and Uhlhaas (2014) suggested that alpha activity is not involved in working memory maintenance as such, but plays an important role in gating of task-relevant working memory items. Since individuals with high working memory capacity displayed stronger alpha desynchronisation throughout the encoding period compared to individuals with low working memory capacity, it can be assumed that parieto-occipital alpha band activity supports working memory processing via visual attention.

The results also provided evidence supporting the involvement of theta oscillations in working memory, as indicated by correlation and causation approaches. Specifically, good working memory performance was associated with stronger event related coherence in the theta frequency band between frontal and parietal areas (maintenance) and within frontal areas (retrieval) (Chapter 4). Theta-band coherence between frontal and parietal areas probably reflects top-down processing that is required to strengthen the activation of memory representations, whereas theta-band coherence within the frontal lobes supports executive control associated with retrieval. These findings are in line with contemporary neuroscience research (Colgin, 2013; Enriquez-Geppert et al., 2013). Furthermore, it was shown that working memory depends on cross-frequency coupling between theta and gamma oscillations and that the number of gamma cycles that can fit into a theta cycle is at certain electrode locations related to individual working memory capacity (Chapter 5), thereby supporting the theta-gamma coding theory (Lisman & Jensen, 2013). However, see Chapter 5 for a discussion regarding the limitatations of the method. The present results also point towards neural efficiency in the gamma frequency band during encoding and maintenance of information, suggesting a reduction in basic neural control needed for performance on the task, or less stimulus directed activity in individuals with high working memory capacity.

A causal role for theta but not gamma oscillatory activity in working memory, particularly in parietal brain areas, was established in three tACS studies (Chapters 6-8).

tACS entrained endogenous theta oscillations, which resulted in improved performance on certain working memory tasks. One might speculate that applying tACS during working memory training would lead to synergistic effects – boosting the effects of training or perhaps even shortening the time needed to obtain significant changes on transfer tasks.

Collectively, these findings provide support for the causal role of theta oscillations in the regulatory component of working memory and point towards their integrative role in organization of brain activity across frontal and parietal areas. Moreover, these findings provide support for contemporary studies showing that tACS represents a valuable tool for the study of the neural basis of working memory (Alekseichuk et al., 2016; Jaušovec et al., 2014; Polanía et al., 2012; Vosskuhl et al., 2015).

10. Povzetek v slovenskem jeziku

Delovni spomin je najpogosteje definiran kot sistem za kratkotrajno hrambo in manipulacijo podatkov (Baddeley, 1992). Delovni spomin je pomemben za višje kognitivne funkcije, kot so reševanje problemov (Swanson, Cooney in Brock, 1993; Seyler, Kirk in Ashcraft, 2003; Ash in Wiley, 2006), sklepanje (Kyllonen in Christal, 1990; Süß et al., 2002; Buehner, Kumm in Pick, 2005;), jezik ter bralno razumevanje (Just in Carpenter, 1992; Cain, Bryant in Oakhill, 2004; Goff, Pratt in Ben, 2005; Oakhill, Yuill in Garnham, 2011). Prav tako so številne študije pokazale, da sta delovni spomin in fluidna inteligentnost močno povezana (Ackerman, Beier, & Boyle, 2005; Burgess, Gray, Conway, & Braver, 2011; Harrison, Shipstead, & Engle, 2015; Unsworth & Engle, 2005; Wiley, Jarosz, Cushen, & Colflesh, 2011). Kapaciteta delovnega spomina je omejena in tako predstavlja enostavno merljiv indikator individualnih razlik v kognitivnih sposobnostih.

Najbolj sprejet je multikomponentni model delovnega spomina (Baddeley in Hitch, 1974**;** Baddeley**,** 2000), katerega v najnovejši različici sestavljajo 4 komponente: fonološka zanka, ki kratkotrajno shranjuje in vzdržuje besedne informacije, vidnoprostorska skicirka, ki aktivno vzdržuje vidno-prostorske informacije, centralni izvršitelj, ki izvaja nadzor nad omenjenima komponentama ter epizodični medpomnilnik, katerega vloga je integracija in shranjevanje multimodalnih reprezentacij. V zadnjem času so vedno bolj priljubljeni modeli delovnega spomina, ki ne predvidevajo ločenega shranjevanja informacij v kratkoročnem in dolgoročnem spominu (D'Esposito in Postle, 2015). Ti modeli predpostavljajo, da tako kratkoročni kot dolgoročni spomin temeljita na isti “bazi podatkov” in da je začasno zadrževanje informacij v delovnem spominu odraz usmerjanja pozornosti na različne reprezentacije v dolgoročnem spominu, ki so lahko pomenske, senzorične ali motorične narave (Anderson et al, 2004;. Cowan 1999; McElree, 2001, Oberauer, 2002).

Funkcijsko slikanje človeških možganov je pokazalo, da je zadrževanje informacij v delovnem spominu povezano z aktivnostjo v prefrontalni (Courtney et al., 1998; D’Esposito et al., 1999; Haxby et al., 2000; Pessoa et al., 2002) in posteriorni parietalni možganski skorji (Honey, Bullmore, & Sharma, 2000; Pessoa et al., 2002; Todd &

Marois, 2004; Mitchell & Cusack, 2008). Prefrontalni korteks najverjetneje nadzira posteriorne predele možganov, s čimer se ojača reprezentacija senzornih informacij, shranjenih na teh področjih (Curtis & D'Esposito, 2003; Postle, 2006; Feredoes et al., 2011). S pomočjo funkcijskega magnetnoresonančnega slikanja (fMRI) so strokovnjaki ugotovili, da oksigenacija krvi (BOLD signal) v intraparietalnem režnju korelira s številom informacij zadržanih v delovnem spominu ter doseže asimptoto, ko je preseženo število informacij, ki jih posameznik lahko zadrži v delovnem spominu (Todd & Marois, 2004; 2005; Xu & Chun, 2006; Cowan, 2011). Elektrofiziološke študije, ki so proučevale kapaciteto delovnega spomina, so to povezavo potrdile (Vogel & Machizawa, 2004; McCollough, Machizawa, & Vogel, 2007; Ikkai, McCollough, & Vogel, 2010). Vendar je treba poudariti, da je delovni spomin zapleten proces, katerega je nemogoče reducirati na posamezna možganska področja (Baddeley, 2012).

Raziskave kažejo, da so možganske električne oscilacije pomembne za vrsto kognitivnih funkcij, vključno z delovnim spominom. Številne elektrofiziološke študije so pokazale, da se možganska aktivnost v theta (4-8 Hz) in gama (30-60 Hz) ritmu poveča med nalogami, ki zahtevajo uporabo delovnega spomina (*theta*: Gevins et al., 1997; Onton et al., 2005; Maurer et al., 2014; *gama*: Gruber et al., 2004; Howard et al., 2003; Roux et al., 2012). V zadnjem času se je povečalo število raziskav, ki proučujejo sinhrone interakcije med prefrontalnimi in parietalnimi možganskimi področji (Yates et al., 2012). Ena izmed takšnih raziskav je s pomočjo magnetoencefalografije (MEG) in elektroencefalografije (EEG) merila sinhronizirano oscilatorno aktivnost nevronskih skupin (v tem primeru so merili fazno sinhronizacijo) v frontalnih, parietalnih in okcipitalnih režnjih med vzdrževanjem vidnih informacij v delovnem spominu (Palva et al., 2010). Vzdrževanje informacij je bilo povezano s fazno sinhronizacijo med fronto-parietalnimi in okcipitalnimi predeli in sicer v alpha (10-13 Hz), beta (18-24 Hz) in gama (30-40 Hz) frekvencah. Ugotovili so tudi, da se je sinhronizacija povečala skladno s povečanjem količine podatkov, ki jih je bilo potrebno ohraniti v delovnem spominu. Individualno kapaciteto delovnega spomina so lahko napovedali s pomočjo sinhronizacije omrežja nevronov, v kateri je vozlišče predstavljal intraparietalni sulkus. Ti rezultati kažejo, da je proces, ki omogoča vzdrževanje vidnih podatkov v delovnem spominu, najverjetneje sinhronizacija električne aktivnosti med oddaljenimi nevronskimi omrežji.

Lisman in Jensen (2013) sta na podlagi meta-analize nevrofizioloških študij delovnega spomina predlagala nevronsko kodo, ki temelji na interakciji med theta frekvenco in gamma frekvenco. Predpostavila sta, da so posamezne informacijske enote predstavljene v različnih ciklih gamma frekvence, ti pa se umeščajo znotraj theta frekvence (Lisman & Idiart, 1995). Od 4 do 8 ciklov game je lahko ugnezdenih v enem theta ciklu, kar omogoča reprezentacijo več informacijskih enot hkrati. Maksimalno število informacijskih enot je omejeno z maksimalnim številom gama ciklov, ki se prilegajo v theta cikel. V prid theta-gama nevronski kodi pričajo številne študije na glodalcih (Bragin et al., 1995; Fuchs et al., 2007; Senior et al., 2008; Colgin et al., 2009; Belluscio et al., 2012) ter določene študije na ljudeh (Axmacher et al., 2010; Holz et al., 2010; Schack et al., 2002).

Na podlagi rezultatov študij, ki kažejo na povezavo med ohranjanjem informacij v delovnem spominu (1) z aktivnostjo v theta, alfa in gama frekvencah ter (2) z interakcijo med temi oscilacijami, sta Roux in Uhlhaas (2014) predlagala teorijo, s katero sta želela integrirati izsledke znanstvenih raziskav na tem področju. Predlagala sta, da ima gama frekvenca splošno vlogo pri aktivnem vzdrževanju informacij, medtem ko je theta bolj pomembna za časovno organizacijo informacij v delovnem spominu. Po drugi strani alfa frekvenca ni vključena pri samem vzdrževanju informacij, ampak je pomembna za aktivno inhibicijo nerelevantnih informacij. Interakcije med nizkimi (theta, alfa) in visokimi (beta, gama) frekvencami omogočajo obdelavo informacij v delovnem spominu. Natančneje, interakcije med alfa in gama frekvencami sodelujejo pri vzdrževanju senzorično-prostorskih elementov v delovnem spominu, medtem ko interakcije med theta in gama frekvencami omogočajo sekvenčno kodiranje informacij v delovnem spominu (Roux in Uhlhaas, 2014). Trenutno ta teorija predstavlja eno od pomembnejših razlag delovanja možganskih oscilacij v delovnem spominu.

Vendar je treba poudariti, da so nevrofiziološke študije na ljudeh, ki kažejo na povečano aktivnost določene možganske oscilacije (ali na povečano fazno poravnavo med dvema oscilacijama) med zadrževanjem informacij v delovnem spominu, v osnovi korelacijske študije, kar dopušča možnost, da je aktivnost oscilacij le stranski proizvod ali posledica aktivnosti nevronov, ki nima nobene funkcije. Za boljše razumevanje nevrofizioloških osnov delovnega spomina je potrebno vspostaviti vzročne povezave med določenimi možganskimi oscilacijami in procesi vkodiranja, kratkoročnega shranjevanja in obdelave podatkov ter priklica. Prav tako je pomembno, da se opredeli, kateri predeli možganov sodelujejo v teh procesih.

Transkranialna stimulacija z izmenjujočim električnim tokom (angleško: transcranial alternating current stimulation; tACS) je ena izmed neinvazivnih oblik možganske stimulacije, ki temelji na aplikaciji šibkih električnih tokov na možgansko skorjo skozi par površinskih elektrod. Številne študije so pokazale, da je tACS varen za uporabo (Fertonani et al., 2015). Izmenjevanje električnega toka v poljubni frekvenci vpliva na možgansko valovanje (Herrmann et al., 2013), kar lahko merimo z EEG napravo, posledice stimulacije pa lahko preverjamo tudi z vedenjskimi nalogami. Prav zato tACS omogoča vspostavljanje vzročnih povezav med možganskimi oscilacijami in kognitivnimi sposobnostmi.

Glavni cilj naloge je, s pomočjo temeljnih raziskav, pridobiti nova znanja na področju nevrološke podlage delovnega spomina, pri čemer sem se osredotočila na vlogo možganskih oscilacij. Zastavljene so bile sledeče/slednje hipoteze:

1) Osebe z višjo kapaciteto delovnega spomina bodo pokazale »nevronsko učinkovitost«, podobno kot se kaže na področju inteligentosti (Neubauer & Fink, 2009).

2) Theta in gama možganski frekvenci, izmerjeni v mirujočem stanju, ter interakcija med tema frekvencama, bosta korelirali z verbalno in prostorsko kapaciteto kratkoročnega spomina. Hipoteza je osnovana v skladu s teorijo theta-gama nevronske kode (Lisman in Jensen; 2013).

3) tACS v theta in gama ritmih bo izboljšal reševanje nalog delovnega spomina, s čimer bom pokazala, da te oscilacije niso le epifenomen. Ti rezultati bodo vzpostavili vzročne povezave med theta in gama oscilacijami in delovnim spominom.

Predstavljenih je pet študij, v katerih sem se raziskovalnega cilja lotila s pomočjo korelacijskih raziskav (študiji 1 in 2) ter raziskav, ki omogočajo vspostavljanje vzročnih povezav (3-5). S pomočjo EEG naprave in tACS-a sem proučevala vlogo možganskih oscilacij v delovnem spominu, s poudarkom na oscilacijah, ki izvirajo iz nevronskih skupin v frontalnih in parietalnih režnjih. Ker sem želela raziskati normalen potek procesov, ki omogočajo kratotrajno zadrževanje informacij, sem v raziskave vključila nevrološko zdrave odrasle osebe.

Analiza rezultatov je pokazala, da se je delno potrdila prva hipoteza: »nevronska učinkovitost« se je pokazala le v gama oscilaciji, ne pa tudi v alfa oscilaciji in theta oscilaciji. Druga hipteza je bila potrjena, vendar so obstajali pomisleki glede zanesljivosti uporabljene metode za določanje individualnih theta in gama frekvenc. Tretja hipoteza je bila delno potrjena, saj so rezultati pokazali, da je tACS v theta frekvenci izboljšal reševanje nalog delovnega spomina, med tem ko za tACS v gama frekvenci ti dokazi niso bili zbrani. Rezultati so nadalje pokazali, da je tACS v theta frekvenci najbolj učinkovit, ko so elektrode postavljene na parietalna območja možganov. To se je pokazalo tako na vedenjskih kot na EEG podatkih. S tem se je potrdila vzročna povezava med theta oscilacijami in delovnim spominom, kar je v skladu s tACS raziskavami (Jaušovec & Jaušovec, 2014; Polanía et al., 2012; Vosskuhl et al., 2015). Prav tako so se potrdili izsledki številnih raziskav, ki kažejo na vlogo frontalnih (Courtney et al., 1998; D’Esposito et al., 1999; Haxby et al., 2000; Pessoa et al., 2002) in parietalnih predelov (Honey, Bullmore, & Sharma, 2000; Pessoa et al., 2002; Todd & Marois, 2004; Mitchell & Cusack, 2008) pri zadrževanju in obdelavi informacij v delovnem spominu.

Te ugotovitve so v skladu s teorijo, ki sta jo predlagala Roux in Uhlhaas (2014), čeprav vsi vidiki teorije niso bili preizkušeni. Rezultati so namreč pokazali, da ima alfa frekvenca vlogo pri filtriranju informacij v fazi vkodiranja, interakcija med theta in gama frekvenco pa je povezana s kapaciteto delovnega spomina. Kot že rečeno, se je potrdila vzročna povezava med aktivnostjo v theta frekvenci v parietalnih območjih in delovnim spominom.

Ker so predvsem tACS raziskave v theta in gama ritmih orale ledino na področju delovnega spomina, so v disertaciji opisane tudi pomanjkljivosti teh raziskav ter smernice za nadaljnje raziskave. Uporabljene so bile inovativne metode za določanje individualnih možganskih frekvenc, ki so bile osnovane na teoretičnih spoznanjih o interakcijah med različnimi možganskimi oscilacijami. Sistematično sosledje študij, tako korelacijskih kot tistih, ki so temeljile na neinvazivni možganski stimulaciji, je obrodilo rezultate, ki predstavljajo doprinos k znanju o nevrobiološki osnovi delovnega spomina.

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