NIBS as a research tool in studying and enhancing episodic memory in the left prefrontal cortex

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Abstract

In the absence of effective treatments for memory disorders including dementia, NIBS methods are being tested for studying and enhancing memory. Anodal transcranial direct-current stimulation (atDCS) is a safe, non-invasive method of stimulating the brain and modulating neural activity through electrodes placed on the scalp. Controversy has surrounded the implementation of atDCS as a research and clinical tool because of inconsistency in effects and a limited understanding of atDCS parameters and mechanisms. Heterogeneity in atDCS parameters across studies could contribute to the inconsistency in effects. Thus, the current research included a systematic methodological investigation of atDCS as a potential research and clinical tool. Two meta-analyses and a set of five methodological experiments analysed the efficacy of atDCS given a consistent set of parameters. In younger adults, atDCS led to a weak and volatile effect under certain conditions that fluctuated with modifications to verbal stimuli and sample size. While there was a robust improvement in memory following atDCS over the left PFC in Experiment 1, this effect did not remain consistent in direct and conceptual replications. The meta-analyses provided support to this investigation by demonstrating that when effect sizes were pooled together across all eligible published studies, the average effect size was close to zero. When only the studies in the current investigation were pooled together, the effect size was larger but also non-significant. Thus, the results inform future considerations of atDCS as a research and clinical tool and provide recommendations for the limited applications of atDCS with a framework for applying effective parameters that take into account individual differences. Furthermore, through the course of the investigation of atDCS, novel findings about episodic memory processes and neural correlates were revealed, confirming the importance of activity in the ventrolateral prefrontal cortex (VLPFC) to episodic memory formation. These findings on VLPFC function were further extended with an investigation of the cognitive mechanisms of atDCS effects on VLPFC

function in Chapter 6 and an examination of the time window and process in the VLPFC that was most crucial to memory formation with repetitive transcranial magnetic stimulation (rTMS) in Chapter 7. Together, the findings contributed to developing a clearer understanding of atDCS effects on episodic memory and the episodic processes that occur in the VLPFC. This understanding can inform future research in NIBS with other cognitive functions and the development of memory interventions that can target the VLPFC.

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Contents

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Acronyms

(in alphabetical order)

ATL	anterior temporal lobe
DI	discrimination index
DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
FA	false alarms
fMRI	functional magnetic resonance imaging
h	hours
MEP	motor-evoked potential
mA	milliamperes
min	minutes
ms	milliseconds
NIBS	non-invasive brain stimulation
PPC	posterior parietal cortex
Pr	proportion (of)
rTMS	repetitive transcranial magnetic stimulation
s	seconds
TPC	temporoparietal cortex
tACS	transcranial alternating current stimulation
tDCS	transcranial direct-current stimulation
VLPFC	ventrolateral prefrontal cortex

Preface

The aim of my PhD was to investigate verbal episodic memory and develop cognitive methods for memory enhancement. Verbal episodic memory is particularly important because a memory must be successfully identified in conscious thought and then communicated as part of social interaction and successful academic and work-related performance. Thus, verbal episodic memory is vital for nearly every aspect of everyday life. I started investigating behavioural enhancements such as guessing (guessing the answer to a question can improve subsequent memory for the answer) while working on a project with Dr Giulia Galli and Maurizio Materassi involving transcranial direct-current stimulation (tDCS), a neurobiological method that could yield memory enhancement (particularly when combined with cognitive tasks). The project began in the midst of a methodological crisis in Psychology and the tDCS field in particular. tDCS has been tested in humans more extensively since the beginning of the 21st century (previously having been studied predominantly in animals) and is known for its safety, accessibility, and usefulness in addressing cognitive questions such as localisation of function. However, there remains little understanding of its mechanisms of action and reliability as a research tool and intervention, particularly for studying and improving episodic memory. Thus, the aim of the project was methodological: to clarify the effects of tDCS with a systematic examination of one of the tDCS parameters (time of administration). After completing the project, the topic of tDCS captured my interest and became the focus of my PhD.

The primary aim of this thesis was to evaluate NIBS, particularly tDCS, as a research tool for studying and improving verbal episodic memory in healthy younger adults. The project involved Experiments 1 and 2 in Chapter 5 that were founded on the work of Dr Giulia Galli (Galli, 2014) and her experiments in tDCS (Medvedeva et al., 2018; Experiment 3) and TMS (Galli, Feurra, Pavone, Sirota, & Rossi, 2017); Dr Galli's previous work suggested that NIBS can modulate verbal memory processes in the left

VLPFC under specific conditions. Experiments 1 and 2 (Chapter 5; Medvedeva et al., 2018) investigated episodic encoding and retrieval in the left VLPFC with atDCS and introduced a significant effect that was subsequently replicated and used to assess the reliability of tDCS as a research tool for addressing specific cognitive questions. The three experiments (Chapter 5: Experiments 1 and 2; Medvedeva et al., 2018: Experiment 3) were later published together (Medvedeva et al., 2018: Experiments 1-3) with another study conducted in the same lab on older adults (Medvedeva et al., 2018; Experiment 4).

All four published experiments became part of another published work (Galli et al., 2018) that also forms part of this thesis (Chapter 4). After the first publication (Medvedeva et al., 2018), I joined Dr Galli and collaborators (Dr Sirota, Dr Vadillo, and Dr Feurra) in an ongoing project assessing tDCS effects on episodic memory using a systematic review and meta-analysis (Galli et al., 2018; Chapter 4). This work helped to address broader issues in the field including the replication crisis and the implementation of tDCS as an intervention. However, the published meta-analysis was revised to include the addition of moderators suggested by the reviewer and more recently-published studies, and I also added two moderators to the revised version. It is important to note that there is overlap in data used between the meta-analyses in Chapter 4 and Chapter 5. The meta-analysis in Chapter 5 aimed to examine the effect on false recognition in Experiment 1 and subsequent replications (Experiments 3, 4, and 5 of Chapter 5 as well as Medvedeva et al., 2018; Experiment 4). On the other hand, the meta-analysis in Chapter 5 aimed to investigate a different outcome measure, correct recognition, in all eligible *published* studies (thus excluding Experiments 3-5 in Chapter 5), and the publication (Medvedeva et al., 2018) became part of the revised meta-analysis after a new search was conducted. The two meta-analyses address different research questions, so although there is overlap in data, it is appropriate that the meta-analyses are independent and thus discussed separately.

The first publication (Medvedeva et al., 2018) also sparked an interest in applying the same systematic investigation (Experiments 1 and 2) to the DLPFC, and while I was working on the meta-analysis, I began working with Dr Feurra and Alexandra Petrovskaya at Moscow Higher Research University. We systematically investigated atDCS effects over the DLPFC at *encoding*, following the design of Experiment 1 (Medvedeva et al., 2018; Chapter 5), and we conducted a replication of the condition in Experiment 1 that showed a significant effect of atDCS over the VLPFC. This work, which extended the results of Experiments 1 and 2, is included in the thesis (Experiment 3; Chapter 5) and is currently being prepared for publication. The results of the experiment, which did not replicate those of Experiment 1 (Chapter 5; Medvedeva et al., 2018), led to closer investigation of the differences between Experiments 1 and 3 that could provide an explanation for the inconsistency. The investigation fostered a collaboration with Dr Oleg Medvedev at University of Waikato in New Zealand, an expert in using a novel and powerful statistical technique called generalisability theory. Using generalisability theory, we were able to establish the reliability of the recognition test used in both experiments and to conclude that neither the lack of reliability of the recognition test nor differences in language could explain differences in results. Ruling out language as an explanation helped to uncover a more plausible explanation involving word characteristics including frequency, and this interpretation is described in the discussion of Experiments 1 and 3.

The next primary aim was to investigate episodic processes in the prefrontal cortex with NIBS, which was partially addressed by the experiments in Chapter 5 and Chapter 6. There was an opportunity to investigate encoding processes in the VLPFC specifically and more directly through a study with rTMS (Chapter 7) after Dr Galli received a British Academy Small Grant. With the help of the grant, we were able to collaborate with Dr Fuggetta and Rebecca Saw at University of Roehampton.

The last experiments conducted for the thesis are Experiment 5 (Chapters 5 and 6) and Experiment 4 (Chapter 5), which were conducted with the help of Ezgi Kosar and Roberta Allegretta. I decided to separate a discussion of the results in Experiment 5 between Chapters 5 and 6 so that I could focus on the contributions to the reliability of the effect (Chapter 5) and a cognitive understanding of the effect (Chapter 6) separately. Chapter 5 included a systematic approach in which the same index of memory performance was measured and analysed in the same way across experiments. To avoid interrupting the systematicity, additional results of Experiment 5 (source accuracy) were discussed in a separate chapter, and these results address a separate question than Chapter 5. While Chapter 5 focuses on the reliability of effects caused by tDCS, Chapter 6 includes a more in-depth examination of interpretations for the effects and whether tDCS can be considered a good research tool for addressing cognitive questions.

A secondary aim of this thesis is to contribute to the resolution of the replication crisis in Psychology through good research practice and systematic study, and this aim was addressed through a discussion of replication issues (Chapter 5); replication studies (Experiments 3 and 4; Chapter 4); pre-registration (Experiment 5); and methodological investigations (Experiments 1-3).

The experiments are presented in order of contribution to the aim of the thesis rather than chronologically. The meta-analysis addresses the first aim of the thesis: investigating tDCS as a research tool and is broad in scope. By including all studies that have investigated episodic memory with tDCS, it includes a discussion of cathodal and anodal tDCS and episodic memory at multiple stages and regions, with verbal and non-verbal material. The remaining chapters address both aims: addressing the efficacy of atDCS as a research tool for investigating verbal episodic memory and investigating verbal episodic memory in the VLPFC. However, the tDCS investigations are constrained to effects of *anodal* tDCS over the VLPFC and DLPFC during *verbal* episodic *encoding* and

retrieval, with a focus on *atDCS effects over the VLPFC at encoding*. Accordingly, the final chapter continues the examination of *encoding* processes in the *VLPFC* using repetitive TMS, addressing the second aim. Thus, the meta-analysis helps to provide a broader context for the remaining work in the thesis.

Chapter 1: General Introduction

Episodic memory refers to memory for personal events and first-hand experiences (Tulving, 1972; 1984) and is a necessary function for everyday life (Squire & Kandel, 1999). It is important to understand episodic memory and associated processes, and this understanding can help to develop cognitive theories and facilitate memory formation in educational and clinical settings. The prefrontal cortex and the hippocampus are arguably the most critical regions in episodic memory: while the hippocampus has long been established as necessary for memory formation and recollection, the prefrontal cortex is gaining support for its role in multiple stages of memory including encoding, consolidation, and retrieval. Encoding is the process of processing and storing information in memory, after which it can be retrieved at a later stage (Eysenck & Keane, 2010). At retrieval, information that has been encoded is re-accessed and can be modified (Rugg, Johnson, & Uncapher, 2015), but consolidation strengthens the memory trace and makes it more stable and resistant to modification (Lechner, Squire, & Byrne, 1999; Squire & Alvarez, 1995).

Unlike hippocampal lesions, prefrontal lesions are not always associated with memory impairment (see **Importance of the prefrontal cortex** below). Thus, causal evidence is still needed to support the causal role of the PFC in memory function. Non-invasive brain stimulation (NIBS), a method of safely and non-invasively stimulating the brain through a weak electric current with transcranial direct-current stimulation (tDCS) or through a magnetically-induced electric field with transcranial magnetic stimulation (TMS), can establish that a region is necessary for a specific function. Existing research with NIBS supports that prefrontal activity is necessary for episodic memory, but the specific role of the prefrontal cortex remains unclear. In addition, NIBS can enhance specific episodic processes, such as recollection, because it can be delivered over a specific region during its involvement in the episodic process (e.g. prefrontal cortex at encoding).

In the same way, NIBS can show the contribution of the PFC to episodic memory formation and recollection and enhance PFC activity during the episodic process, leading to improved episodic memory function. With NIBS as a potential memory intervention, the prefrontal cortex may be a particularly optimal target because cortical sites are more effectively stimulated than subcortical sites such as the hippocampus. In addition, prefrontal dysfunction is part of disorders including dementia and frontal lobe epilepsy that can impair episodic memory function. There is evidence that the prefrontal cortex is important for maintaining normal memory function when other memory-related regions do not function properly. In other memory disorders such as mild cognitive impairment (MCI), the prefrontal cortex remains intact, while other regions including the hippocampus are impaired. Patients with MCI show increased PFC activation compared to healthy older adults during memory tasks (Erk, Spottke, Meisen, Wagner, Walter, & Jessen, 2011; Liang, Wang, Yang, Jia, & Li, 2011), suggesting that recruiting the PFC may serve as a compensatory mechanism for accessing additional cognitive resources (Grady et al., 1994). NIBS may be able to enhance this beneficial prefrontal activation, leading to better memory performance and improved memory function (Turriziani, Smirni, Zappalà, Mangano, Oliveri, & Cipolotti, 2012). Thus, enhancing prefrontal cortex function can possibly lead to enhanced episodic function, and NIBS can potentially serve as a neurorehabilitation tool for memory disorders.

Importance of Prefrontal Cortex

The prefrontal cortex seems to play the most important role in executive function and goal-directed behaviour, as evident from patients with lesions. Since before the 20th century, the prefrontal cortex seemed irreplaceable for behavioural control. However, the role of the prefrontal cortex in memory was less clear. For example, in the famous case of Phineas Gage, the railroad worker was injured by a rod that passed through the left eye and out of the skull (Harlow, 1848, as cited in Macmillan & Lena, 2010), damaging much of

the prefrontal cortex (Van Horn, Irimia, Torgerson, Chambers, Kikinis, & Toga, 2012). He experienced radical changes in personality and behaviour, reflecting impairments in goal-directed behaviour and possibly a loss in impulse control and response inhibition. However, he showed seemingly intact short-term and long-term episodic memory.

Patients have shown deficits in memory since the beginning of the 20th century (Elder & Miles, 1902; Penfield, 1938), but these deficits were subtle and did not receive much attention until the late 20th century (Fuster, 1973; Neill, 1976). Patients with frontal lobe lesions do not have symptoms of amnesia (Wheeler, Stuss, & Tulving, 1995 in Nyberg, Cabeza, & Tulving, 1996). Instead, they have specific impairments in recall and recognition. For example, Milner and colleagues (1985) showed that patients with lesions to the frontal lobe showed reduced abilities in identifying the order and frequency of memories. Even animal studies of prefrontal lesions showed no consistent impairments in short-term or long-term memory (Kolb, Nonneman, & Singh, 1974; Nonneman, Voigt, & Kolb, 1974; Rosenkilde, Bauer, & Fuster, 1981). Initial examinations of delayed spatial memory in the rat following ventrolateral prefrontal cortex (VLPFC) lesions found no relationship with memory (Nonneman, Voigt, & Kolb, 1974; Kolb, Nonneman, & Singh, 1974), but later recordings of single-cell activity in the ventral prefrontal cortex showed a connection with short-term memory deficits after lesions (Rosenkilde, Bauer, & Fuster, 1981).

The prefrontal cortex was thought to be involved with short-term memory or components of memory that required cognitive control, such as strategic encoding and retrieval. VLPFC and dorsolateral prefrontal cortex (DLPFC) lesions lead to impairments in working memory (Tsuchida & Fellows, 2009), executive functions, and various verbal learning tasks including memory for order, frequency, and associations (Centeno, Thompson, Koep, Helmstaedter, & Duncan, 2010).

Neuropsychological studies of memory seemed to constrain the role of the PFC to cognitive control, including strategic recollection, working memory, and emotion regulation, since deficits in the DLPFC were found for tasks requiring the use of top-down control (i.e. selective attention and memory monitoring), and deficits in the VLPFC were found for tasks that required response inhibition. This is partly due to limitations of the neuropsychological tests in measuring deficits. Thus, children with frontal lobe epilepsy show strong deficits in attention and working memory and subtle deficits in verbal memory, with increased false alarms (Hernandez et al., 2003).

Patients with DLPFC lesions exhibit impairments in attending to novel stimuli that naturally attract attention in healthy controls and goal-related stimuli that receive more attention due to top-down control by the DLPFC on sensory information. Lesions lead to greater distractibility and impaired performance in tasks that require selective attention, particularly in the presence of distractors. In turn, there is an absence of the memory advantage for novel stimuli that is present for healthy controls, so patients are impaired in recollecting novel stimuli better than familiar stimuli. They also show deficits in spontaneous recall for remote and recent events, showing an inability to organise information according to temporal order, context or strategy (strategic encoding and retrieval; Szczepanski & Knight, 2014).

Imaging studies revealed that the dorsolateral prefrontal cortex (DLPFC, BA 9/46) is associated with a variety of higher-order executive functions, including metamemory, working memory**,** cognitive control (task switching and response inhibition), and attention (Schmolck et al., 2011; Kobayashi, 2009). Like the VLPFC, the DLPFC also organises a variety of functions (i.e. language, behaviour) and integrates sensory and motor input based on temporal context, thus explaining its role in working memory and executive functions such as planning and forming schemas (Fuster, 2001).

The strong relationship between memory and cognitive control is sensible. Episodic memory is necessary for simulating and predicting future events and planning appropriate responses activities (Suddendorf & Corballis, 1997; Botzung, Denkova, & Manning, 2008). Episodic memory is active when remembering rich details (including context, time, and place) and re-experiencing events, particularly personally-relevant experiences (Tulving 1972; 1984; 1998; 2005). Episodic memories can also include information about the individual's thoughts, feelings, perceptions, and context at a specific time (Irish, Lawlor, Coen, & O'Mara, 2011; Irish et al., 2011), and this informs future decisions, goals, plans, and responses. Therefore, episodic memory is a key element of executive function involved in remembering a variety of important details necessary for future planning and decision making (Cohen, 2008).

Unlike the role of the DLPFC, the role of the VLPFC in verbal memory appears to be independent of cognitive control. The ventrolateral division of the PFC was established as functionally distinct when Broca discovered that patients with VLPFC lesions showed speech impairments. Although Broca proposed that the left VLPFC, specifically the pars opercularis and triangularis of the IFG, was necessary for language production and access to lexical representations, this area may be associated with a more domain-general process such as selection from competing representations or response override, as shown in participants who struggle with incongruent trials in the Stroop task and other conflict tasks (Thompson-Schill et al., 2002). Broca's area is specific to language processing or engages in multiple functions. It seems that Broca's area is part of a larger language network, since damage to Broca's area alone does not always lead to aphasia, and damage outside of Broca's area can lead to aphasia (Szczepanski & Knight, 2014). Moreover, patients with language deficits may not be able to perform verbal memory tasks, but they may show impaired memory independent of language (Riege et al., 1980; Stuss et al., 1994; Whitehouse, 1981).

Upon examination of patterns in patient lesions, Markowitsch (1995) hypothesised a role of the VLPFC in retrieval, and subsequent neuroimaging studies showed activation in the VLPFC at encoding (Fletcher, Shallice, & Dolan, 2000) as well as retrieval (Monchi, Taylor, & Dagher, 2000). fMRI studies led to the conclusion that the VLPFC is active during successful word encoding. The VLPFC consists of the anterior surface (BA 45/47), including the anterior inferior frontal gyrus, and the posterior surface (BA 45/44), including the posterior inferior frontal gyrus. For example, at verbal episodic encoding, the anterior (BA 45/47) and posterior part (44/46) were active in encoding-related semantic and phonological processing, respectively (Kirchhoff, Wagner, Maril, & Stern, 2000). In addition, the VLPFC is associated with a variety of linguistic tasks including semantic, phonological, and syntactic processing (Nozari & Thompson-Schill, 2015; Nozari, Mirman, & Thompson-Schill, 2016). Thus, the anterior surface is associated with semantic processing, whereas the posterior surface is associated with phonological processing. More specifically, the anterior VLPFC was associated with retrieving, selecting, organising, and maintaining words and their semantic attributes (Fletcher & Henson, 2001).

The VLPFC is generally associated with elaborative encoding, memory for order, and cognitive control processes at encoding and retrieval (Badre & Wagner, 2007). Thus, although the VLPFC is engaged during multiple domain-general cognitive functions, it seems necessary for verbal episodic memory, which is the focus of the thesis. In fact, the VLPFC may interact with the hippocampus to ensure the formation of long-term verbal memories (Burke, Long, Zaghloul, Sharan, Sperling, & Kahana, 2014).

NIBS has helped to establish causal relationships between the prefrontal cortex and aspects of episodic memory. NIBS has supported hemisphere-specific functional distinctions: while the left PFC is active in encoding and verbal memory, the right PFC is active in retrieval and non-verbal memory (Flöel et al., 2004; Gagnon et al., 2011; Innocenti et al., 2010; Miniussi, Cappa, Sandrini, Rossini, & Rossi, 2003; Rossi et al.,

2001; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003). NIBS has also supported the observation that hemispheric distinctions can be blurred in older adults and patients (Manenti, Cotelli, & Miniussi, 2011; Manenti, Cotelli, Robertson, & Miniussi, 2012; Solé-Padullés et al., 2006; Turriziani et al., 2012), who recruit prefrontal areas bilaterally because of cognitive decline (Ford & Kensinger, 2017; Rajah & D'Esposito, 2005). NIBS has supported functional distinctions between the dorsolateral and ventrolateral divisions of the PFC: while the DLPFC appears to have a selective role in memory for relationships (Epstein, Sekino, Yamaguchi, Kamiya, & Ueno, 2002; Hawco et al., 2017), perhaps due to a role in domain-general control processes such as selective attention (Sandrini, Rossini, & Miniussi, 2008) and manipulation of information (Veltman, Rombouts, & Dolan, 2003), the VLPFC appears active in verbal encoding generally (Blumenfeld, Lee, & D'Esposito, 2014; Galli, Feurra, Pavone, Sirota, & Rossi, 2017). See Chapter 2, Figure 2.0.1, for the position of the VLPFC and DLPFC with respect to other sites, and Chapter 4, Table 4.2.1, for the coordinates used to stimulate the sites. NIBS has also shown the causal role of activity in the VLPFC and DLPFC for distinct memory processes. The DLPFC has been shown to be important for encoding (Manenti, Cotelli, & Miniussi, 2011; Rossi et al., 2001; Rossi et al., 2010), reconsolidation (Sandrini, Censor, Mishoe, & Cohen, 2013; Sandrini, Brambilla, Manenti, Rosini, Cohen & Cotelli, 2014), and retrieval (Penolazzi, Stramaccia, Braga, Mondini, & Galfano, 2014; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003), with greater involvement of left DLPFC in encoding and reconsolidation and a greater involvement of the right DLPFC at retrieval (Balconi, 2013; Manenti, Tettamanti, Cotelli, Miniussi, & Cappa, 2010; Miniussi, Cappa, Sandrini, Rossini, & Rossi, 2003; Penolazzi, Stramaccia, Braga, Mondini, & Galfano, 2014). Delivering tDCS over the left DLPFC during encoding (Javadi & Cheng, 2013; Javadi & Walsh, 2012; Lu, Wang, Chen, & Xue, 2015; Manenti, Cotelli, Calabria, Maioli, & Miniussi., 2013) and reconsolidation (Sandrini et al., 2014) led to improved memory performance. tDCS over

the right DLPFC at encoding can also improve memory performance for verbal and non-verbal material (Lafontaine, Théoret, Gosselin, & Lippé, 2013; Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2013), reflecting the importance of both hemispheres for successful recollection. Delivering tDCS over the left and right DLPFC between encoding and retrieval could have targeted the consolidation phase, leading to enhanced consolidation processes and subsequent recognition (Gray, Brookshire, Casasanto, & Gallo, 2015).

The *left* VLPFC has been shown to be necessary for encoding (Galli, Feurra, Pavone, Sirota, & Rossi, 2017; Kahn, Pascual-Leone, Theoret, Fregni, Clark, & Wagner, 2005; Köhler, Paus, Buckner, & Milner, 2004; Machizawa, Kalla, Walsh, & Otten, 2010), particularly semantic and phonological processing (Gough, Nobre, & Devlin, 2005; see Nozari & Thompson-Schill, 2016 for a review). Delivering tDCS over the VLPFC during semantic or phonological processing facilitates performance on language tasks such as naming (Nixon et al., 2004; Pisoni, Papagno, & Cattaneo, 2012; Sehm, Kipping, Schäfer, Villringer, & Ragert, 2013). Delivering tDCS over the VLPFC during long-term episodic encoding also enhances performance in memory tasks (Meinzer et al., 2012; Medvedeva et al., 2018 Experiment 3; Pisoni et al., 2015a). There is also evidence for a causal role of the left VLPFC in retrieval (Wais, Kim, & Gazzaley, 2012), although the contributions of left VLPFC activity at reconsolidation and retrieval are less clear because of a lack of studies with NIBS. In contrast, the right VLPFC does not appear to play a large role in episodic encoding, reconsolidation, or retrieval. Few studies have compared stimulation of the right vs left VLPFC because there is little evidence for a role of the right VLPFC in verbal memory. Instead, the right VLPFC appears to be associated with inhibitory control (Anderson & Weaver, 2009) and thus is not a common site in examinations of episodic memory (Badre & Wagner, 2007; Ester, Sprague, & Serences, 2015; Kahn, Pascual-Leone, Theoret, Fregni, Clark, & Wagner, 2005; Linden, 2007). Kahn and colleagues (2005) found that interrupting activity in the right but not left VLPFC with TMS led to an

enhancement in response accuracy at encoding and retrieval, perhaps reflecting an advantage of disrupting response inhibition rather than episodic processes.

NIBS has established causal relationships between other regions and episodic memory, showing potential for memory function in these regions to be enhanced (see Chapter 4, Figure 4.1.2 for locations and functions). The left anterior temporal lobes appear to be causally involved in semantic encoding (Boggio et al., 2009; Chi, Fregni, & Snyder, 2010; Pisoni et al., 2015b). Delivering tDCS over the left but not right anterior temporal lobes can reduce false recognition by increasing literal vs categorical processing (Boggio et al., 2009; Chi, Fregni, & Snyder, 2010). There is evidence from TMS and tDCS studies for a causal role of both hemispheres of the parietal cortex in episodic encoding (Flöel et al., 2012; Jacobson, Goren, Lavidor, & Levy, 2012; Jones, Gözenman, & Berryhill, 2014) and the left hemisphere at retrieval (Chen, Lo, Liu, & Cheng, 2016; Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2010; Pergolizzi & Chua, 2015; Pisoni et al., 2015b), although the role at retrieval appears to be stronger than at encoding. Delivering tDCS over the left parietal cortex during encoding (Jacobson, Goren, Lavidor, & Levy, 2012; Jones, Gözenman, & Berryhill, 2014) and retrieval (Manenti, Tettamanti, Cotelli, Miniussi, & Cappa, 2010; Pergolizzi & Chua, 2015; Pisoni et al., 2015b) can enhance memory performance, demonstrating the role of the left parietal cortex in episodic processes and the potential for tDCS to improve memory function. Although promising approaches demonstrate that under certain conditions, episodic memory can be facilitated (Brem, Ran, & Pascual-Leone, 2013), these conditions are often elusive and difficult to identify and replicate (Berryhill, Peterson, Jones, & Stephens, 2014; Minarik et al., 2016). There is often little evidence or justification for choosing stimulation sites (Jeong, Chung, & Kim, 2015; Cantone et al., 2014), and direct replications of tDCS studies in other fields have not always been successful (e.g. Vannorsdall, van Steenburgh, Schretlen, Jayatillake, Skolasky, & Gordon, 2016). An additional complication is applying results to patients and

older adults with cognitive decline, who can undergo neurological or neurodegenerative changes (Davis & van Koningsbruggen, 2013; Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012). The successful use of NIBS depends on interactions between technical and experimental parameters, but there is strong evidence that NIBS can be used to address memory research questions and induce long-term improvements in memory function under certain conditions.

Importance of Studying Episodic Memory

Episodic memory is an important cognitive function for everyday functioning in nearly every aspect of human life, and connections between memory, language, and consciousness enable effective communication and social interaction. Episodic memory is one of the most important types of memory because of its relevance to forming personal identity and other constructs that are based on first-hand experience (Williams, Conway, & Cohen, 2008).

Episodic memory is an important function to examine in research; it interacts with other cognitive functions and can help improve broad theories of cognition, such as whether cognition is situated in the individual or in the interactions between the individual and the environment (e.g. Barsalou, 2003). In turn, even basic and theoretical cognitive research in episodic memory can greatly benefit clinical studies in multiple ways. Diagnostic tools and interventions can be developed based on an understanding of the basic cognitive and neural mechanisms of episodic function. Understanding the processes involved in successful memory formation and recollection in the healthy brain could lead to improvements in interventions to slow cognitive decline and degeneration. For example, NIBS can target a specific function. In addition, identifying the essential and compensatory areas involved in memory formation can help to guide treatments and surgeries to maximise retention of memory abilities in patients. There is a possibility that regions like the prefrontal cortex can compensate for the functions of more essential

memory regions through neuroplasticity, as evident in older adults and cases of brain damage (Grady et al., 2003), and these regions should be considered as targets for focal memory interventions. In addition, surgeries could be designed to avoid regions of the prefrontal cortex by using diffusion tensor imaging (DTI) to map the functional networks of the PFC for each individual.

Aims of the Thesis

There were two primary aims of the thesis: 1) assessing tDCS as a research tool for investigating and enhancing episodic memory 2) investigating episodic memory processes in the prefrontal cortex. An additional aim was contributing to resolving the replication crisis and increasing high-quality research in the field by engaging in good research practice and relevant activities including preregistration, transparency, and methodological investigations.

The first aim of investigating episodic memory processes in the VLPFC and DLPFC was addressed throughout the thesis, with a greater focus on verbal encoding processes in the VLPFC but comparisons with retrieval in the VLPFC and encoding in the DLPFC. Although Chapter 4 had a broad scope, including all eligible tDCS studies of episodic memory, it included a systematic review of tDCS studies of episodic memory over the PFC and an analysis of the left and right PFC as moderators of tDCS effects in the meta-analysis. Chapter 5 investigated episodic memory processes in the VLPFC and DLPFC using tDCS: Experiments 1 and 2 included investigations of encoding and retrieval, respectively, in the VLPFC, while Experiment 3 compared contributions of the VLPFC and DLPFC to encoding, and Experiments 4 and 5 were replication studies (direct and conceptual, respectively) of a significant condition in Experiment 1. Chapter 6 further investigated encoding processes in the VLPFC using tDCS, and Chapter 7 investigated these processes using TMS.

The second aim of assessing tDCS as a research tool was also addressed throughout the thesis, particularly in Chapters 4-6. Chapter 4 aimed to examine the reliability of tDCS effects across published studies, while Chapter 5 aimed to examine the reliability of tDCS effects across the studies conducted in this thesis. In addition to explaining the effects in Chapter 5, Chapter 6 aimed to show how tDCS can be applied to more complex designs and the development of cognitive theories.

Chapter 2: Foundations of Non-Invasive Brain Stimulation

Overview

The chapter introduces the methods of repetitive TMS and tDCS, referencing other magnetic and electrical stimulation methods in context. NIBS includes TMS and tDCS, distinct methods of safely and non-invasively stimulating the brain, including the prefrontal cortex. TMS is a more established method and can be used to understand the effects of tDCS, as demonstrated from initial studies of tDCS that will be discussed. The effects and cellular and cognitive mechanisms are described in terms of the motor cortex and visual cortex, since motor and visual cortex stimulation produce clearer, more straightforward physiological and cognitive responses that can be used to understand stimulation over the prefrontal cortex. The cellular mechanisms are discussed in terms of studies with pharmacology that have examined effects of inhibiting or exciting ion channels and receptors. The similarities and differences between the techniques are reviewed, followed by a discussion of how they can be implemented in cognitive experiments, including studies of episodic memory. The relative safety of the techniques has been established and safety considerations are reviewed, followed by a discussion of the advantages and limitations of the techniques for studying cognitive neuroscience and being applied as interventions. Finally, the effects of tDCS and TMS over the prefrontal cortex are discussed in terms of physiological effects and prefrontal cortex anatomy. Cognitive effects are discussed more in detail in Chapter 3.

TMS

Based on the principle of electromagnetic induction, transcranial magnetic stimulation generates a volatile magnetic field that painlessly and non-invasively penetrates the scalp (Hamada & Rothwell, 2015). This is caused by the strong, rapid, perpendicular flow of electrical current through a coil of wire that generates an electrical field within the cortical tissue with currents that flow parallel to the coil (Walsh &

Rushworth, 1999). The changing magnetic field generates a complementary electric field and associated currents in conductive elements nearby, like the skull. Thus, the electric field forms based on an interaction of the magnetic field with charges between the scalp and skull that increase scalp conductivity (Walsh & Rushworth, 1999). The large current pulse from the TMS coil generates a magnetic field that reaches and subsides from 1 Tesla and greater within 1 ms. Thus, the rapid movement of the current through the coil leads to a pulse duration of only 1 ms (Walsh & Rushworth, 1999). The rapidly changing magnetic field leads to induction of weak electric currents, and this causes changes in neuron polarisation and activity. The magnitude of the effect on neuron polarisation depends on the magnetic field's intensity and rate of change. The process is similar to electrical stimulation which excites neuronal axons in superficial structures not located deeply in the brain (like the cerebellum or cingulate). When it induces an electric field in the brain, it focally, painlessly, and noninvasively depolarizes neurons.

Effects of TMS. Single pulse TMS delivers an excitatory pulse, leading to action potentials and objective sensory and motor responses in basic functions such as perception and movement. When delivered over the motor cortex independent of a task (offline TMS), the pulse leads to a motor-evoked potential (MEP) and involuntary reflex in the contralateral hand, and this response can be accompanied by an increase in BOLD response (Bohning et al., 2000). This response can be used to find an individual's threshold for motor cortex excitability, and stimulation intensity can be adjusted according to the minimum intensity that evokes the response. When delivered over the visual cortex, the pulse can lead to phosphenes (perception of light that is absent) or facilitation of perception, depending on stimulation intensity. At low intensity, TMS over the visual cortex can lead to blind spots but not phosphenes and at high intensity, TMS can lead to the perception of phosphenes (Hallett, 2000). Like MEPs for the motor cortex, phosphenes can be used to identify visual cortex excitability, and intensity can be adjusted based on

participant perception of phosphenes (Gerwig, Kastrup, Meyer, & Niehaus, 2003). However, at specific intervals, a single pulse can lead to lack of visual perception entirely. However, when delivered during a task (online TMS), single pulse TMS can interfere with neural function; a single pulse over the motor cortex can slow reaction time in a motor task (Day, Thompson, Dick, Nakashima, & Marsden, 1987).

Moreover, when delivered over the visual cortex during a task, a single pulse can interfere with perception. Amassian and colleagues (1989) found that visual perception of letter triads was disrupted when a pulse was delivered 80-100 ms post-stimulus onset but not 40-60 or 120-140 ms post-stimulus onset, suggesting that processes necessary for the task (letter recognition and information transfer from visual cortex) occurred and were disrupted within 140 ms of stimulus onset.

The lack of visual perception may occur as part of the ‘virtual lesion effect’: TMS can cause a large population of neurons to fire simultaneously and repetitively, and an increase in general activation can compete with and disrupt specific, task-related activation, impairing function. This also suggests that there are differences between offline and online TMS effects. Specifically, one pulse independent of a task (offline TMS) may excite the system. When neurons associated with the task fire concurrently with the TMS pulse (online TMS), however, the additional non-task-related activation can induce disorder rather than facilitating organised processing. In this way, certain threshold of neuron firing can lead to a disruption of normal task-related activation. Amassian and colleagues (1989) suggested that in their study, a single pulse of TMS indirectly and directly led to neuron excitation and that concurrent neuron firing led to impaired perception between 80-100 ms.

Thus, TMS can act as a temporary virtual lesion when delivered over a specific area. However, TMS does not seem to impair performance by abolishing neural activity in the stimulation site. A single pulse can facilitate neural activity and increase evoked

activity within 500 ms, but after, activity can be decreased for as long as several seconds (Moliadze et al., 2003). Stimulation intensity can modulate these effects, with greater intensity leading to earlier inhibition at 100-150 ms and then enhancement (Miniussi, Harris, & Ruzzoli, 2013). Walsh and Cowey (2000) proposed that when delivered concurrently with a cognitive task, TMS introduces noise or disorder in the neural system by activating neurons that may not be directly relevant for the task, since TMS indiscriminately activates neurons in the stimulation site and is unlikely to activate the same neurons as engaged by the task. Among organised task-related activity, the noise can be considered random and in turn, can lead to slower or worse performance by competing with task-related activity or cognitive resources (Miniussi, Harris, & Ruzzoli, 2013). However, TMS-induced activity can still overlap with task-related activity if TMS activates task-related neurons that are oriented toward the electric field.

TMS seems to depolarize neurons based on their orientation (Amassian, Eberle, Maccabee, & Cracco, 1992). TMS depolarizes neurons that are positioned horizontally, activating both excitatory glutamatergic and inhibitory GABAergic pathways. Thus, pyramidal neurons positioned radially are influenced indirectly through synaptic transmission with the horizontal cells or TMS effects on level I interneurons, which indirectly activate GABA receptors and suppress dendritic calcium, leading to dendrite inhibition and inhibitory postsynaptic potentials pyramidal neurons (Murphy et al., 2016; Kapogiannis & Wassermann, 2008). In addition, TMS may activate cortical neurons through axon bends and terminals rather than directly, perhaps because of lower membrane threshold and stronger electric field at these sites. In addition, stimulation may target longer axons with greater diameters because of lower threshold for stimulation (Nagarajan, Durang, & Warman, 1993). These activations may increase intracellular calcium through depolarization effects on calcium channels rather than action potentials, thus showing changes in cortical excitability in depolarized activity that leads to activation of calcium

channels and NMDA receptors. Although TMS may exert effects through NMDA receptors, it is not dependent on them because it may act through presynaptic activity (Banerjee, Sorrell, Celnik, & Pelled, 2017).

TMS is thought to add random noise to the neural network and lower the signal-to-noise ratio because it appears to generate random patterns of neuron firing (Harris, Clifford, & Miniussi, 2008; O'Shea & Walsh, 2007; Walsh & Rushworth, 1999). Noise can occur in every stage of processing, from stimulus detection by neurons in the region to the behavioural response, and information may be better processed with an intermediate level of noise compared to no noise at all since neurons can be more receptive to input, including task-related input (Miniussi, Harris, & Ruzzoli, 2013). Noise can be beneficial if it adds to the target signal, which occurs when TMS activates neurons oriented toward the electric field that are also activated by the task, and with optimal noise, the noise and signal can become synchronised and the signal can become stronger (Miniussi, Harris, & Ruzzoli, 2013). Neurons associated with the task will be correlated with performance and contribute to the signal, whereas response variability across trials may be associated with neurons engaged in unrelated, random activity that contributes to noise (Miniussi, Harris, & Ruzzoli, 2013). The cognitive performance, consisting of accuracy and reaction time, may be determined by signal-to-noise ratio (Miniussi, Harris, & Ruzzoli, 2013). By generating random patterns of neuron firing, TMS may increase neural noise and lower the strength of the target signal (Miniussi, Harris, & Ruzzoli, 2013).

For example, Ruzzoli, Marzi, and Miniussi (2010) found that TMS impairs perceptual discrimination of motion direction by increasing neural noise but does not lower the strength of the target signal. They stimulated a visual area sensitive to motion direction (V5/MT) and a visual area associated with phosphene induction when stimulated (V1/V2) and found impairment in correct discrimination of motion direction for V5/MT compared to a control site (vertex) for higher levels of motion coherence (when

participants had 75% or higher accuracy on the baseline measure of the task). Higher levels of motion coherence were associated with lower levels of task-induced neural noise, since the dots were presented as moving in a random motion vs a synchronised, directed motion. They suggested that TMS does not lower the signal strength but rather increases neural noise and decreases perceptual discrimination by increasing response variance. They found no differences in perceptual awareness, suggesting that TMS affected perception rather than higher-order functions such as response selection. In another study, Harris, Clifford, and Miniussi (2008) found that TMS interacted with the level of visual image noise to reduce signal strength.

However, single-pulse TMS may not be strong enough to modulate higher-order cognitive functions such as perceptual discrimination and memory, unlike repetitive TMS. Repetitive TMS involves the rapid delivery of multiple, repeated pulses within hundreds of milliseconds usually with effects that outlast the period of stimulation. The series of pulses is known as a *train,* and trains can be delivered between 1 and 50 Hz for 10-1000 ms (Walsh & Rushworth, 1999). In episodic memory, high-frequency rTMS is usually delivered at 20 Hz for 500 ms, so ten pulses are delivered within half a second. While a single pulse of TMS can temporarily excite a region, evoking a visible motor movement, repetitive TMS (Theta Burst Stimulation) can suppress cortical excitability for longer periods of time, up to 30-60 min (Hamada & Rothwell, 2015). Repetitive TMS can cause longer-lasting changes of neuron activity at synapses. For example, rTMS in the motor cortex leads to modulation of movement and in the striatum leads to modulation of neurotransmitter release such as dopamine. Repetitive TMS can also lead to long-term alterations of the functions of stimulated cortical regions (Nevler & Ash, 2015).

While short bursts of high frequency stimulation can lead to long term potentiation in synapses between the stimulated cells and the cells that they stimulate, longer bursts of low-frequency stimulation (1 Hz for 15 min) led to long term depression and a suppressed

EPSP wave at the synapse lasting for hours (Purves et al., 2004). Thus, in the cerebral cortex, high-frequency stimulation leads to excitation, whereas low-frequency stimulation leads to inhibition.

However, TMS is sensitive to baseline neural activation. In line with the state-dependency principle (Miniussi, Harris, & Ruzzoli, 2013), offline and online TMS can disrupt or facilitate cognitive performance depending on the baseline excitability of the neuron population (Silvanto & Pascual-Leone, 2008). Thus, TMS is affected by baseline cortical excitability and whether it is delivered online or offline with respect to the task.

It is clear that the effects of TMS interact with baseline activation in the system: the MEP amplitude is increased after voluntary muscle contraction, facilitating TMS-induced neuron firing. On one hand, the motor evoked potential is larger with an earlier onset after baseline muscle contraction compared to rest, because there is a higher level of motor neuron activity and activation can be easily increased. (Hallett, 2007). On the other hand, stimulating the motor cortex during simultaneous voluntary muscle movement leads to inhibition of motor movement and an inhibitory silent period in the EMG rather than an excitatory effect of TMS. (Nevler & Ash, 2015). TMS seems to affect the neurons that are less active in the stimulation site, with lower TMS-induced evoked activity but higher spontaneous activity for stimulation sites that are more strongly active at baseline. For example, the presentation of a red or green screen led to phosphenes in the presented colour after TMS over the occipital cortex, and priming the visual cortex with a specific motion orientation led to enhanced detection of motion in that direction but not the opposite direction (Silvanto, Muggleton, Cowey, & Walsh, 2007). Moreover, TMS can lead to temporary synaptic changes in motor reflexes after training, called training-induced plasticity. Training involves moving the finger in the opposite direction of the involuntary reflex induced by the TMS pulse, and after multiple training trials, the thumb moves in the

trained direction without conscious effort (post-training directional change; Rosenkranz, Nitsche, Tergau, & Paulus, 2000).

Subthreshold modulation of neuron activity before TMS can reverse the expected effects. When baseline corticospinal excitability is increased, 1-Hz rTMS leads to a reduction in excitability, whereas when baseline excitability is suppressed, 1-Hz rTMS leads to an increase (Siebner et al., 2004). It seems that over the motor cortex, low-frequency rTMS (1 Hz) inhibits cortical excitability, whereas high-frequency (>5 Hz) rTMS leads to cortical excitability (Hallett, 2007). Silvanto and Muggleton (2008) showed similar results on the visuo-motor region V5/MT: after offline rTMS and online TMS separately, performance was disrupted in the motion-detection task. However, if 1-Hz of online TMS was delivered after the offline stimulation, performance was facilitated. These effects may be reversed when a cognitive function is targeted, depending on whether the region inhibits or facilitates performance on a given task.

Longer rTMS administration can increase general neural activation by increasing spontaneous neuron firing and modulating timing in spike timing dependent potentiation, causing presynaptic activity that leads to long-term potentiation (Banerjee, Sorrell, Celnik, & Pelled, 2017). This increase in cortical excitability can enhance NMDA-dependent after-effects, in which subsequent activation of postsynaptic NMDA receptors could lead to long-term changes in plasticity at synaptic connections (Banerjee, Sorrell, Celnik, & Pelled, 2017; Huang, Chen, Rothwell, & Wen, 2007). rTMS can also lead to action potentials by activating sodium and calcium gated channels, leading to an influx of intracellular sodium and calcium (Banerjee, Sorrell, Celnik, & Pelled, 2017). Since TMS has state-dependent effects, increased baseline cortical activity would improve modulatory effects of rTMS. For example, with increased neural activity in presence of further input, such as tactile stimulation, rTMS can have greater modulation (Murphy et al., 2016).

Transcranial Direct-Current Stimulation (tDCS)

Transcranial direct-current stimulation is safely, non-invasively stimulates the cerebral cortex by delivering a constant current (usually 1-2 mA) through two electrodes that are usually placed on the scalp. One electrode delivers a positive charge (anode), while the other electrode delivers a negative charge (cathode), and together the electrodes generate a dipole field in which current flows between the electrodes and leads to a stronger ion concentration underneath the electrodes. Positive ions flow away from the cathode and toward the anode, concentrating under the anode and leading to greater positive charge and increased cortical excitability, while negative ions flow toward the cathode and lead to a greater concentration of negative charge and increased cortical inhibition (Kuo & Nitsche, 2012; Reinhart, Cosman, Fukuda, & Woodman, 2017).

Cortical excitability is modulated through the effect of the tDCS-induced electric field on neuron membrane potentials (Bindman, 1964; Purpura & McMurtry, 1965). The flow of positive ions toward the anode increases excitability of large populations of neurons under the electrode by increasing the potential. The resting neuron membrane potential is -70 mV, and if the potential becomes more positive by 15 mV, the neuron fires, delivering an action potential to another neuron and increasing its susceptibility to fire (Kalat, 2016; Purves et al., 2004). The simultaneous firing of large populations of neurons leads to an increase in overall neural activity that can facilitate function in the region. While the anode depolarises membrane potentials, the electric current is not strong enough to induce an action potential (Reti & Chang, 2015). Similarly, the flow of negative ions toward the cathode leads to hyperpolarisation of membrane potential and decreased neuron excitability, decreasing the susceptibility of the neuron to fire and deliver a signal to another neuron. The neuron that fires is the presynaptic cell, and the neuron that receives the signal is the postsynaptic cell (Kalat, 2016). The signal can be excitatory, leading to stronger receptivity to input in the postsynaptic cell, respectively. Long-term synaptic and

metabolic changes occur and stabilize synaptic strength when two adjacent cells cause persistent excitation or inhibition in each other (Hebb, 1949): long-term potentiation refers to excitation and long-term depression refers to inhibition (Purves et al., 2004; Stagg & Nitsche, 2011). The persistent excitation can be induced naturally by a response to the environment or artificially by external stimulation (e.g. tDCS). Neuron signalling and communication is the basis for learning, so tDCS may be particularly beneficial for facilitating functions associated with learning, as discussed below. It is important to note that the ion channel can be opened by neurotransmitters including excitatory glutamate and inhibitory GABA, which increase permeability to positive and negative ions, respectively, and allow them to alter resting membrane potential. Altering channel permeability by increasing glutamate and GABA levels may affect tDCS modulations, as discussed below.

Thus, tDCS effects are polarity-specific: if the anode electrode is active on the target site, the stimulation is known as anodal tDCS, whereas active cathodal stimulation is called cathodal tDCS (Purpura & McMurtry, 1965; Nitsche & Paulus, 2000). Successful application depends on multiple factors, including the appropriate position of both electrodes with constant current strength over a sufficiently long duration.-The electric current must successfully pass through the scalp, and the suggestion is for the electrodes to be at least 4 cm apart to reduce shunting, which refers to current flow over the surface of the scalp rather than the cortex (Moliadze et al., 2010). Both electrodes must be in contact with the organism, but researchers have also been able to effectively modulate brain activity by placing just one electrode (usually called active or target) on the scalp and the second electrode (usually called reference or return) on another part of the body (i.e. shoulder or leg). However, the reference electrode is necessary for the proper functioning of the active electrode because the opposite polarities of the two electrodes generate a dipole electric field (Nasseri, Nitsche, & Ekhtiari, 2015). The position of the reference electrode influences the orientation of the electric field and the effect (increasing or

decreasing excitability). For example, Nitsche and Paulus (2000) found significant effects when using a bilateral montage with the return electrode on the contralateral forehead, whereas Priori and colleagues (1998) placed the return electrode on the chin, and the differences in return electrode placement could explain differences in effects (Nitsche et al., 2003). Changes in the location of the return electrode could lead to a change in current direction: a change from the upper arm to the lower arm could lead to current flow over parietal rather than frontal regions (Thair, Holloway, Newport, & Smith, 2017).

The *extracephalic* site of the reference electrode can be the muscle of a limb or part of the face (cheek) because positioning the electrode on other sites may pose a greater risk. For example, positioning either electrode on the neck may be unsafe because homeostatic systems that regulate breathing and heart rate could be affected. In addition, the flow of the current could be extended to the heart, although the levels of current reaching the heart would be far below safe thresholds if maximum tDCS current strength was 2 mA or lower (Parazzini, Rossi, Rossi, Priori, & Ravazzani, 2012). Placing the electrode on a limb muscle, however, is thought to be safe, with no effects on respiratory or cardiovascular function when the target electrode was placed on a midline frontal site (Fz, international 10-20 system) and the return electrode was placed on the right leg (Vandermeeren, Jamart, & Ossemann, 2010).

tDCS effects on motor cortex. Nitsche and Paulus (2000) found changes in motor cortex excitability as measured by MEPs after anodal and cathodal tDCS, and they found that after sufficiently long durations and current strengths, the changes in excitability continued after the stimulation stopped. They stimulated the motor cortex and recorded MEP amplitudes at baseline, immediately after the end of stimulation, and 5 min after the end of stimulation. After-effects were defined as changes in MEP amplitudes that occurred after the stimulation ended. When atDCS was delivered for 1 mA for 5 min over

the motor cortex and adjacent sites, only motor cortex atDCS and cathodal tDCS led to significant changes in MEP size that lasted for 5 min before returning to baseline.

When atDCS was delivered for 1 mA with duration varying between 1-5 min, there were significantly higher MEP amplitudes (compared to baseline) for three min following stimulation for 4-5 min and after-effects for one minute after three-minute stimulation. When atDCS was delivered for 5 min between 0.2-1 mA, current strength of at least 0.6 mA led to one-minute after-effects, 0.8 mA led to two-minute after-effects, and 1 mA led to three-minute after-effects. Nitsche and Paulus (2000) concluded that increasing current strength and stimulation duration would increase after-effects, and a minimum of 3 min at 1 mA or 5 min at 0.6 mA was needed for inducing after-effects. They also concluded that effects during the stimulation were due to changes in resting membrane potential, while after-effects could be due to changes in spontaneous neuron firing. However, in previous studies with animals, cancellation of brain activity by inducing hypothermia did not lead to changes in tDCS-induced excitability, implicating long-lasting mechanisms (Gartside, 1968 in Nitsche & Paulus, 2000). Moreover, Bindman, Lippold, and Redfearn (1964) found evidence of long-term depression and changes in evoked potentials and spontaneous firing rate in anesthetised rats, with atDCS increasing the size of the potential and firing rate and cathodal tDCS decreasing it. Five to ten min of stimulation led to 1-5 h of after-effects, with an increase in excitability for atDCS and a decrease in excitability for cathodal tDCS.

The study by Nitsche and Paulus (2000) illustrated the importance of duration and current strength for inducing immediate effects and after-effects that outlasted the period of stimulation. Accordingly, Nitsche and colleagues found longer after effects after longer durations and higher current strength. While 5-7 min of 1 mA stimulation led to only several minutes of after-effects, 9 min led to after-effects lasting over an hour, 13 min led to 60-90 min (Nitsche & Paulus, 2001), and 35 min led to after-effects of several minutes

(Nitsche et al., 2003). Monte-Silva and colleagues (2013) found significant increases in motor cortex excitability after 13 min of atDCS but decreases after 26 min. Moreover, Batsikadze and colleagues (2013) found that 20 min of 1 mA of cathodal tDCS led to decreases in excitability lasting 90-120 min after stimulation termination, while 2 mA of cathodal and anodal tDCS led to increases in excitability with after-effects lasting 90-120 min and 60-90 min, respectively.

The non-linear increase in after-effects as a function of duration and intensity- and duration-dependent reversals in expected polarity-specific effects highlights the complex nature of tDCS in interactions with the state of the neural system. There is a possibility that because the neural system adjusted to the constant input through homeostatic mechanisms, longer durations of cathodal tDCS had a more transient after-effect (Miniussi, Harris, & Ruzzoli, 2013).

Nitsche and colleagues (2004) also examined the mechanisms of after-effects by facilitating or impairing membrane receptivity with channel blockers, since spontaneous firing and changes in resting membrane potentials could lead to synaptic changes that are facilitated by NMDA receptors. They administered a voltage-dependent sodium ion channel blocker (carbamazepine) to interfere with atDCS and an NMDA-channel blocker (dextromethorphan) to interfere with plastic changes in the motor cortex. They found that after-effects of anodal and cathodal tDCS were abolished by the NMDA channel blocker, whereas only after-effects effects of atDCS were abolished by the channel-blocking drug. Similarly, Liebetanz, Nitsche, Tergau, and Paulus (2002) found that atDCS and cathodal tDCS after-effects were abolished by an NMDA receptor antagonist (Nitsche, Fricke, & Henschke, 2003), and Antal and Paulus (2011) found longer atDCS after-effects after the administration of d-cycloserin, an NMDA receptor agonist. Since neural activity depends on the frequency of firing and thus membrane potential, with more positive potentials leading to increased firing and negative potential leading to decreased firing, tDCS effects

may depend on ion channel permeability. The results suggested that atDCS immediate *and* after-effects were dependent on the flow of sodium (Antal, Paulus, & Nitsche, 2009) or calcium (Nitsche, Nitsche, Klein, Tergau, Rothwell, & Paulus, 2003) through the membrane and the ability to alter membrane potential (Nitsche et al., 2004). Specifically, tDCS could act on voltage sensitive calcium and sodium channels that are dependent on NMDA receptor activation (Coussens, Kerr, & Abraham, 1997; Mayer, Westbrook, & Guthrie, 1984; Rosenmund, Feltz, & Westbrook, 1995). LTP and LTD may be dependent on NMDA receptors, so the NMDA receptor drug would block changes in synaptic strength that were facilitated by NMDA receptor interactions with tDCS. In turn, Nitsche and colleagues (2004) found that GABA receptor agonist lorazepam led to increased and longer atDCS after-effects as evident from increased MEP amplitude, although this effect occurred after a delay, possibly because administering GABA terminates the start of long-term potentiation (Gaiarsa, Caillard, & Ben-Ari, 2002; Fujii, Jia, Yang, & Sumikawa, 2000; Meredith, Floyer-Lea, & Paulsen, 2003), whereas reducing GABA causes long-term potentiation. Reduction of GABA increases plasticity (Nitsche et al., 2005; Stagg, Bachtiar, & Johansen-Berg, 2011), so animal studies show an increase in plasticity when tDCS lowers free GABA in the cortex of the stimulation site (Stagg et al., 2009). Moreover, blocking NMDA glutamatergic excitation and GABAergic inhibition abolishes tDCS after-effects but not initial effects (Nitsche et al., 2003; Stagg & Nitsche, 2011). Thus, neocortical plasticity appears to depend on glutamatergic and GABAergic interneurons, which depend on NMDA receptors and intracellular calcium (Anwyl, 1999; Mattson, 2008; Nakanishi, 1994). Stagg and Nitsche (2011) found that plasticity was not easily modulated by tDCS in the motor cortex, but multiple spaced sessions of tDCS could lead to changes in plasticity and increases in the duration of after-effects (depending on the interval between sessions and the number of sessions). The electrical current modulates the resting membrane potential over time, possibly increasing plasticity with multiple sessions

as well as longer durations (Nitsche et al., 2007). tDCS appears to modulate concentrations of inhibitory GABA and excitatory glutamate (Filmer, Dux, & Mattingley, 2014; Nitsche & Paulus, 2011; Ruohonen & Karhu, 2012; Stagg, Bachtiar, & Johansen-Berg, 2011), perhaps through subthreshold depolarization and oscillatory activity (Atallah & Scanziani, 2009; Das, Holland, Frens, & Donchin, 2016; Duncan, Wibking, & Northoff, 2014). This modulation of GABA and glutamate could be the mechanism through which tDCS synchronizes neural networks and promotes connectivity (Stagg et al., 2014).

In addition, tDCS modulates neurons depending on their morphometry and orientation with respect to the electric field, and an attempt to polarize the axon, whether at the soma, bend, or terminal, would be weaker if the neuron is not facing the electric field. Thus, level IV pyramidal neurons parallel to the field would be most strongly affected, while other neuron subpopulations can be influenced weakly or not at all (Tranchina & Nicholson, 1986). tDCS mainly affects level IV pyramidal neurons oriented parallel to the electric field, and modulation is stronger for these neurons than any other sub-population, particularly for level V pyramidal neurons with larger soma volumes (Bindman et al., 1964). The direction of tDCS effects (depolarization or hyperpolarization) depends on the orientation of the electrical field relative to the orientation of neurons (Nitsche, Polanía, & Kuo, 2015). By modulating membrane potential, tDCS may lead to changes at synapses, junctions between individual neurons in a cortical site. These changes in turn could lead to network-level effects, representing indirect modulations of tDCS on neural activity (Nitsche, Polanía, & Kuo, 2015). A synapse between two neurons (e.g. neuron A to neuron B) starts with an action potential in the pre-synaptic neuron (neuron A), which enables the delivery of a signal to the post-synaptic neuron (neuron B; Kalat, 2016). When oriented toward the cathode, the postsynaptic potential can be suppressed, and when oriented toward the anode, the postsynaptic potential can be facilitated, as shown by studies on hippocampus slices in animals (Bikson et al., 2004; Lian et al., 2003; Pelletier & Cicchetti,

2015). Thus, tDCS can indirectly modulate postsynaptic potentials by modulating membrane thresholds: increasing the membrane potential over time can lead to an "excitatory feedback loop" (Das, Holland, Frens, & Donchin, 2016; Stagg & Nitsche, 2011). However, effects in deeper structures are reversed in polarity because of the dipole sink (negative charges underneath the field). This can lead to hyperpolarization near the surface and depolarization deeper below the surface (Purpura & McMurtry, 1965). These orientation and polarity-specific changes can last for hours, depending on stimulation intensity and duration (Das, Holland, Frens, & Donchin, 2016).

tDCS can also modulate visual-evoked potentials: while 5 min did not have any effect, 15 min of cathodal tDCS led to immediate effects and after-effects 10 min after stimulation ended, decreasing amplitudes of visual-evoked potentials, and anodal tDCS led to after-effects but not immediate effects, increasing amplitudes 10 min after stimulation termination (Antal, Varga, Kincses, Nitsche, & Paulus, 2004).

tDCS modulates neuron activity in the visual cortex: There was a loss in contrast sensitivity after cathodal tDCS was delivered for 7 min but no effect of anodal tDCS (Antal, Nitsche, & Paulus, 2001). Antal and colleagues (2001; 2006) suggested that because the visual stimulus could be easily perceived, there was a ceiling effect that prevented further enhancement of visual perception with atDCS. Antal and colleagues (2004) also found modulations of visual oscillations by tDCS, with increases and decreases in beta and gamma power following anodal and cathodal tDCS, respectively.

While tDCS does not appear to induce phosphenes, the illusory perception of bright light when it is absent, tDCS modulates phosphene threshold: Antal and colleagues (2003b) found that atDCS increased susceptibility for perceiving phosphenes induced by TMS, while cathodal tDCS decreased it, showing that tDCS modulates visual cortex excitability. tDCS also modulated susceptibility for perceiving *moving* phosphenes with the same polarity-specific effects when delivered over the motion perception area (V5;

Antal, Kincses, Nitsche, & Paulus, 2003a). After-effects for stationary and moving phosphene threshold lasted for up to 10 min (Antal, Kincses, Nitsche, & Paulus, 2003a; Antal, Kincses, Nitsche, & Paulus, 2003b).

Antal and colleagues (2004b) also found a modulation of visuomotor discrimination after cathodal tDCS: cathodal tDCS facilitated motion perception in a complex task (low motion coherence, random dot motion) but impaired performance on a simple task (high motion coherence, uniform dot motion). Thus, after cathodal tDCS, participants were better able to discriminate the direction of the motion when coherent motion was presented among randomly-moving dots than among dots that moved uniformly. In contrast, atDCS facilitated performance for high motion coherence but not low motion coherence. In addition, cathodal tDCS enhanced correct tracking movements in the visuomotor task, perhaps because the motion perception demands were more complex, but there was no effect of anodal tDCS. The study suggests that cathodal tDCS may allow for a sharper target signal (neural activity associated with the task; Javadi, Brunec, Walsh, Penny, & Spiers, 2014) by decreasing overall neuron activity in the region and thus decreasing noise. Because of its complexity, the low motion coherence task may have led to activation of efficient as well as inefficient neural patterns, leading to higher levels of neural noise than the low motion coherence task (Antal et al., 2004b; Miniussi, Harris, & Ruzzoli, 2013).

Baudewig, Nitsche, Paulus, and Frahm (2001) found changes in BOLD response immediately and 5 min after cathodal but not anodal tDCS during a motor task, with reduced responses in the supplementary motor area but not the stimulation site in the primary motor cortex. They suggested that cathodal tDCS led to decreases in neural activity in related cortical networks and associated responses rather than the stimulated network and primary neural input.

Hoy and colleagues (2013) proposed that there was no effect of 2 mA compared to 1 mA on working memory task because homeostatic mechanisms were triggered by constant excessive input and prevented further neuron depolarisation. Bonaiuto and Bestmann (2015) proposed that polarity-specific tDCS effects vary with intensity because of differences in baseline neuron activity: at low intensity, cathodal stimulation could reduce noise and bias due to baseline activity, but at high intensity (>1 mA), cathodal stimulation could be excessive and inhibit neuron activity to the extent that neurons cannot respond to input and fire. Thus, accuracy on a cognitive task would increase at low intensities of cathodal tDCS and decrease at high intensities. Similarly, as anodal tDCS intensity increased, accuracy decreased because of increased neural noise. The results of Bonaiuto and Bestmann also highlight an important point: increasing neuron activation due to tDCS, as measured by fMRI activity, may not always be beneficial (Bonaiuto & Bestmann, 2015).

Merton, Morton, Hill, and Marsden (1982) were among the first to test evoking a muscle reflex using bearable methods: a single pulse of high voltage current through transcranial electrical stimulation. This was in contrast to previous, more painful methods that elicited multiple electrical bursts and contractions on scalp muscles, as in the case of Gualtierotti and Patterson (1954). However, then magnetic rather than electrical means were introduced by Barker, Jalinous, and Freeston (1985), and stimulating the motor cortex evoked a motor potential that led to a muscle reflex. When developed, transcranial magnetic stimulation became the optimal solution for stimulating the cortex and evoking muscle responses.

While tDCS and TMS are both methods of safely, non-invasively stimulating the brain and inducing an electric field that modulates neuron activity, there are key differences between the methods and associated research.

First, TMS is a well-established technique that has led to important discoveries including an increased understanding of function-region associations and basic mechanisms of cognitive function. On the other hand, tDCS is a relatively new tool for addressing research questions in cognitive neuroscience, and the mechanisms of action are still being uncovered. Both methods have been thoroughly studied through the motor cortex, yet even the physiological effects of tDCS on MEPs and cerebral blood flow remain more complex and inconsistent than the effects of TMS. tDCS seems to affect deeper neurons such as those in subcortical structures and possibly corticospinal neurons, whereas most TMS methods affect only cortical neurons (Classen et al., 1998). In addition, tDCS affects neurons of a different orientation than TMS. Thus, the two methods could have different cellular mechanisms and in turn, different cognitive effects.

For example, TMS was used to induce involuntary movements of the thumb that were consistent in direction, and Classen and colleagues (1998) trained participants for 15-30 min to move the thumb in the opposite direction. When delivering TMS over the motor cortex again, they found that the thumb moved in the trained direction for the first 5 min before returning to the same direction as baseline. They showed that training could induce plasticity in the motor cortex that was affected by TMS, and they found weaker effects after stimulating the motor cortex with tDCS to induce involuntary movements, with smaller and non-significant changes toward the trained direction after training. In participants who had undergone TMS and tDCS, there was a training-induced change in direction after TMS but not tDCS. They argued that tDCS differed from TMS in that it activated more neurons at the axon rather than at the bend, where excitability was less dependent on additional input. In addition, although tDCS was thought to lead to stronger direct activation of corticospinal neurons, plasticity could be cortical rather than subcortical (the training-induced plasticity could be unaffected because of cortical mediation). Moreover, Rosenkranz, Nitsche, Tergau, and Paulus (2000) delivered atDCS

or cathodal tDCS to the motor cortex during the last 5 min of training the thumb to move in the opposite direction as a TMS-induced twitch. They found that both polarities led to a reduced post-training directional change, suggesting that tDCS interfered with motor learning and plasticity mechanisms. They suggested that by exciting the motor cortex, atDCS led to stronger activation of the dominant response, while cathodal tDCS led to reduced learning for the new movement, thus strengthening the dominant, competing response.

Nonetheless, both methods seem to induce noise in the neural system, although during a task, TMS can induce more random noise by activating neurons that are not involved in the task, while tDCS would likely lead to firing of the neurons involved in the task because they are already active and close to threshold. TMS has high temporal and spatial resolution that is comparable to fMRI and EEG, but TMS can provide causal rather than correlational evidence. tDCS can also provide causal evidence, but its temporal and spatial resolution are much lower compared to TMS (Nitsche, Polanía, & Ruff, 2015).

In tDCS, the current flows between the two electrodes, whereas in TMS, the current flows in loops around the coil, with stronger current near the centre of the coil and weaker current at the circumference for a figure-of-eight coil (Rossi et al., 2009). In TMS, an electric charge generates a magnetic field that in turn, generates an electric field in the cortex, causing ions to flow without the need for an active current or penetration of the skull with ions (Rossi et al., 2009). On the other hand, tDCS releases an electric charge to create the electric field, injecting ions through the skull with a strong current due to the low conductivity of bone (Rossi et al., 2009). In this way, the charge can reach the neurons and stimulate them. Thus, tDCS has higher current density than TMS, and this current density can cause transient pain and affect the skull (Rossi et al., 2009).

On the other hand, there is no evidence that tDCS can increase seizure threshold, unlike TMS. While single pulse TMS is relatively safe, repetitive TMS can induce seizures

because it causes neurons to fire repetitively and continuously over a short period of time (Hallett, 2000). TMS can also induce muscle twitches, headaches, nausea, and auditory sensitivity (Hallett, 2000; see Safety considerations).

Safety Considerations

TMS and tDCS are considered relatively safe for patients as well as healthy individuals, although the risk increases under certain conditions, and risks are greater for delivering TMS under those conditions (Antal et al., 2017; Rossi et al., 2009). There is no established risk for delivering safe levels of TMS to healthy individuals without pre-existing conditions or contraindications. The main risk for individuals with implants, trauma, or an altered physiological or neurological state is that long-term and adverse effects are unknown (Rossi et al., 2009). There are contraindications against implanted metal or devices, including cochlear implants and brain electrodes. Although TMS may remain safe for the patient according to mechanical models (Golestanirad et al., 2012), it could disrupt proper functioning of the device (Rossi et al., 2009). In addition, there are risks of inducing seizures for individuals with lesions; current alcohol dependence; a current state of sleep deprivation; or a history of epilepsy (Rossi et al., 2009). Sleep deprivation and alcoholism can modify the state of the neural network, leading to a below-average baseline activation and increasing risk (Rossi et al., 2009). Consequently, certain prescribed medications or psychiatric drugs or can lower seizure threshold, such as anti-depressants (Rossi et al., 2009). In addition, taking or withdrawing from psychoactive drugs or substances (e.g. cocaine) would increase a risk for seizures following TMS (Rossi et al., 2009). Thus, TMS poses a risk for individuals taking these medications (Rossi et al., 2009). Other contraindications include pregnancy and heart disease (Rossi et al., 2009). Although no adverse effects were reported for TMS delivered during pregnancy (Klirova et al., 2008), the strength of the magnetic field could directly affect the foetus (Rossi et al.,

2009). Heart disease could be a risk because TMS can temporarily increase heart rate and blood pressure (Foerster, Schmitz, Nouri, & Claus, 1997).

There are only a few possible side effects of single-pulse TMS and low-frequency rTMS, including transient pain in the head (headache, tooth pain) and hearing changes (Rossi et al., 2009). Less is known about other forms of TMS such as paired-pulse TMS and theta-burst stimulation (Rossi et al., 2009). Temporary aches can also occur following high-frequency rTMS. While seizures are rare in single-pulse and low-frequency TMS, high-frequency rTMS can induce seizures in epileptic patients and other acute side effects in all individuals such as a temporary acute state of hyperactivity and temporary hormonal changes (Rossi et al., 2009). However, hormonal changes usually involved increases in cortisol or other stress-related hormones, and a study with multiple sessions of prefrontal rTMS reported no hormonal changes (Rossi et al., 2009). Pain is reported to be transient, and in multiple-session prefrontal TMS, pain declined with each daily session (Anderson et al., 2009). Mania was a greater risk for individuals with major depression and bipolar depression following left prefrontal stimulation (Xia et al., 2008), so healthy individuals are not likely to experience hypomania following TMS (Rossi et al., 2009).

tDCS should not be performed for individuals with skull or brain implants, since the possible interactions of implants and tDCS are still largely unknown (Antal et al., 2017). When tested with implanted electrodes from deep brain stimulation, tDCS did not damage the device and was established as safe (Bikson et al., 2016; Kühn & Heubl, 2011). However, the greater risk may arise from working with patients in an uncontrolled environment without a supervisory clinician (Antal et al., 2017). While there is no known risk for delivering stimulation to pregnant women (Shenoy et al., 2015; Sreeraj et al., 2016; Vigod et al., 2014), the risk to benefit ratio indicates that tDCS should not be conducted in pregnant women in usual neuroenhancement studies although previous studies (Antal et al., 2017). Although tDCS appears safe with pharmacological drugs,

certain drugs such as anticonvulsants can interfere with tDCS effects (Antal et al., 2017) by decreasing baseline neuron excitability. As with TMS, the state of the individual should be assessed, and individuals with intoxication or sleep-deprivation should not undergo stimulation (Antal et al., 2017). For example, tDCS can increase neural excitability after sleep deprivation, increasing risk of adverse effects (Antal et al., 2017). As with TMS, there may be a risk of mania in individuals with depression due to increased cortical excitability, so depression and other psychiatric disorders should be screened and assessed for risk (Antal et al., 2017).

Nonetheless, no severe adverse effects for tDCS have been identified, only mild dermatological symptoms and sensations (Antal et al., 2017). tDCS can induce tingling, burning, and itching at stimulation and transient aches post-stimulation (Antal et al., 2017). Thus, pre-existing skin conditions should be identified prior to the stimulation session to avoid adverse reactions (Antal et al., 2017). Any abnormal, inflamed, or irritated tissue should be avoided (Antal et al., 2017). Moreover, the electrodes should not be placed directly on regions involved in cardiovascular or regulatory functions (see introduction to tDCS: Transcranial Direct-Current Stimulation section). Nitsche and colleages (2003) also noted that serum neuron specific enolase concentrations did not change after measurement in blood samples, providing support for the safety of tDCS. Neuron specific enolase concentrations can be increased in patients with acute seizures (generalised convulsive status epilepticus) and reflects damage to neurons, so it can serve as a biomarker for neuron injury (Oh, Lee, Na, Park, Choi, & Kim, 2003).

Designing Experiments with NIBS

Because so little is known about the mechanisms and magnitude of tDCS effects over time, there is no standardisation of implementing tDCS in research or clinical settings. Safety guidelines have specified that the maximum tDCS intensity is 4 mA over an hour per day (Antal et al., 2017), which still leaves a range of possible durations and

intensities. Furthermore, tDCS parameters can vary systematically depending on the targeted stimulation site and associated cognitive function. For example, the prefrontal cortex and higher-order cognitive functions may require longer durations of tDCS (Fregni et al., 2005; Fregni, Liguori, Fecteau, Nitsche, Pascual-Leone, & Boggio, 2008a; Guo, Zhang, Da, Sheng, & Zhang, 2018; Price & Hamilton, 2015).

There are several important factors in tDCS research: stimulation site, time of administration, individual differences, and assessment. Researchers may determine the exact region for based on previous evidence from neuroimaging, neuropsychology (patient lesions), and TMS (Fregni et al., 2005; 2008a; 208b). There may also not be a clear mapping of physiological tDCS effects to cognitive effects. For example, stimulating the motor cortex and visual cortex appears to yield distinct effects from stimulating regions involved in higher-order cognitive functions. While stimulating the visual cortex led to changes in visual-evoked potentials, the effects on specific components were less clear, with cathodal tDCS increasing amplitudes of the P70 but no effect of atDCS.

Montage is another important parameter that is not standardised, and researchers use different montages for studying the same cognitive function. Nasseri, Nitsche, and Ekhtiari (2015) proposed the categorisation of electrode placement into several different montages, including unilateral and monopolar, in which one hemisphere is targeted. The target electrode is placed on a cortical region, and the return electrode is placed on an extracephalic site. The location of the stimulation site is commonly a coordinate on the 10-20 International EEG system (Jasper, 1958), an estimated coordinate system for cortical regions originally designed for the EEG cap (see Figure 2.0.1 for common stimulation sites using the system and Figures 2.02-2.04 for the montages used in this thesis). The cortical regions (parietal, temporal, frontal, and occipital) are determined for each individual based on head size: the circumference and distance from the anterior to posterior parts of the head are measured based on skull landmarks (nasion and inion bones), and 10% or 20% of

these measurements are used to estimate the location of a region from a certain landmark (commonly the centre of the head; see Klem, Lüders, & Jasper, 1999 for more information). Then the target electrode is placed on the cortical region. For example, the left VLPFC could be estimated by taking 10% of the distance between the nasion and the inion (e.g. 30 cm) and then 15% of the circumference (e.g. 40 cm): the first measurement (3 cm) would be used to find the distance from the nasion to the centre of the forehead (3 cm above the nasion), and from the centre of the forehead, the second distance (6 cm) would be measured across the left side of the forehead to reach the estimated coordinate for the left VLPFC (6 cm left of the centre of the forehead). Nasseri, Nitsche, and Ekhtiari (2015) suggested that monopolar montage only occurs when the references/return electrode is placed extracephalically, away from the scalp, because there can be an effect on brain function even over sites thought to be neutral (e.g. orbitofrontal cortices, Willis, Murphy, Ridley, & Vercammen, 2015). In bilateral bipolar montage, two regions are targeted with the aim of inhibiting one and exciting the other. In bipolar balanced, both electrodes are placed on the same region but in opposite hemispheres. In bipolar nonbalanced, the electrodes are placed over two different regions. The rationale for bipolar nonbalanced may be to facilitate cognitive function in one region by inhibiting a similar function in a competing region (e.g. Jacobson, Goren, Lavidor, & Levy, 2012). By using different montages, researchers can investigate functional lateralization (hemispheric differences) and region-specific processes that do not depend on the opposite hemisphere. However, while using a unilateral montage allows for the isolating of a specific region and attributing a function to it, using a bilateral montage can leave questions about whether the effect was caused by inhibition of the contralateral region or facilitation of the excitatory region, or a combination of both (e.g. Boggio et al., 2009; Mordillo-Mateos et al., 2012). Thus, studies with the same design but different montages cannot be uniformly compared (Klaus & Schutter, 2018; Sehm, Kipping, Schäfer, Villringer, & Ragert, 2013). Few

studies have compared the effects of bipolar vs unipolar montage, but a recent study (Zich et al., 2017) suggests that bipolar montage may be ineffectual or even detrimental when the opposite hemisphere is also functionally relevant to the task. Thus, it is important to select a well-reasoned montage that can then be linked to a specific function.

Figure 2.0.1. Position of VLPFC (F7) and DLPFC (F3) with respect to other sites in the 10-20 EEG system.

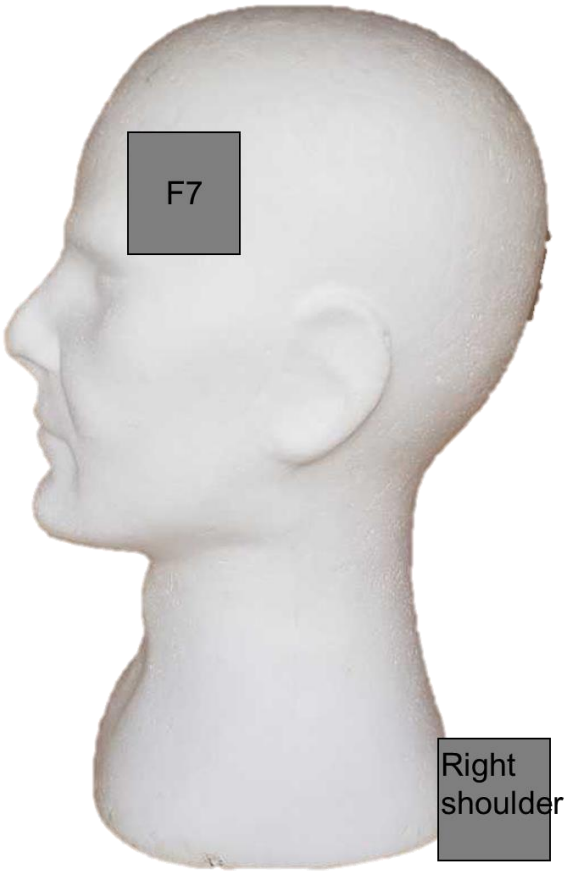

Figure 2.0.2. Montage for Chapter 5: Experiments 1 and 2.

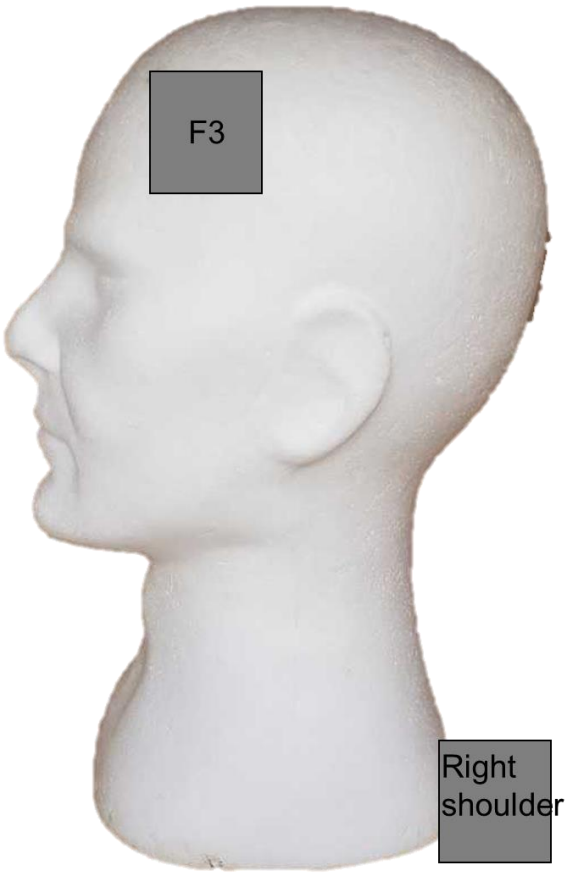

Figure 2.0.3. Montage for Chapter 5: Experiment 3 DLPFC.

Note: The montage applies for Online Encoding DLPFC, Offline Encoding DLPFC, and Sham. Montage for the VLPFC group was identical to Experiments 4 and 5.

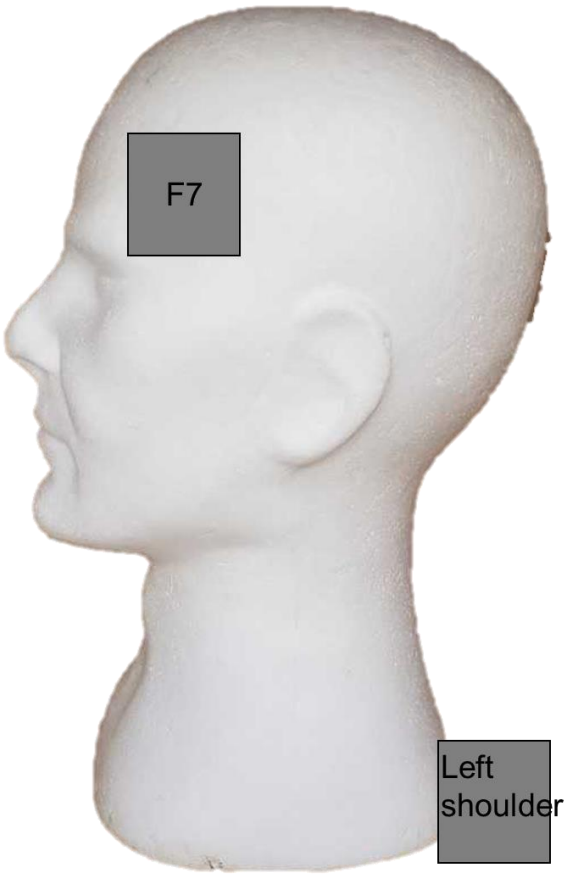

Figure 2.0.4. Montage for Chapter 5: Experiments 4 and 5.

Note: the main distinction in montage between Experiments 1-2 and 4-5 is the placement of the reference electrode on the right vs left shoulder, respectively.

In addition, studies have varied in the size of electrodes used and current strength (usually ranges from 0.5 to 2 mA), which affects current density and the strength of tDCS effects. The electrodes can be different sizes, usually ranging from 12.25 to 35 cm^2, and increasing the size of the return electrode relative to the active electrode can reduce the current density (= current strength/electrode area) and functional effect (Nitsche, Polanía, & Kuo, 2015). Nitsche and colleagues (2015) argued that the current strength must be increased for larger electrodes (e.g. 7 x 5 cm) compared to smaller electrodes (i.e. 3.5 x 3.5 cm) so that the effect of the stimulation remains consistent. Thus, the effects of delivering stimulation through smaller electrodes at 2 mA cannot be compared to stimulation in larger electrodes at the same current strength. In turn, the effects of tDCS cannot be accurately compared across studies without the same current density, and it is necessary to establish a

fixed current density for future work, a concern that has been highlighted in previous research (Das, Holland, Frens, & Donchin, 2016).

tDCS can be administered concurrently with a task (online) or independently (offline), and effects can vary depending on online or offline administration. While atDCS appears to increase excitability and facilitate physiological effects over the motor cortex, it may not always facilitate performance when delivered concurrently with a motor task. Instead, offline tDCS before the motor task may facilitate subsequent performance. Online tDCS may exert a different effect compared to offline effects because the magnitude of the effect may be dependent on the baseline state of the targeted neuron population (Miniussi, Harris, & Ruzzoli, 2013). A baseline activation that is at an optimal level may lead to optimal tDCS-induced enhancement or impairment, whereas a baseline activation that is too high or too low may prevent further tDCS-induced activation or inhibition, respectively (Miniussi, Harris, & Ruzzoli, 2013).

Moreover, there is a distinction between effects during the stimulation, immediately after (immediate effects), and for a period of time after (after-effects). Antal and colleagues found that performance on a visual perception task improved at all three intervals, suggesting that tDCS leads to effects early after administration and these effects can be long-lasting, outlasting the period of stimulation. tDCS research commonly cites the finding of a minimum of 5-minute tDCS duration for after-effects (Nitsche & Paulus, 2000). However, longer durations, such as ten or twenty min, can increase tDCS after-effects, although not in a linear way (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Bonaiuto & Bestmann, 2015). In addition, it is vital to consider after-effects when implementing duration and time of administration so that the stimulation site can be attributed to a specific memory process (i.e. encoding, retrieval). Thus, combining online and offline tDCS durations (e.g. Manenti, Cotelli, Robertson, & Miniussi, 2012), a

decision that occurs frequently in tDCS research, could obscure effects of time of administration.

In addition, the delay between stimulation termination and test is a crucial factor for any tDCS study because of after-effects. If there is a delay of less than an hour (i.e. Medvedeva et al., 2018; Experiment 3), there is no certainty that the stimulation has affected encoding but not retrieval. Thus, the conclusion can be made that if the behavioural modulation of tDCS outlasts after-effects, the effect is strong and tDCS shows promise for inducing long-term, stable changes. Studies can ensure that after-effects are not driving behavioural modulations by using biomarkers such as MEP amplitude measurements or BOLD activation (Baudewig, Nitsche, Paulus, & Frahm, 2001; Antal, Polanía, Schmidt-Samoa, Dechent, & Paulus, 2011). Previous studies have established the appropriate intervals for assessment, after which tDCS no longer has an after effect. For example, Nitsche and Walsh (2000) found that for short durations, after-effects last only several min. Thus, a cognitive assessment could be conducted after a five-minute delay. In addition, studies can assess cognitive performance after tDCS at more than one interval (e.g. immediately and at a delay) to measure the robustness of tDCS effects on cognition (Di Lazzaro et al., 2014; Ljubisavljevic, Maxood, Bjekic, Oommen, & Nagelkerke, 2016; Sandrini et al., 2014).

Assessments of tDCS effects. Individual differences and assessment test are among the factors that are important to consider when assessing tDCS effects on cognition. Studies in humans and animals (Bennabi et al., 2014; Berryhill, Peterson, Jones, & Stephens, 2014) have revealed that individual differences and experimenter effects can heavily bias or obscure tDCS modulations by adding unsystematic variation and noise, and large, homogeneous samples are needed to counteract these limitations. In the presence of low power and weak effect sizes, differences in age, education, and baseline cognitive function may be clouding significant findings with noise. Thus, sampling from a

population that is similar in age, handedness (right handed), education level, and cognitive abilities could help to reduce relevant individual differences and help true tDCS effects to emerge (Berryhill, Peterson, Jones, & Stephens, 2014).

tDCS does not have effects when performance is at floor or ceiling, which occurs when participants are under- or over-motivated or when the task is too easy or difficult (Bonaiuto & Bestmann, 2015; Berryhill, Peterson, Jones, & Stephens, 2014). Thus, tDCS is sensitive to response variability and participant motivation. For example, tasks may become more challenging with age, so tDCS effects may be more visible in older populations (Berryhill, Peterson, Jones, & Stephens, 2014). However, analyses could distinguish easy from difficult trials, through baseline accuracy and response time (faster and more accurate trials could be considered easier) and focus on a subset of trials.

Researchers have begun to implement suggestions to control for individual cognitive differences by recruiting homogeneous populations that are similar in age and cognitive performance. Researchers have measured baseline performance on tasks of working memory and attention to control for individual differences in cognition, since performance correlates between multiple cognitive tests, including language tasks, and working memory capacity differences could explain differences in performance on other tasks (London & Slagter, 2015; Westwood & Romani, 2018). Berryhill and colleagues (2015) urged identifying other important individual differences that could influence the specific cognitive function being examined, such as education (Berryhill & Jones, 2012).

The ideal design for tDCS is a randomized-control trial, in which a control group receives placebo intervention (resembles stimulation but has no effect) and the experimental group receives the intervention (real, active stimulation). Control conditions vary between studies. The control condition can be no stimulation/stimulator turned off (e.g. Marshall et al., 2004); tDCS over another stimulation site (Boggio et al., 2008; Medvedeva et al., 2018; Experiment 3; Woods et al., 2016); tDCS for a shorter duration

(e.g. 30 s; Zwissler et al., 2014; Gandiga, Hummel, & Cohen, 2006); tDCS at the beginning and end of a task (e.g. 30 s at the start and 30 s at the end; Ambrus, Al-Moyed, Chaieb, Sarp, Antal, & Paulus, 2012; Sandrini, Manenti, Brambilla, Cobelli, Cohen, & Cotelli, 2016); or constant tDCS over a low current (e.g. 0.1 mA; Gaynor & Chua, 2016; Miranda, Faria, & Hallett, 2009). The best control condition may be a short duration of tDCS over the same stimulation site, because even a low current can produce some cortical modulation (Nitsche et al., 2000), and tDCS over a different stimulation site can have some non-specific modulation of cognition (Lu, Wang, Chen, & Xue, 2015; Nitsche, Polanía, & Kuo, 2015).

Blinding is an important consideration for minimising bias, particularly when testing the efficacy of an intervention. However, while commonly reported in clinical trials, blinding success is rarely reported in cognitive studies. A questionnaire to measure participants' awareness of the condition is essential to measure the integrity of the blinding (Antal et al., 2017). Although double-blinding is ideal because of possible experimenter bias, most studies use a single-blind design to avoid participant bias (Bennabi et al., 2014; Lally et al., 2013). In single blind studies, the experimenter but not the participant is aware of the experimental conditions. Thus, the experimenter administers the tDCS will full awareness of the setting being sham or active tDCS. In double-blind studies, both the experimenter and the participant are unaware of the experimental conditions and are unable to guess the condition based on cues or sensations. Double blinding can be achieved by obscuring the settings on the stimulator (through "Study Mode" on the Neuroconn stimulator) and assigning arbitrary codes (e.g. 1 or 2) for each condition (Zwissler et a., 2014; Teo et al., 2011; Lally et al., 2013). Then, the experimenter selects that condition (1 or 2) on the machine.

However, studies can vary in experimental design, including a between-subjects, parallel design, or a within-subjects, crossover design. Like other within-subjects designs,

crossover studies are advantageous because they minimise individual differences. Nonetheless, researchers can control for individual differences in parallel designs by recruiting from a homogeneous population and measuring related cognitive functions , as stated previously. An important consideration with crossover designs is minimising carry-over effects between the tDCS and sham group. Thus, researchers with crossover designs have taken care to space the sessions at least 24 h apart (Heimrath et al., 2012; Nitsche et al., 2008) and counterbalance (e.g. Fregni et al., 2008b; Lafontaine, Théoret, Gosselin, & Lippé, 2013). If the within-subjects conditions are not counterbalanced or appropriately spaced, differences in conditions could not be clearly attributed to tDCS effects. Another consideration is that participants who undergo both Sham and tDCS stimulation within a short period could identify their conditions because they would be able to compare sensations and note that sensations are stronger in the tDCS condition (Woods et al., 2016). However, a blinding success questionnaire at the end of the experiment can assess whether participants in the crossover design were able to identify the experimental condition.

Parameters of TMS.

Coils. The position and shape of the coil affects the electrical field produced in the brain. The current size depends on the size of the coil, and a diameter of 8 cm stimulates 2-4 square centimetres. This would be ideal for stimulating superficial (e.g. cortex) areas but not deeper structures.

Whereas the newly-developed H-coil safely reaches a depth of 4-6 cm and enables the stimulation of deeper structures, figure-of-eight and round coils are considered superficial since they only reach 1-3 cm within the cortex (Nevler & Ash, 2015). A round coil has strongest current strength in the peripheral edges, whereas the centre contains no activity at all. On the other hand, a coil that forms a figure-of-eight (two adjacent circular coils) creates a rapidly changing magnetic field at right angles to the coil, with the

strongest current at the intersection of the circles (centre of the coil; Hallett, 2007; Hamada & Rothwell, 2015). Thus, coils can be adapted depending on the desired effects on the cortex.

Baseline excitability. In addition, the intensity of the coil needs to be adjusted based on baseline cortical excitability. Researchers can determine an individual's cortical excitability by using the active motor threshold, which is the minimum stimulation intensity required to elicit an MEP (Klomjai, Katz, & Lackmy-Vallée, 2015). It is not possible to measure resting motor threshold, or the level of resting excitability.

Advantages and limitations of tDCS and TMS. An advantage of tDCS and TMS for research is that they provide evidence for causal relationships between functions and brain regions, whereas fMRI and EEG data only demonstrate correlational relationships. Specifically, they can specify the contribution of activity in a region to a specific function, and TMS can be more precise in helping to specify the location and time window of this activity. NIBS also serves as a biomarker for synaptic and network-level changes (Bartrés-Faz, Rossi, & Pascual-Leone, 2016): the baseline state of neural activation can be estimated, and functional connectivity between regions can be examined. In addition, changes in cortical excitability and synaptic plasticity can be examined at multiple levels: neural, anatomical, and behavioural.

Chapter 3: Foundations of Episodic Memory

Overview

Episodic memory can best be understood as a concept in the context of established models including the levels of processing framework (Craik & Lockhart, 1972) and the working memory model (Baddeley & Patterson, 1971). The current chapter will introduce the concept of episodic memory and associated processes, in the real world and in the laboratory, using neural models and cognitive theories. First, the importance of episodic memory in the prefrontal cortex will be discussed in the context of cognitive research and clinical relevance. Next, episodic memory will be defined as a concept that can be distinguished from other forms of memory, and the processes of memory formation and recollection will be described in terms of current cognitive models. In the context of these models, the standard methods of examining episodic memory in research will be discussed, followed by a critical view of the validity of these methods in representing real-world memory phenomena. Finally, a new target of memory research and treatment, the prefrontal cortex, will be discussed in detail in terms of its functional and clinical significance. Overall, the chapter will introduce the cognitive and neurological foundations of memory that are necessary for understanding the development of a promising new research and clinical tool: NIBS, which was introduced in the previous chapter.

The Definition of Episodic Memory

Episodic memory involves unique events that can be distinguished based on spatio-temporal context, and these different aspects (space, time, occurrences; ‘where’, ‘when’, ‘what’) are associated and bound together in a single memory trace (Rugg, Johnson, & Uncapher, 2015). Episodic memory is a form of declarative, long-term memory for personally-relevant and experienced events. In addition to the event or episode, it includes spatial and temporal context and autonoetic (‘self-knowing’) consciousness, in which person places the self in the memory and may re-experience the event (Tulving, 1984).

Episodic memory is unique in that using autonoetic consciousness, an individual can re-create a past event and imagine future events in a realistic way, resembling "mental time travel" (Tulving, 2002a; Tulving, 2002b).

Distinction between declarative and non-declarative memory. Declarative memory refers to memory that can be consciously stored and retrieved, such as verbal material that can be 'declared' or pictorial material that may be voluntarily recollected (Hasselmo, 2011). In addition to personal, episodic information, declarative memory includes general, factual knowledge (semantic memory) and non-verbal but conscious spatial and visual memory (Paller, 2009). On the other hand, non-declarative memory consists of unconscious, implicit memory processes: procedural memory, including motor skills; priming, involving implicit learning for patterns; and classical conditioning, involving the creation of associations between a physiological reflex and a stimulus without conscious awareness (Ullman, 2015). Although episodic memories can form without conscious awareness (incidental learning), recollection usually occurs consciously (Droege, 2013; Tulving, 1984), in contrast to non-declarative memory in which memorisation and recollection occur unconsciously. Thus, consciousness is an important part of episodic memory.

Episodic memory is distinct from other kinds of declarative memory, such as semantic memory, in that it includes autonoetic consciousness and memory traces grounded in a specific context. While semantic memory also involves long-term memory and a sense of knowing, Tulving (1972; 2005) argues that only episodic memory includes a sense of autonoetic consciousness. In addition, knowledge can become decontextualized in semantic memory. With repeated exposure in different contexts, knowledge becomes independent of context because the source becomes less important as long as the knowledge is reliable. In a semantic memory test, memory judgements can be completed

through familiarity alone, without accessing contextual or recollective detail (Rugg, Johnson, & Uncapher, 2015).

Unlike autobiographical memories, episodic memories are distinct from concepts of the self, decontextualized knowledge about a person's life and identity, and representations of the self in the past (Conway & Williams, 2008).

Distinctions between short-term and long-term memory. Episodic memory is distinct from short-term declarative memory, such as visual working memory, in that memories are long-lasting and durable, whereas short-term memories can only retain short spans of information (e.g. the start of a sentence) and are forgotten within minutes and even seconds (Baddeley, 2001). In contrast to long-term memories, short-term memories are vulnerable to distraction and time (Murdock, 1962; Bjork & Whitten, 1974; Baddeley, Thomson, & Buchanan, 1975). In addition, studies with patients show selective impairment for long-term memory but not short-term memory (Glanzer & Cunitz, 1966; Graf et al., 1984; Penfield & Milner, 1958; Corkin, 1984), suggesting distinct cognitive systems for each form of memory. The distinction between long-term and short-term memory is important in the context of studying episodic memory: tasks with short retention intervals or spans of information cannot be considered to study long-term episodic memory (Hasselmo, 2011). This issue is elaborated further in **Tasks.**

Overview of Episodic Memory Processes in the PFC: Cognitive, Anatomical, and Neurobiological Level

At the basic cognitive level, memory processes include encoding, storage, consolidation, and retrieval. Encoding is the process of processing and storing incoming information in memory, after which it can be retrieved at a later stage. Encoding can occur through sensory processing, like perceiving, and semantic processing, like reading and listening. This online processing leads to forming a lasting, accurate memory and may be just as important for the resilience of a memory as the consolidation processes that follow

(Rugg, Johnson, & Uncapher, 2015). Because the memory trace can be manipulated through re-accessing and reconstructing the event (adding or changing details), consolidation stabilizes the memory so that it is longer-lasting and no longer as vulnerable to manipulation and decay. Although consolidation begins soon after encoding, retrieval can occur multiple times as the memory is consolidated over hours and even years. Retrieval is the process of accessing the stored memory trace, and during this process the memory is reconstructed through a neural reinstatement of the same sensory information that was present at encoding (Hayes, Nadel, & Ryan, 2007; Johnson, McDuff, Rugg, & Norman, 2009). The iterative process of memory formation supports the idea of grounded cognition (Barsalou, 2008): the brain does not merely process information in terms of a static knowledge and representational system. Instead, the sensory areas capture new representations from the environment and integrate them with the existing knowledge system as a form of updating. The integration of new and existing knowledge demonstrates how learning occurs with experience, and when the updated knowledge is needed for perception, the brain may reactivate these new representations (Shastri, 2002).

Episodic memory does not activate a unique network of regions, since there is some overlap with autobiographical and semantic memory. The prefrontal cortex, particularly the dorsolateral region, has been attributed to autonoetic consciousness and self-awareness during retrieval (Wheeler, Stuss, & Tulving, 1997). In addition, multiple regions of the medial temporal lobes, including the hippocampus, map onto information for the event and associated spatial and temporal details (Hasselmo, 2011). However, the same regions enable re-experiencing an event and recollecting contextual details, an act of memory that is uniquely episodic. Specifically, the hippocampus and the prefrontal cortex interact at recollection to re-instate the same neural representations of sensory information as at encoding (Gordon, Rissman, Kiani, & Wagner, 2013; Preston & Eichenbaum, 2013).

The neurobiological correlates of encoding and retrieval reveal that the memory trace is stored in distributed networks, not only the prefrontal cortex and medial temporal lobes. In fact, Lashley (1950) discovered the presence of a distributed network when he pioneered searching for the neural representation of a memory trace, called the engram. In studies with animals, he searched for a physical part of the brain, such as the cerebral cortex, that could hold memories. In some cases, removing parts of the cerebral cortex had no effect on learning, while in other cases, any removal of cortical tissue led to impairments in learning. Lashley concluded that the engram was not present in any specific part of the brain after the removal of cortical tissue in rats led to memory impairment, regardless of the specific lesion site. Nonetheless, episodic memory relies on anatomical connections between the cerebral cortex, perirhinal and entorhinal cortex, and hippocampus. The prefrontal cortex and medial temporal lobes integrate and retrieve sensory representations from other regions, and consolidation of long-term memories relies on these two regions. A key limitation of Lashley's work was an absence of attention to the synaptic level, which was initially discovered by Hebb (1949). Hebb demonstrated the importance of synaptic interactions to learning, leading to a connection between anatomical and synaptic processes underlying memory formation.

Synaptic interactions lead to associations between stimuli with close proximity in time and space, for example, the distinct sensory features that form a distinct episodic experience (Mayford, Siegelbaum, & Kandel, 2012). The associations formed through synaptic connections underpin classical conditioning, encoding for emotional events, and binding in episodic memory: associations are forged between various discrete sensory features to form a single trace, starting from a synaptic level to the systems-level in the hippocampus (Eichenbaum, 2016). For example, in rats in a new environment undergo repeated firing of hippocampal cells coding for each location so that a map of the environment forms (Moser, Rowland, & Moser, 2008). The stabilization of this map

depends on modifications in synaptic strength that can be disrupted by certain drugs (Rezvani, 2006). In emotional memory, an increase in emotional valence activates the amygdala and leads to increased firing and long-term potentiation (Bocchio, Nabavi, & Capogna, 2017). Thus, fear can be conditioned and then extinguished by modulating synaptic plasticity with drugs and genetic modifications (Davis, 2011; Nabavi et al., 2014).

Prior to encoding (perception), information is gathered through the senses and then encoded in different ways: visually, acoustically, or semantically. Various parts of the brain, particularly posterior sensory cortices, are associated with collecting the input, and these areas can be unimodal (modality-specific, i.e. visual) or polymodal (integrating sensory information from multiple modalities, i.e. audiovisual). During this process, the prefrontal cortex can exert top-down control over sensory input through attentional mechanisms (Fuster, 2001; Helfrich, Huang, Wilson, & Knight, 2017; Pessoa, 2010). In turn, only selected information is processed at the level of its identity (i.e. semantic meaning). Then the hippocampus binds these sensory experiences (O'Reilly & Rudy, 2001). Memory consists of associations from various cortical areas, so a cortical synapse network records these associations so that the sequence can be replayed during recollection (Hasselmo, 2011). At retrieval, the stored memory trace is re-activated by an environmental or internal cue (e.g. familiar face) and the encoding sequence of sensory representations is reinstated at a neural and cognitive level (Rugg, Johnson, Park & Uncapher, 2008). Consolidation of this neural sequence occurs over days and years, ensuring that the integrated memory trace is durable and resilient to interference (Abel & Lattal, 2001; Frankland & Bontempi, 2005).

Attentional and perceptual processes leading to memory. Memory consists of features (parts of an event: location, time, context) that are processed by neurons in different regions, (O'Reilly, 2010) and then bound together in a single trace, and the engram is in the synaptic connections between those neurons. The pattern of activation in

distributed networks reflects the sensory inputs from visual, auditory, tactile, and motor modalities (Bauer, Magg, & Wermter, 2015).

Specialised neurons from primary sensory cortices, such as photoreceptors in the primary visual cortex, detect environmental input, such as light, and these inputs are processed in sensory association areas in the posterior parietal and anterior prefrontal cortices and integrated into sensory experiences such as images and sounds (Eysenck, 2015). The prefrontal cortex exerts top-down control over allocation of attentional resources to different parts of the environment depending on goals and tasks, and some stimuli receive more attention than others (Eysenck, 2015). In turn, the stimuli that are attended to are processed at the level of their identity and semantic features, whereas the irrelevant stimuli are only processed at the level of superficial features such as colour, shape, and pitch. The DLPFC receives visuospatial and motor input from the posterior parietal cortex, and the VLPFC receives visual and semantic information from ventral posterior and temporal sensory regions, which enables processing the stimulus at the level of its identity (Miller, 2000; Blumenfeld & Ranganath, 2017).

These processes are relevant to memory because the prefrontal cortex maintains goal-related representations and is sensitive to context to achieve the goal, in turn sensitizing the primary and association areas to some information but not others (Pace-Schott, 2011). In this way, the prefrontal cortex regulates posterior sensory association cortices. Specifically, the DLPFC is associated with sensory information through attention networks with the parietal cortex. Like the VLPFC, it may be associated with emotional processing (Ochsner & Gross, 2005), affecting emotional reactivity by modulating perceptual attentional systems and selectively responding to sensory input (Sturm et al., 2016). Thus, emotional memories may be stronger. For example, Penolazzi and colleagues (2010) found that stimulating the left DLPFC with atDCS led to improved recall for

unpleasant images, whereas stimulating the right DLPFC led to an improved recall pleasant images.

At this stage, information enters a temporary sensory store, from which it can decay within 0.5 and 1.6 s. Within 55 ms, visual attention can shift to relevant features of the environment and ignore irrelevant features, and the input can enter visual storage (Poghosyan & Ioannides, 2008; Moholm, Ritter, Javitt, & Foxe, 2004). This is an instant store for sensory representations before they are processed further through selective attention, which enables the rapid visual discrimination of multiple items perceived for a brief period of time (Shiffrin, 1975). Broadbent (1957) proposed that words cannot be processed within iconic storage because they exceed the limited capacity, and thus they must be selected to enter working memory, whereas other, filtered-out stimuli are not processed further. Thus, information in iconic storage can be maintained temporarily without further processing (Smith, Bentin, & Spalek, 2001) for a brief duration. The auditory store can reinstate input of longer durations, such as 2-4 s (Cowan, 1984; 1995) and even longer (Sams, Hari, Rif, & Knuutila, 1993).

During visual encoding and working memory, the prefrontal cortex receives visual input from the primary visual area, and during semantic encoding, the prefrontal cortex receives input from a variety of areas depending on the modality (visual, auditory) and content (emotional, motor). The prefrontal cortex relies on sensory cortices for early semantic processing, not just comprehension and later processes, demonstrating that semantic processing too is modality-specific (e.g. motor areas activated for action words; visual areas for colours; emotion areas recruited for emotional content; Binder & Desai, 2011).

Episodic Memory Processes in the PFC.

Levels of processing. Attentional and perceptual processes determine whether the information enters long-term storage. If the information is processed superficially, it is not

likely to be remembered, even if it is attended to. However, information processed at the level of its identity and meaning is likely to be remembered. The levels of processing framework (Craik & Lockhart, 1972) specifies that information can be processed in two different ways at encoding: deep or shallow. The framework predicts that information will be memorised and subsequently recollected better if it is processed at a deeper, semantic level. Thus, the information will be more resilient, durable, and better integrated with existing memories through elaboration. Although deep and shallow processing can occur simultaneously, deep processing requires more attentional resources, so while background information can be processed at a shallow level, only the focus of attention can be processed deeply. Thus, there must be sufficient cognitive resources to process the information at a deeper level. Semantic processing may require the pre-existing semantic network be active and maintained in working memory. Accordingly, divided attention interferes with deep encoding and leads to shallower encoding.

Spreading activation model. The model of spreading activation (Reisberg, 2015) in the semantic network is similar to Hebbian learning in synaptic interactions: a semantic representation is activated in memory, and this representation provides the input for neighbouring representations to become active. Stored representations can become activated by input (e.g. a similar representations) and these representations activate others that are adjacent in time, space, or association strength. More strongly-associated representations may become active above threshold and become sources of activation, leading to the subsequent activation of other associations. More weakly-associated representations could remain active below threshold after input but could become more responsive to further input. Thus, parallel processing that results in activation of a representation via multiple different sources could lead to above-threshold activation and firing in the neuron that contains the representation. The presence of an additional retrieval cue may facilitate the memory search in the network by providing parallel input to the

target information since the original cue may only have a weak connection to the target (thus providing weak input and keeping the target at subthreshold activation). Thus, more retrieval cues increase the likelihood of activating the target so that it becomes active and 'found' in memory. Spreading activation is visible in lexical-decision tasks and semantic prime tasks in which participants must indicate whether pairs of letter strings represent words or not: decisions are faster for semantically-related rather than unrelated words, suggesting that the associated word is already weakly activated by the first word (subthreshold input) and can be more easily identified in memory (second subthreshold input, intentional search, leading to above-threshold firing). In addition, the process of spreading activation can be manipulated and inhibited through executive control to start the memory search and avoid false memories (Reisberg, 2015).

Ursino, Cuppini, and Magosso (2010) proposed a model for how lexical and semantic codes interact on a synaptic level in the context of grounded cognition. They found that semantic representations for objects are constructed based on features (input) that are processed in terms of similar stored representations that are reactivated together with the sensorimotor neural pattern and higher-order sensory processing in the cerebral cortex. In turn, the completion of the semantic pattern (with all object features) can lead to the activation of the corresponding word (lexical unit). On the other hand, given the word as input, the lexical network can activate corresponding semantic representations. These processes occur through gamma band synchronisation: features of the same object oscillate in phase, whereas features for different objects are not synchronous in gamma oscillation. In particular, common features include strong synaptic connections to other common features but do not activate distinctive features, whereas distinctive features are intermediately interconnected and can activate other distinctive features as well as common features. Thus, the synaptic weights for distinctive features are stronger than for common features, and distinctive features can more strongly activate corresponding lexical

codes for words. In turn, presynaptic and postsynaptic activity within the gamma band (10-20 ms) drives the formation of synaptic connections that can be excited or inhibited within the semantic network (depending on the frequency of co-occurring features and objects within a task). Language comprehension as well as memory is influenced by spreading activation and semantically-related concepts (McEvoy, Nelson, & Komatsu, 1999).

HERA model. The hemispheric encoding/retrieval asymmetry (HERA) model proposes that the left prefrontal cortex is associated with verbal information at encoding and retrieval, whereas the right prefrontal cortex is selectively involved in retrieval (Nyberg, Cabeza, & Tulving, 1996). This model was further developed as the hemispheric asymmetry reduction in older adults model (HAROLD), proposing that prefrontal functional asymmetry is reduced in older adults, leading to difficulties in memory processes and engagement of contralateral regions that may serve to compensate for the deficits of the functionally-necessary hemisphere (Cabeza, 2002).

Rossi and colleagues (2001) found impairment in picture encoding following TMS to the left DLPFC and in retrieval following stimulation to the right DLPFC, supporting the idea of hemisphere-specific processes in the DLPFC. Similarly, Sandrini and colleagues (2003) found an impairment in recognition of unrelated word pairs following TMS to the left and right DLPFC at encoding and following stimulation of the right DLPFC at retrieval.

Flöel and colleagues (2004) delivered TMS to the left and right anterior VLPFC (BA 45/47; Machizawa, Kalla, Walsh, & Otten, 2010) at encoding of abstract shapes and words, and they found impaired recognition selectively for words following TMS to the left hemisphere and for pictures following TMS to the right hemisphere. This supports the material-specific roles of the left and right VLPFC at encoding.

Gagnon and colleagues (2011) found faster reaction times to hits when delivering paired-pulse TMS over the left DLPFC (F3) at encoding and over the right DLPFC (F4) at

retrieval, reflecting a facilitatory effect on memory when inhibiting the DLPFC and confirming the hemisphere-specific roles of the DLPFC at encoding and retrieval. In addition, they found material-specific effects for the right but not left DLPFC, with greater false alarms for random shapes than for words.

Working memory. Baddeley and Hitch (1974) developed the idea of the short-term store with the working memory model, which contains independent, modality-specific rehearsal loops for auditory (phonological), visual, and spatial (visuo-spatial sketchpad) information, a modality-independent mechanism of attention (central executive), and an episodic buffer (mechanism for interacting with long-term memory). At the working memory stage, the information enters the brain temporarily until it transitions from short-term memory into long-term memory. The prefrontal cortex maintains, manipulates, integrates, and monitors information that can be separated in time. In addition, it can manipulate the maintained information to coincide with current goals, forming associations over time and space (Miller, 2000). The VLPFC appears to be engaged in maintaining information in working memory, while the DLPFC can manipulate information that is maintained in working memory by the VLPFC. For example, the VLPFC is engaged when a set of letters is kept in mind, while the DLPFC is engaged when the sequence of letters is listed in backward order (Blumenfeld & Ranganath, 2006).

Simply rehearsing the information does not ensure that it will be remembered, because information can be maintained within working memory. To ensure that the information is resistant to time, distraction, and forgetting, new information must be integrated with existing memories through elaboration, which develops associations between new and old information (Craik, 1983; Dark & Loftus, 1976; Shiffrin & Atkinson, 1969).

Unitary vs multi-store models: Episodic memory vs short-term memory. In between encoding and retrieval, the predominant view is that there is a transfer from short-

term memory to long-term memory (Baddeley, 2003; Norris, 2017). However, another established view states that short-term memory and long-term memory interact before a transfer, through temporary activations of long-term memory when required for processing that requires prior knowledge, such as a semantic network or phonological information in linguistic tasks (Burgess & Hitch, 2005; Penney, 1989). This is to provide evidence for cases in which short term memory does not always disappear after distraction, delay, and lack of rehearsal, and that rehearsal is not common in everyday memory, so it cannot be the main pathway for transfer to long-term memory. The evidence comes from the activation of a long-term semantic network during working memory tasks and the reliance on long-term memory regions such as the hippocampus for short-term relational tasks. For example, phonological similarity between words in a set disrupts immediate serial recall, demonstrating that prior phonological knowledge was accessed through long-term memory and affected short-term memory processing. In addition, false memory paradigms (Roediger & McDermott, 1995) demonstrate increased false memory for semantically similar words, so processing can rely on the existing semantic network. However, evidence from amnesic patients still supports the multi-store model, since patients showed differential performance for tasks that could not be performed with distractions (short-term memory) vs tasks that engaged long-term memory (Foerde, Knowlton, & Poldrack, 2006).

Reinstatement theory. An aspect of the event can serve as a cue at retrieval and can cause a partial reinstatement of the original encoding activity, and the hippocampus processes this activity to determine whether it matches stored activity (Rugg, Johnson, & Uncapher, 2015). Based on any overlap, the hippocampal representation is activated and the entire pattern of activity re-occurs. Once the stored representation is activated, the hippocampus reactivates details bound to other regions and then presents the complete conscious event, which is controlled by task-related, goal-relevant processes in the prefrontal cortex (Moscovitch, Cabeza, Winocur, & Nadel, 2016).

However, because there are fine details that may need to be distinguished (e.g. two different faces), the hippocampus may need to differentiate between patterns within a region rather than between regions. Thus, the regions that were active at encoding should be activated at retrieval, having stored associations of space, time, and other contextual details that can distinguish the event from others.

Recollection occurs if a pattern of cortical activity at retrieval matches the stored representation of activity in the hippocampus. The hippocampus records and stores the pattern of activity elicited by various distinct regions at encoding. In the established model introduced by Norman and O'Reilly (2003), the CA3 in the hippocampus contains a representation of cortical activity from encoding that is re-activated at retrieval by a retrieval attempt, and this leads to a replay of the original cortical activity. The retrieval attempt does not have to perfectly match because the CA3 can complete the pattern, so even partially overlapping activity between retrieval and the encoded representation can reactivate the entire representation and the activity at encoding. Memories are only partial representations of the original event, and not all features of an event are encoded. There could be different representations of the same episode, with greater detail for some aspects than for others, depending on which aspects were attended-to and stored at encoding. Thus, retrieval may be a constructive process such that additional information and interpretation are integrated into the memory.

Consolidation. Initially, retrieval of an event can be an iterative process, recollecting details that were present at encoding and filling in context with pre-existing templates. Memory is constructive and re-constructive, with information flowing from long-term memory to working memory and back again, each time being updated in the context of new information and re-integrated with that information (Reisberg, 2015). However, memories are gradually transferred from a volatile state in which disruption can occur to a more stable state in which they become resistant to disruption (Frankland &

Bontempi, 2005). A complete memory involving detail and context depends on the activation and re-activation of hippocampal-cortical networks: semantic and general information is available from the cortex, and spatio-temporal context and detail are available in the hippocampus. Throughout consolidation, the neural networks supporting the memory trace are strengthened and reorganised (Stickgold, 2005). While the hippocampus integrates information into a cohesive memory trace for recent memories and is active during recall, for remote memories this function may be transferred to the prefrontal cortex, specifically when connections between cortices are strengthened. Through online reactivation (e.g. information needed for a task or goal) or offline (sleep or altered states of consciousness like daydreaming), storage and recall can become dependent on the cortex instead of the hippocampus (Wang, de Oliveira Alvares, & Nader, 2009). Thus, the storage of remote memories may be supported by the prefrontal cortex, whereas storage of more recent memories involves the hippocampus. However, evidence suggests that the memories do not remain in a consolidated state permanently, and a memory can be reactivated, modified, and reconsolidated.

Reconsolidation has been studied with NIBS by re-activating the memory with an old/new recognition task. Sandrini and colleagues (2013; 2014) used a cue (blue bag) at learning and 24 h later to reactivate the memory. On the first day, the experimenter took words written on pieces of paper from a white bag and gave them to participants to memorise, and participants were instructed to place the words in a blue bag. On the second day, participants were shown the blue bag in the same room and asked to describe the procedure but not list any words. In another group (control), participants were not shown the blue bag or asked to describe the procedure, and they were in a different room. At retrieval, which took place 24 h later, participants were asked to recall as many words as possible. They showed that the reminder cue was sufficient to reactivate the memory and induce reconsolidation, which led to higher recall than in the control group. Sandrini and

colleagues (2013) delivered low-frequency rTMS over the right DLPFC during reconsolidation or one hour later, and they found an enhancement in recall only for the reconsolidation group. They also found no effect of rTMS for a control group that did not have the reminder cue. Sandrini and colleagues (2014) delivered atDCS over the left DLPFC during reconsolidation or a control condition (no reminder cue) and found that atDCS led to increased recall in both groups 24 h later and 28 days later. The effect of atDCS in the control condition suggests that the broader context (university) may have been sufficient to reactivate the memory (Sandrini et al., 2014) or that atDCS may have an offline effect independent of memory reactivation.

Innocenti and colleagues suggested that because there were no effects of rTMS on encoding judgements, a disruption of memory consolidation led to impairment on the memory test. Rossi and colleagues (2011) found that rTMS after the offset of a presented visual scene led to impairment in retrieval, and they suggested that the left DLPFC was involved in top-down control over maintenance and consolidation of the scene to enable the transfer from the episodic buffer to long-term memory.

Episodic Memory in the Laboratory and PFC involvement

Tasks. In the laboratory, episodic memory is studied through a model assuming that each trial in a task is a distinct, nonoverlapping event (even if the trial is repeated). Unlike other memory tasks in which context may be irrelevant or forgotten, participants are encouraged to engage with the context of each event. Even if each trial includes the same background (a perceptual feature), the participant is assumed to generate unique impressions for most of the trials, which will assist in later recollection. In addition to measuring item memory, episodic tasks can examine these impressions directly by varying perceptual features between trial. Then participants can be asked to state what they remember about the trial or to select the correct feature from multiple options. Episodic tasks can encourage generating impressions connected to autonoetic consciousness by

asking participants to indicate whether each item is pleasant or unpleasant or whether each item is personally relevant to them, thus activating self-awareness or the concept of the self. However, the connection to the self-concept does not make a memory autobiographic, because it retains the context-bound characteristics of episodic memory and is recent (unlike autobiographical episodic memories).

Episodic memory can be measured through various cognitive tasks. Each episodic task includes an encoding and retrieval phase. At encoding, a set of items is presented, and participants may be instructed to interact with the items (i.e. make judgements) or memorise them. At retrieval, participants are instructed to list the items they can remember (recall) or identify them from a set of presented and unpresented items (recognition). Participants may be asked to provide additional details for each item, including colour, order in the set, and judgement made. These details reflect memory for the recollected detail, testing that participants can identify the experiment as the source. Testing source memory as part of an episodic task can index recollection for contextual details, while recall and recognition may only index memory for the item (Johnson, 2005; Yonelinas, 2010).

It is important to note that different tasks measure different aspects of episodic memory such as temporal order (Farrell, 2012; Lu, Wang, Chen, & Xue, 2015), location (Köhler et al., 1998), and both (Hayes, Ryan, & Schnyer, 2004). In these tasks (e.g. what-where-when), participants may be unable to rely on semantic strategies, engaging episodic strategies to a greater extent (Cheke & Clayton, 2013). Thus, some episodic measures correlate, such as recall and the ‘what-where-when’ test of contextual detail (Cheke & Clayton, 2013; 2015). Others measure episodic memory but may not measure the same aspect (Johnson, 2005), so it is important to consider the task that is best-suited to the episodic process of interest.

Encoding tasks and levels of processing. There are different kinds of episodic memorisation and retrieval depending on how the information is processed and later tested. Encoding can be manipulated by asking participants to attend to different features of the items, such as perceptual or semantic characteristics. For example, with semantic judgements participants must attend to the meaning of the word, whereas with orthographic judgements participants must attend to the letters in the word. For pictures, participants may be asked to name the object (semantic judgement) or indicate the colour of the background (perceptual judgement). In this way, the instructions are used to manipulate levels of processing (deep or shallow; Craik & Lockhart, 1972; Windey, Gevers, & Cleeremans, 2013, Zwaan, 1996). Shallow encoding tasks such as alphabetical judgements or syllable counting usually involve structural or phonological analysis. Other tasks may require judgements about pitch, typography, colour, capitalization, font, or rhyme. Deep encoding tasks usually involve a semantic judgement such as living or non-living. Other tasks involve constructing or reading a sentence (Craik & Tulving, 1975). It is important to note that although deep encoding of words or pictures may involve the semantic network, episodic rather than semantic memory is engaged. Although participants may hear the items of the experiment in other contexts, such as a conversation, they are asked to constrain their retrieval only to the context of the experiment (Hasselmo, 2011). This reliance on specific context and contextual details distinguishes episodic tasks from other memory tasks.

Deep encoding leads to higher accuracy and a higher proportion of confident responses in memory tasks. Thus, participants remember more items and rate their memory for these items with high confidence. Nonetheless, participants are still able to recognise and even recall words that involved shallow encoding (Kirsner, 1973). Higher recollection could occur because deep encoding increases processing for individual items (item-specific encoding), and the items could become more distinct in memory and easily

retrieved (Moscovitch & Craik, 1976; Winograd, 1981). Deep encoding may also allow for encoding associations and the item-context relationship (Galli et al., 2014), linking each item to the semantic network and resembling relational encoding (encoding for relationships between items). While shallow encoding can involve associations, these would be between the item and perceptual features. In both cases, deep encoding increases elaborative processing, which facilitates integration with previous memories and generates retrieval cues. These retrieval cues in turn increase the accessibility of the memory trace (Craik & Tulving, 1975).

For example, a form of deep encoding known as semantic analysis can be activated by asking categorical or sentence questions ("Would the word fit the following sentence: The girl placed the ___ on the table?" for a target word "vase"). Semantic questions ("Is the word a type of fish?" for target word "salmon") led to higher levels of memory than phonemic ("Does the word rhyme with park?" for a target word "dark") or orthographic features ("Does the word start with S?" for a target word "snake"; Craik & Tulving, 1975). In addition, when Craik and Tulving (1975) presented different kinds of semantic questions (simple, medium, or complex), filling in the blanks to the most complex sentences led to higher recall for the words. While all types of sentences involved conceptual processing, the most complex sentences were remembered best because they activated larger, richer cognitive structures. Sentences such as "She cooked the FOOD" were considered simple, while complex sentences included: "The great bird swooped down and carried off the struggling WORM".

Galli (2014) proposed that deep and shallow encoding may engage different mechanisms and regions of the brain. Rather than engaging distinct regions, however, shallow encoding may activate a subset of the regions involved in deep encoding, specifically the left VLPFC and left anterior hippocampus (Otten, Henson, & Rugg, 2001), which are associated with semantic encoding in long-term memory (Blumenfeld &

Ranganath, 2007). While the VLPFC appears to be strongly engaged in deep and shallow encoding in verbal tasks, the DLPFC appears to be more engaged for deep vs shallow encoding. Medvedeva and colleagues (2018; Experiment 3) did not find an effect of atDCS over the left VLPFC on deep or shallow encoding. However, Galli and colleagues (2017) showed that rTMS to the left VLPFC disrupted deep and shallow encoding, and the magnitude of impairment did not appear to differ for items that were encoded in deep vs shallow encoding. In contrast, Innocenti and colleagues (2010) showed that deep but not shallow encoding was disrupted by rTMS to the left DLPFC, although reaction time at retrieval increased for both deep and shallow encoding. There was no effect of rTMS on the right DLPFC, providing support for hemisphere-specific effects as proposed by the HERA model. Innocenti and colleagues (2010) suggested that activity in the DLPFC was necessary for successful retrieval of deep and shallow items, but the levels of processing effect was abolished by rTMS because of rTMS sensitivity to the state of the neural network and greater DLPFC activation during deep encoding.

Takahashi, Ohki, and Kim (2007) showed similar fMRI activation between deep and shallow encoding in the VLPFC but greater activation for deep than shallow encoding in the DLPFC. They also found functional and anatomical connections to the left temporal cortex, supporting the idea that the VLPFC may control retrieval of sensory representations in the posterior regions (such as the temporal cortex) that enables successful recollection, particularly for the superficial features encoded in a shallow task such as colour, whereas the DLPFC may manipulate information maintained by the VLPFC.

In support for the greater role of the VLPFC than DLPFC in shallow encoding, Blumenfeld and colleagues (2007) found that the VLPFC but not DLPFC activity during working memory maintenance for word triplets predicted long-term memory. However, both VLPFC and DLPFC activity during working memory manipulation of the triplets

(backward order) predicted long-term memory, providing support for the interpretation of Takahashi and colleagues (2007) that the VLPFC may be involved in more domain-general maintenance processes, while the DLPFC may be involved in manipulation of information that is maintained or accessed in working memory.

The role of the DLPFC in memory-related control processes and strategic retrieval is supported by a study that found DLPFC involvement in self-initiated elaboration strategies. Hawco and colleagues (2013) examined the effects of rTMS over the DLPFC in memory for semantically-related and unrelated word pairs, either in a condition with explicit instruction (identify the relationship between the words) or without it. They examined the DLPFC because of its role in spontaneous initiation of elaboration in encoding, and they predicted worse memory accuracy for the absent-instruction condition for related word pairs. Their hypothesis was supported in that the They found a correlation between the use of strategies and direction of rTMS effects, such that rTMS reduced recall for those who used multiple elaborative strategies and increased recall for those who did not use many strategies. They concluded that their results supported the role of the DLPFC in initiation of strategies, and the rTMS effects could be explained by individual differences.

Moreover, Hammer and colleagues (2011) examined executive function in the DLPFC during errorless vs errorful learning, which makes retrieval challenging in identifying correct items vs errors. They used a mixed design in which each tDCS group (cathodal, anodal) also received sham stimulation, and they used a word stem completion task to manipulate errorless vs errorful learning. Each participant completed errorless and errorful learning tasks: in the errorful condition the participant guessed words to complete a three-letter fragment, and then the target word was revealed. The most frequent guess was used as a distractor for the recognition test. In errorless learning, the first three letters were shown and then the target word was revealed, without participants guessing. Then

participants were asked to use the word in a sentence, to match deep encoding between the two conditions. Whereas anodal stimulation had no effect, cathodal stimulation led to decreased memory accuracy following errorful learning but not errorless learning (for which there was no effect). They concluded that errorless learning is more beneficial in general, and the results confirm the role of the DLPFC in memory-related cognitive control. They concluded that cathodal stimulation reduced the memory-related cognitive control processes, specifically monitoring at retrieval, rather than memory processes in general, which explains the lack of effect of cathodal tDCS for errorless learning. The lack of conflicting information could reduce processing demands for the PFC such that modulation is not evident.

However, there is support for the specific role of the VLPFC in semantic encoding rather than domain-general control processes. Meinzer and colleagues (2012) delivered atDCS over the left VLPFC during a semantic naming task and found improved naming and decreased activity during the task that was specific to the stimulation site rather than adjacent regions rather than adjacent regions involved in domain-general control processes (left DLPFC and right VLPFC). During a control task in which participants said the word "rest", there was increased activation at the stimulation site and increased connectivity with regions in the language network (perisylvian areas including insula, posterior temporal cortex, and inferior parietal cortex). Participants were instructed to name members of a category as part of a semantic retrieval task or say the word "rest" in a control task that enabled measurement of resting-state fMRI.

The VLPFC may be active at both deep and shallow encoding because of its role in semantic processing and item-specific encoding, thus enabling recollection for the item within a semantic network or without a context, respectively. Specifically, the anterior VLPFC may show greater activation during deep encoding because of its role in semantic elaboration (Badre et al., 2005), whereas the posterior VLPFC may show greater activation

at shallow encoding because of its role in phonological processing (Nozari & Thompson-Schill, 2016; Nozari et al., 2016). Thus, the VLPFC may show greater activation for deep than shallow encoding when a more anterior region is stimulated, as in the study by Vidal-Piñeiro and colleagues (2015) with offline continuous theta-burst stimulation leading to an increase in the stimulation site (left anterior VLPFC) activation during deep but not shallow encoding.

Intentional vs incidental encoding. In addition, memorisation can be manipulated such that it is intentional or incidental. Participants may be instructed to memorise the items for the subsequent test, or the memory test may come as a surprise. By assigning a learning task without specific instruction to memorise, participants can learn a set of material without being aware of a subsequent memory test. Memory performance is generally better on intentional than incidental memory tasks, perhaps because deep encoding can be engaged automatically as a strategy (Bastin & Van der Linden, 2005; Craik & Rose, 2012; Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003). At encoding, the pre-existing semantic network may be active and maintained in working memory (Galli et al., 2014). Thus, reading a word may automatically access its semantic meaning, and the sole act of intending to memorise may lead to similar results as in deep encoding if the default strategy is to process words at the level of their meaning (Craik & Lockhart, 1972; Ekuni, Vaz, & Bueno, 2011). This also explains why recall is possible after shallow encoding (Kirsner, 1973).

In addition, there is an important distinction between incidental and implicit memory: even memory that is incidental includes conscious processes, specifically autonoetic consciousness. It is never a question that incidental memory can be episodic, even though the memorisation may not be conscious, because the individual consciously engages with the material, unlike in implicit memory, in which the individual may not be aware of the event taking place because it occurs so rapidly or without attention. In fact,

most everyday encoding processes are incidental, since individuals do not make an effort to memorise each event and conversation that occurs, yet they can remember and re-experience it consciously.

The VLPFC and DLPFC also show distinctive sensitivity to experimental manipulations such as incidental vs intentional encoding and shallow vs deep processing. While the DLPFC may be selectively active in intentional memorisation (Wimber, Heinze, & Richardson-Klavehn, 2010), the VLPFC may be active at both intentional and incidental encoding (Uncapher, Boyd-Meredith, Chow, Rissman, & Wagner, 2015). The DLPFC could be selectively active at intentional memorisation because of domain-general control mechanisms that must be engaged (Badre, 2008; Sallet et al., 2011). For example, in working memory tasks, the DLPFC increases in activation as distractions increase task difficulty (Kim et al., 2015; Wu et al., 2017). For example, Jiang and Kanwisher (2003) asked participants to indicate whether colours matched (match), and in a separate task they asked them to indicate the opposite response (no match) when the colours matched. The latter task, which involved greater interference because of incompatibility between the response and perception, was associated with greater activation in the DLPFC. However, the VLPFC was active in both tasks. Because the VLPFC was active in the easier task as well as the difficult task with interference, control operations may not be active as for the DLPFC.

Item-specific vs relational encoding. In addition to shallow and deep encoding, there is another dichotomy worthy of discussion: item or relational memory, which affects encoding and retrieval. Item-specific memory involves processing each word separately and is thought to increase distinctiveness of each item, whereas relational memory involves processing forming relationships between items in a set. For example, associative memory is a form of relational encoding which involves explicit memorisation for associations, such as pairs of words or groups of items. Although both item and relational

encoding can involve deep semantic encoding, relational encoding is thought to rely more strongly on the semantic network and item encoding may overlap more with shallow encoding (Addis & McAndrews, 2006; Spataro, Mulligan, Bechi Gabrielli, & Rossi-Arnaud, 2017; Staresina, Gray, & Davachi, 2008; Zimmer & Steiner, 2003). Item memory is often thought to be linked to shallow encoding because pure item memory involves binding an item without linking it to semantic or visual context (Lepage, Hawco, & Bodner, 2015). Moreover, strong semantic similarity between the items during relational encoding may lead to increased false recognition and recall, in contrast to item-specific encoding. An increase in shallow encoding during item encoding could explain the decrease in false recognition and increase in distinctiveness and memory for item details. On the other hand, relational and item-specific encoding both increase the number of items recollected. In fact, early studies of the two processes suggest that together, item-specific and relational encoding may lead to higher memory performance than either alone (e.g. Hunt & Einstein, 1981). The memory advantages of both may be linked to an increase in elaboration and greater subsequent integration with previous memories. Item-specific encoding may increase memory accuracy, although perhaps at the cost of remembering more information, while relational encoding can increase the quantity of information memorised, but details can be confused among items. In relational encoding, new memories can be easily integrated with previous information at the cost of greater memory errors.

The VLPFC may be more engaged in item-specific encoding, while the DLPFC is more engaged in relational encoding (Blumenfeld & Ranganath, 2007). Blumenfeld and colleagues (2011) asked participants to memorise pairs of words by imagining them separately (item-specific encoding) or together (relational encoding), and they found selective DLPFC activation during relational but not item-specific encoding, while the VLPFC was active during both. Similarly, Murray and Ranganath (2007) presented two

object words sequentially per trial and asked participants to indicate whether the second object word was living or non-living (item-specific encoding) or whether the second object could fit inside the first. They found that DLPFC activity was selective for relational encoding and correlated with successful recognition for relational trials. While VLPFC activity was greater during relational encoding, it correlated with successful recognition for item-specific and relational trials. Blumenfeld and colleagues (2014) found that after instructing participants to indicate whether each word was concrete or abstract, facilitating item-specific encoding, rTMS over the middle VLPFC but not DLPFC led to recognition impairment. rTMS over the DLPFC led to non-significant enhancement.

Retrieval tasks and recollection. In free recall, participants are presented with auditory or visual lists of words in a sequence and then are asked to list them, not necessarily in order. The temporal dimension of episodic memory is only tested when participants are requested to list the words in order, or when the experimenter scores recall based on order information. This test can follow immediately after the item presentation or after a delay. Because there is a short-term memory component in immediate free recall (listing words from the end of the list), episodic memory specifically is thought to be active in delayed free recall and in immediate free recall only when words from the start of the list are listed (Hasselmo, 2011). Thus, tasks with shorter lists of words (>15), such as Raven's Auditory Verbal Learning Test (a neuropsychological test), are considered short-term episodic tasks.

Innocenti and colleagues (2013) found that following rTMS over the DLPFC and intra-parietal lobe, immediate recall performance was worse, specifically the primacy effect and recency effect, respectively. The memory impairment over the DLPFC likely reflects long-term memory, while the memory impairment over the intra-parietal lobe likely reflects short-term memory, in line with the expected contributions of these regions to long-term and short-term memory. The DLPFC may be involved in short-term and long-

term memory, while the intra-parietal lobe may only be associated with short-term memory.

Rami and colleagues (2003) delivered rTMS to the DLPFC in young men at high (5Hz for 10s at a time) or low (1 Hz for 10s at a time) frequency, and they found lower recall for detail in the Rivermead Behavioural Memory Test after high but not low frequency rTMS. They also delivered rTMS to the right cerebellum and found no effects. rTMS was delivered at the start of the Rivermead Behavioural test, which requires participants to read and memorize a story over 30 s and then recall as much detail as possible. However, the Rivermead Behavioural Memory Test would be considered a short-term memory task, supporting the role of the DLPFC in short-term memory.

In recognition tasks, participants are presented with a set of presented and unpresented items and are asked to indicate which item they have seen or heard previously. At test, they may see the correct item paired with one or multiple distractors and select the item they remember, or they may see one item at a time and indicate whether it is old or new. Recognition may rely on familiarity and recollection processes. Episodic memory is thought to be engaged during recollection of episodic details, so recognition tests may also include subjective (confidence ratings) and objective (source memory) measures of recollection. Participants may be asked to rate their confidence on a memory response on a scale from ‘low’ to ‘high’ confidence. Alternatively, they could be asked whether they ‘remember’ the event and associated details (e.g., seeing the word on the screen and remembering the font) or whether they ‘know’ that the event occurred (e.g., feelings of familiarity but no memory of seeing the word). For example, following deep encoding, participants are more likely to rate responses as ‘remember’ and ‘very confident’. Responses based on recollection are rated with high confidence and include contextual or spatiotemporal details, whereas responses based on familiarity may have low confidence and can be based on ‘knowing’ rather than ‘remembering’ (Hasselmo, 2011). However,

while patients with amnesia and damage to the hippocampus generally perform better on recognition than recall tasks, they show impairments in responses based on familiarity as well as those based on recollection (Manns, Hopkins, & Squire, 2003).

Thus, recognition and episodic recollection can rely on both familiarity and recollection processes, although these processes may be anatomically distinct, as supported by neuroimaging evidence. For example, Kirwan and colleagues (2008) found recollection-based activity in the left medial and right ventrolateral PFC but familiarity activation in the hippocampus and right perirhinal cortex. They presented 360 words to participants and asked them to make an animacy judgement for words presented in green and a size judgement for words presented in red. In the subsequent surprise recognition task, participants were asked which judgement was made for a given word (size or animacy) if they indicated having memory for the word. Kirwan and colleagues (2008) identified recollection-based activity on source trials that had strong item memory and high confidence responses, while familiarity-based activity was associated with lower confidence ratings and lower source accuracy. While the hippocampus and right perirhinal cortex showed graded activation according to confidence (reflecting memory strength), the right perirhinal was not active for high-confidence responses. The right VLPFC was selectively active for recollection-based responses. They concluded that medial temporal regions may be important for memory strength, while the prefrontal cortex may be important for recollection.

The example of the study above demonstrates that memory can be indexed in different ways, with varying degrees of temporal and spatial detail. In addition, the study reflects the idea that recognition indexes item memory more than relational memory, particularly when one item at a time is presented. Recall and associative recognition, on the other hand, may index relational memory and rely on anatomically distinct regions. In turn, the VLPFC may be more active than the DLPFC in a recognition task, while the

DLPFC may be more active in a recollection-based task, perhaps because the DLPFC encodes contextual details and binds various sensory features of the event (Lee, Blumenfeld, & D'Esposito, 2013; Naghavi & Nyberg, 2005). Studies have found differences in DLPFC and VLPFC activation between recall and recognition tests, possibly because recognition tests may be insensitive to effects of relational encoding and performance may be enhanced by item-specific encoding, whereas free recall performance may be enhanced by relational encoding.

Generalisability and ecological validity of laboratory memory studies. It is generally assumed that the memory processes that occur in the laboratory are similar to those that occur in everyday life. Indeed, fMRI studies find overlapping activation between more laboratory-based tasks like recognition tests and more naturally-occurring memories like autobiographical events, in the hippocampus and medial temporal lobe (Cabeza et al., 2004; Chen, Gilmore, Nelson, & McDermott, 2017). However, debates have arisen about the relevance of phenomena studied in the laboratory to the real world, even questioning the existence of certain constructs. Everyday memory is context-bound (Cohen, 2008), usually to social and interpersonal context (at encoding and retrieval), and not constrained to remembering original events and making overt responses. In addition, it is purpose-driven and designed to achieve specific goals (Cohen, 2008): creating and maintaining the concept of the self (autobiographical memory), planning and forming intentions, and completing planned tasks within space and time (spatial and prospective memory). These aspects should be captured in memory experiments. In fact, the dichotomies faced in episodic memory theory are often blurred in the real world.

For example, relational and item memory rarely occur separately in naturalistic memory. Relational memory is engaged in multiple naturalistic contexts, forming associations in time and space (Blumenfeld & Ranganath, 2007; Murray & Ranganath, 2007). Forming relational associations involves accessing the meaning and possibly

unique characteristics of individual items to find shared semantic features (Hunt & Einstein, 1981). In deep encoding, relational and item encoding can coincide as the item's meaning is accessed and associated to a semantic network (Lepage, Hawco, & Bodnar, 2015). Thus, in real-world memory, it is likely that relational and item memory are often engaged simultaneously, and laboratory tasks may have difficulty disentangling the two.

Franzen and Wilhelm (1996) argued that neuropsychological tests should resemble the real-world environment (verisimilitude: e.g. reading material could be taken from age-appropriate but not widely-known books) and results should be able to predict the level of everyday functioning in parallel abilities (veridicality: e.g. a reading test should predict impairments in everyday reading).These concepts of verisimilitude and veridicality were applied by Kvavilashvili and Ellis (2004) as representativeness and generalisability, respectively, to memory experiments.

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The process studied in the laboratory should reflect the real-world process as a construct and with a similar context, and the results should be able to explain the process as it occurs in the real world. The experimental context, stimuli, task, and variables should be as close to the natural context and phenomenon as possible. Thus, episodic memory studies are thought to be ecologically valid through accurately representing the real-world phenomena and context (representativeness) and yielding generalisable results (generalisability; Kvavilashvili & Ellis, 2004). For example, conducting a study in a

classroom rather than a laboratory and using words rather than meaningless strings of letters would be more natural than artificial, and thus more representative. In addition, the results should be generalisable: applicable to the phenomena in the real world and able to explain it. However, field studies with high representativeness can lack ecological validity if they do not include the proper controls, leading to low generalisability (Kvavilashvili & Ellis, 2004). Thus, experimental research in the laboratory can be high in representativeness and generalisability by accurately simulating an everyday process (e.g. associative memory through naming objects), using naturalistic materials (e.g. words or pictures), and including a robust experimental design. For example, the distinctiveness effect has long been established as improving recognition with a variety of stimuli, even when recognition was tested a week later (Cohen & Carr, 1975). Watier and Collin (2012) found that the distinctiveness effect applied for associations between faces and names. The stimuli (faces and names) were representative of memorable phenomena in the real world (high representativeness), and the findings showed that distinctive faces or names are more memorable after a brief meeting with strangers (high generalisability).

Chapter 4: Assessing tDCS as a Research Tool: A Systematic Review and Meta-Analysis of the Effects of tDCS on Episodic Memory

Abstract

There is promising evidence that NIBS, including tDCS, leads to facilitation and enhancement of long-term memory processes such as encoding, retrieval, and consolidation, under specific conditions. However, these specific conditions are unclear since previous studies have used different parameters (largely unsystematically) and found varying modulations of tDCS (no effect or modulation of memory performance or reaction time). It is clear from theoretical explanations and models of tDCS effects that tDCS parameters interact with cognitive task characteristics and individual differences (e.g. age) to determine the final modulation. Thus, this meta-analysis examined the pooled effect of polarity-specific tDCS on long-term episodic memory and investigated moderation effects based on parameters of tDCS (e.g. stimulation site) and episodic tasks (e.g. recall vs recognition). The included studies tested older or younger adults and were methodologically-sound in using appropriate tDCS designs (e.g. control group and blinding) and established episodic memory procedures (i.e. long-term memory tasks). The meta-analysis showed no significant effects of anodal or cathodal tDCS on hits or associated reaction times. However, the moderation analyses revealed significant moderations of retrieval task, stimulation duration, and stimulation site. In conclusion, the results confirm the importance of tDCS- and task- parameters in determining tDCS modulations and emphasise the need for standardisation in tDCS use that has been noted by other tDCS researchers and theorists.

Introduction

tDCS is a rapidly-developing potential memory intervention that has already been tested in animals, healthy adults, and patients with memory disorders. Investigating episodic memory with tDCS is relatively new, while TMS is a more established research

tool. While the facilitatory effects of TMS on cognitive function are still being explored, anodal tDCS seems to be a promising method for increasing neuron excitability in a way that enhances memory function. However, the excitement over the advantages of this technique may be blown out of proportion. Parkin, Ekhtiari, and Walsh (2015) argued that claims by tDCS researchers may be unfounded, contributing to unregulated use of the machine by the public due to high accessibility. There is a need for regulation in the field and also regulation in the world so that people do not improperly use the easily-accessible device (Santarnecchi et al., 2013), which may be easier if claims are not over-exaggerated (Walsh, 2013).

There is a need to increase high-quality research in the tDCS field rather than facilitating the propagation of false positives and claims that urge application of tDCS to practical settings. There is a lack of standardisation, and adverse effects and cognitive effects are still being uncovered, particularly in the long-term. For example, Sandrini and colleagues (2014; 2016) found enhanced memory effects lasting up to nearly a month after stimulation termination. Thus, application to various populations and real-world situations may be premature and unwise, particularly when there is no evidence for an effect of tDCS beyond the material or after-effects longer than several minutes (Walsh, 2013). For example, tDCS effects over the motor cortex in stationary participants may not be present for participants who are moving. Modelling is important for understanding long-term effects and translation of tDCS effects in healthy young adults to other populations. It is also important to conduct meta-analyses because individual studies can be pooled to calculate an average effect, which is more reliable than the effect of any single study. Without a strong understanding of safety characteristics, translation of tDCS research to children and patients with certain conditions (e.g. epilepsy) could be careless and detrimental (Walsh, 2013).

An increasing number of studies has investigated tDCS effects, and the number of tDCS studies grows exponentially with every year (Polanía, Nitsche, & Ruff, 2018). However, the understanding of tDCS and its cognitive effects may not be proportional to the number of investigations. Evidence for effects of tDCS has been mixed, with some studies showing enhancements in memory and others showing impairments. Meta-analyses of tDCS effects have also shown inconsistent effects and a large proportion of heterogeneity, and examinations of the heterogeneity have not always led to explanations with expected moderators (e.g. current density or duration).

In their meta-analysis, Brunoni and Vanderhasselt (2014) compared active tDCS and rTMS to sham on working memory accuracy and reaction times and found faster reaction times following tDCS and improved accuracy following rTMS but not tDCS (33 experiments from twelve articles). Moderators included type of stimulation, gender, study design, working memory load, population type (healthy vs clinical), current density (0.28 vs >0.57), and stimulation site. The authors found significant effects of type of stimulation, study design, and population type: there were stronger effect sizes for rTMS on correct and error responses and for clinical samples and parallel design on correct responses only.

In another meta-analysis, Summers, Kang, and Cauraugh (2016) found significant effects of tDCS on motor and cognitive function in older adults (N = 25), and there was a high fail-safe, indicating that a large number of studies with null results would be required to yield non-significance in the meta-analysis. In addition, there was no significant publication bias, suggesting that the results of individual studies were unbiased. Although the confidence intervals for individual studies were relatively large, suggesting a lack of precision, the overall effect size had a narrow interval. It was unclear whether the heterogeneity was explained by the included moderators, but nearly factors in the moderation analysis were significant. There were significant effects for cognitive and motor functions and for all brain regions examined, including the DLPFC. There were also

significant effects for memory and language tasks but not problem-solving tasks. Both online and offline tDCS yielded significant effects for motor and cognitive function, although there was a greater number of online studies. However, most of the conducted moderator analyses included small subsamples (N<10), so the results may not be reliable.

Dedoncker and colleagues (2016) also commented on the heterogeneity of tDCS parameters and effects, an especially critical issue in the presence of growing research. They examined single-session crossover studies and found significantly improved performance and faster reaction time on cognitive tasks, with greater accuracy for patients and faster reaction time for healthy controls. There were no effects of cathodal tDCS on accuracy or reaction time, and there were no moderation effects. Anodal tDCS effects were significantly moderated by increased current density and gender (female) in healthy individuals and online administration in patients.

Hill, Fitzgerald, and Hoy (2016) found no overall effects of tDCS but also examined current density (< 0.029 or > 0.029), stimulation duration (<10 min or >10 min), sample (clinical or healthy), and time of administration (online or offline) as moderators of working memory. Higher current density and longer durations increased effect sizes for accuracy (current density) and reaction time (duration), respectively. In addition, there was an interaction between time of administration and sample: atDCS decreased reaction times and increased accuracy when delivered offline in healthy adults and online in adults with neuropsychiatric conditions.

Westwood & Romani (2018) found no significant effects of anodal tDCS on picture naming and word reading, but they examined multiple moderators: time of administration (online vs offline), current density (0.28 vs > 0.057) and stimulation duration (<15 vs >20 min). Time of administration and duration showed significant moderation effects, with larger effects on reaction time for shorter stimulation duration and on accuracy for offline vs online tDCS.

Horvath, Forte, and Carter (2015) did not conduct moderator analyses but conducted meta-analyses on sub-samples based on task: they did not find effects of tDCS on any measure including verbal and visual episodic memory. They further divided working memory studies based on working memory load. However, Price and Hamilton (2015) criticised the authors' sub-division of studies rather than examining them, and most subsamples included only 3-5 studies, so the verbal and visual episodic memory analyses were underpowered.

In line with previous tDCS moderator analyses, time of administration, current density, and duration may be among the most important moderators of tDCS effects, with increased current density and duration associated with larger effects. However, there are inconsistencies in the meta-analyses concerning the significance of overall effects and which time of administration is most effective, and these could vary depending on the cognitive function examined. The nature of tDCS as well as the nature of the studies contributes to these inconsistencies: tDCS exerts polarity-specific effects, so it can potentially inhibit (with the cathode) or facilitate (with the anode) the function of a region depending on whether excitatory or inhibitory pathways are activated. Although it is possible to estimate the baseline activity of the region and subsequent increases in activation by tDCS, it remains unclear which specific pathways and associated functions are targeted by tDCS, since it indiscriminately modulates activation of large populations of neurons and this modulation changes non-linearly in magnitude (and often polarity) over time (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). In the past twenty years, through an increasing number of studies tDCS effects on function have been explored by implementing different tasks and measuring behavioural modulations (Polanía, Nitsche, & Ruff, 2018). However, the neurobiological effects of tDCS do not always clearly map onto behavioural or cognitive effects. For example, studies over the motor cortex have found non-linear increases in MEPs over time (Nitsche, Polanía, & Kuo, 2015). In addition,

although the effects of tDCS are promising in some studies, they are more subtle than other stimulation methods (e.g. transcranial magnetic stimulation) and thus more difficult to control and manipulate through experiments. Finally, reverses in tDCS effects can occur based on current strength (1 mA compared to 2 mA; Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). Unreliable effects can occur in part because multiple parameters of tDCS and the experiment interact with individual and population differences to determine the final modulatory effect: inhibitory, excitatory, or neither. This interaction contributes to the difficulty of implementing and validating tDCS as an established research tool for cognitive as well as clinical research.

The effects of tDCS on tests of episodic memory have been mixed partly because of differences in methodological aspects such as experimental design, cognitive tasks implemented, populations recruited. As previously discussed, the question of which conditions need to remain consistent has been asked since the beginning of tDCS research (Nitsche & Paulus, 2000; Nitsche et al., 2005; Saturnino, Antunes, & Thielscher, 2015), and many authors have emphasised the need for standardisation in parameters (e.g. Das, Holland, Frens, & Donchin, 2016). Specifically, although tDCS can also modulate other indexes of memory performance (i.e. false recognition and associated reaction times), anodal tDCS can lead to increases and cathodal tDCS leads to decreases in hits, a common outcome measure examined in episodic memory tasks that reflects accurate recollection.

Several studies investigated the effects of anodal and cathodal tDCS and found effects on hits (Flöel et al., 2012; Gaynor & Chua, 2016; Gray et al., 2015; Javadi & Cheng, 2013; Jones, Gözenman, & Berryhill, 2014; Leach et al., 2018; Leshikar et al., 2017; Lu, Wang, Chen, & Xue, 2015; Manuel & Schnider, 2016; Marián et al., 2018; Matzen et al., 2015; Pergolizzi & Chua, 2015; Pisoni et al., 2015a; Sandrini et al., 2014; 2016; Smirni et al., 2015). Most of these studies have found increases in hits in recall and

recognition tasks after anodal but not cathodal tDCS, which impaired or had no effect by comparison.

Moreover, most studies delivered anodal tDCS over the left DLPFC and found significant effects, although the posterior parietal cortex (PPC), temporoparietal cortex (TPC), and anterior temporal lobe (ATL) have also been targeted. Sandrini and colleagues (2014; 2016) found increased recall up to 28 days later after atDCS over the left DLPFC for 15 min between encoding and retrieval (stimulation was delivered 24 h after encoding during reconsolidation). Gray and colleagues (2015) found increased hits in a source recognition task for words in red font but not pictures when atDCS was delivered between encoding and retrieval over the left and right DLPFC but not the PPC. Javadi and Cheng (2013) also found improved word recognition after anodal tDCS but no effect of cathodal tDCS when delivered over the left DLPFC for 20 min between encoding and retrieval. Lu and colleagues (2015) found enhanced recognition for Chinese characters after atDCS was delivered before a visual discrimination study task over the left LPFC (CP3) but not the occipital cortex. Over the occipital cortex, atDCS led to increased hits for the visual discrimination task at study but not the recognition test. Leshikar and colleagues (2017) and Leach and colleagues (2018) found increased recall in older and younger adults for face-name associations after 25 min of atDCS over the left DLPFC during encoding.

Pergolizzi and Chua (2015) found enhanced word recognition after atDCS was delivered for 20 min (mostly during retrieval) over the right PPC. Jones and colleagues found increased verbal recall after atDCS delivered over the PPC for 15 min mostly during encoding, but this effect was not replicated in a subsequent study. Flöel and colleagues (2012) found an increase in object-location recall after delivering anodal tDCS for 20 min during encoding over the right temporoparietal cortex (CP4). England and colleagues found an increase in recall for locations after atDCS over the left PPC for 20 min before encoding. Pisoni and colleagues (2015a) found increased face-name recognition after

atDCS was delivered over the left ATL for 15 min during retrieval. Matzen and colleagues (2015) found increased recall for face-name associations after atDCS was delivered over the left VLPFC for 30 min during encoding.

Fewer studies have examined effects of cathodal tDCS, but they have found mixed results ranging from impairment to enhancement. With proportion of hits, a study by Elmer and colleagues (2009) supported the idea that cathodal tDCS can interfere with the amount of information recollected; they found decreased verbal recall after cathodal tDCS was delivered for five min. However, this may not be a sufficiently long duration to make conclusions about the effects of cathodal tDCS, which may change across duration and current strength (Bonaiuto & Bestmann, 2015).

However, a few studies found decreased hits after anodal tDCS or increased hits after cathodal tDCS, showing that the direction of effects is not always consistent. Gaynor and Chua (2016) found that anodal tDCS over the left PFC (CP3) led to decreased word recognition when delivered for 25 min mostly during encoding. Smirni and colleagues (2015) found that cathodal tDCS led to increased verbal recognition when delivered over the right DLPFC for 20 min between encoding and retrieval, while atDCS had no effect, and Marián and colleagues (2018) found that atDCS over the right DLPFC lowered recall for Swahili-Hungarian word pairs when delivered for 15 min between encoding and retrieval.

Moreover, studies have found effects over the DLPFC depending on valence and material. Penolazzi and colleagues (2010) found a selective effect of atDCS over the right DLPFC for pleasant but not unpleasant or neutral images, with increased recognition after atDCS was delivered for 20 min mostly during encoding. Similarly, after 15 min of atDCS over the left DLPFC, Balzarotti and Colombo (2016) found increased recall for pleasant images only. When delivering atDCS for 24 min mostly during encoding, Manuel and

Schnider (2016) found decreased verbal recognition for stimulation over the left DLPFC, while there was increased recognition for nonverbal stimuli over the left PPC.

Although few studies have reported successful modulations of other indices, effects have been reported on composite indices of performance (d': Jacobson, Goren, Lavidor, & Levy, 2012; d: Javadi & Walsh, 2012; Wong et al., 2018; DI: Manenti et al., 2017; A': Leach et al., 2018); reaction time (Lafontaine, Théoret, Gosselin, & Lippé, 2013; Manenti, Cotelli, Calabria, Maioli, & Miniussi., 2013); or false recognition (Boggio et al., 2009 ; Díez et al., 2017; Medvedeva et al., 2018; Pergolizzi & Chua, 2015; 2016; Pisoni et al., 2015a; b; Zwissler et al., 2014). Notably, most studies that reported effects on composite indices did not report that the effect was specific to hits or false alarms, so it remains unclear from these studies whether hits are modulated by tDCS. Thus, anodal tDCS can lead to improved performance in both recognition and recall tasks (Flöel et al., 2012; Meinzer et al., 2012), while cathodal tDCS can exert the opposite effect (Javadi, 2011; Javadi & Walsh, 2011). However, modulations have been inconsistent even when similar parameters were implemented (e.g. Matzen et al., 2015 vs Pisoni et al., 2015b). These findings and the parameters that have influenced them are reviewed in Table 4.2.1.

Stimulation site and time of administration may be one of the most important parameters and among the first to be determined in designing a tDCS experiment, but it remains unclear which stimulation site and time of administration are most effective. Episodic memory processes rely on a distributed cortical network that can include regions in the temporal, frontal, and parietal lobes. For example, the ATLs were identified as critical regions in encoding for categorical information and semantic retrieval (Boggio et al., 2009; Chi, Fregni, & Snyder, 2010; Nikolin et al., 2015; Pisoni et al., 2015a). In line with their hypotheses, Boggio and colleagues (2009) found a selective modulation of false recognition after anodal tDCS to the left ATL, concluding that their results confirmed the role of the left ATL in semantic encoding and that tDCS could successfully modulate

memory improvement. On the other hand, Chi and colleagues (2010) found that impairing the left ATL led to a reduction of visual false memory with no effect on hits. They concluded that their results confirm the role of the left ATL in semantic memory, specifically categorical visual encoding, so impairing the left ATL would lead to more verbatim encoding and less false recognition.

These two studies aimed to examine the effect of impairing the same region yet found completely contradictory results. Chi (2010) explained this discrepancy by arguing that tDCS effects were dependent on task and the baseline state of neural activity; Boggio and colleagues used a semantic task whereas Chi used visual shapes (not as semantic), and Chi implemented the same offline tDCS duration but a longer online duration so that it covered the entire task. Nonetheless, both studies additionally examined the same montage: anodal tDCS on the left ATL and cathodal tDCS on the right ATL, and similar stimulation sites (T3), although Chi and colleagues stimulated a slightly more ventral region (between T7 and FT7). The reason for discrepant effects likely lies in a combination of factors and individual differences.

Pisoni and colleagues (2015a) found a selective modulation of hits following anodal tDCS at test over the ATL. They explained their conflicting results with task differences: in contrast to Boggio and colleagues (2009), they did not use a semantic task designed to elicit false memory. Nikolin and colleagues (2015) attempted to stimulate the medial temporal lobe but through a more parietal region (T9), but they did not find significant effects of tDCS on episodic memory tasks, although analyses on the serial position effect of recall suggested impaired long-term memory (greater recency effect but not primacy effect). Nonetheless, the ATL was functionally and causally related to semantic processing.

The studies designed tDCS administration to maximise offline effects, online effects, and after-effects, thus disentangling when tDCS had an effect. In addition, these

studies are illustrative of the complexity of tDCS interactions with parameters and tasks. Although these studies were similar in population and task, in that they were conducted in younger adults and implemented recognition tasks, these and other factors have varied and also play a role. Few studies have examined (Manenti, Cotelli, Calabria, Maioli, & Miniussi., 2013) and found effects (Leshikar et al., 2017; Medvedeva et al., 2018) on older adults. However, research in other domains suggests that tDCS effects may be equal if not greater for older adults compared to younger adults (Berryhill, Peterson, Jones, & Stephens, 2014). Manenti and colleagues (2013) presented the first study to compare memory-enhancing effects of atDCS on both hemispheres of the DLPFC and parietal cortex in younger and older adults. Although they did not report any specific hypotheses, it could be hypothesised that there would be a hemisphere-specific effect for older adults but not younger adults in line with the HAROLD model of functional asymmetry in older adults. Similar to previous studies, they delivered partially offline and partially online tDCS at retrieval in the hope of increasing after-effects, and they found bilateral effects for younger adults but not older adults, who showed improved recognition only after atDCS to the left hemisphere. Only a handful of studies in episodic memory examined tDCS effects on older adults, and only one other study has directly compared older and younger adults with a similar procedure (Medvedeva et al., 2018). Flöel and colleagues (2012) and Sandrini and colleagues (2014; 2016) also found enhancing effects of tDCS, in delayed recall. Both Sandrini (2016) and Flöel (2012) delivered online encoding atDCS, but Flöel (2012) stimulated the right TPC and delivered atDCS for longer (20 vs 15 min), while Sandrini (2016) delivered offline encoding atDCS as well, confounding offline and online effects. Like Sandrini (2016) and Manenti (2013), Sandrini (2014) delivered tDCS to the DLPFC, but the time of administration was consolidation (24 h after encoding).

Thus, in addition to the lack of clarity surrounding online and offline effects, it is unclear whether the magnitude of tDCS modulation differs for older and younger adults.

This could be relevant to increasing research with older adults and facilitating clinical application, since tDCS could be ineffective with younger adults because cognitive function is generally strong and there is little room for modulation. In other domains, such as working memory, research suggests that tDCS differentially modulates task performance between younger and older adults, with greater effects for older adults (Berryhill, 2015). This could be because older adults struggle with the tasks, and because tDCS is sensitive to baseline network activity, modulations could be greater for challenging tasks in which the network is more engaged in effortful activity.

In line with this proposal emphasising the importance of task difficulty, researchers have found differences in tDCS effects depending on the cognitive task (as seen in the above example). Specifically, there could be differences between recall and recognition, as several studies have demonstrated. Two studies directly compared tDCS effects on recall and recognition: Jones and colleagues (2014) found enhancements in recall under certain conditions but ceiling effects for recognition prevented tDCS from increasing performance. Similarly, Matzen and colleagues (2015) found increased recall for names but no tDCS effects on recognition. In contrast, Nikolin and colleagues (2015) did not find effects on recall or recognition, but it is important to note that Nikolin used a short-term episodic recall task (Rey Auditory Verbal Learning Test), so the task could have been less challenging and facilitated by short-term memory or verbal fluency.

It is sensible to expect limited (if any) effects of tDCS on the outcome measure; not because there is an absence of a real effect, but because of the heterogeneity in methods and modulations reported. Meta-analyses can be weakened by dissimilarity in studies, particularly if there is a low sample size of studies, as is the case here. Even the reported effects could be weak when converted to the same effect size, given the limitations of exploratory research, including low sample size and lack of systematic variation. Since standard protocols have not been established, there can be a lack of clear rationale or

justification for decisions made, which further weakens the experimental design and methodological rigour.

Nonetheless, this is the first meta-analysis and systematic review conducted on studies of tDCS on episodic memory in healthy older and younger adults. Thus, the aim of the meta-analysis was to provide a summary effect size and provide evidence of parameter-specific modulations, enabling a better understanding of the state of the field and an idea of future directions for research, particularly that which strives for clinical application. Specifically, the findings could be applied to development of standardised tDCS parameters and experimental designs. The more the parameters interact with participant characteristics and engagement, the more important they may be in determining tDCS effects (Berryhill, Peterson, Jones, & Stephens, 2014; Miniussi, Harris, & Ruzzoli, 2013). Thus, it can be expected that stimulation site, time of administration, retrieval task, and age would yield larger moderation effects than current density, montage, and delay. The evidence for tDCS effects seems to be in favour of a longer stimulation duration because tDCS modulates cortical excitability over time (Nitsche et al., 2000); recall tasks that are more challenging (Berryhill et al., 2015); and the older population who could benefit more from tDCS modulation (Heise, Niehoff, Feldheim, Liuzzi, Gerloff, & Hummel, 2014; Manenti, Cotelli, Robertson, & Miniussi, 2012). There may also be support for a larger current density because the current strength would be strong over the entire surface area (Polanía, Nitsche, & Ruff, 2015).

Aims. There are few systematic or replication-based studies to provide evidence for the efficacy of tDCS and the importance of specific parameters, so the aim of this meta-analysis was to provide a pooled effect size for tDCS effects across episodic memory studies and identify which parameters underlie stronger tDCS effects.-Specifically, the meta-analysis aimed to provide a pooled effect of polarity-specific tDCS (anodal and cathodal) on hits and associated reaction times. In addition, the meta-analysis investigated

several tDCS parameters and task characteristics as moderators: stimulation site; time of administration; current density; montage; retrieval task; age of participants. Only studies that administered one session of tDCS were included in the primary meta-analyses, mainly because studies examining multiple sessions of tDCS on episodic memory were scarce. However, a secondary, exploratory meta-analyses was conducted on a small sample of eligible multiple-session studies. The results of the latter meta-analysis are included below the main results.

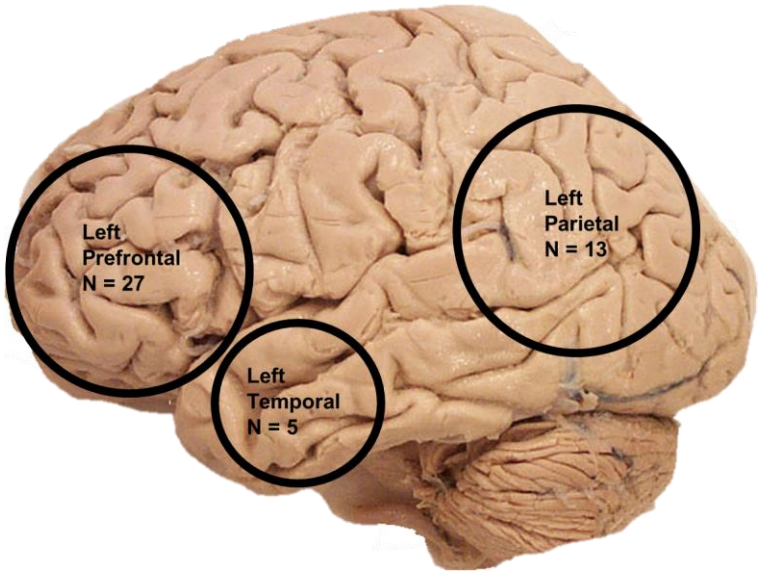

Figure 4.1.1. Most frequent stimulation sites in the current systematic review and meta-analysis. N denotes how many effect sizes targeted the stimulation site.

From "Human brain, lateral view", by G. G. del Caño, 2004 (https://www.flickr.com/photos/euskalanato/1971828859). Copyright [2004] by Gontzal García del Caño. Adapted with permission (https://creativecommons.org/licenses/by-nc-sa/2.0/).

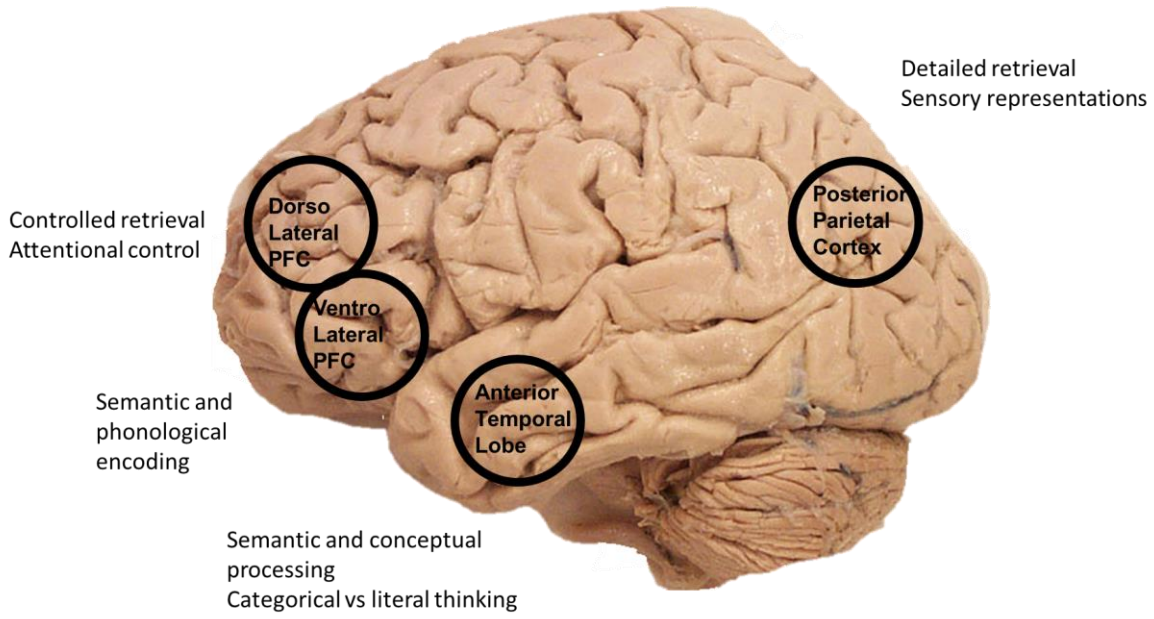

Figure 4.1.2. Common stimulation sites in tDCS research of episodic memory and their functions.

From "Human brain, lateral view", by G. G. del Caño, 2004 (https://www.flickr.com/photos/euskalanato/1971828859). Copyright [2004] by Gontzal García del Caño. Adapted with permission (https://creativecommons.org/licenses/by-nc-sa/2.0/).

Method

Literature review. A systematic literature review was conducted through MEDLINE (PubMed), Web of Science, and Scopus (EBSCO) databases, from the first available date to September 2018. The following keywords were selected based on previous tDCS meta-analyses: ("tDCS" OR "transcranial direct current stimulation" OR "NIBS") AND memory. Additional searches were conducted in retrieved articles and previous tDCS reviews and meta-analyses.

Eligibility criteria. The meta-analysis included published, methodologically-sound studies of single-session tDCS on episodic memory tasks in healthy younger and older adults. Specifically, studies were included if they were published in English; a control group and appropriate blinding was implemented; the samples were healthy younger or

older adults (>18 years old); and the outcome measure (hits) was available in the article or upon request. Studies were excluded if they did not include long-term episodic memory tasks. For example, short-term episodic measures such as the RAVLT and digit span (i.e. <15 items in the list) were excluded from analysis. In addition, tasks with immediate recall and recognition within the study cycle were considered short-term (Gavett & Horwitz, 2011). Thus, the episodic tasks tested memory for material learned within the encoding context (rather than semantic, decontextualized knowledge) and included a sufficient number of stimuli and delay between study and test. Tasks with lists of greater than 25 items or with a five-minute delay following lists of 15-25 items met this criteria. If studies included short-term memory tasks, those measures were excluded from analysis. Consequently, if studies did not include long-term memory tasks, they were excluded. Only published papers were included. The recommendation for meta-analyses is to include unpublished as well as published work, but particularly in the tDCS field where published work can be methodologically questionable, unpublished work may be even more susceptible.

The outcome measure was hits, which were calculated as the percent of correctly recalled or recognised items with respect to the total number of items. Other outcome measures were not examined because they were recognition-specific (i.e. false alarms) or were calculated based on recognition-specific measures (i.e. d', discrimination index). A secondary outcome measure was reaction time for hits, because this measure was not collected in recall or available from the authors for recognition. Thus, separate meta-analyses were conducted for tDCS effects on hits and reaction times.

Meta-analyses were conducted for the effects of anodal and cathodal tDCS vs sham on hits and associated reaction times. Hedges' *g* (Hedges & Olkin, 1985) was the measure of effect size, calculated based on standard mean differences, because it provides a more unbiased estimate for small sample sizes (compared to Cohen's *d*; Borenstein, Hedges,

Higgins, & Rothstein, 2009). Dependency needs to be considered in crossover designs, so the standard deviation of the sham group was used to calculate standardised mean differences and an assumed correlation of $r = .50$ was used to estimate the correlation between dependent variables, given that this information was not available for most studies (only 12). The assumed correlation was supported by a smaller meta-analysis (anodal vs sham on hits) on the twelve studies with dependency information ($r = .55$) and sensitivity analyses using more extreme correlations ($r = .30$, $r = .70$) showed similar results.

Moderation analyses included six *a-priori* factors: stimulation site, stimulation duration, montage, current density, time of administration, and retrieval task. There were also four *post-hoc* factors, two of which were suggested by a reviewer: participant age, delay between stimulation and test, levels of processing, and encoding task.
Most moderators included only two levels: retrieval task was coded as recall or recognition; stimulation duration was coded relative to 10 min (≤10 min or >10 min; Hill, Fitzgerald, & Hoy, 2016); current density was coded relative to 0.029 mA/cm^2 (≤0.029 or >0.029; Hill, Fitzgerald, & Hoy, 2016); montage was coded as unilateral or bilateral; age was coded as younger or older adults (Berryhill, Peterson, Jones, & Stephens, 2014); levels of processing was coded as deep or shallow (Craik & Lockhart, 1972); and encoding task was coded as intentional or incidental (Silas & Brandt, 2016; Téllez-Alanís & Cansino, 2004).

Multiple levels were included in stimulation site (seven levels: left and right frontal; left and right parietal; left and right temporal; midline occipital; Brunoni & Vanderhasselt, 2014) and time of administration (seven levels: offline encoding, online encoding, online retrieval, online encoding and retrieval, between encoding and retrieval, partly offline but mostly online retrieval, partly offline but mostly online encoding; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). The partly offline conditions lasted less than 5 min and then online stimulation continued through the task, following most

studies that delivered offline and online stimulation in the same condition. In addition, there were multiple levels of delay between stimulation and test, coded with four levels: the test was less than 5 min after end of the stimulation, or the delay was between one hour and 24 h, or the delay was more than 24 h. Previous tDCS studies suggest that there could be differences between immediate and delayed memory tests (e.g. Sandrini et al., 2014; Sandrini et al., 2016). Although moderation results are available for all meta-analyses, only moderator results for ten or more effect sizes are considered reliable (Higgins & Green, 2008).

Data extraction. Means and standard deviations for hits and reaction times were extracted from each study and requested from authors if unavailable. Outcome measures were averaged across conditions that were unrelated to moderators (i.e. retrieval task) or experimental conditions. These conditions that were not of interest included: valence of stimuli, encoding instructions, number of repetitions at encoding, semantic relatedness at encoding, stimulus modality, recollection task, and number of repetitions of presented stimuli between study and test).

Half of studies (N = 14) included a crossover design with the conditions of interest (stimulation site, time of administration, and delay between tDCS and test), so these conditions were treated as independent data. Although the assumptions of the meta-analysis are violated by calculating distinct effect sizes for the same set of data, the model included random effects at the study level, controlling for dependencies within the data. This enabled the use of a substantial set of data and preservation of individual effect sizes. The results were confirmed and the analysis was further validated by a separate analysis in metaSEM, which computes the model of random effects using a different strategy.

Characteristics of the studies. Methodological quality was assed following the standard method of Higgins and Green (2008): studies were single or double-blind, randomised, and sham-controlled. Although the control groups differed in the way sham

stimulation was applied, studies reported that the stimulation resembled the sensations of the experimental group stimulation. Thus, the sham groups were appropriate, in spite of variability.

Table 4.2.1

Overview of studies

Study	**Exp**	**Total sample size**	**Age**	**Design** (active/ control)	**Encoding task**	**Findings**	**Montage Polarity[1]**	**Anode || Cathode**	**Duration (min)**	**Current Density (mA/cm^2)**	**Phase**	**Retrieval task**
Boggio et al., 2009	1	30	Y	Parallel[2]	Intentional deep	No effect on hits Reduced false alarms after bilateral and unilateral atDCS	Bilateral and unilateral a-tDCS	T3 || T4	10	0.06	5 min before and 5 min during encoding and retrieval	Recognition
Elmer et al., 2009	1	20	Y	Crossover	Intentional N/A	No effect on hits (long-term retrieval) Reduced hits after cathodal tDCS to left DLPFC	a-tDCS, c-tDCS	F3 || mastoid (n=10) F4 || mastoid (n=10)	5	0.05	During short-term encoding and retrieval; long-term retrieval offline	Recall

Penolazzi et al., 2010	1	12	Y	Crossover	Intentional deep	No effect on hits Increased recall for pleasant images after right DLPFC atDCS and for unpleasant images after left DLPFC atDCS	Bilateral	Between F3 and C3 || between F4 and C4 Between F3 and C3 || between F4 and C4	20	0.03	5 min before and 15 min during encoding	Recall
Flöel et al., 2012	1	20	O	Crossover	Incidental shallow	Increased hits in delayed recall after atDCS to right temporoparietal	a-tDCS	CP4 || LSO	20	0.03	During encoding	Recall
Jacobson, Goren, Lavidor, & Levy, 2012	1	24	Y	Parallel (12/12)	Intentional shallow	Increased d' after atDCS over left intraparietal sulcus	Bilateral	P3 || P6 P6 || P3	10	0.04	7 min before and 3 min during encoding	Recognition
Javadi and Walsh, 2012	1	16	Y	Crossover	Intentional shallow	Increased accuracy after anodal	a-tDCS, c-tDCS	F3 || RSO RSO || F3	20	0.08	During encoding	Recognition

						tDCS and decreased accuracy after cathodal tDCS					
Javadi and Walsh, 2012	2	16	Y	Crossover	Intentional shallow	Decreased accuracy after cathodal tDCS	a-tDCS, c-tDCS	F3 || RSO RSO || F3	20	0.08	During retrieval	Recognition
Javadi and Cheng, 2013	1	30	Y	Crossover	Intentional deep	Increased hits after atDCS to left DLPFC No effect of cathodal tDCS	a-tDCS, c-tDCS	F3 || RSO RSO || F3	20	0.12	Between encoding and retrieval (during memory reactivation in the *consolidation group*)	Recognition
Lafontaine, Théoret, Gosselin, & Lippé, 2013	1	11	Y	Crossover	Intentional shallow	No effect on hits Faster RT after atDCS over the right DLPFC	Bilateral	F3 || P4 F4 || F3	15	0.04	Before encoding	Recognition
Manenti, Cotelli, Calabria,	1	64	Y (n=32)	Crossover	Intentional deep	No effect on hits	a-tDCS	F3 || RSO and F4 ||	6	0.04	2 min before and 4	Recognition

Maioli, & Miniussi., 2013			O (n=32)			Faster RT after atDCS to left DLPFC in older adults and to left and right DLPFC in younger adults		LSO (n=16) P3 || RSO and P4 || LSO (n=16)			min during retrieval	
Jones, Gözenman, & Berryhill, 2014	1	20	Y	Crossover	N/A	Increased hits in recall after atDCS to PPC	a-tDCS	P3 || RC	15	0.04	3 min before and 12 min during encoding	Recognition & recall
Jones, Gözenman, & Berryhill, 2014	2	20	Y	Crossover	N/A	No effect on hits	a-tDCS	P3 || RC	15	0.04	Between encoding and retrieval	Recognition & recall
Jones, Gözenman, & Berryhill, 2014	3	20	Y	Crossover	N/A	No effect on hits	a-tDCS	P4 || LC	15	0.04	3 min before and 12 min during encoding	Recognition & recall
Jones, Gözenman, &	4	20	Y	Crossover	N/A	No effect on hits	c-tDCS	P4 || LC	15	0.04	3 min before and 12	Recognition & recall

Berryhill, 2014											min during encoding	
Sandrini et al., 2014	1	36	O	Parallel (24/12)	Intentional shallow	Increased hits after tDCS over left DLPFC after 2 and 28 days	a-tDCS	F3 || RSO	15	0.04	Between encoding and retrieval (during memory reactivation in the *reminder group*)	Recall
Zwissler et al., 2014	1	96	Y	Parallel (48/48)	Intentional N/A	No effect on hits Increased false recognition after atDCS and decreased false recognition after cathodal tDCS	a-tDCS (n= 24)/ c-tDCS (n=24)	F3 || RS RS || F3	15	0.03	5 min before and 10 min during encoding	Recognition
England et al., 2015	1	12	Y	Crossover	Intentional shallow	No effect on recognition Increase in location	a-tDCS	P3 || P4 P4 || P3	20	0.08	Before encoding	Recognition

						recall after atDCS over left PPC						
Gray et al., 2015	1	96	Y	Parallel (72/24)	Incidental deep	Increased hits after atDCS over left and right DLPFC for font source test alone	a-tDCS	F3 || RSO (n=24) F4 || LSO (n=24) P5 || RSO (n=24)	20	0.06	Between encoding and retrieval	Recognition
Lu, Wang, Chen, & Xue, 2015	1	20	Y	Crossover	Intentional shallow	Increased hits after atDCS to left LPFC	Bilateral	FC5 || FP2	20	0.06	Before encoding	Recognition
Lu, Wang, Chen, & Xue, 2015	2	17	Y	Crossover	Intentional shallow	No effect on hits Increased accuracy in visual encoding judgment	Bilateral	Oz || FP2	20	0.06	Before encoding	Recognition
Matzen et al., 2015	1	24	Y	Parallel (12/12)	Intentional shallow	Increased hits for recall but not recogniti on	a-tDCS	F9 || RUA	30	0.18	During encoding	Recognition and recall
Nikolin et al., 2015[3]	1	16	Y	Crossover	Intentional N/A	No effect on hits	HD-tDCS	P9 F3 CP5	20	0.18	5 min before and 15	Recognition & recall

						Increased rate of learning					min during encoding	
Pergolizzi and Chua, 2015 [69]	1	52	Y	Parallel (26/26)	N/A	No effect on hits Increased false recognition after atDCS over left PPC	Bilateral	CP3 || CP4	10	0.06	5 min before and 5 min during retrieval	Recognition
Pergolizzi and Chua, 2015	2	72	Y	Parallel (48/24)	N/A	Increased hits after atDCS over right PPC Increased false recognition after atDCS over left PPC	Bilateral	CP3 || CP4 (n=24) CP4 || CP3 (n=24)	20	0.06	5 min before and 15 min during retrieval	Recognition
Pisoni et al., 2015a	1	44	Y	Parallel (30/14)	Intentional shallow	Increased hits after atDCS over left ATL Decreased false recognition after atDCS	Bilateral	P3 || P4 (n=15) T3 || T4 (n=15)	15	0.04	During retrieval	Recognition

						over left PPC						
Pisoni et al., 2015b	1	12	Y	Crossover	Intentional shallow	No effect on hits Increased false recogniti on after atDCS over left ATL	a-tDCS	T3 || RSO	20	0.08	14 min before and 6 min during encoding	Recall
Pisoni et al., 2015b	2	12	Y	Crossover	Intentional shallow	No effect on hits No effect on false recogniti on	c-tDCS	T3 || RSO	20	0.08	14 min before and 6 min during encoding	Recall
Pisoni et al., 2015b	3	12	Y	Crossover	Intentional shallow	No effect on hits Decrease d false alarms after atDCS over left VLPFC	a-tDCS	F5 || RSO	20	0.08	14 min before and 6 min during encoding	Recall
Smirni et al., 2015	1	20	Y	Crossover	Incidental deep	Increased hits after cathodal tDCS over right but not left DLPFC	c-tDCS	F3 || RS F4 || LS	20	0.03	Between encoding and retrieval	Recognition

Smirni et al., 2015	2	16	Y	Crossover	Incidental deep	No effect on hits	a-tDCS	F3 || RS F4 || LS	20	0.03	Between encoding and retrieval	Recognition
Sandrini et al., 2016	1	28	O	Parallel (14/14)	Intentional shallow	Increased recall after 2 and 28 days after atDCS over left DLPFC	a-tDCS	F3 || RSO	15	0.04	During encoding	Recall
Balzarotti and Colombo, 2016	1	42	Y	Parallel (28/14)	Intentional N/A	No effect on hits overall Increased hits for pleasant but not neutral or unpleasant images after atDCS over left DLPFC	a-tDCS (n= 14)/ c-tDCS (n=14)	F3 || LM LM || F3	15	0.03	5 min before and 10 min during encoding	Recall
Chen, Lo, Liu, & Cheng, 2016	1	36	Y	Crossover	Intentional shallow	No effect on recognition Decrease in source accuracy after	a-tDCS (n= 18)/ c-tDCS (n=18)	P3 || RC RC || P3	10	0.04	2 min before and 8 min during retrieval	Recognition

						cathodal tDCS over left PPC						
Gaynor and Chua, 2016	1	72	Y	Parallel (48/24)	Intentional deep	Decreased hits after atDCS to left PFC	Bilateral and unilateral a-tDCS	F3 || RSO (n=24) CP3|| CP4 (n=24)	25	0.06	5 min before and 20 min during encoding	Recognition
Manuel and Schnider, 2016	1	26	Y	Crossover	Intentional N/A	Increased hits for non-verbal stimuli after atDCS over PPC and decreased hits for verbal stimuli after atDCS over left but not right DLPFC	Bilateral	F3 || RSO and F4 || LSO (n=13) P3 || RSO and P4 || LSO (n=13)	24	0.03	4 min before and 20 min during encoding	Recognition
Pergolizzi and Chua, 2016	1	54	Y	Parallel (36/18)	Intentional deep	No effect on hits but decreased false	Bilateral	CP3 || CP4 (n=18) F3 || F4 (n=18)	20	0.06	5 min before and 15 min	Recognition

						alarms for atDCS over PPC but not DLPFC					during retrieval	
De Lara et al., 2017[6]	1	30	Y	Crossover	Intentional deep	No effect on hits but moderate support for the null hypothesis	HD-tDCS	AF3	20	0.33	12 min before and 8 min during encoding (n=15) or 15 min before and 5 min during retrieval (n=15)	Recall
Díez et al., 2017	1	65	Y	Parallel (43/22)	Intentional deep	No effect on hits but decreased false alarms for atDCS over ATL compared to Sham for associative but not	a-tDCS (n= 22)/ c-tDCS (n=21)	FT9 || RS RS || FT9	20	0.06	7 min before, 8 min during and 2 min after encoding	Recognition

						categorical lists						
Habich et al., 2017	1	43	Y	Parallel (22/21)	Intentional N/A	No effect on hits but increased hits for midlist words in low performers	a-tDCS	F3 || RSO	20	0.03	5 min before encoding, 10 min during encoding /test cycles, 5 min after encoding	Recognition & recall
Leshikar et al., 2017	1	42	Y	Parallel (21/21)	Incidental shallow	Increased hits in recall but not recognition on day 1 (immediate) and day 2 (delayed)	a-tDCS	F3 || RUA	25	0.14	4 min before and 21 min during encoding	Recognition & recall
Manenti et al., 2017	1	22	O	Parallel (11/11)	Intentional N/A	Increased recognition accuracy (DI) for atDCS compared to sham on day 3 and day 30 but no	a-tDCS	F3 || RSO	15	0.04	Between encoding and retrieval	Recognition & recall

						effect on day 1 or free recall						
Prehn et al., 2017	1	40	Y (n=20) O (n=20)	Crossover	Incidental shallow	No effect on hits	a-tDCS	T6 || Left frontopolar cortex[4]	20	0.02	During encoding	Recall
Leach et al., 2018	1	96	Y (n=24) O(n=24)	Parallel (24/24)	Incidental shallow	Increased hits and recognition accuracy (A') for younger but not older adults	a-tDCS	F3 || RUA	25	0.14	4 min before and 21 min during encoding	Recognition & recall
Marián et al., 2018	1	66	Y	Parallel (33/33)	Incidental shallow	Decreased hits for atDCS compared to sham	Bilateral	F4 || Cz	15	0.08	Between encoding and retrieval	Recall
Marián et al., 2018	2	52	Y	Parallel (27/25)	Incidental shallow	No effect on hits	Bilateral	F4 || Cz	15	0.08	Between encoding and retrieval	Recall
Medvedeva et al., 2018	1	49	Y	Parallel (32/17)	Intentional deep	No effect on hits Decreased false alarms after	a-tDCS	F7 || RS	10	0.06	Before (n=15) and during (n=17) encoding	Recognition

						atDCS over VLPFC online encoding						
Medvedeva et al., 2018	2	49	Y	Parallel (31/18)	Intentional deep	No effect on hits	a-tDCS	F7 || RS	10	0.06	Before (n=15) and during (n=16) retrieval	Recognition
Medvedeva et al., 2018	3	31	Y	Crossover	Incidental deep and shallow	No effect on hits	a-tDCS	F7 || RS (n=15) P3 || RS (n=16)	15	0.04	During encoding	Recognition
Medvedeva et al., 2018	4	22	O	Parallel (11/11)	Intentional deep	No effect on hits Increased accuracy (DI) after atDCS over VLPFC	a-tDCS	F7 || RS	10	0.06	During encoding	Recognition
Meier and Sauter, 2018	1	32	Y	Parallel (16/16)	Incidental shallow	No effect on hits	a-tDCS	F3 || RSO	20	0.09	During encoding	Recognition
Wong et al., 2018	1	48	Y	Parallel (24/24)	Intentional deep	No effect on hits	a-tDCS	F3 || RSO	20	0.06	Between encoding and retrieval	Recognition
Wong et al., 2018	2	48	Y	Parallel (24/24)	Intentional deep	No effect on hits	a-tDCS	F3 || RSO	20	0.06	Between encoding and retrieval	Recognition

Wong et al., 2018	3	120	Y	Parallel (80/40)	Intentional deep	No effect on hits	a-tDCS	F3 || RSO (n=40) F4 || LSO (n=40)	20	0.06	Between encoding and retrieval	Recognition
Wong et al., 2018	4	80	Y	Parallel (40/40)	Intentional deep	No effect on hits Increased accuracy (d) for the morning	a-tDCS	F3 || RSO	20	0.06	Between encoding and retrieval	Recognition

Note: Y = young adults; O = older adults; NR = not reported; N/A = not applicable; a-tDCS = anodal tDCS, c-tDCS = cathodal tDCS, RSO = right supraorbital area; LSO = left supraorbital area; RC = right cheek; LC = left cheek; RS = right shoulder; LS = left shoulder; RUA = right upper arm; LM = left mastoid; all stimulation sites follow the International 10-20 EEG electrode placement coordinates (see Chapter 2, Designing Experiments with NIBS); [1] '/' denotes polarity is varied between subjects, ',' denotes polarity is varied within subjects. [2]Number of participants per group not available in the paper.[3]High-Definition tDCS.[4]9.5 x 9.5 cm^2 electrode size.

Results

3033 eligible studies were identified, and these were screened for title. 2877 articles were excluded based on title because they did not examine episodic memory, and the remaining 156 were screened based on abstract. 103 articles were excluded based on abstract because they were not empirical studies or did not meet the inclusion criteria for implementing *one* session of tDCS on a *long-term* episodic memory task with *healthy* younger or older adults. The excluded studies implemented multiple sessions of tDCS, examined effects in a clinical sample, implemented a different method of non-invasive stimulation, or used a short-term memory task or a shorter duration of tDCS than established. Of the remaining 53 articles, 13 were examined based on the full text because of methodological reasons. The excluded studies implemented a different method of stimulation, a short-term memory task, or a shorter stimulation duration; included the same data as published in another study; and did not compare with a control group. Data were extracted from the remaining forty studies or requested from the authors if not available, and two articles were excluded because the authors did not provide the unavailable data. A meta-analysis was conducted on the remaining 38 eligible studies.

The studies were assessed for quality based on the criteria for randomized-control trials, and the majority of the studies included an acceptable sham group, randomly assigned participants into two groups (including sham), and blinded the participant and/or the experimenter to the tDCS condition (active or sham). Thus, the studies were methodologically sound and are appropriate for the meta-analysis.

Effects of anodal tDCS. Three extreme outliers on the higher end of the spectrum (>±5) were excluded due to possible reporting error, and they were removed from analyses (the extreme size of the reported effect sizes were unlikely to reflect a true effect, but because the effect sizes were extracted from published papers and the analysis had already started at this point, authors were not contacted for a correction). Thus, the final sample

size for effects was k = 115. There were positive and negative effect sizes for individual studies in the comparison of atDCS vs sham on proportion of hits. However, these effect sizes were relatively small, and the average effect size was in a positive direction but close to zero Hedge's g = 0.11, 95% Cl[-0.02,0.23] and not significant z = 1.63, p = .102. Thus, there was no significant effect of atDCS on proportion of hits in recognition or recall tasks when compared to Sham. However, there was a significant proportion of heterogeneity across effect sizes $Q(114) = 246.88$, $p<.001$, $\sigma^2 = 0.111$. Thus, moderation analyses were conducted to test whether any of the selected moderators would explain differences in effect sizes.

Of the 114 studies, 37 included data for reaction times based on a recognition task. Thus, a meta-analysis was conducted on 37 effect sizes to compare anodal tDCS and Sham on reaction times for hits. Like the effect of atDCS on hits, the effect of atDCS on reaction times was small but in the opposite direction (increasing reaction time) g = 0.06, 95% Cl[-0.11, 0.24] and non-significant z = 0.70, p = .482. However, there was no significant proportion of heterogeneity in effect sizes $Q(34) = 44.31$, p = .161, $\sigma^2 = 0.06$, and there were no significant effects of the moderators of interest.

Effects of cathodal tDCS. The meta-analyses comparing cathodal tDCS and Sham included much smaller sample sizes than the meta-analyses for anodal tDCS (k = 13 for proportion of hits; k = 8 for reaction times). Like effect sizes for anodal tDCS, effect sizes for cathodal tDCS were close to zero in individual studies. The average effect size was not significant z = -0.87, p = .383, although it was in the expected negative direction g = -0.26, 95% Cl[-0.85, 0.33]. The effect of cathodal tDCS on reaction times was also not significant z = 0.81, p = .421 but demonstrated the expected increase in reaction times g = 0.22, 95% Cl[-0.32, 0.76]. There was a significant proportion of unexplained heterogeneity for memory accuracy $Q(12) = 74.84$, $p<.001$, $\sigma^2 = 0.73$ and response times $Q(7) = 25.02$, $p<.001$, $\sigma^2 = 0.32$. Moderator analyses are reported below (See Table 4.3.1).

Moderator analyses. Stimulation site, time of administration, stimulation duration, and task were the only significant moderators. Specifically, stimulation site explained a significant proportion of heterogeneity for cathodal tDCS effects on memory accuracy $Q(4) = 11.74$, $p = .019$, and time of administration showed a significant moderation effect for cathodal tDCS effects on response times $Q(3) = 23.33$, $p<.001$. Specifically, effect sizes were higher and cathodal tDCS showed a greater impairment of memory accuracy over left parietal sites $g = -0.69$, $p = .011$, and effect sizes were larger and reaction time was slower when cathodal tDCS was delivered entirely online encoding $g = 1.36$, $p<.001$. However, the moderation analyses included small sample sizes. While sample size for stimulation site was within the acceptable range ($k = 13$), the subset of left parietal sites included only one effect, and time of administration included less than ten effect sizes ($k = 8$). Thus, both moderation effects should be interpreted with caution.

There were also significant moderation effects of stimulation duration $Q(1) = 4.96$, $p = .026$ and task $Q(1) = 5.50$, $p = .019$ for anodal tDCS effects on memory accuracy. Specifically, recall tasks and longer stimulation durations had larger effect sizes, $g = 0.23$, $p = .025$ and $g = 0.16$, $p = .019$, respectively, than recognition tasks and stimulation duration under ten min, indicating that memory accuracy was higher following atDCS under these conditions. It is interesting to note that while recognition tasks were associated with smaller but still positive atDCS effects $g = 0.06$, $p = .483$, stimulation duration under 10 min led to worse accuracy $g = -0.19$, $p = .005$. In addition, there was a significant moderation effect of levels of processing ($k = 91$) for anodal tDCS on hits, with larger, positive effect sizes for shallow $g = 0.28$, $p = .028$, compared to deep encoding $g = -0.10$, $p = .075$. However, there were no significant moderators of atDCS effects on reaction times, in line with the lack of significant unexplained heterogeneity.

Table 4.3.1.

Results of moderation analyses

Moderator / Sub-group	***G***	**LL**	**UL**	***z***	***P***	***k***	***Q***	***Df***	***p***
Moderators of memory accuracy - anodal tDCS									
Stimulation site							6.81	6	.339
Left frontal*	0.19	0.01	0.37	2.12	.034	61			
Left parietal	-0.02	-0.16	0.12	-0.29	.776	19			
Left temporal	-0.04	-0.46	0.38	-0.19	.852	9			
Midline occipital	0.22	-0.27	0.71	0.87	.382	1			
Right frontal	-0.14	-0.31	0.03	-1.64	.100	10			
Right parietal	-0.14	-0.35	-0.07	-1.33	.185	7			
Right temporal	0.04	-0.12	0.20	0.51	.607	8			
Montage							1.47	1	.225
Unilateral*	0.18	0.01	0.35	2.04	.042	84			
Bilateral	-0.05	-0.26	0.15	-0.51	.608	22			
Time of stimulation							8.37	6	.213
0 - Entirely offline before encoding	0.18	-0.06	0.42	1.44	.150	5			
1 - Partly offline, partly online during encoding	0.35	-0.47	1.16	0.84	.401	11			
2 - Entirely online during encoding	0.09	-0.07	0.25	1.13	.257	44			
3 - Offline between encoding and retrieval	0.20	-0.06	0.45	1.51	.131	32			
4 - Partly offline, partly online during retrieval	0.58	-0.50	1.67	1.06	.290	2			
5 - Entirely online during retrieval	-0.01	-0.28	0.27	-0.06	.956	17			
6 - Online during encoding and retrieval†	-0.47	-1.00	0.07	-1.72	.086	4			

Retrieval task*							**5.54**	**1**	**.019**
Recognition	0.05	-0.10	0.21	0.68	.497	73			
Recall*	0.24	0.03	0.45	2.24	.025	42			
Level of processing*							**6.79**	**1**	**.009**
Deep†	-0.10	-0.21	0.01	-1.78	.075	46			
Shallow*	0.28	0.03	0.53	2.20	.028	45			
Encoding task							0.30	1	.586
Intentional	0.13	-0.04	0.31	1.47	.143	74			
Incidental	0.05	-0.07	0.18	0.87	.384	41			
*Stimulation duration**							4.91	1	.027
≤ 10 min**	-0.19	-0.33	-0.06	-2.79	.005	18			
> 10 min*	0.17	0.03	0.31	2.32	.020	97			
Current density							1.42	1	.234
≤ 0.029 mA/cm^2	-0.02	-0.14	0.10	-0.29	.768	19			
> 0.029 mA/cm^2†	0.15	-0.01	0.30	1.88	.061	96			
Delay							2.25	3	.523
Less than 5 min	0.09	-0.07	0.25	1.08	.279	12			
Between 5 and 60 min	0.02	-0.10	0.13	0.31	.759	42			
Between 61 min and 24 h	0.11	-0.08	0.29	1.14	.252	22			
More than 24 h†	0.38	-0.06	0.81	1.70	.090	15			
Age							0.68	1	.409
Younger	0.04	-0.07	0.16	0.76	.449	96			
Older*	0.42	0.00	0.83	1.97	.049	19			

Moderators of memory accuracy - cathodal tDCS

*Stimulation site**							11.74	4	.019
Left frontal	-0.45	-1.38	0.48	-0.95	.343	8			
Left parietal*	-0.69	-1.23	-0.16	-2.56	.011	1			
Left temporal	-0.03	-0.61	0.55	-0.10	.916	1			
Right frontal	0.80	-0.39	1.98	1.32	.187	2			
Right parietal	-0.19	-0.64	0.26	-0.82	.413	1			
Time of stimulation							3.04	5	.694
Partly offline, partly online during encoding	-0.91	-2.56	0.73	-1.09	.277	3			
Entirely online during encoding	0.62	-0.19	1.44	1.49	.136	2			
Offline between encoding and retrieval	-0.13	-0.44	0.19	-0.80	.424	4			
Partly offline, partly online during retrieval***	-2.37	-3.42	-1.32	-4.43	<.001	1			
Entirely online during retrieval*	-0.69	-1.23	-0.16	-2.56	.011	1			
Online during encoding and retrieval	-0.14	-0.62	0.35	-0.56	.577	2			
Retrieval task							0.36	1	.551
Recognition	-0.45	-1.57	0.67	-0.79	.430	8			
Recall	-0.09	-0.36	0.17	-0.68	.499	5			
Level of processing							1.11	1	.292
Deep	-0.13	-0.44	0.19	-0.80	.424	4			
Shallow	-1.07	-2.52	0.38	-1.44	.149	4			
Encoding task							0.14	1	.710
Intentional	-0.31	-0.97	0.36	-0.90	.367	11			
Incidental	0.07	-0.52	0.67	0.25	.806	2			
Stimulation duration							**0.06**	**1**	**.803**
≤ 10 min	-0.41	-0.95	0.14	-1.46	.145	3			
> 10 min	-0.23	-1.00	0.55	-0.57	.569	10			

Current density							2.46	1	.117
≤ 0.029 mA/cm^2	0.55	-0.36	1.46	1.19	.235	3			
> 0.029 mA/cm^2	-0.49	-1.13	0.14	-1.52	.128	10			
Delay							0.03	2	.986
Less than 5 min	-0.03	-0.61	0.55	-0.10	.916	1			
Between 5 and 60 min	-0.27	-1.42	0.88	-0.46	.646	6			
Between 61 min and 24 h	-0.21	-0.58	0.16	-1.10	.272	2			
Moderators of response times - anodal tDCS									
Stimulation site							0.69	4	.953
Left frontal	0.02	-0.21	0.24	0.14	.888	20			
Left parietal	-0.08	-0.29	0.13	-0.75	.452	7			
Left temporal	0.26	-0.35	0.88	0.84	.399	2			
Right frontal	-0.08	-0.36	0.20	-0.57	.570	4			
Right parietal	0.00	-0.29	0.28	-0.03	.973	4			
Montage							1.61	1	.205
Unilateral	0.02	-0.17	0.21	0.22	.827	33			
Bilateral[†]	0.35	-0.02	0.72	1.83	.067	4			
Time of stimulation							3.31	5	.652
Entirely offline before encoding	-0.04	-0.71	0.64	-0.11	.916	1			
Partly offline, partly online during encoding[†]	0.33	-0.00	0.67	1.95	.051	5			
Entirely online during encoding	0.06	-0.29	0.41	0.35	.726	14			
Offline between encoding and retrieval	-0.15	-0.43	0.12	-1.10	.271	5			
Partly offline, partly online during retrieval	0.07	-0.43	0.57	0.28	.782	1			
Entirely online during retrieval	-0.05	-0.35	0.26	-0.30	.766	11			

Retrieval task							1.41	1	.235
Recognition	0.02	-0.15	0.19	0.24	.808	34			
Recall	0.32	-0.22	0.86	1.16	.245	3			
Level of processing							**5.33**	**1**	**.021**
Deep	-0.11	-0.26	0.04	-1.43	.153	21			
Shallow[†]	0.22	-0.03	0.46	1.74	.083	10			
Encoding task							2.99	1	.084
Intentional	0.10	-0.10	0.30	0.97	.330	31			
Incidental	-0.11	-0.34	0.12	-0.96	.339	6			
Stimulation duration							0.04	1	.844
≤ 10 min	0.08	-0.57	0.74	0.25	.804	10			
> 10 min	0.08	-0.11	0.28	0.85	.393	27			
Current density							0.05	1	.151
≤ 0.029 mA/cm^2	0.10	-0.38	0.58	0.42	.678	8			
> 0.029 mA/cm^2	0.04	-0.15	0.22	0.39	.695	29			
Delay[b]							1.70	2	.428
Less than 5 min	0.21	-0.52	0.94	0.57	.569	3			
Between 5 and 60 min	0.07	-0.18	0.33	0.57	.570	16			
Between 61 min and 24 h	0.02	-0.45	0.49	0.07	.940	7			
More than 24 h									
Age							0.85	1	.355
Young	0.06	-0.13	0.24	0.60	.547	32			
Elderly	0.08	-0.51	0.66	0.25	.801	5			

Moderators of response times - cathodal tDCS[b]

Stimulation site							0.57	2	.751
Left frontal	0.26	-0.45	0.97	0.72	.472	6			
Left temporal	-0.08	-0.66	0.50	-0.26	.792	1			
Right frontal	0.16	-0.49	0.81	0.48	.631	1			
Time of stimulation***							**23.33**	**3**	**<.001**
Partly offline, partly online during encoding	0.03	-0.35	0.41	0.13	.896	2			
Entirely online during encoding***	1.36	0.83	1.89	5.00	<.001	1			
Offline between encoding and retrieval	-0.09	-0.38	0.20	-0.61	.541	4			
Partly offline, partly online during retrieval	-0.03	-0.53	0.47	-0.11	.916	1			
Retrieval task							0.22	1	.637
Recognition	0.29	-0.37	0.96	0.86	.390	7			
Recall	-0.08	-0.66	0.50	-0.26	.792	1			
Level of processing							0.20	1	.652
Deep	0.22	-0.03	0.46	1.74	.083	4			
Shallow	0.01	-0.30	0.31	0.04	.968	4			
Encoding task							0.16	1	.693
Intentional	0.28	-0.40	0.96	0.82	.414	6			
Incidental	-0.02	-0.48	0.44	-0.10	.924	2			
Current density							1.93	1	.165
≤ 0.029 mA/cm^2	0.66	-0.69	2.01	0.96	.338	3			
> 0.029 mA/cm^2	-0.05	-0.28	0.18	-0.42	.677	5			

Delay							0.71	2	.702
Less than 5 min	-0.08	-0.66	0.50	-0.26	.792	1			
Between 5 and 60 min	0.47	-0.39	1.33	1.08	.281	4			
Between 61 min and 24 h	-0.13	-0.50	0.24	-0.71	.479	2			
More than 24 h									

Note: *g* = effect size; LL = lower limit of the 95% CI; UL = upper limit of the 95% CI; *z* = *z*-score associated with the *g* value in the same row; *p* = *p*-value associated with the *z*-score in the same row; *k* = number of effect sizes contributing to *g* in the same row; *Q* = result of the *Q*-test for moderation; *df* = degrees of freedom of the *Q*-test for moderation; *p* = *p*-value of the *Q*-test for moderation. Significant moderator analyses are denoted in bold. [a] The two effect sizes in the Right parietal condition of memory accuracy - cathodal tDCS belong to the same study. Consequently, these two effects sizes cannot be collated using a multi-level model. The reported effect size and 95% CI was computed with a univariate meta-analysis. [b] The moderator analysis included less than ten effect sizes and is thus less reliable than the other moderator analyses. [†] $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$.

Publication bias. Publication bias was tested through funnel plot asymmetry, and because of dependence between effect sizes, a mixed-effects multi-level model was fitted to the distribution, similarly to the conducted moderator analyses. The standard error served as the moderator for each comparison, following the meta-analyses: anodal vs sham on hits; anodal vs sham on reaction times; cathodal vs sham on hits; and cathodal vs sham on reaction times. Significant funnel plot asymmetry was found only for effects of anodal tDCS on hits, b = 3.48, 95% Cl [2.03, 4.93], z = 4.71, p<.001, suggesting publication bias. Asymmetry demonstrates whether studies with greater standard error and in turn, less precision, were associated with inflated effect sizes. Thus, a greater proportion of effect sizes at the boundary for significance would indicate publication bias. The shaded area represents non-significance in a two-tailed t-test given a specific error and effect size. As shown in Figure 4.3.1, the effect sizes for anodal tDCS effects on hits were disproportionately skewed toward the edge of significance, where a lower number of studies is expected. This suggests the possibility of selective publication for significant but not null findings. There was no significant publication bias for the effects of cathodal tDCS on hits b = 0.09, 95% Cl[-4.84, 5.02], z = 0.04, p = .970, or reaction times, b = -6.73, 95% Cl[-28.46, 15.00], z = -0.61, p = .544 (See Figures 4.3.2 and 4.3.4). There was also no evidence of publication bias for effects of anodal tDCS on reaction times, b = 2.32, 95% Cl[-0.36, 4.99], z = 1.70, p = .090 (See Figure 4.3.3).

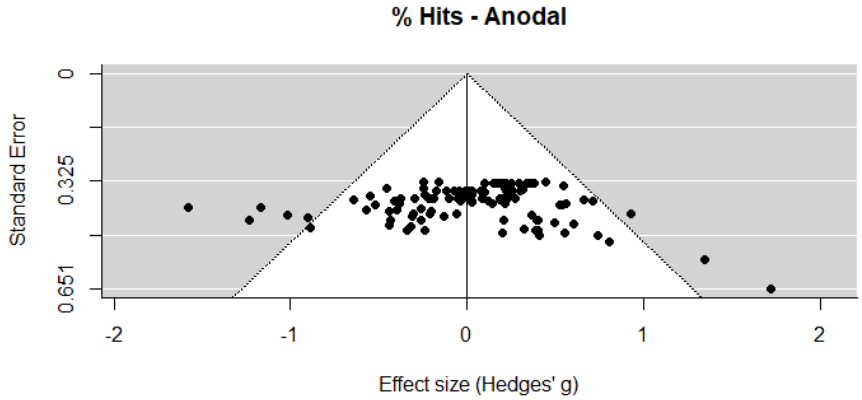

Figure 4.3.1. Funnel plot asymmetry for effects of Anodal tDCS vs Sham on proportion of hits.

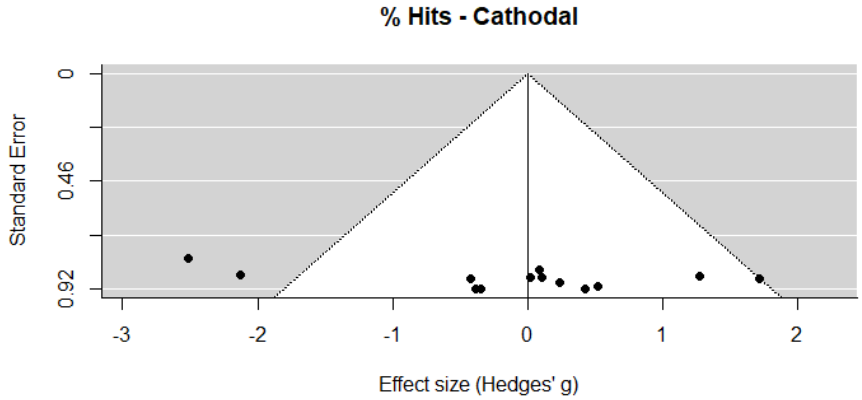

Figure 4.3.2. Funnel plot asymmetry for effects of Cathodal tDCS vs Sham on proportion of hits.

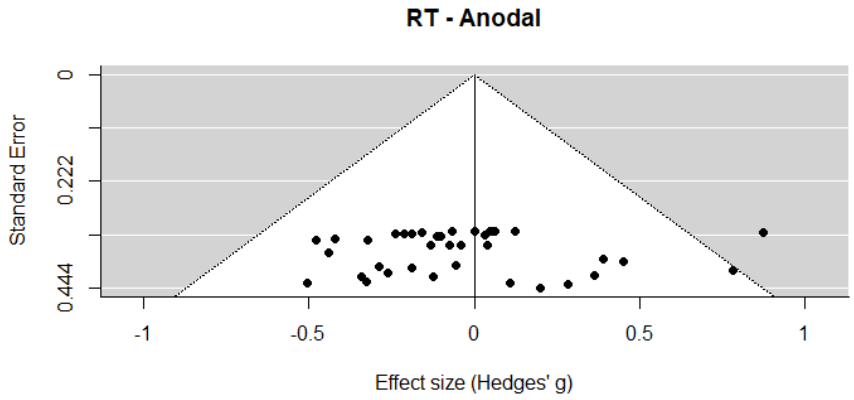

Figure 4.3.3. Funnel plot asymmetry for effects of Anodal tDCS vs Sham on reaction times for hits.

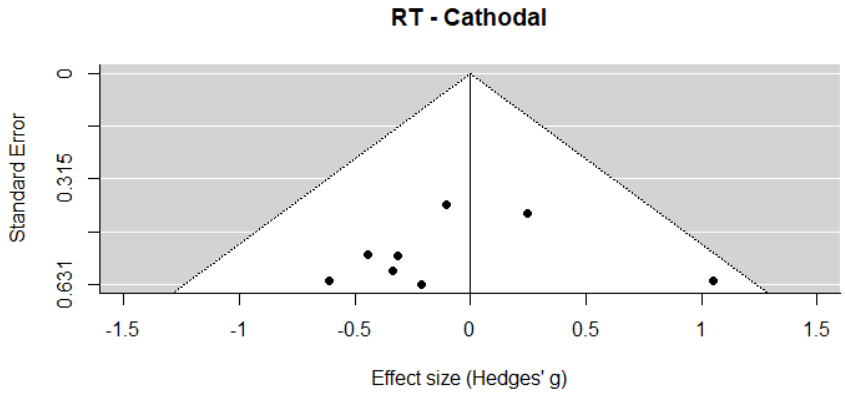

Figure 4.3.4. Funnel plot asymmetry for effects of Cathodal tDCS vs Sham on reaction times for hits.

Multiple sessions. An exploratory meta-analysis was conducted on a small sample of multiple-session tDCS studies on long-term episodic memory. Studies were excluded for not examining long-term episodic memory and for examining working memory or cognitive training instead. In addition, studies were excluded for including a clinical sample. This resulted in a sample size of three studies, and data were not available or provided upon request from one of the studies. Thus, the final sample size included two studies (Kulzow et al., 2018; Meinzer et al., 2014) with effect sizes available for proportion of hits but not reaction times (recall tasks were used in both). The meta-analysis found a significant effect of anodal tDCS compared to Sham on memory accuracy z = 7.39, p<.001 in a positive direction g = 0.65, 95% Cl [0.48, 0.82]. Since there were only two effects, moderator analyses were not conducted.

Discussion

The results revealed no significant effects of anodal or cathodal tDCS on proportion of hits or associated reaction times. Nonetheless, the non-significant effects were in the expected direction: positive effects showed that atDCS increased accuracy, and negative effects showed that cathodal tDCS decreased accuracy, and both polarities of tDCS increased reaction time. Significant moderators included stimulation site (cathodal

tDCS effects on hits), stimulation duration (atDCS effects on hits), retrieval task (atDCS effects on hits), and time of administration (cathodal tDCS effects on reaction times). Although montage (unilateral or bilateral) was not a significant moderator, it remains an important parameter that is closely related to stimulation site and influences the modulation over the targeted region (see Chapter 2, Designing Experiments with NIBS**).** However, strong conclusions can only be made for the moderation effects in anodal tDCS effects on hits, since there was a sufficient number of effects (>10) overall and within each condition. Moderation effects revealed stronger effects of atDCS in increasing memory accuracy following longer durations (>10 min) and at recall compared to recognition tasks. These effects are supported by previous findings that demonstrate longer after-effects after 10 min of tDCS (Nitsche et al., 2003), and recall tasks may be more challenging, increasing the engagement of the stimulated region and leading to greater effects on memory performance (Berryhill, Peterson, Jones, & Stephens, 2014). The small sample sizes in the moderator analyses and within each condition also suggest a need for more research on cathodal tDCS and its effects.

It is important to note that individual and condition-specific (e.g. left parietal) effects for anodal and cathodal tDCS were in both positive and negative directions. For each condition in the moderator analysis, effects varied widely but were mostly close to zero, leading to heterogeneity in effect sizes. Effect sizes are usually not affected by the biases of individual studies (although publication bias may occur, as in the current study), and the average effect size is not usually biased by the number of studies included in the analysis (although a larger sample size is better). Thus, the distributions also show that there was no consistent relationship between number of effects and effect size. This is important because a large number of effects (k = 60) were included in the left frontal condition, but although there was a significant effect, there was no significant moderation.

The greater modulation for recall tasks is in line with state-dependent effects during online stimulation: greater baseline activation of the stimulation site by the cognitive task can lead to stronger modulations, and the stimulation site can be more strongly engaged by a more challenging task. In line with the proposal of state-dependent effects, the difference between recall and recognition may be more critical for stimulation at retrieval than encoding (Miniussi, Harris, & Ruzzoli, 2013). Although no moderation effect was found for encoding task, effect sizes were stronger for intentional encoding in both cathodal and anodal tDCS.

Levels of processing was also a significant moderator. However, the unexpected direction of the effect, with negative, smaller effect sizes for deep encoding and higher, positive effect sizes for shallow encoding suggests that further research is needed to understand effects of atDCS on levels of processing. It remains puzzling that there was a larger effect for shallow than deep encoding since the left DLPFC, thought to be more associated with deep encoding, was the predominant stimulation site and there were an equal number of deep and shallow encoding studies. There was no significant moderation effect of stimulation site, however, suggesting that perhaps the levels of processing effect was driven by strong interactions between shallow encoding and associated regions. On one hand, deep encoding can engage certain regions of the brain (e.g. DLPFC) more and facilitate state-dependent tDCS effects (Blumenfeld & Ranganath, 2007). On the other hand, there may be greater potential for tDCS to modulate cognition after shallow encoding tasks because performance is generally lower (Berryhill, Peterson, Jones, & Stephens, 2014). It seems clear that the effects of tDCS on deep and shallow encoding depend on the extent to which the stimulation site is engaged in each process and the extent to which tDCS generally enhances low compared to high performance. For example, more perceptual and attentional areas of the brain such as the parietal cortex may be engaged in shallow encoding tasks that require attention to perceptual detail. The ATL

may be selectively engaged in deep encoding (Boggio et al., 2009), while the VLPFC may be engaged in shallow as well as deep encoding (Matzen et al., 2015; Pisoni et al., 2015b).

The moderation effect of duration seems to be reliable and is in line with findings demonstrating that longer durations may lead to stronger tDCS modulations, although not in a linear function. Thus, it is also important to consider the maximum effective duration. Current safety guidelines suggest durations below 60 min (Antal et al., 2017), and most included studies that stimulated for over 10 min used durations between 15 and 20 min. It is possible that the optimal duration is between 10 and 15 min, although 20 min may be necessary depending on the cognitive task. It is also notable that although there was no significant effect for cathodal tDCS on hits, effect sizes were stronger for longer durations, reflecting the importance of longer durations.

The effects of various parameters on reaction times for cathodal and anodal tDCS are less clear, particularly because some studies report that faster reaction times accompany higher accuracy, while other studies report slower reaction times. It is notable that although there was no significant overall effect of anodal or cathodal tDCS on reaction time, both polarities showed a positive effect size, indicating increased reaction time. The effect size was numerically higher for cathodal tDCS, perhaps indicating a more consistent increase in reaction time across studies. Moreover, the significant moderation effect indicated a greater increase in reaction time when cathodal tDCS was delivered entirely online encoding. It is sensible that both cathodal and anodal tDCS lead to increased reaction time when delivered during the task (online encoding) because anodal tDCS could lead to greater processing (e.g. semantic elaboration, see Chapter 5, Experiment 1: Discussion) while cathodal tDCS could lead to more effortful processing. Cognitive research seems to suggest more efficient processing associated with faster reaction times, while slower reaction times can indicate the use of a more complex or inefficient strategy (Innocenti et al., 2010). Future research is needed to understand how tDCS and associated

parameters modulate reaction times and whether reaction time is a reliable measure of tDCS effects.

Based on the results of the meta-analysis, the suggestion is to examine each parameter of tDCS and interactions between parameters systematically, within the domain of episodic memory. It is sensible to postulate that tDCS parameters would be specific to a certain cognitive function, such as episodic memory. Thus, findings from studies over the motor cortex or other cognitive domains may not always be applicable to episodic memory. Thus, episodic memory may need a series of rigorous, high-quality methodological studies to establish basic parameters for investigating cognitive functions. In this way, tDCS can become a better research tool and can be used effectively to answer complex questions about function-region relationships and the nature of a specific process.

In addition, good practices could be encouraged with the support of journals to publish null findings. Reproducibility could be increased by sharing data online after publication and thoroughly reporting statistical analyses, including exclusion of outliers and multiple comparisons. In addition, a widespread practice of pre-registration, including a record of a-priori hypotheses and experimental design, would help to ensure the rigour of each new investigation. Replicability could be enhanced by increasing transparency in reporting of methods, particularly any experimental conditions included or analysed that were not significant.

Limitations and future directions. There were several limitations, including sample size. Specifically, the relatively low number of effects in the cathodal tDCS meta-analyses and moderation analyses prevented the presentation of any conclusive evidence. Although the atDCS analyses included larger sample sizes, the measure of heterogeneity was likely to be less reliable, since the presence of publication bias together with results of previous work (Héroux, Loo, Taylor, & Gandevia, 2017) are suggestive of questionable research practices. Heterogeneity can be influenced by a low sample size of included

studies and questionable research practices in individual studies, and heterogeneity in turn affects the results of moderator analyses (Linden, 2018; Linden & Hönekopp, 2018). Although the current meta-analysis could not address the issue of questionable research practices directly, there is evidence that such practices occur in the tDCS field (Héroux, Loo, Taylor, & Gandevia, 2017), including hypothesizing after results are known (HARKing; Kerr, 1998), adjusting sample size unsystematically in the middle of data collection, p-hacking, and selective reporting (Simmons, Nelson, & Simonsohn, 2011). Even with a relatively small sample size, the meta-analysis was the first of its kind to provide evidence, if only preliminary, for the importance of specific tDCS parameters and the need for higher methodological standardisation in the field. However, the meta-analysis only examined published studies. In the presence of publication bias, future studies should include unpublished work. Moreover, the meta-analysis only examined the effects of tDCS on hits Although this enabled a comparison of recognition and recall tasks, tDCS can also modulate different indices of memory, such as false recognition or learning across multiple sessions (Boggio et al., 2009; Simonsmeier et al., 2018). Thus, future meta-analyses should investigate effects of tDCS on false recognition and associated reaction times. As the number of studies examining multiple sessions increase, meta-analyses can combine a larger number of effect sizes to make stronger conclusions about the effects of tDCS at multiple sessions. In addition, future meta-analyses should include a larger and more homogeneous sample of studies that examined the same stimulation site and region.

Finally, the meta-analysis included an exploratory analysis of multiple sessions of tDCS. There were few studies available in episodic memory that examined tDCS effects over multiple sessions. However, the results suggested that tDCS effects may be beneficial over multiple sessions, in line with findings in other domains (e.g. working memory; Talsma, Kroese, & Slagter, 2016), possibly because tDCS may have greater modulations

on learning than retrieval (Simonsmeier et al., 2018). In addition, tDCS important for studies implementing multiple sessions. Future research should confirm this in the episodic memory field and systematically examine the effects of tDCS at multiple sessions.

Future studies in the field should begin systematic, methodologically-targeted studies to better understand the parameters of tDCS that are important for episodic memory. In addition, future studies should examine effects of tDCS across multiple sessions, measuring learning as well as final memory performance. Replications of previous tDCS studies could be conducted, and any studies investigating a similar research question could conduct a closer conceptual replication to the original study. As the number of studies increases, particularly with methodological aims or multiple-sessions of tDCS, another meta-analysis should be conducted to better and more specifically evaluate the efficacy of the tDCS across regions, tasks, and populations.

Conclusion. Although there is little evidence in healthy populations to support that tDCS can be an effective clinical tool, tDCS can certainly be a useful and valuable research tool in episodic memory if developed appropriately. This meta-analysis may serve to suggest an increase in systematic, methodological investigations with larger sample sizes, fewer conditions within the same experiment, and examinations of specific tDCS parameters such as voltage and time of administration (see Chapter 5).

Chapter 5: Assessing tDCS as a Research Tool: A Systematic Investigation of the Effects of tDCS on Episodic Memory

Abstract

Anodal transcranial direct-current stimulation (atDCS) may be a promising research and clinical tool in the field of episodic memory, but effects of atDCS on episodic recall and recognition have been inconsistent, partly due to variation in the time at which atDCS is delivered with respect to the memory task. Specifically, studies over the DLPFC and other cortical regions have examined online effects as well as combinations of offline and online atDCS. atDCS has led to effects when delivered online and offline with respect to the memory task, at encoding and retrieval (i.e. during the study phase). In addition to time of administration, studies have varied widely in other important methodological parameters such as memory task and atDCS current strength. Thus, standardisation of methodology is important for the future use of atDCS, and the following experiments have identified consistent parameters for standardisation. Specifically, five experiments served as a systematic and methodological investigation into the effects of different timings of atDCS administration on episodic recognition in the VLPFC and DLPFC. Three experiments (and two direct replications) examined and found effects of atDCS when delivered online encoding over the VLPFC, also identifying the importance of language and stimuli in episodic memory experiments with atDCS. Reliable effects of atDCS were found at online encoding but not at any other time of administration (offline encoding, offline retrieval, or online retrieval). In contrast, weak effects were found over the DLPFC at offline but not online encoding. Thus, the results of the experiment emphasise the importance of individual parameters and interactions between them, advise future atDCS research and attention to good research practice, and further understanding of the mechanisms whereby atDCS can modulate cognition. In addition, the findings confirm the important roles of the VLPFC and DLPFC in episodic memory.

Overview

The current chapter addresses the reliability of tDCS as a research tool with a methodological investigation of effects of timing of administration. If tDCS reliably reveals causal relationships between episodic memory as indexed with a cognitive task and a specific region, there should be an effect of tDCS on memory performance for regions strongly associated with episodic memory, especially the VLPFC which has previously been shown to be necessary to successful memory formation through rTMS studies. Nonetheless, regions can be critical at different phases in memory: encoding, consolidation, or retrieval. With subtle effects of tDCS, it is unclear whether VLPFC activity would be impacted more at encoding or retrieval. Previous rTMS studies have not targeted the VLPFC at retrieval, only at encoding. Thus, the first set of studies aimed to identify *when* tDCS would lead to an effect on memory performance, if any effect would be present at all. The second set of studies aimed to replicate and extend the significant effect of tDCS over the VLPFC when delivered during encoding. The effects of tDCS on recognition rather than recall were examined because previous TMS studies have found effects at recognition, although fMRI and intracranial EEG studies have also reported activation at recall.

Introduction

Previous studies in developing memory interventions using atDCS have targeted the DLPFC, a region thought to be functionally related to nearly every episodic process (Fletcher, Shallice, & Dolan, 1998; Fletcher, Shallice, Frith, & Dolan, 1998) based on activation found in fMRI studies (Karlsgodt et al.., 2005). Further justification arises from TMS disruption of the DLPFC, which can lead to impaired memory (Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003; Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2010), and patients with DLPFC lesions, who show selective impairments of retrieval. Episodic memory has been extensively studied in the left DLPFC with tDCS, given that the left PFC

is associated with verbal encoding (Nyberg, Cabeza, & Tulving, 1996) and the DLPFC is associated with controlled retrieval (Fuster, 2000). However, the DLPFC may not be the optimal region for stimulation. Despite countless investigations of tDCS effects over the DLPFC, no conclusions could be drawn regarding enhancement of memory processes in the DLPFC, as demonstrated in previous systematic reviews (e.g. Manenti, Cotelli, Robertson, & Miniussi, 2012; Kim, Ekstrom, & Tandon, 2016). In fact, the meta-analysis moderator results (Chapter 4) did not show a significant moderation effect of stimulation site, although the left PFC was associated with a significant positive effect of atDCS.

However, the optimal stimulation site remains unknown, and it remains unclear whether atDCS would lead to cognitive outcomes over the site, given the current inconsistency in findings over the DLPFC and other episodic regions (e.g. PPC and ATL). The methodological rigour of tDCS research in general may be weaker due to a lack of standardisation in the field (see Chapter 4, meta-analysis). Specifically in the episodic memory field, findings may be inconsistent because of a heterogeneity in the timing of administration of tDCS with respect to the memory task and stimulation site. Episodic memory research with fMRI has demonstrated that different functionally-relevant regions are active at distinct times: the left VLPFC and ATL may be active at encoding (Hales & Brewer, 2011), while the left DLPFC and posterior parietal cortex may be more active at retrieval (Achim & Lepage, 2005; Sohn, Goode, Stenger, Carter, & Anderson, 2003; Takahashi, Ohki, & Kim, 2007).

Studies over the DLPFC. The timing-related heterogeneity and inconsistency in findings is clear in tDCS effects over the DLPFC in particular. When delivered *during* the memory test, DLPFC atDCS led to increased recognition accuracy in some studies (Sandrini et al., 2016; Balzarotti & Colombo, 2016) and decreased recognition accuracy in others (Manuel & Schneider, 2016). For example, Pergolizzi and Chua (2016) found that DLPFC stimulation *during* the memory test improved recognition. However, Lafontaine

(2013) found that stimulation delivered *before* the memory test did not improve face recognition. Stimulation *before* the study phase led to improved recognition accuracy in some studies (Lu, Wang, Chen, & Xue, 2015; Pisoni et al., 2015). However, the specific modulation was different: Lu and colleagues (2015) found an increase in correct recognition, whereas Pisoni and colleagues (2015) found a decrease in false recognition.

Thus, while tDCS studies have examined DLPFC modulations at encoding and retrieval, multiple times of administration have been used (i.e. tDCS at offline *and* online encoding), and results have been mixed. It remains unclear *when* tDCS leads to enhanced memory in the DLPFC. Most previous studies have not clearly defined and isolated the time of administration, implementing a mixture of offline and online tDCS without controlling for carryover effects to retrieval. For example, Balzarotti and Colombo (2016) delivered tDCS at online encoding and at offline encoding, while Javadi and Walsh (2011) delivered tDCS at offline encoding, online encoding *and* retrieval. This could contribute to the inconsistency in modulations found over the DLPFC, with some studies reporting an enhancement in recognition (Sandrini et al., 2016; Balzarotti & Colombo, 2016) or recall (Javadi & Walsh, 2011), while others report an impairment (Manuel & Schneider, 2016) or no effect (Balzarotti et al., 2013). In addition, as demonstrated previously by the systematic review and meta-analysis (Chapter 4), the task and associated material can also interact with time of administration to influence tDCS modulations. Balzarotti and Colombo (2016) found an effect of atDCS specific to pleasant but not neutral images, while Javadi and Walsh (2011) found an enhancement on word recall but no significant effect on word recognition.

Another factor that could explain the inconsistency in results and interact with time of administration is the specific role of the DLPFC in encoding and retrieval. The role of the DLPFC in controlled processing has long been established from fMRI and TMS evidence (Macdonald, Cohen, Stenger, & Carter, 2000; Milham, Banich, & Barad, 2003;

Vanderhasselt, De Raedt, Baeken, Leyman, Clerinx, & D'haenen, 2006). However, while the DLPFC is consistently active at encoding and retrieval (Mitchell & Johnson, 2009), interrupting activity in the DLPFC does not always lead to a disruption in memory performance (Balconi & Ferrari, 2012; Gagnon, Schneider, Grondin, & Blanchet, 2011). The inconsistency in rTMS effects suggests that inhibiting the DLPFC can have enhancing or impairing effects depending on the degree to which the task engages executive function (e.g. Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2010). This observation is in line with the theory that the neural network must be active for greater neuromodulation (Silvanto, Muggleton, Cowey, & Walsh, 2007). For example, the DLPFC could be engaged at intentional but not incidental encoding, since intentional encoding may involve more controlled encoding processes. In addition, the findings of fMRI studies have found that DLPFC activation does not always predict subsequent recollection (Anderson et al., 2004; Blumenfeld & Ranganath, 2006; Blumenfeld & Ranganath, 2007; Buckner, Koutsaal, Schacter, Wagner, & Rosen, 1998; Clark & Wagner, 2003; Otten & Rugg, 2001). Thus, the DLPFC could be engaged in more general processes such as top-down modulation of attention that increase the likelihood of successful encoding but not necessarily retrieval (Sandrini, Rossini, & Miniussi, 2008).

Studies over the VLPFC. The VLPFC may be a more optimal site than the DLPFC because of consistent evidence from other domains that implicate a strong role in episodic memory. The VLPFC is also active at encoding and retrieval, but rTMS studies provide more conclusive evidence about the importance of its contribution to episodic memory. Disrupting VLPFC activity has consistently led to memory impairment, particularly in direct comparison with the DLPFC (Blumenfeld et al., 2014; Galli, Feurra, Pavone, Sirota, & Rossi, 2017). Galli and colleagues (2017) found that disrupting the VLPFC but not the DLPFC at encoding led to worse verbal recognition performance, which is in line with the role of the VLPFC in semantic processes that may lead to

successful encoding. Nonetheless, few studies have examined the effects of anodal tDCS on episodic memory when delivered over the left VLPFC, perhaps because the VLPFC has been studied more in other contexts (e.g. working memory and emotion regulation) and functional distinctions between the VLPFC and DLPFC are not yet well-understood (Blumenfeld et al., 2007).

Two of these studies have targeted sites near the inferior frontal gyrus because of previous fMRI activation in face-name encoding tasks. Matzen and colleagues (2015) investigated atDCS effects at online encoding for face-name associations and found significant improvements in recall for names but not face-name associative recognition. Similarly, Pisoni and colleagues (2015a) examined atDCS effects at offline and online encoding for proper names during a face-name task and found lower false recognition for unpresented names but no effects on recall. The inconsistency in results with Matzen and colleagues (2015) could be due to differences in task: Pisoni and colleagues (2015) examined recollection for names alone rather than face-name pairs, and the VLPFC is active specifically for semantic or phonological associations during recognition (Park & Rugg, 2008). In addition, the DLPFC may be more active for non-verbal material (faces) and recall (Epstein et al., 2002). In contrast to the other two studies, Medvedeva and colleagues (2018; Experiment 3), who conducted the study on which the current investigation is based, found no significant effects of online encoding atDCS over the VLPFC on verbal recognition. However, Matzen (2015) and Pisoni (2015a) instructed participants to memorise the words, while the memory test was a surprise for participants in Medvedeva and colleagues (2018). Thus, implementing an incidental memory task could obscure online tDCS effects, which may be state-dependent and require greater engagement from the stimulated region. Although the VLPFC is active at incidental and intentional encoding (Cohen & Berkman, 2013; Dove, Manly, Epstein, & Owen, 2008), online tDCS effects may be too subtle and dependent on baseline network activation to

modulate incidental encoding. It is notable that Galli and colleagues (2017) found rTMS effects using an incidental memory task, but rTMS modulates action potentials, whereas at a much subtler level, tDCS modulates resting membrane potential. Thus, tDCS may be a more successful approach for intentional rather than incidental encoding. In contrast, rTMS may be equally effective in disrupting intentional and incidental encoding.

It is unlikely that the differences between the studies were due to significant differences in other factors. Instead, it is possible that other factors interacted with task and time of administration to yield varying tDCS effects. All three studies implemented methodologically-rigorous designs, so the difference in results should not be due to differences in quality. The studies implemented relatively long durations of tDCS (Matzen: 30 min; Pisoni: 20 min; Medvedeva: 15 min), in line with the findings of the meta-analysis that durations of longer than 10 min increase tDCS effects. Although they implemented similar current strength (1.5 - 2 mA), Pisoni (2015a) and Medvedeva (2018) used 5 x 7 cm^2 electrodes, whereas Matzen and colleagues (2015) used 3.5 x 3.5 cm^2 electrodes, which led to higher current density. As the systematic review (Chapter 4) demonstrated, the interaction of current density with other factors such as time of administration could lead to differences in behavioural modulation. Specifically, higher current density could increase the strength of tDCS effects, and together with long durations, Matzen and colleagues could have increased the behavioural modulation, although it is not clear why there would be a modulation for recall but not recognition. Importantly, the three studies implemented different coordinates: Matzen and colleagues (2015) positioned the active electrode above the IFG (F9), while Pisoni and colleagues (2015a) targeted the site below the IFG (F5) and Medvedeva and colleagues (2018; Experiment 3) stimulated a site thought to be at the pars opercularis, the anterior IFG (F7). The subtle differences in stimulation site between Pisoni (2015a) and Matzen (2015) since the anterior IFG (possibly targeted by F5) is associated with semantic processing and the posterior IFG (F9)

is associated with phonological processing. Since names are more less semantic than vocabulary words (no inherent meaning or categorization), they could be better encoded and subsequently recalled through phonological rather than semantic encoding. In addition, Matzen and colleagues (2015) might have increased focality for the stimulation site by using smaller electrodes, decreasing the likelihood that an adjacent site was directly stimulated. While Medvedeva and colleagues (2018; Experiment 3) likely targeted the anterior IFG, the posterior IFG could have also been captured given the large size of the electrodes. Nonetheless, an effect on phonological or semantic processing would have been visible in associated task performance (shallow and deep processing, respectively).

Accordingly, what effects could result from stimulating the VLPFC with anodal tDCS? The findings of Pisoni and colleagues (2015a) and Galli and colleagues (2017) suggest that VLPFC modulations may affect semantic processing and perhaps subsequent false recognition. As mentioned previously, Pisoni and colleagues (2015a) found decreased false recognition following atDCS facilitation of VLPFC processing. Similarly, Galli and colleagues (2017) found a significant increase in false recognition following disruption of the VLPFC, although this was a weaker effect and did not correspond to the time window in which memory impairment was greatest. Implementing tDCS with an intentional encoding task could lead to effects in shallow and deep encoding tasks, following the same design as Medvedeva and colleagues (2018). While Innocenti and colleagues (2014) found differential effects of high-frequency rTMS on deep and shallow encoding when delivered over the DLPFC (greater impairment for shallow), Galli and colleagues (2017) found a similar magnitude of impairment following rTMS at deep and shallow encoding tasks, as demonstrated by the lack of a significant interaction. Nonetheless, fMRI research reveals that although the VLPFC is active at shallow and deep encoding, activation may be greater for deep encoding. This observation is in line with the

function of the VLPFC in semantic elaboration, which is thought to be engaged in deep but not shallow encoding (Bradshaw & Anderson, 1982; Lockhart & Craik, 1990).

Together, the findings suggest that VLPFC modulation through tDCS is dependent on an intentional, semantic encoding task and may affect subsequent recognition when delivered online encoding. However, tDCS could have modulated the VLPFC when delivered at retrieval rather than encoding. The possibility that tDCS affected retrieval cannot be ruled out, since Matzen (2015) and Pisoni (2015a) started the memory tests almost immediately after tDCS administration and after-effects could occur. Although after-effects may not lead to strong behavioural modulations when the stimulation duration is short (>5 min), longer durations can lead to prolonged neurobiological and even behavioural modulations, as demonstrated by effects of offline tDCS on encoding and retrieval (England et al., 2015; Jacobson, Goren, Lavidor, & Levy, 2012; Lafontaine, Théoret, Gosselin, & Lippé, 2013; Lu, Wang, Chen, & Xue, 2015; Pisoni et al., 2015b).

Evidence from neuroimaging suggests that unlike the DLPFC, the VLPFC may be active at encoding and retrieval. However, this finding is yet to be confirmed by rTMS research, which has predominantly targeted the VLPFC at encoding. Thus, whether the VLPFC can be modulated at encoding and retrieval remains an important question for further research. In addition, the DLPFC and VLPFC may be active at encoding and retrieval through control operations, as suggested from single-cell recordings of DLPFC and VLPFC neurons (Kennerley & Wallis, 2009), and the DLPFC may exert top-down control over the VLPFC in working memory tasks (Wolters & Raffone, 2008). On the other hand, the DLPFC may be less critical to verbal memory formation in general as suggested by TMS studies comparing inhibitory effects on the DLPFC vs the VLPFC. Galli and colleagues (2017) found no consistent impairment when rTMS was delivered over the DLPFC, and Blumenfeld and colleagues (2014) even found enhancements when the DLPFC was disrupted. The development of future memory interventions and answers

to research questions could benefit from an understanding of the VLPFC and possible interactions with the DLPFC.

Aims. To the author's knowledge, no study has systematically compared tDCS effects over the VLPFC and DLPFC, and no study has systematically compared the effects of online vs offline stimulation in episodic memory, and this is necessary to understand the cognitive mechanisms of tDCS and develop future application for research and patient interventions. The aims of this study were to further an understanding of tDCS effects on critical regions to episodic memory formation by systematically examining the effects of timing of administration. The current investigation also served to specify relevant interactions between parameters such as task, time of administration, and stimulation site in tDCS research. The effect of tDCS time of administration on recognition accuracy was investigated through four experiments over the VLPFC and DLPFC (see Table 5.0.1). Specifically, Experiment 1 examined the effects of delivering tDCS offline or online with respect to encoding, and Experiment 2 compared offline and online effects with respect to retrieval. While Experiments 1 and 2 investigated the VLPFC, Experiment 3 investigated tDCS over the DLPFC at encoding. Given a significant effect of the tDCS in Experiment 1 (tDCS at online encoding over the VLPFC), the significant condition was included in Experiment 3 and Experiment 4 for replication. Greater tDCS modulations were expected for the VLPFC than the DLPFC at encoding, and with the implementation of an intentional memory task, an effect of tDCS at online encoding was expected for the VLPFC. In addition, a successful replication of Experiment 1 (Online Encoding over the VLPFC) was expected in Experiments 3 and 4. Together, these experiments inform theories of memory processes in the VLPFC and DLPFC and the development of standardised application procedures of tDCS.

Table 5.0.1

Overview of experiments

Experiment	atDCS Groups	Major research question	Major distinctions
Exp 1	Online Encoding[b] Offline Encoding Sham	When is atDCS effective over the VLPFC at encoding?	Time[a]: atDCS delivered at encoding atDCS duration: 9 min Stimuli: randomly-selected English words Stimulation site: VLPFC
Exp 2	Online Retrieval Offline Retrieval Sham	When is atDCS effective over the VLPFC at retrieval?	Time[a]: atDCS delivered at retrieval
Exp 3	Online Encoding[b] Online Encoding (DLPFC) Offline Encoding (DLPFC) Sham	Comparison of atDCS effects over the VLPFC and DLPFC at encoding	Stimulation site: atDCS delivered over DLPFC Stimuli: Russian translation of words
Exp 4	Online Encoding[b] Sham	Replication of Experiment 1	Recognition test: inter-trial interval longer
Exp 5	Online Encoding[b] Sham	Effects of atDCS in a false memory task	Stimuli: semantically-related words atDCS duration: 20 min

Note: [a]Time refers to time of administration with respect to the memory phase. Online encoding is the main experimental group, in which atDCS was delivered over the VLPFC during the encoding phase. The parameters of Experiment 1, including Stimuli, atDCS duration, Stimulation site, and Time serve as the base for the remaining experiments, so distinctions from these parameters in subsequent experiments are outlined in the fourth column.

Experiment 1: atDCS over the VLPFC During Encoding

Method.

***Participants*.** Eighteen participants were recruited per group (online, offline, sham) and randomly allocated, and 46 remained after exclusion (16 in the Online tDCS group, 14 in the Offline tDCS group and 16 in the Sham group). Eligible participants were right-handed Native English speakers with normal-to-corrected vision and no history of major neurological or psychiatric disease. In addition, the participants were screened for contraindications to tDCS (DaSilva, Volz, Bikson, & Fregni, 2011), including history of seizures and pregnancy. The groups were similar in age (*M* Age = 24, *SD* = 5, range = 19-41) and gender (9 male), and there were no significant differences in age or gender. Participants provided informed consent, and ethical approval was obtained from Kingston University's ethics committee. Upon completion of the experiment, participants received £13 or course credits.

Exclusions. Five participants did not complete the memory test because they did not attend the second session, so these participants were not part of the final sample size and their data were not included in the analysis. No participants were excluded for being ineligible, and complete data were available from the remaining 49 participants. Outliers of two standard deviations from the mean in either direction were removed (*N* = 3), leaving a final sample size of 46 (Online *N* = 16; Offline *N* = 14; Sham *N* = 16) for data

analysis. Although the final sample size was relatively small, the main results did not differ when the outliers were included (except for significant response bias). Thus, the results are reported without outliers.

Materials. A pool of 248 words was selected from a standardised set (MRC psycholinguistic database; Coltheart, 1981). The words were similar in frequency (*M* = 24.47, *SD* = 46.46; Kučera & Francis, 1967) and number of letters (*M* = 6.17, *SD* = 1.96). The study phase included 160 words that were randomly selected from the pool, and the test phase included the remaining 81 words to serve as new, unstudied items. The practice tasks (study and test) included the remaining seven words for the study and test lists. Stimuli were presented in MATLAB version 7.0 (Mathworks) and Cogent Toolbox version 1.32 (Cogent, www.vislab.ucl.ac.uk/Cogent/). Stimuli were presented in white uppercase Helvetica font on a grey background and subtended at a visual angle of 1.6° vertically and 4.3-11.6° horizontally at a viewing distance of approximately 55 cm. Data analyses were conducted in SPSS version 24 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY).

Procedure. Participants were given the instructions for the study phase and completed the practice to ensure that they understood the task. Subsequently, participants were asked to read magazines for 10 min (reading task), and the task was timed with a timer. During this task, participants in the offline encoding group received active stimulation and those in the offline sham group received sham stimulation, while the other groups did not receive any stimulation. Finally, participants started the study task. Participants were instructed to indicate whether each word was pleasant or unpleasant using the keys A and L, respectively. These keys were not counterbalanced. In addition, participants were instructed to try to memorise the word. During the study task, participants in the online encoding group received active stimulation and those in the online sham group received sham stimulation.

In the first 10 min of the experiment, participants were as part of a reading task. If participants were in the offline encoding group, they would receive stimulation at this time. Then they completed the study phase, in which they were instructed to memorise each word and judge whether it was pleasant or unpleasant as part of a learning task. In each trial, a fixation cross or word was presented on a grey background. The fixation cross was presented for 500 ms initially followed by the word for 1000 ms, and then a blank screen for 1000 ms before the next trial. Words were presented in four blocks of 40, and participants received three breaks of 20 s each. The study task lasted ten min.

In the second session 24 h later, participants performed the reading task again before completing the test phase, in which they judged whether each word was previously studied (old) or new as part of a recognition test. In each trial of the test, the fixation cross was presented for 500 ms initially followed by the word for 500 ms, and between trials a blank screen was presented for 1000 ms. The 40 words from each block of the study phase were randomly ordered within the same blocks at test, and 27 additional new words were interspersed within the four blocks. Participants received two breaks, and each occurred after 67 words had been presented.

Experimental design. To examine the effects of different timings, 3 groups were established that varied only in when the stimulation was administered, and participants were randomly assigned to each group. In the online atDCS group, the stimulation was delivered for the entire duration of the study task, whereas in the offline group the stimulation was delivered for the duration of the reading task (active stimulation). In the sham group (the control group), the stimulation was turned off after 30 s and delivered at the start of the study task or reading task (sham stimulation). This procedure ensured that participants felt the physical tingling sensation associated with the stimulation and that the duration was not long enough to induce changes in cortical excitability. Thus, memory performance could be attributed to the stimulation rather than participants' knowledge of

the stimulation parameters and to which group they were assigned (control or experimental). The sham group was further separated into two conditions: online encoding sham and offline encoding sham. At offline encoding sham, sham stimulation was delivered at the start of the reading task but lasted only 30 s, while at online encoding sham, sham stimulation was delivered at the start of the study task and shortly turned off. The response hand was counterbalanced for the recognition task but not the encoding task, since encoding response was not a dependent variable of interest.

tDCS parameters. The anode and cathode electrodes were placed on the head and shoulder, respectively, at both experimental sessions and remained until the end of the session. However, stimulation was delivered at various times depending on group. For Experiment 1, stimulation was only delivered in the first experimental session, during the reading task (offline encoding tDCS) or the study phase (online encoding tDCS). Stimulation was delivered through a Neuroconn battery-powered stimulator (DC-STIMULATOR PLUS, Neuroconn, Germany) through 5 x 7 cm^2 electrodes. Electrodes were soaked in saline for at least 20 min before use, and impedances were kept below 20 kΩ. The anode (active electrode) was placed on the left temple, corresponding to F7 (International 10-20 system, see Chapter 2, Designing Experiments with NIBS, and Figure 2.0.2), and the cathode electrode was used as a reference and placed on the contralateral (right) shoulder so that it would not affect brain activity. Through these electrodes a current of 2 mA was delivered for approximately 10 min, equivalent to the duration of the reading and study tasks. In the sham group, the stimulation lasted only 30 s. The study was single-blind: participants were not aware of their experimental condition, but the experimenter was fully aware. Note: Blinding success was not tested by asking participants to indicate whether they believed that they received real stimulation. However, blinding success was tested in subsequent experiments (Experiments 3-5).

Analysis. False alarms were defined as incorrect responses to new words (falsely recognising items as "old"), and misses were incorrect responses to studied words (forgetting that an item had been presented earlier and selecting "new"). Hits were correct responses to studied words (correctly responding "old") and correct rejections were correct responses to new words (correctly responding "new").

Participant responses were classified into proportions of false alarms; hits; correct rejections; or misses. However, since the sum of the proportion of hits and misses was 1 (as was the sum of the proportion of false alarms and correct rejections), only the proportion of hits (Pr Hits) and false alarms (Pr FA) were examined. Discrimination ability was used as a measure of recognition accuracy (Pr Hits – Pr FA; Snodgrass & Corwin, 1988). Average reaction time was calculated using the average reaction times for hits and false alarms for each subject: (RT Hits + RT False Alarms)/2, and then individual average reaction times were averaged for each group. Response bias (Br) was calculated as Pr FA/(1- (Pr Hits – Pr FA); higher values reflected more conservative responding, whereas lower values reflected more liberal responding (Snodgrass & Corwin, 1988).

One-way ANOVAs were conducted for each measure of accuracy: discrimination ability, proportion of hits, and proportion of false alarms. In addition, one-way ANOVAs were conducted for average reaction times and reaction times for hits and false alarms separately. Finally, a one-way ANOVA was conducted on response bias. Significant effects were followed up with planned contrasts between each stimulation group and Sham (one-tailed).

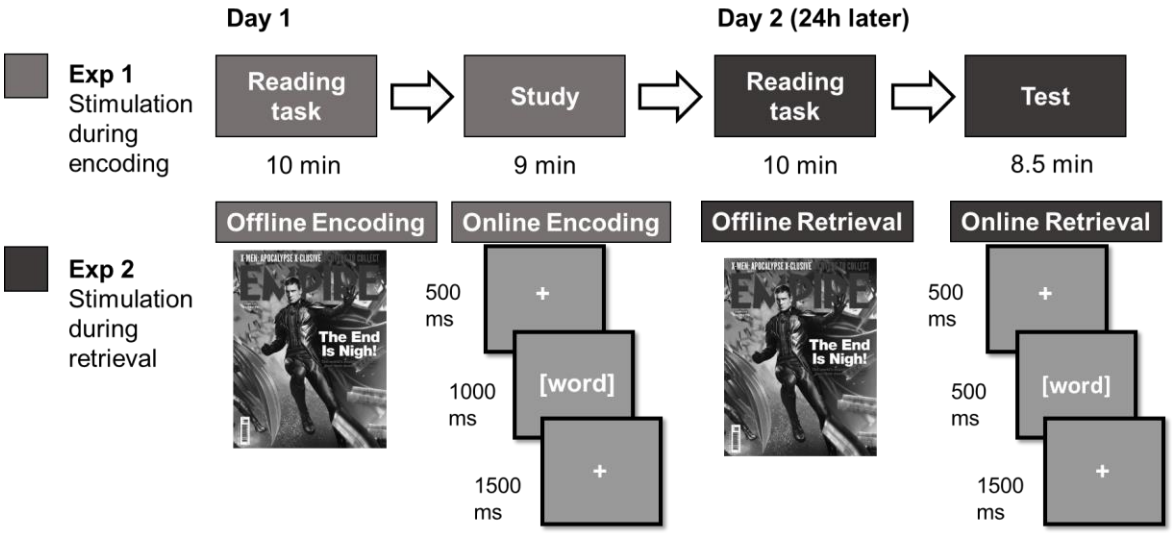

Figure 5.1.1. Procedure for Experiments 1 and 2.

Results.

Effects of tDCS during administration. The assumption of homogeneity of variance was met for encoding reaction time; Levene's test was not significant $F(2,43) = 1.03$, $p = .366$. Accuracy was significantly above chance for all experimental groups, *t*s > 5.85. and there was no significant difference in accuracy between items rated pleasant and unpleasant, *t*s<.074. There was a significant difference between groups in reaction time at encoding, $F(2,43) = 3.71$, $p = .033$, $\eta_p^2 = .147$. Planned contrasts revealed significant differences between Sham and Online tDCS $t(43) = 2.72$, $p = .009$ but not Offline tDCS $t(43) = 1.12$, $p = .134$. Specifically, encoding reaction time was longer for Online tDCS ($M = 851.15$, $SD = 140.49$) than for Sham ($M = 742.98$, $SD = 96.73$).

Effects of tDCS on retrieval. The assumption of homogeneity of variances was only violated for discrimination ability $F(2,43) = 4.41$, $p = .017$. Levene's test was likely significant due to unequal sample sizes, so Brown-Forsythe's *F* is reported. There was a significant effect of tDCS on discrimination ability $F(2,30.61) = 6.66$, $p = .004$, $\eta_p^2 = .303$.There was significantly higher discrimination ability in the Online tDCS group $t(43) = -3.60$, $p<.001$ but not the Offline tDCS group $t(43) = -0.85$, $p = .100$ compared to Sham. Thus, Online tDCS increased recognition accuracy ($M = 0.30$, $SD = 0.09$) compared to

Sham (*M* = 0.13, *SD* = 0.13), but there was no effect of Offline tDCS (*M*= 0.17, *SD* = 0.18).

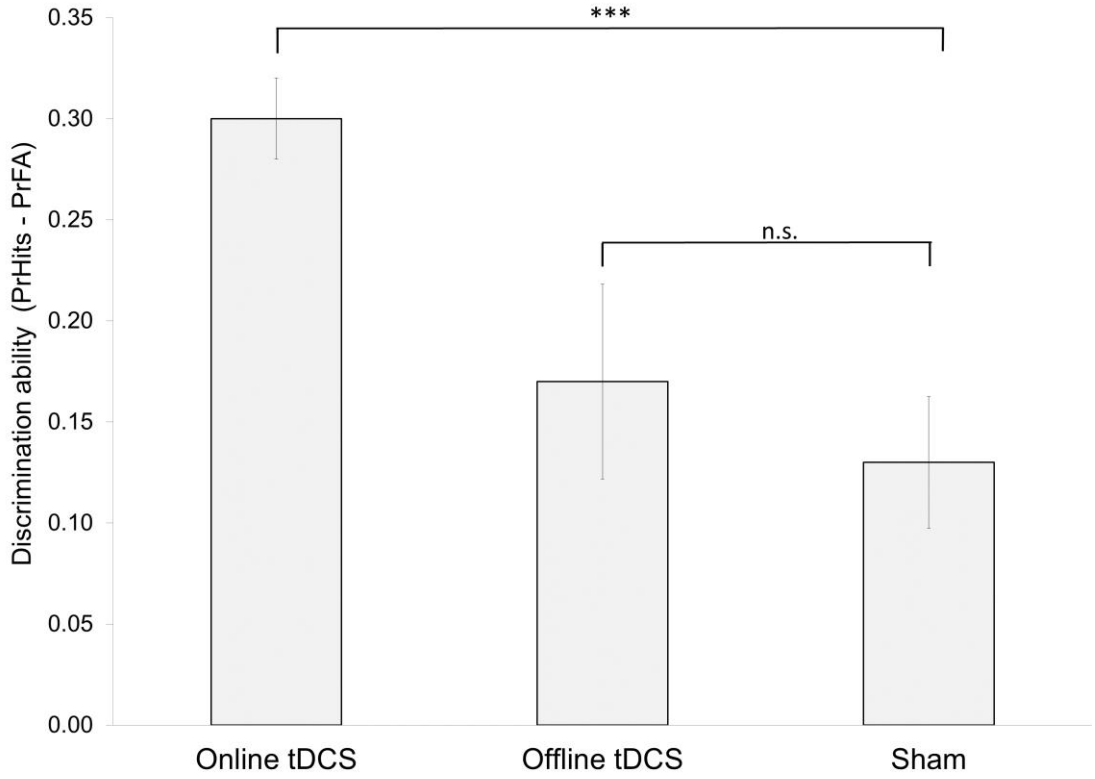

Figure 5.1.2. Discrimination ability as a function of experimental group.

Note: Discrimination ability is a measure of accuracy and ranges from 0 to 1. * denotes significance at p<.05; ** denotes significance at p<.01; and *** denotes significance at p<.001. Online tDCS = tDCS was delivered for the entire duration of the study task. Offline tDCS = tDCS was delivered for the entire duration of the reading task, before the study task. Sham = tDCS was delivered for 30 s before the stimulator was turned off; half of the group received stimulation at the beginning of the study task, and the other half received stimulation at the beginning of the reading task.

There was not a significant difference in proportion of hits $F(2,43) = 1.02$, $p = .366$, $\eta_p^2 = .045$, but there was a significant difference in proportion of false alarms $F(2,43) = 8.74$, $p = .001$, $\eta_p^2 = .289$. Again, there was a significant difference between Sham and Online tDCS $t(43) = 4.00$, $p<.001$ but not Offline tDCS $t(43) = 0.88$, $p = .097$.

Specifically, there were fewer false alarms for Online tDCS (*M* = 0.34, *SD* = 0.11) than for the Sham group (*M* = 0.57, *SD* = 0.19).

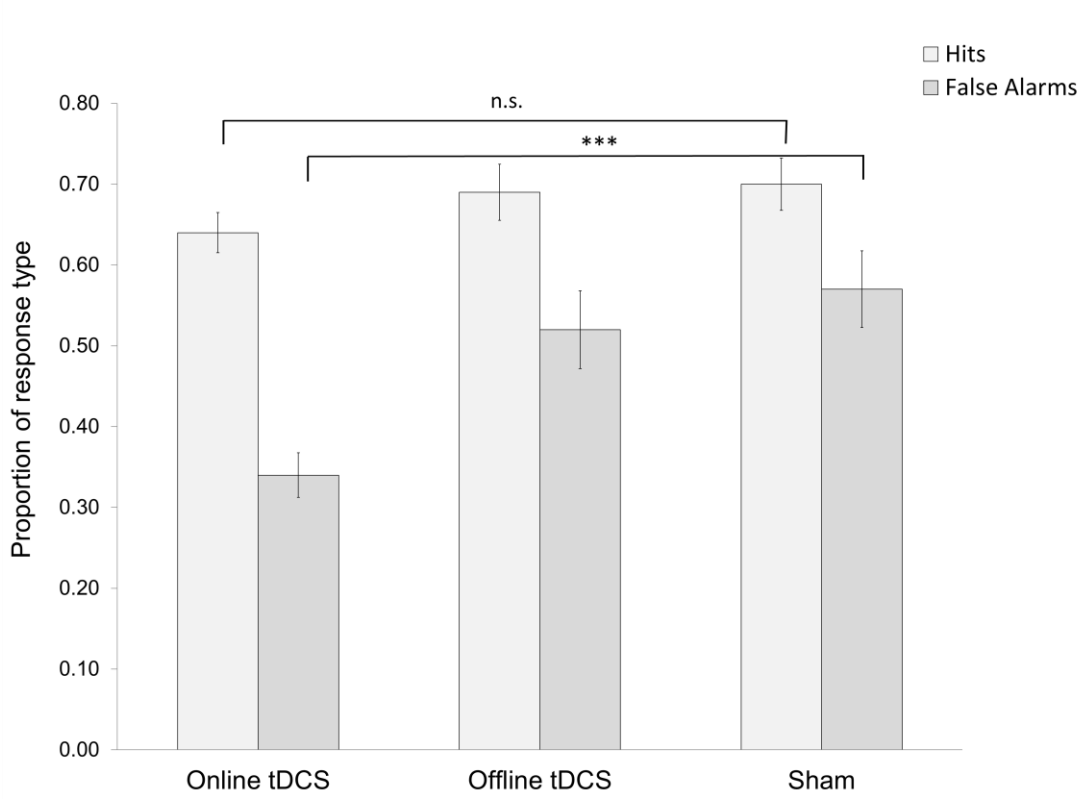

Figure 5.1.3. Discrimination ability for each response type as a function of experimental group.

Note: Proportion of hits and false alarms are shown. * denotes significance at p<.05; ** denotes significance at p<.01; and *** denotes significance at p<.001.

There was a significant difference between the groups in response bias $F(2,43) = 5.12$, $p = .01$, reflecting a difference between Sham and Online tDCS $t(43) = 2.99$, $p = .003$. It seems that participants in the Online group were responding more liberally (*M* = 0.49, *SD* = 0.14) than those in the Sham group (*M* = 0.65, *SD* = 0.15). In addition, there was a significant difference between the groups in average reaction time $F(2,43) = 5.35$, $p = .008$, reflecting increased reaction times for the Online group compared to Sham $t(43) = -2.99$, $p = .003$. Specifically, there was a significant difference in reaction times for hits, $F(2,43) = 5.28$, $p = .009$, and reaction times for false alarms, $F(2,43) = 5.29$, $p = .009$,

reflecting slower reaction times in Online tDCS for hits, $t(43) = 2.95$, $p = .005$, and false alarms, $t(43) = 2.99$, $p = .005$, compared to Sham.

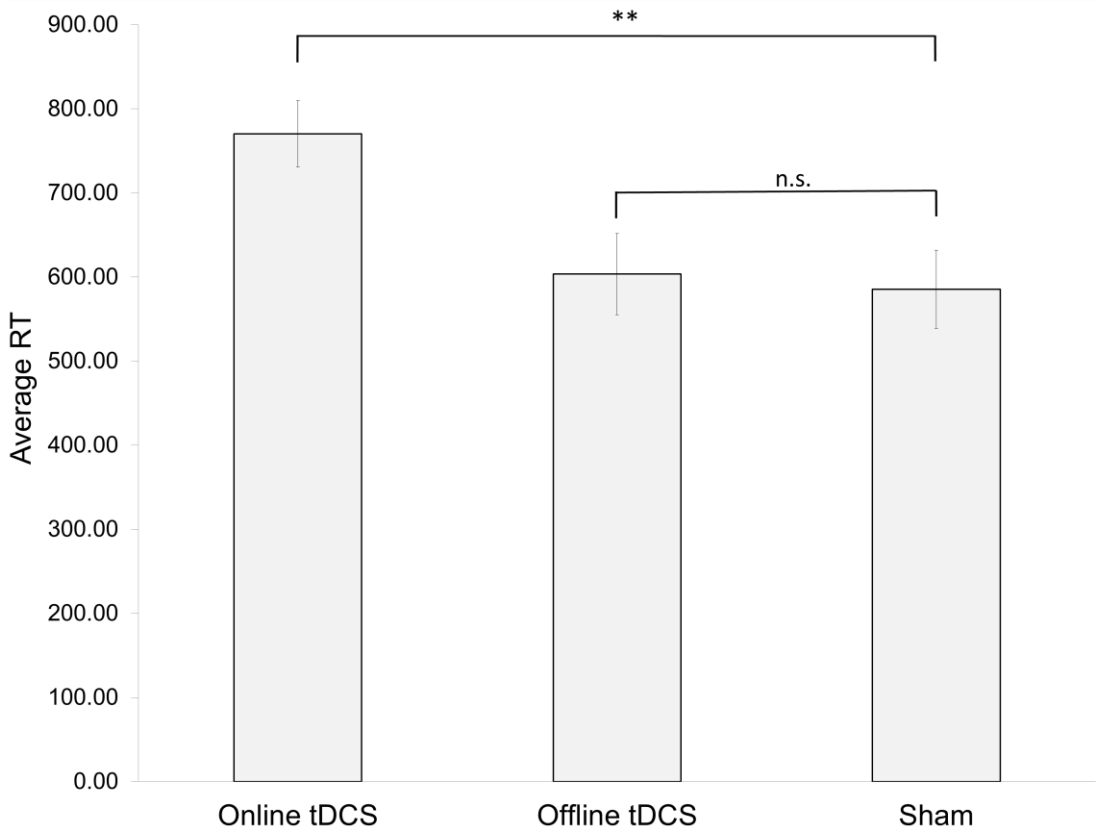

Figure 5.1.4. Average reaction time as a function of experimental group.

Note: * denotes significance at p<.05; ** denotes significance at p<.01; and *** denotes significance at p<.001.

Given the significant effect of atDCS over the VLPFC during administration, leading to increased reaction times, and on retrieval, leading to increased accuracy and reaction time, it was of interest to investigate whether atDCS effects fluctuated throughout the experiment, particularly in the presence of non-linear atDCS effects over time (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015) and previous findings that atDCS effects differed across blocks (Antal, Nitsche, Kincses, Kruse, Hoffman, & Paulus, 2004; Kincses, Antal, Nitsche, Bártfai, & Paulus, 2004).

An exploratory analysis was conducted to determine whether the effect of atDCS differed across blocks. A mixed ANOVA was conducted with group (online tDCS, offline tDCS, Sham) as the between-subjects factor and block (block 1, 2, 3) as the within-subjects factor on recognition accuracy. There was no significant effect of Block for recognition accuracy, $F(2, 86) = 2.66$, $p = .076$, $\eta^2_p = .058$, nor was there a Group x Block interaction, $F(4, 86) = 0.64$, $p = .638$, $\eta^2_p = .029$. However, there was a significant effect of Group, $F(2,43) = 5.00$, $p = .011$, $\eta^2_p = .189$, reflecting higher recognition accuracy for Online tDCS. There was also a main effect of Group for proportion of false alarms, $F(2,43) = 7.06$, $p = .002$, $\eta^2_p = .247$, and a main effect of Block, $F(1.72, 74.13) = 6.43$, $p = .004$, $\eta^2_p = .130$, Greenhouse Geisser-corrected value $\varepsilon = .862$ for violation of sphericity $\chi^2(2) = 7.33$, $p = .026$, reflecting higher false alarms for the third block compared to the second and first blocks. There was also no significant effect of Group, $F(2,43) = 0.58$, $p = .565$, $\eta^2_p = .026$, or Block, $F(2,86) = 0.62$, $p = .538$, $\eta^2_p = .014$, for proportion of hits, and there was no significant Group x Block interaction effect, $F(4,86) = 0.48$, $p = .750$, $\eta^2_p = .022$.

Given that the effect of Online tDCS was specific to false alarms rather than hits, it is possible that participants were encoding distinctive features of items, which led to fewer false alarms. Distinctive features may be more likely in low-frequency words, as shown in previous studies (Brown, Lewis, & Monk, 1977; Hunt & Einstein, 1981; Malmberg, Steyvers, Stephens, & Shiffrin, 2002). Thus, an exploratory analysis was conducted on the Online Encoding and Sham groups to determine whether accuracy for low-frequency words (1-10) presented at encoding differed from high-frequency words (>10). Words at test were separated into high and low (~50 trials per participant) frequency, and then participants in each group were compared in proportion of hits for high- vs low-frequency words. A two-way ANOVA was conducted with experimental group (Online tDCS, Sham) and frequency (Low, High) as the between-subject factors. There was a significant effect

of frequency, $F(1,30) = 20.02$, $p<.001$, $\eta^2_p = .400$ and a significant frequency x group interaction, $F(1,30) = 8.33$, $p = .007$, $\eta^2_p = .217$, but no significant effect of group, $F(1,30) = 2.28$, $p = .142$, $\eta^2_p = .071$. The significant interaction revealed that while there was a higher hit rate for low-frequency words in both groups, the difference in hit rate between low- and high-frequency words was only significant for the Sham group, $t(15) = 4.79$, $p<.001$, $d = 1.22$. Notably, only two participants in the Sham group showed lower accuracy for low than high-frequency words. Although there was no significant difference between low-frequency and high-frequency trials for VLPFC tDCS, $t(15) = 1.24$, $p = .234$, it is notable that over half of the participants ($N = 11$) demonstrated numerically-higher accuracy for low-frequency than high-frequency words.

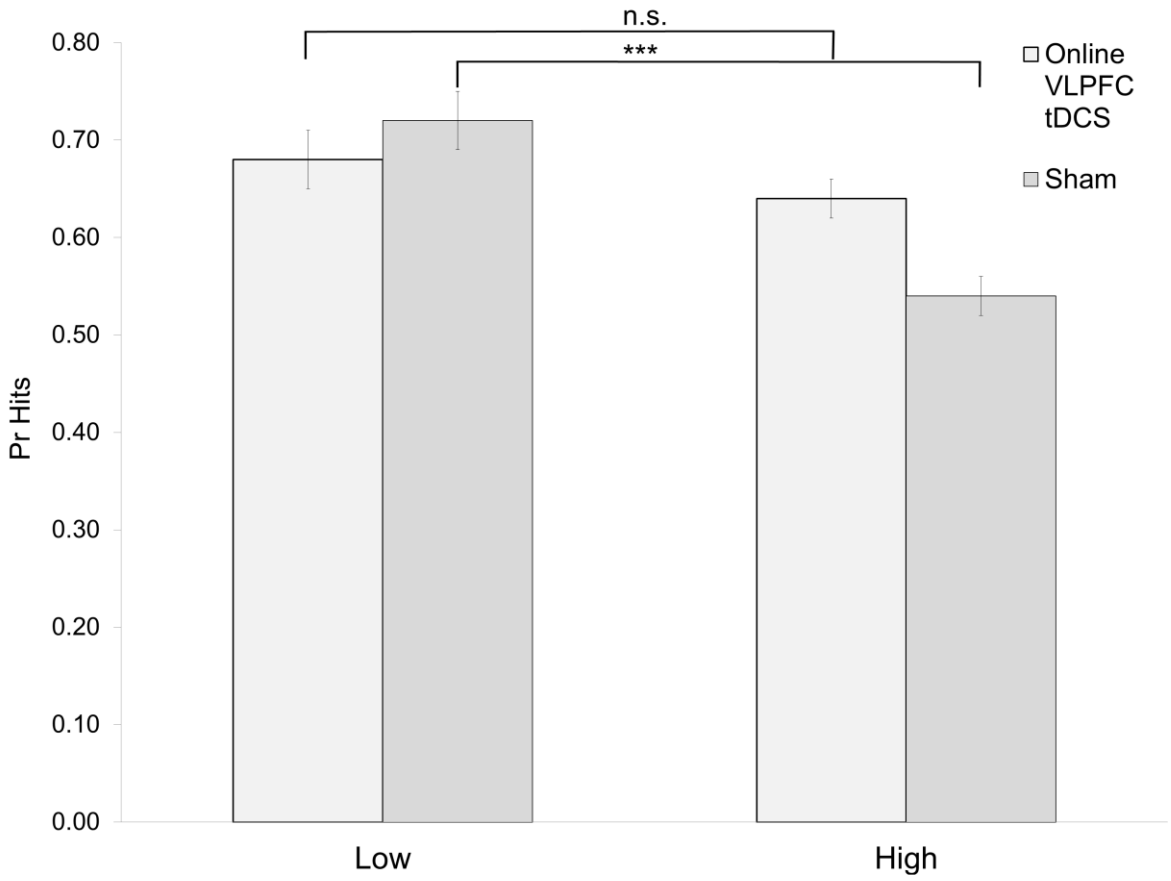

Figure 5.1.5. Proportion of hits for low- and high-frequency words for each group.

Discussion. A significant improvement in recognition accuracy was found when atDCS was delivered online but not offline at intentional, deep encoding, and an examination of hits and false alarms separately suggested that there was a selective

decrease in false recognition following atDCS. The effect of atDCS appears to be specific to intentional encoding, since in a previous experiment, there was no effect of atDCS when delivered online at incidental encoding (Medvedeva et al., 2018; Experiment 3). The effect of atDCS on recognition accuracy seems to be robust, as confirmed by a similar study conducted in the same lab with older adults (Medvedeva et al., 2018; Experiment 4). However, since the reduction in false alarms was not replicated with older adults (Medvedeva et al., 2018; Experiment 4), the robustness of the effect on false alarms remains to be examined.

An effect of atDCS was found at online encoding over the VLPFC during deep encoding and intentional memorisation, while Medvedeva and colleagues (2018; Experiment 3) did not find an effect of atDCS on deep or shallow encoding in an incidental task. The results suggest that the VLPFC may be more engaged during intentional encoding, and this engagement is important for a successful atDCS modulation, supporting the idea of state-dependent online effects (Miniussi, Harris, & Ruzzoli, 2013).

An effect of atDCS at online encoding over the VLPFC was found during a shallow, intentional encoding task when Pisoni and colleagues (2015) instructed participants to memorise face-name associations. Pisoni and colleagues (2015b) also found a selective decrease in false alarms for names. However, they stimulated a more posterior area (F5) closer to the pars opercularis (BA 44) and DLPFC, which may correspond to the posterior VLPFC that is involved in phonological processing. Thus, it remained unclear whether semantic processing in the anterior VLPFC could be modulated by atDCS. It was also unclear from their results whether the effect of tDCS on the VLPFC was from offline or online stimulation. They delivered tDCS for 20 min, with offline tDCS for 14 min and online tDCS for 6 min, covering the entire duration of the encoding task.

The current study provides clearer evidence that tDCS effects may occur during online encoding but not during offline encoding. Although it could be argued that tDCS

had carryover effects from offline to online encoding (since there was not a delay between offline encoding tDCS and the task), the absence of a tDCS effect at offline encoding suggests that even if there were carryover effects, the after-effects were not strong enough to modulate behavioural performance.

Few other studies with neuromodulation in *younger* adults reported selective modulations of false alarms when stimulating the VLPFC: rTMS studies over the VLPFC reported effects on hits and false alarms, while previous tDCS studies have found modulations of false alarm rates in other regions including the DLPFC and ATL. Blumenfeld, Lee, and D'Esposito (2014) found a selective increase in false alarms after rTMS over the VLPFC but not DLPFC, supporting the role of the VLPFC in item-specific semantic memory. They suggested that there was a high degree of interference and similarity because of items in similar categories with similar features, but item-specific encoding in the VLPFC could have led to a greater focus on distinctive features of the items, which could improve discrimination between semantically-similar old and new items at retrieval. Indeed, many of the words in the current study could be clustered into broad categories (i.e. animals, professions; see Figure 5.1.6), leading to an increase in semantic similarity that could possibly be mediated by item-specific encoding in the VLPFC. An increase in VLPFC activation through atDCS could have facilitated semantic elaboration processes that distinguished between semantically-similar items at encoding, leading to fewer false alarms for semantically-similar new items at retrieval.

The selective modulation of false alarms but not hits suggests that atDCS may have modulated semantic elaboration rather than a memory-specific process. By increasing elaboration, atDCS could have increased item-specific encoding and processing for distinctive features, which can lead to a selective decrease in false alarms (Hunt & Einstein, 1981). The increase in reaction time at encoding suggests that participants engaged in greater elaboration, in line with previous studies that have shown longer

processing for items that were deeply encoded (e.g. Innocenti et al., 2010). However, the reason for the increase in reaction time at retrieval is less clear. Innocenti and colleagues (2010) suggested that increased reaction time represented a less efficient strategy. However, increased reaction time could mean greater interference because of high semantic similarity, and participants in the Online atDCS group would have elaborated common features, as well. atDCS could have led to fewer false alarms at the cost of higher response time.

Participants in the atDCS group could have benefitted from additional elaborative processing, although not only for the items with distinctive features (low-frequency words). It is notable that in contrast to the Sham group, the atDCS group did not show differences in accuracy between low- and high-frequency words, although low frequency words may have more distinctive features and be better encoded. Perhaps atDCS increased processing for distinctive features in high- as well as low-frequency words. Support for this account arises from the distinctiveness effect, in which processing distinctive, unique features of an item (such as whiskers on a cat) leads to better memory for the item, particularly in the presence of items with common features (ears on animals; Hunt & Einstein, 1981; Israel & Schacter, 1997). Similarly, the bizarreness effect shows that unexpected or unusual words or sentences within a list can lead to increased memory accuracy for the bizarre items (Einstein & McDaniel, 1987) when they are interspersed with common items (mixed list) but not when bizarre items are presented alone (pure list; Waddill & McDaniel, 1998). It is possible that these effects occurred for the Sham group, in which participants showed increased recognition accuracy for low-frequency compared to high-frequency items. At test, the distinctiveness heuristic (Israel & Schacter, 1997) can lead to decreased false alarms because the absence of expected distinctive information in memory for an item can serve as an indication that the item was not presented at study. However, when pictures, which include more distinct features, are presented with words in

a within-subjects design, the advantage for pictures over words can disappear because the absence of memory for distinctive features does not mean that an item has not been presented; it could have been presented as a word (Schacter, Israel, & Racine, 1999; Dodson & Schacter, 2002). Moreover, the advantage for bizarre items can disappear when participants use different strategies that lead to more equal processing of common and bizarre items at encoding or more cues for common items at retrieval (McDaniel, DeLosh, & Merritt, 2000; Wollen & Cox, 1981; although see Geraci, McDaniel, Miller, & Hughes, 2013 for an alternate account). In this experiment, low-frequency items could be the equivalent of the pictures or bizarre items, and atDCS could serve as the manipulation that leads to more equal processing of the distinctive and common items. The advantage for low- over high-frequency words in the control group suggests that participants were engaging in greater distinctive encoding for the low-frequency items, but perhaps they were not using the distinctiveness heuristic (as evidenced by the high proportion of false alarms); instead, the items that were distinctively-encoded were simply more memorable (Hunt & Einstein, 1981). In the Online tDCS group, however, participants could have been using the distinctiveness heuristic if all items were distinctive, which is possible if atDCS increased processing for distinctive features (as in a picture-only condition; Schacter, Israel, & Racine, 1999). Perhaps by increasing semantic elaboration, atDCS increased distinctive processing for all the presented items, and this helped to reject unpresented items that lacked the expected distinctive information at test (distinctiveness heuristic). This account is tested in Chapter 6. Previous studies have shown that attending to unique or distinctive features of each item in a list leads to better recollection and decreased false recognition (Huff & Bodner, 2013; McCabe et al., 2004), regardless of whether the item is common and distinctive features are readily available. Perhaps together with atDCS-induced elaboration, the presence of a high proportion of low-frequency items with distinctive features encouraged the use of this strategy.

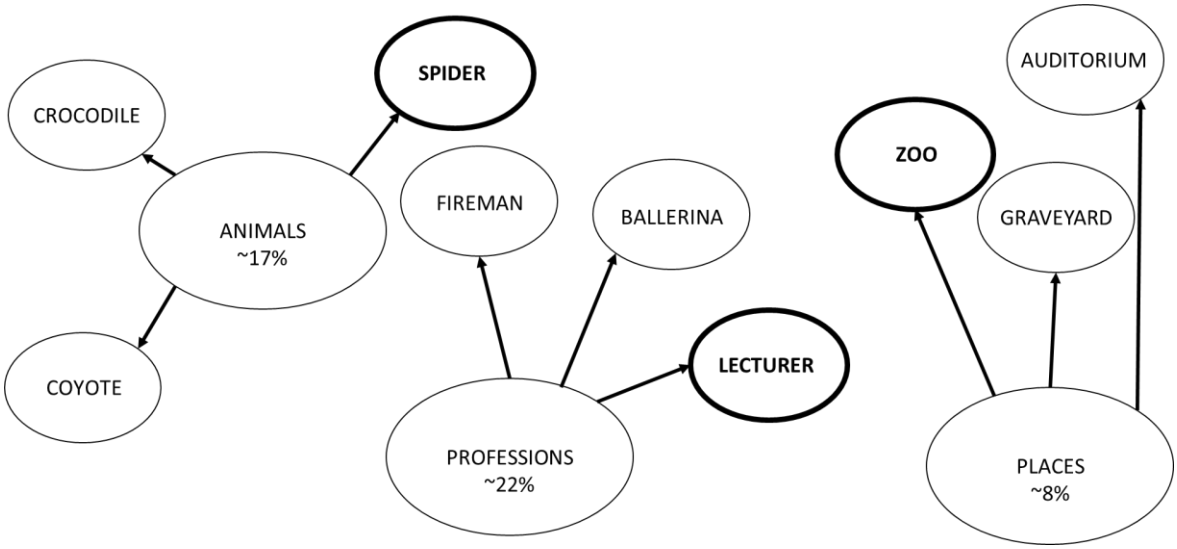

Figure 5.1.6. Predominant categories of the verbal stimuli in Experiment 1.

Note: Percentages denote the minimum percentage of words that could fit in the category, and words that are common exemplars for each category are in bold.

In addition, VLPFC activity may be important for resolving semantic interference. Pisoni, Papagno, and Cattaneo (2012) examined the semantic interference effect, which shows longer reaction times for naming objects within the same semantic category compared to objects in different semantic categories. Pictures within the same semantic category were presented sequentially to induce the semantic interference effect. Pictures were presented with labels, and participants were asked to name the pictures without labels as fast as possible. atDCS lowered the effect when delivered over the left VLPFC, corresponding to BA 44/45 (between T3-Fz and F7-Cz) and increased the effect when delivered over the left superior temporal gyrus, decreasing and increasing reaction time, respectively, for naming in semantically related compared to semantically unrelated sets.

The effect of tDCS did not appear to vary between blocks when measured at encoding or retrieval, although there is evidence that tDCS effects during the task can lead to an initial increase in performance and then subsequent decrease as homeostatic mechanisms are engaged (Fricke, Seeber, Thirugnanasambandam, Paulus, Nitsche, &

Rothwell, 2010). It would be interesting to more closely examine the effects of atDCS over time in episodic encoding by examining the sub-processes that could occur, such as working memory and semantic processing. While atDCS is delivered, working memory and semantic naming could be examined throughout the encoding phase and then analysed as predictors of successful recollection.

While Javadi (2011) found that tDCS effects differed within a trial, with greater effects of atDCS over the DLPFC in the first second than that the later part of the trial, tDCS modulations occur over minutes rather than seconds. The effects of atDCS over the VLPFC may occur throughout the trial and blocks, since the VLPFC appears to be active throughout the presentation of the word on the screen (Burke et al., 2014; Mainy et al., 2007), and the degree of VLPFC engagement in semantic elaboration may vary based on the word.

A selective effect on false alarms has also been observed in previous tDCS research with the left ATL, a region associated with semantic processing and false memory. Using the same face-name task and tDCS parameters (i.e. 20 min of stimulation), Pisoni and colleagues (2015) found increased false alarms after atDCS over the left ATL, a finding that was replicated by Chi and colleagues (2010) in a visual false memory task. Like Chi and colleagues (2010), Boggio and colleagues (2009) used a false memory task but with verbal stimuli and found a *reduced* false alarm rate when delivering atDCS partly offline and partly online. They proposed that because atDCS was delivered over a relatively large region (35 cm^2 electrodes), it could have activated competing regions that in turn inhibited the ATL. While differences in task together with differences in baseline neural activation and neuron orientation could have explained the inconsistencies in results, it remains unclear how atDCS can selectively modulate false alarms.

Thus, the results confirm the role of the VLPFC in episodic memory. For the first time in tDCS research, the causal relationship between the VLPFC and semantic item

encoding is established. The results add to the handful of tDCS studies that examined the VLPFC in episodic memory and extend the results of Medvedeva and colleagues (2018; Experiment 3) in particular. The results also support the role of the VLPFC in semantic processing. Although the anterior and posterior VLPFC could not be disentangled because both regions could be captured by the large electrode, it is likely that the anterior VLPFC was selectively engaged by the task and modulated by atDCS because judgements at encoding encouraged attention to semantic rather than phonological characteristics.

Although the DLPFC could also be captured with a large electrode, the current study suggests that tDCS effects were specific to the VLPFC and not the DLPFC, since previous studies over the DLPFC that have found enhancements due to tDCS showed increases in the proportion of hits or general accuracy rather than false alarms (Gray et al., 2015; Leach et al., 2018; Lu, Wang, Chen, & Xue, 2015; Manenti, Cotelli, Robertson, & Miniussi, 2012). However, the DLPFC and VLPFC should be compared to ensure that this is the case. While there is a suggestion that activity in the anterior VLPFC was most prominent, other sub-regions of the VLPFC could be affected by the electrode, and future studies can examine fMRI activation in these regions during atDCS. Nonetheless, in line with the state-dependent principle, only the regions associated with the task should be active and modulated on a cognitive level. The mid-VLPFC could be more active during interference-based tasks, and the posterior VLPFC could be more active during phonological processing and other structural shallow encoding tasks. Future studies can compare the effects of atDCS on different subregions of the VLPFC by using different tasks, and future studies can compare deep and shallow encoding using an intentional memorisation task.

The effect of atDCS on deep and shallow encoding during an intentional task was not compared in the current experiment. Although it remains unclear whether the effect of atDCS over the VLPFC in an intentional task would extend to shallow encoding, the

plausibility of an effect on shallow encoding is supported by studies demonstrating the causal role of the VLPFC in phonological processing (Galli, Feurra, Pavone, Sirota, & Rossi, 2017; Machizawa, Kalla, Walsh, & Otten, 2010: Nixon et al., 2004; Sehm, Kipping, Schäfer, Villringer, & Ragert, 2013). Thus, there is a possibility of tDCS modulation for shallow as well as deep encoding in an intentional task. The VLPFC may be modulated by atDCS in shallow encoding if phonological processing is required by the task, leading to engagement of the posterior VLPFC. Future studies can compare deep and shallow encoding in an intentional task over the VLPFC using atDCS. Future studies should also compare effects of cathodal and anodal tDCS over the VLPFC to identify the conditions under which cathodal tDCS can lead to inhibition vs facilitation depending on the cognitive task. Finally, since older adults did not show a reduction in false alarms following atDCS, future research should investigate this further and determine whether the cognitive mechanisms of atDCS effects differ between younger and older adults.

Experiment 2: atDCS over the VLPFC During Retrieval

Method.

***Participants*.** As in Experiment 1, 54 participants (18 per group) were recruited and randomly assigned to each group (Online tDCS, Offline tDCS, Sham). The final sample included 49 participants (16 in the Online group, 15 in the Offline group and 18 in the Sham group) after exclusion (See Exclusions). Exclusion criteria were the same as Experiment 1. The groups in Experiment 2 did not significantly differ in age (*M* age = 22, *SD* = 3, range 19-30) or gender (42 females). All participants provided informed consent before starting the experiment and were compensated upon completing the experiment (£13 or course credits). The study was conducted in accordance with ethical approval from Kingston University.

Exclusions. Five participants were excluded before outlier removal. Two participants were ineligible due to neurological conditions, and technical issues occurred during the experimental session. One participant did not complete the experiment, and two participants experienced excessive discomfort during the stimulation. Criteria for outlier rejection was the same as in Experiment 1, but no outliers were identified.

***Experimental design*.** The materials, tDCS parameters, and procedure for the experiment were identical to Experiment 1 except that stimulation was delivered at retrieval rather than encoding. The procedure for data analysis was also identical. In the online atDCS group, the stimulation was delivered for the entire duration of the retrieval task whereas in the offline group the stimulation was delivered for the duration of the reading task that took place on the second day immediately before the test. In the sham group, the stimulation was delivered at the start of the reading task or test.

Results. Accuracy was significantly above chance for all groups, *t*s>2.41. The assumption of homogeneity of variances was met for each dependent variable, and there were no significant differences in any measure. There was no effect of tDCS on reaction

times at encoding $F(2,46) = 0.46$, $p = .636$, $\eta_p^2 = .020$, or average reaction times at retrieval, $F(2,46) = 0.49$, $p = .618$, $\eta_p^2 = .021$ (See Figure 5.2.2). There were no significant differences in recognition accuracy $F(2,46) = 0.09$, $p = .915$, $\eta_p^2 = .004$ (See Figure 5.2.1), or response bias $F(2,46) = 1.32$, $p = .277$, $\eta_p^2 = .054$. Finally, there were no significant group differences in proportion of hits, $F(2,46) = 1.45$, $p = .245$, $\eta_p^2 = .059$; proportion of false alarms, $F(2,46) = 1.39$, $p = .261$, $\eta_p^2 = .057$; or associated reaction times for hits $F(2,46) = 0.34$, $p = .717$, $\eta_p^2 = .015$, and false alarms, $F(2,46) = 0.65$, $p = .528$, $\eta_p^2 = .027$. Means for each measure are presented in Tables 5.3.4 and 5.3.5.

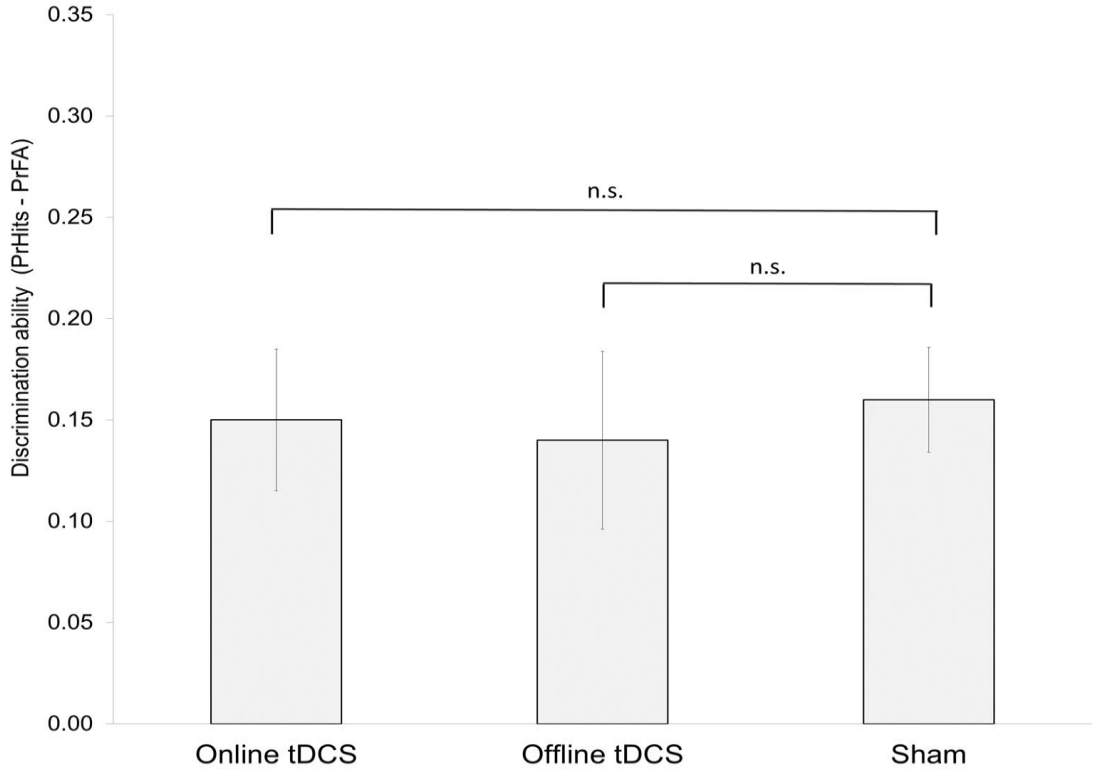

Figure 5.2.1. Discrimination ability as a function of experimental group.

Note: Discrimination ability is a measure of accuracy and ranges from 0 to 1. * denotes significance at p<.05; ** denotes significance at p<.01; and *** denotes significance at p<.001. Online tDCS = tDCS was delivered for the entire duration of the recognition test. Offline tDCS = tDCS was delivered for the entire duration of the reading task on Day 2, before the recognition test. Sham = tDCS was delivered for 30 s before the stimulator was turned off; half of the group received stimulation at the beginning of the recognition test, and the other half received stimulation at the beginning of the reading task on Day 2.

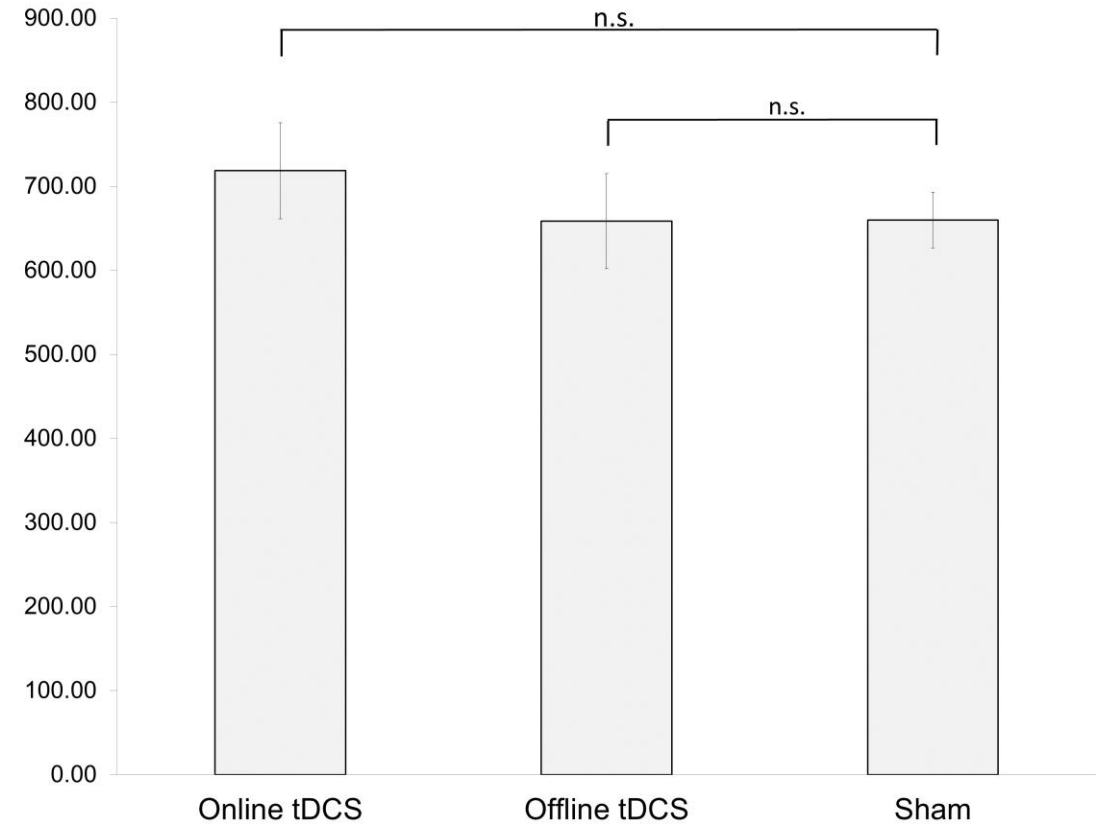

Figure 5.2.2. Average reaction time as a function of experimental group.

Discussion. No significant effects on recognition accuracy were found when atDCS was delivered over the left VLPFC before or during retrieval. While this is surprising given the role of the VLPFC in controlled retrieval, especially for semantic information, atDCS effects may be state-dependent (Miniussi et al., 2008), and the VLPFC may not have been sufficiently active at retrieval. Previous studies suggest greater VLPFC activation at retrieval during interference or other cases in which control processes are needed (e.g. Souza, Donohue, & Bunge, 2009). For example, King and colleagues (2005) found increased VLPFC activation at retrieval during contextual interference, when events at study were presented in only two different contexts, whereas the activation was absent when each event at study was presented in a distinct context.

Few previous studies have investigated the effects of neuromodulation over VLPFC activity at retrieval, and most of these studies have investigated working memory. In rTMS studies of working memory retrieval, the VLPFC appears to play a significant

role regardless of control processes. However, two studies have examined the effects of rTMS over the mid-VLPFC in long-term retrieval. Although the mid-VLPFC is thought to be more involved in selection of relevant responses, both the anterior and mid-VLPFC are thought to be involved in control operations at retrieval. Wais, Kim, and Gazzaley (2012) lend support to the role of the VLPFC in controlled retrieval during interference: there was a greater memory impairment during visual distraction when mid-VLPFC activity was disrupted with rTMS. Similarly, Hindy and colleagues (2009) found that after rTMS disruption of mid-VLPFC activity, participants moved the computer mouse toward the incorrect response in the absence of strong target-cue associations and available contextual information, suggesting that the mid-VLPFC is necessary during semantic interference and contextual ambiguity.

In addition, there could be other regions with greater contributions for successful retrieval. Indeed, while the VLPFC may be consistently active at semantic retrieval, VLPFC activity is not always associated with successful retrieval (Blumenfeld & Ranganath, 2007). A meta-analysis of regions associated with recollection found that the largest cluster associated with successful retrieval was the left PPC, followed by the DLPFC and finally the VLPFC (Spaniol, Davidson, Kim, Han, Moscovitch, & Grady, 2009). The left PPC and bilateral DLPFC were associated with greater activation at successful retrieval than encoding. In contrast, the left VLPFC was associated with greater activation at successful encoding than retrieval.

Previous tDCS studies have found evidence for a role of the parietal cortex in episodic retrieval: Pergolizzi and Chua (2015) found increased false recognition after atDCS to the bilateral posterior parietal cortex (CP3 and CP4) during a false memory task, and during an item memory task (2016) they found decreased false recognition after atDCS over the left PPFC (CP3) compared to stimulation over the DLPFC (F3). Pisoni and colleagues (2015b) also found decreased false recognition after atDCS over the left PPC

(P3). Chen and colleagues (2016) found no effects of anodal or cathodal tDCS on recognition, but they found reduced source accuracy after cathodal tDCS over the left PPC. Finally, Manenti and colleagues (2010) found impaired verbal recognition when rTMS was delivered over the left PPC, and the magnitude of impairment correlated with PPC fMRI activation at encoding. These studies are in line with fMRI evidence that the posterior parietal cortex is associated with correct source memory and recollection for detail (Vilberg & Rugg, 2008), possibly because of top-down control over attention at retrieval (Hutchinson et al., 2012).

To the author's knowledge, no prior study has directly investigated the effects of rTMS or tDCS on episodic retrieval in the anterior VLPFC. The current study supports the finding that VLPFC activity may be more crucial for encoding than retrieval, although it would be interesting to compare the results of the current study with rTMS studies examining effects of interrupting *anterior* VLPFC activity at retrieval. Although rTMS effects may be stronger, rTMS should also have no effect on recognition accuracy when delivered over the VLPFC at retrieval, replicating the results of the current study.

It is not likely that atDCS improved retrieval in Experiment 1 through effects on reconsolidation because the offline retrieval condition in Experiment 2 resembles previous reconsolidation studies (Sandrini, Censor, Mishoe, & Cohen, 2013; 2014), and the reading task on the second day could resemble a reminder cue, reminding participants of the procedure on the first day and thus reactivating the memory. However, unlike other studies that have delivered NIBS at encoding and suggested effects on consolidation (Innocenti et al., 2010; Rossi, Hallett, Rossini, & Pascual-Leone, 2011), the current study does not find evidence for an effect on consolidation or reconsolidation. Nonetheless, this idea can be better supported by a future study that compares atDCS effects when atDCS is delivered during encoding or immediately after. In addition, future studies can examine the effects of

atDCS on the VLPFC during reconsolidation using standard procedures for reactivating the memory (Sandrini et al., 2014).

Experiment 3: atDCS over the VLPFC and DLPFC During Encoding

Method.

***Participants*.** The aim was to recruit 31 participants per group. Thus, 124 young adults were recruited for the experiment, but 113 participants remained in the final sample size. The included participants (female = 58, male = 39, *M* age = 20.46) were right-handed Native Russian speakers with normal-to-corrected vision and no history of major psychiatric or neurological disease (27 in the VLPFC group, 31 in the Offline group, 27 in the Online group, and 28 in the Sham group). There was a significant difference in age $F(3,89) = 3.99$, $p = .010$, between VLPFC ($M = 19.23$) and DLPFC Sham ($M = 21.71$) $p = .015$. However, there were no significant differences in age between the other groups. The study was conducted in accordance with the ethical guidelines of Moscow Higher Research University, and participants who completed the experiment received 500 roubles as compensation.

Exclusions. Data from 11 participants were excluded from analysis because 1) the participant was feeling unwell 2) there were technical issues 3) the participant was left-handed and 4) experimenter error with the protocol. On the same basis as Experiment 1 and 2, sixteen outliers were excluded, leaving a final sample size of N = 97 (VLPFC N = 25; Offline N = 25, Online N = 24, Sham N = 23).

Experimental Design. The procedure was identical to Experiment 1, except that all materials (information sheet, consent form, stimuli) were translated to Russian and relevant pictorial reading material was selected for the reading task. tDCS settings (including 2 mA delivered over 10 min) were nearly identical to Experiment 1 except that the DLPFC was the stimulation site for each condition (Online, Offline, Sham), and the Online Encoding condition from Experiment 1 included as an additional condition

(VLPFC). In the DLPFC conditions, the active electrode was placed over F3 (International 10-20 EEG system; see Figure 2.0.3). Participants in the VLPFC group received stimulation in the same way as the Online group in Experiment 1, during the study phase over F7. The position of the cathode electrode was distinct from Experiments 1 and 2 and identical to Experiments 4 and 5: over the ipsilateral (left) shoulder. The materials were identical to Experiment 1: the stimuli were translated to Russian and matched in frequency (mean word frequency = 40.38, *SD* = 58; Lyashevskaya & Sharov, 2009) based on the word that best reflected the concept. Stimulation was delivered through a battery-powered, constant-current stimulator (Brainstim, EMS, Bologna, Italy). In addition, participants were asked to describe the sensations that they felt during the stimulation and indicate whether they believed they received real or placebo stimulation. Finally, the data analysis procedure was identical to Experiment 1.

Participants were randomly assigned to one of four groups: Online DLPFC tDCS, Offline DLPFC tDCS, VLPFC, and DLPFC Sham. The Online and Offline groups received online and offline tDCS, respectively, over the DLPFC. Half of the Sham group was assigned to receive sham tDCS online encoding, while the other half received sham tDCS offline encoding, in both cases over the DLPFC. The VLPFC group received online encoding tDCS over the VLPFC.

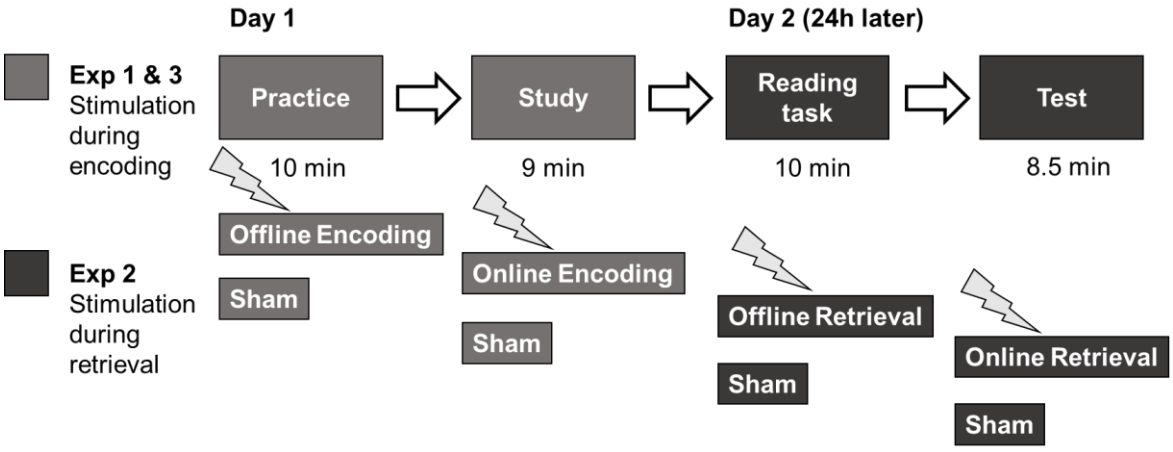

Figure 5.3.1. Time of atDCS administration for Experiments 1-3.

Note: For Experiments 1 and 2, atDCS was delivered over the VLPFC only. For Experiment 3, atDCS was delivered over the VLPFC and DLPFC for Online Encoding but only over the DLPFC for Offline Encoding.

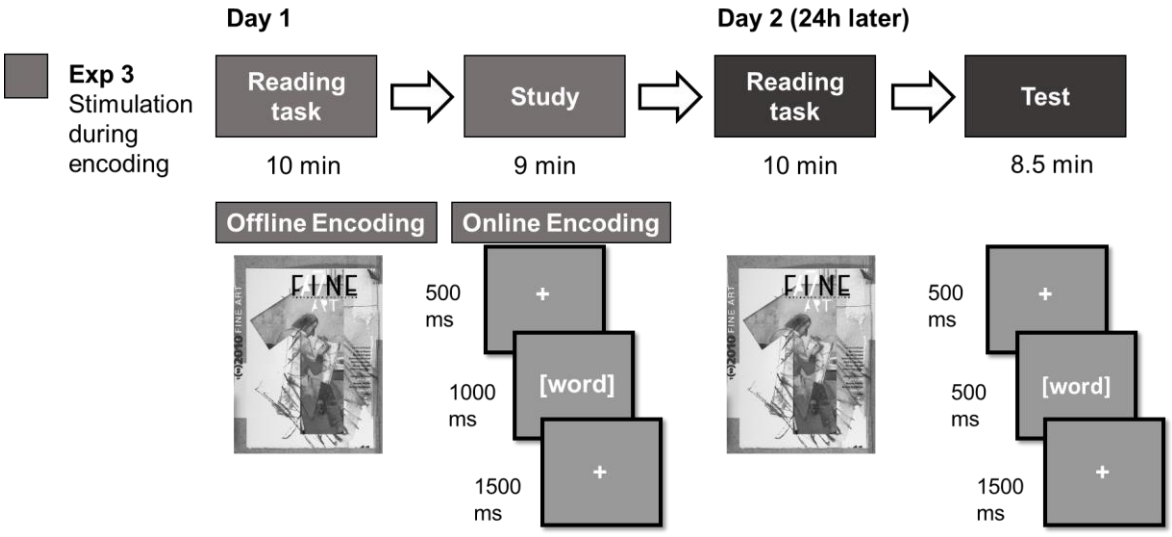

Figure 5.3.2. Procedure for Experiment 3.

Note: atDCS was delivered at offline or online encoding over the DLPFC (Offline DLPFC tDCS and Online DLPFC tDCS groups, respectively) and at online encoding over the VLPFC (VLPFC tDCS). Sham atDCS was delivered at offline or online encoding over the DLPFC.

Results. Sensations data were available for 45 participants, but the majority of participants (69%) felt only a weak tingling or no sensations. Only 13% of participants described an unpleasant feeling or weak pain, while 18% of participants felt burning. The frequency distribution for sensations is presented in Figure 5.3.3. Blinding responses were available for 64 participants. Blinding was successful: 80% of participants believed that they received real stimulation on the first day.

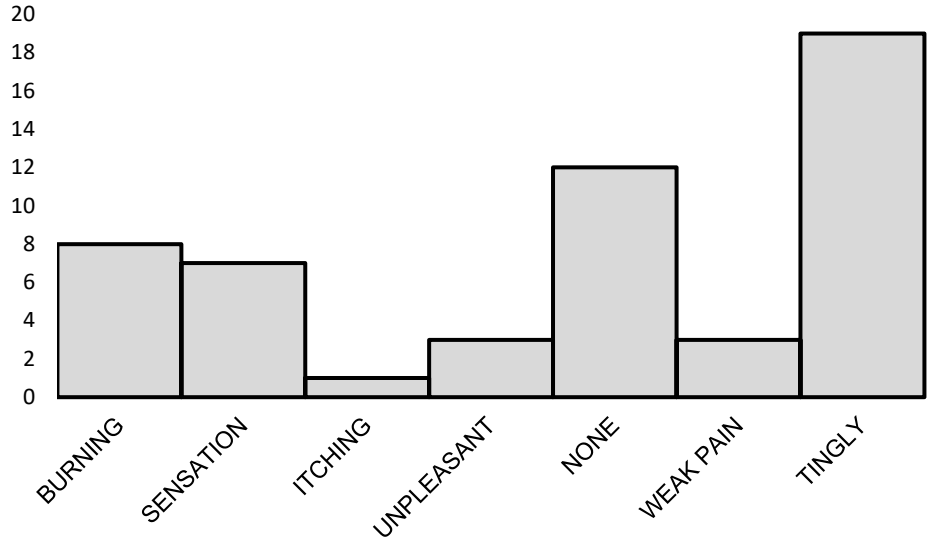

Figure 5.3.3. Frequency of sensations reported by participants.

Accuracy was significantly above chance (Chance $N = 25$) for each group: Online DLPFC $t(23) = 8.74$, $p<.001$; VLPFC $t(24) = 8.41$, $p<.001$; Offline $t(24) = 5.65$, $p<.001$; and Sham, $t(22) = 3.88$, $p = .001$. Levene's test was significant for Online DLPFC $F(1,47) = 34.72$, $p<.001$; VLPFC $F(1,48) = 37.20$, $p<.001$; Offline $F(1,48) = 73.08$, $p<.001$; and Sham, $F(1,46) = 65.71$, $p<.001$.

The assumption of homogeneity of variances was violated for all dependent variables except proportion of false alarms and response bias: recognition accuracy $F(3,93) = 2.84$, $p = .042$; average reaction time $F(3,93) = 4.61$, $p = .005$; Hits $F(3,93) = 3.47$, $p = .019$; RT for Hits $F(3,93) = 4.80$, $p = .004$; RT for False Alarms $F(3,93) = 4.55$, $p = .005$. Levene's test was not significant for response bias $F(3,93) = 2.27$, $p = .086$ and proportion of false alarms $F(3,93) = 2.40$, $p = .073$

Levene's test and frequency distributions suggested that most data did not follow a normal distribution. Thus, non-parametric statistics may be more appropriate than an ANOVA. However, to enable comparison with previous experiments, parametric statistics (Brown-Forsythe's F statistic) are reported in text for corresponding dependent measures. There were no differences in significance between parametric and non-parametric statistics

for the dependent measures with abnormal distributions. In addition, Kruskal-Wallis test results are reported after the main results.

There was not a significant difference between the groups in recognition accuracy $F(3,79.78) = 2.37$, $p = .076$, $\eta_p^2 = .082$, response bias $F(3,93) = 2.15$, $p = .100$, $\eta_p^2 = .065$, or average reaction time $F(3,74.26) = 0.70$, $p = .556$, $\eta_p^2 = .028$. There were also no significant differences between the groups in proportion of hits $F(3,76.88) = 1.37$, $p = .259$, $\eta_p^2 = .051$, or associated reaction times $F(3,75.56) = 0.49$, $p = .694$, $\eta_p^2 = .019$. However, there was a significant difference in proportion of false alarms $F(3,93) = 2.85$, $p = .042$ but not associated reaction times $F(3,70.82) = 0.91$, $p = .439$, $\eta_p^2 = .037$. Planned contrasts for false alarms revealed significant differences between VLPFC tDCS and Sham $t(93) = 2.78$ and between Offline DLPFC tDCS and Sham $t(93) = 2.14$, $p = .018$, with higher false alarm rates for VLPFC tDCS and Offline DLPFC tDCS. However, there were no significant differences between Online tDCS and Sham $t(93) = 1.36$, $p = .178$.

Kruskal-Wallis four-sample tests showed no significant differences for Hits $\chi^2(3) = 2.36$, $p = .502$; False Alarms $\chi^2(3) = 7.16$, $p = .067$; RT for Hits $\chi^2(3) = 1.68$, $p = .641$; or RT for False Alarms $\chi^2(3) = 2.25$, $p = .522$. There were no significant differences in discrimination ability $\chi^2(3) = 4.53$, $p = .209$, average reaction time $\chi^2(3) = 1.95$, $p = .582$, and response bias $\chi^2(3) = 5.03$, $p = .169$.

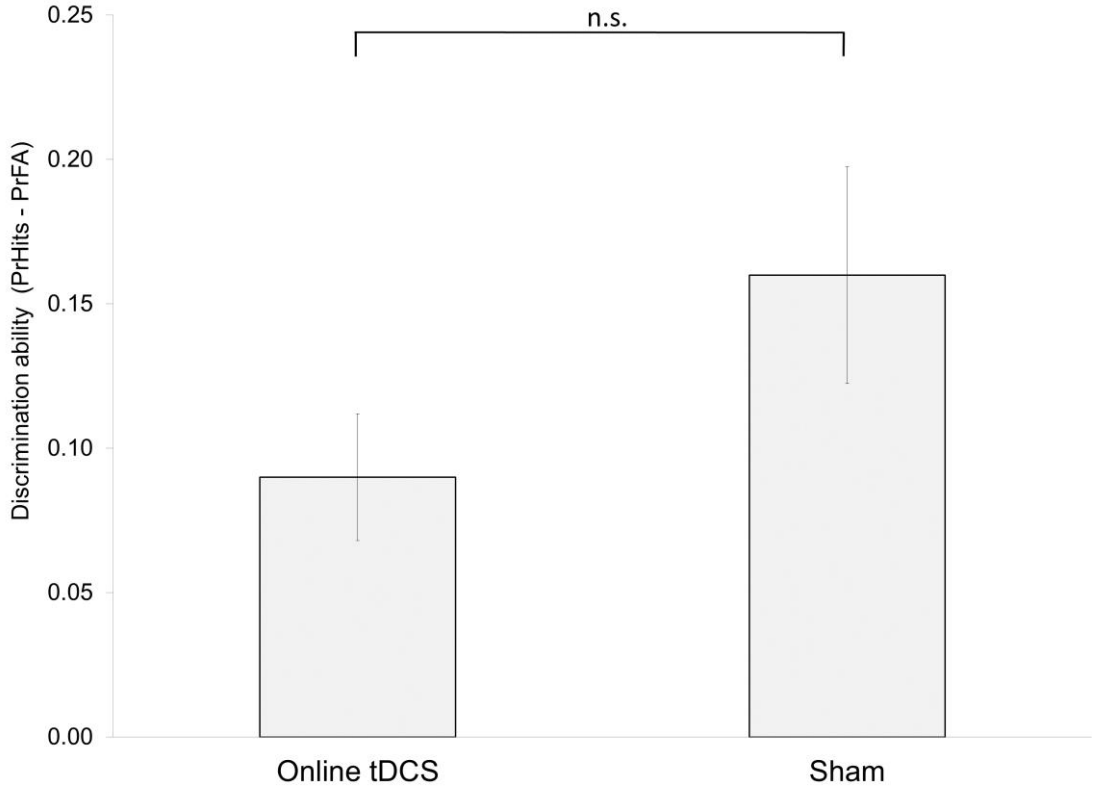

Figure 5.3.4. Discrimination ability for Online VLPFC tDCS and Sham.

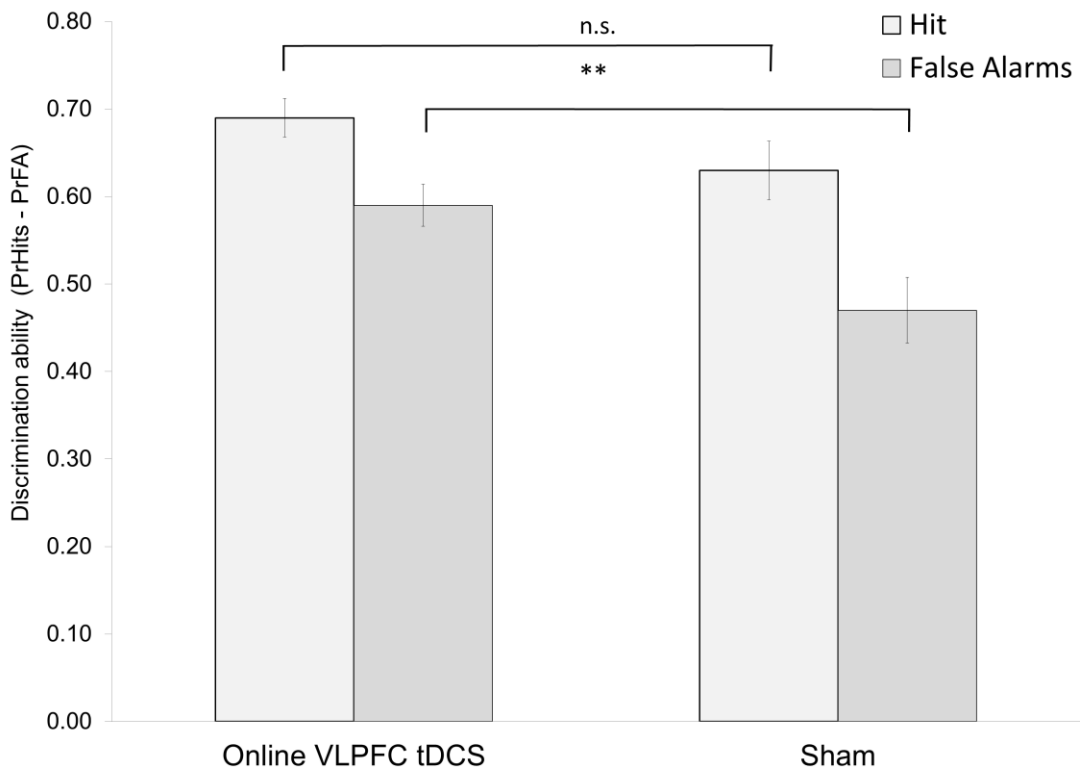

Figure 5.3.5. Discrimination ability across response type for Online DLPFC tDCS and Sham.

Note: Proportion of hits and false alarms are presented for each group.

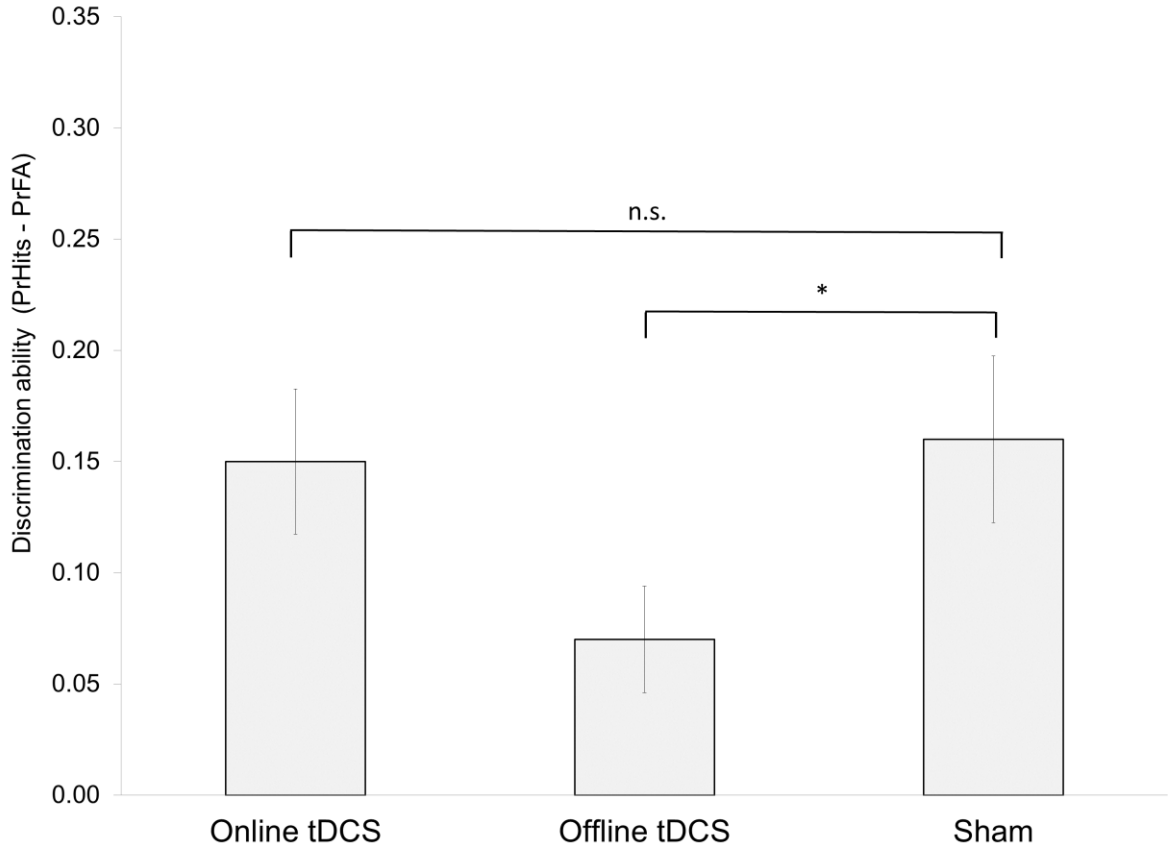

Figure 5.3.6. Discrimination ability as a function of DLPFC experimental group.

Note: Online tDCS = Online DLPFC tDCS; Offline tDCS = Offline DLPFC tDCS; and Sham = DLPFC Sham.

The analysis of low- and high-frequency words was conducted in a subset of participants with available data at study and test (Online Encoding VLPFC N = 15; Sham N = 19) and revealed that a smaller number of low-frequency words (1-10) was presented at study and test for each participant (~33). However, there was a significant effect of frequency, $F(1,32) = 22.93$, $p<.001$, $\eta_p^2 = .417$, but not group, $F(1,32) = 0.74$, $p = .397$, $\eta_p^2 = .023$, on the proportion of hits. There was no significant frequency x group interaction, $F(1,32) = 2.55$, $p = .120$, $\eta_p^2 = .074$, reflecting that partgicipants in both groups showed fewer hits for low- than high-frequency words (see Figure 5.3.7).

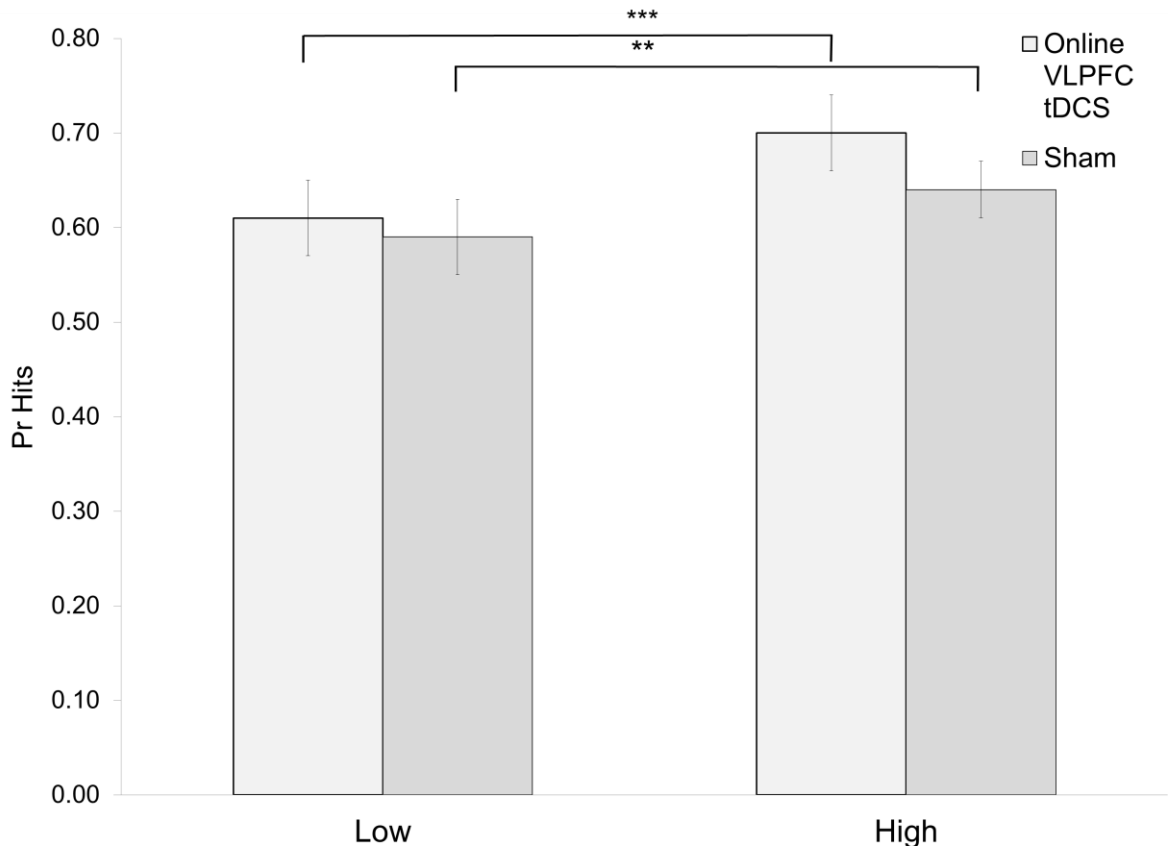

Figure 5.3.7. Proportion of hits for low- and high-frequency words for each group.

Exploratory analysis with Generalizability Theory. The effect of atDCS over the VLPFC did not replicate the effect found in Experiment 1, and one of the possible explanations could be differences in language and another could be weaknesses in the memory test that assesses tDCS effects. While episodic memory tests have previously been examined and compared in terms of validity, few studies have examined the reliability of the standard laboratory memory task. Reliability measurements have generally used Classical Test Theory, which includes test-retest and inter-rater reliability, but Classical Test Theory is limited in that it can only identify one source of error (e.g. time or person; Bloch & Norman, 2012). Another technique developed by Cronbach (1967) called Generalizability Theory is superior for establishing reliability by separating the main measurement (e.g. individual performance) and breaking down the error component into multiple sources, such as language (Russian and English) and trial (different words; Cronbach, 1967). Generalizability Theory can also identify the error variance due to

differences in language and demonstrate how this variance affects the reliability of the measurement. Thus, an exploratory analysis was conducted using Generalizability Theory to understand whether baseline memory performance was biased by different languages and words, and this could help to understand why the two experiments differed in memory performance for the tDCS group.

First, accuracy data were extracted from the Sham groups in Experiments 1 and 3, consisting of trial-by-trial accuracy (1=correct or 0=incorrect/no response) for old words including 120 trials. To satisfy sample size requirements for a reliability study (Atilgan, 2013) additional data were taken from Experiment 4 Sham, and Experiment 3 Online Encoding, because both experiments used the same memory test. For Experiment 3 Online Encoding, atDCS was applied, but there was no significant effect on recognition accuracy, $p>.05$. Thus, trials from the Online Encoding condition could be combined with Sham.

A nested person (P) by trial (T) design was implemented, where an equal number of participants ($N = 61$) were nested in each language (L) (Russian or English), expressed as P:L x T. Generalisability theory was applied following recommendations of Cardinet, Johnson, and Pini (2010) with EduG 6.1-e software (Swiss Society for Research in Education Working Group, 2006). G theory is applied by 1) defining the measurement design 2) estimating variance components by conducting a classical ANOVA 3) calculating the overall reliability (G-coefficient) of the recognition test and 4) conducting a D-study to calculate variance estimates for different measurement designs (Russian and English) separately to improve the reliability of the test. Thus, a standard G study was conducted to evaluate the overall reliability and generalisability of the test scores across persons and trials (see Bloch & Norman, 2000; Medvedev et al., 2017). Then in a D-study one of two languages was removed as a level from the model, and generalisability analysis was conducted for Russian and English separately to compare unique effect of each language on reliability estimates (e.g. G-coefficients).

G-study. A standard ANOVA was used to estimate basic variance components for G-theory analyses shown in Table 5.3.1. The subsequent G-study separates object of measurement (person) from sources of measurement error such as trials and their interactions with person and language while accounting for the levels of each potential error source with reference to the object of measurement. This way G theory prevents inflation of variance resulting in more accurate reliability and error estimates.

Table 5.3.2 includes G-study results and shows the G coefficient of 0.92 (conservative cut-off is 0.80), demonstrating that the recognition test reliably discriminates between individuals and test scores can be generalizable across person and trial populations. The largest amount of error variance was explained by interaction between person, trial and language while language alone had a negligible effect on test scores.

Thus, person x trial in language produced the largest amount of error, perhaps because different people interacted with different words uniquely, and after accounting for the error, the effect of language was negligible. While the recognition test with the set of words cannot be generalised to every language because language is a fixed rather than dynamic construct, the test can be reliably applied for Russian and English speakers.

D-study. Additional evidence that language had no effects on test scores was obtained when Russian and English speakers were analysed separately, which produced comparable G coefficients in each language (G>.91). See Table 5.3.3.

Table 5.3.1.

Classical ANOVA for individual by trial nested in language

				Components				
Source	SS	df	MS	Random	Mixed	Corrected	%	SE
P(L)	162.12	78	2.08	0.02	0.02	0.02	7.5	0.00
L	20.72	1	20.72	0.00	0.00	0.00	0.9	0.00
T	25.70	119	0.22	0.00	0.00	0.00	0.1	0.00
LxT	24.83	119	0.21	0.00	0.00	0.00	0.2	0.00
PxT(L)	1773.77	9282	0.19	0.19	0.19	0.19	91.2	0.00
Total	2007.15	9599					100%	

Note: [a]Corrected components are calculated using Whimbey's correction to classical ANOVA estimates. [b]SE refers to the mixed effects.

Table 5.3.2

G study for individual by trial nested in language

Source of variance	Differ-entiation variance	Source of variance	Relative error variance	% relative	Absolute error variance	% absolute
P(L)	0.02		.....		.....	
L	0.00		.....		.....	
	.....	T	.....		0.00	0.2
	.....	LxT	0.00	0.2	0.00	0.2
	.....	PxT(L)	0.00	99.8	0.00	99.6
Sum of variances	0.02		0.00	100%	0.00	100%
Standard deviation	0.13		Relative SE: 0.04		Absolute SE: 0.04	
Coef_G relative				0.92		
Coef_G absolute				0.92		

Table 5.3.3

G study for English and Russian separately

Source of variance	Differ-entiation variance	Source of variance	Relative error variance	% relative	Absolute error variance	% absolute
P	0.02		.....		.....	
	.....	T	.....		0.00	0.6
	.....	PxT	0.00	100.0	0.00	99.4
Sum of variances	0.02		0.00	100%	0.00	100%
Standard deviation	0.12		Relative SE: 0.04		Absolute SE: 0.04	
Coef_G relative			0.91			
Coef_G absolute			0.91			

Note: G study for English.

Source of variance	Differ-entiation variance	Source of variance	Relative error variance	% relative	Absolute error variance	% absolute
P	0.02		.....		.....	
	.....	T	.....		0.00	0.0
	.....	PxT	0.00	100.0	0.00	100.0
Sum of variances	0.02		0.002	100%	0.002	100%
Standard deviation	0.13		Relative SE: 0.04		Absolute SE: 0.04	
Coef_G relative			0.91			
Coef_G absolute			0.91			

Note: G study for Russian

Table 5.3.4.

Means for accuracy measures across groups for Experiments 1-3

	Online tDCS		Offline tDCS		Sham	
	M	*SD*	*M*	*SD*	*M*	*SD*
Experiment 1 ***N*** (VLPFC encoding)	**16**		**14**		**16**	
Pr discrimination	0.30	(0.08)	0.17	(0.18)	0.13	(0.13)
Br response bias	0.49	(0.14)	0.62	(0.15)	0.65	(0.15)
Pr hits	0.64	(0.10)	0.69	(0.13)	0.70	(0.13)
Pr false alarms	0.34	(0.11)	0.52	(0.18)	0.57	(0.19)
Experiment 2 ***N*** (VLPFC retrieval)	**16**		**15**		**18**	
Pr discrimination	0.15	(0.14)	0.14	(0.17)	0.16	(0.11)
Br response bias	0.53	(0.17)	0.61	(0.19)	0.52	(0.15)
Pr hits	0.60	(0.17)	0.68	(0.14)	0.60	(0.12)
Pr false alarms	0.45	(0.16)	0.54	(0.22)	0.44	(0.16)
Experiment 3 ***N*** (DLPFC encoding)	**24**		**25**		**23**	
Pr discrimination	0.15	(0.16)	0.07	(0.12)	0.16	(0.18)
Br response bias	0.61	(0.14)	0.60	(0.12)	0.56	(0.17)
Pr hits	0.68	(0.10)	0.63	(0.12)	0.63	(0.16)
Pr false alarms	0.53	(0.18)	0.57	(0.14)	0.47	(0.18)

Note: *Means and standard deviations are shown for average reaction time, reaction time for hits, and reaction time for false alarms for each experiment. Sample sizes (N*) are also shown for each experiment. *For Experiment 3, the means are shown for stimulation over the DLPFC.*

Table 5.3.5

Reaction times at retrieval for each group across Experiments 1-3

	Online tDCS		Offline tDCS		Sham	
	M	*SD*	*M*	*SD*	*M*	*SD*
Experiment 1 ***N*** (VLPFC encoding)	**16**		**14**		**16**	
Average RT	770.25	(157.06)	603.42	(180.91)	585.58	(185.82)
RT Hits	769.55	(147.68)	605.31	(174.45)	590.75	(189.95)
RT FA	770.94	(170.58)	601.51	(188.05)	580.42	(182.85)
Experiment 2 ***N*** (VLPFC retrieval)	**16**		**15**		**18**	
Average RT	718.52	(228.38)	658.54	(219.22)	659.78	(140.45)
RT Hits	715.58	(216.63)	664.89	(225.76)	667.62	(149.47)
RT FA	721.48	(243.80)	652.22	(214.75)	651.91	(134.57)
Experiment 3 ***N*** (DLPFC encoding)	**24**		**25**		**23**	
Average RT	501.49	(144.91)	503.00	(103.62)	535.72	(156.16)
RT Hits	504.82	(151.20)	505.85	(104.71)	532.52	(142.72)
RT FA	498.17	(139.84)	500.16	(103.66)	538.91	(171.43)

Note: Means and standard deviations are shown for average reaction time, reaction time for hits, and reaction time for false alarms for each experiment. Sample sizes (N) are also shown for each experiment. *For Experiment 3, the means are shown for stimulation over the DLPFC.*

Table 5.3.6.

Reaction times during tDCS administration (encoding)

	Online tDCS		Offline tDCS		Sham	
	M	*SD*	*M*	*SD*	*M*	*SD*
Experiment 1 (VLPFC encoding)	851.15	(140.49)	789.17	(92.07)	742.89	(96.73)
Experiment 2 (VLPFC retrieval)	825.78	(194.20)	800.42	(177.24)	773.82	(93.30)
Experiment 3 (DLPFC encoding)	720.98	(68.32)	731.33	(61.05)	742.36	(96.62)

Note: Means and standard deviations for reaction times at encoding are shown for each group across Experiments 1-3. For Experiment 3, the means are shown for stimulation over the DLPFC.

Discussion. It is important to note that although average word frequency was similar between Experiments 1 and 3, there was a greater proportion of low-frequency words (1-10) in Experiment 1 than in Experiment 3. However, Experiment 1 showed that atDCS effects on memory accuracy did not differ for low-frequency and high-frequency words. Thus, differences in results between experiments could not be driven by differences in the proportion of low-frequency words. It is possible that individuals were able to focus more on features that were common to the word set independent of word frequency.

Contrary to the expectation of reduced false recognition following atDCS to the VLPFC, Experiment 3 found the opposite effect: increased false recognition. Despite the procedure being identical and verbal stimuli being similar, there were two notable differences: language and characteristics of the stimuli.

Language was mostly ruled out as a factor that explained differences between Experiment 1 and Experiment 3. However, the characteristics of the stimuli differed and could explain differences in results. Although the words were matched as closely as possible in frequency, with similar average frequency and standard deviation, it is important to note that there was a greater proportion of low-frequency words in

Experiment 1 than in Experiment 3. While this may not have had a large effect on encoding in the Sham group, as evident in similar false alarm rates in Experiment 1 and Experiment 3, the higher proportion of low-frequency words could have encouraged item-specific encoding in Experiment 1 because of more distinctive features, whereas the lower proportion of low-frequency words in Experiment 3 could have led to processing of more common semantic features and thus greater relational encoding.

Both experiments suggest that atDCS influenced semantic elaboration, encouraging processing of the features available for each word. If the features were distinctive, which is more likely for low-frequency words, the word could be encoded as unique and distinct from other words. However, if the features were common, which is more likely for high-frequency words, the word could be better encoded in relation to other similar words. Since the pleasantness judgement was designed to draw attention to the words rather than serve as a specific encoding task (relational or item-specific), participants could have encoded the words using item-specific or relational encoding. It remains unclear which strategy was used unless participants are asked or tested using a task that would reveal how the words were encoded (e.g. Blumenfeld & Ranganath, 2007). However, previous research suggests that the DLPFC is selectively engaged at relational encoding and the VLPFC is more engaged at item-specific encoding, and the lack of effect over the DLPFC at online encoding suggests that perhaps relational processing was not as prevalent. It is more likely that item-specific encoding occurred in both experiments, but in one experiment, more distinctive features were processed, whereas in the other experiment, more common features were processed because there was a fewer number of highly distinctive (infrequent words).

With more common features processed, there could have been greater false alarms in Experiment 3 because the VLPFC is involved in temporal clustering (Dubrow & Davachi, 2016). For example, in a false memory task in which semantically-similar items

are presented sequentially, VLPFC activation is associated with a greater proportion of false alarms (Atkins & Reuter-Lorenz, 2011). Future studies could test whether an increased false alarm rate after atDCS over the VLPFC may be due to temporal clustering by using a false memory task.

There were other characteristics that could have differed between Russian and English words, such as orthography and phonology. Unusual or infrequent orthography and phonology lead to distinctiveness at encoding or retrieval, and participants are better able to distinguish between old words and new words because of strong differences in characteristics, leading to fewer false alarms (Roediger, Watson, McDermott, & Gallo, 2001). However, it is important not to exaggerate differences associated with language, since this was likely not the source of differences in results. Previous atDCS studies that have found effects over the VLPFC took place in Italy (Pisoni et al., 2015a), England (Medvedeva et al., 2018; Experiment 3), and the USA (Matzen et al., 2015) with Italian and English words, respectively. However, the results of Experiment 1 corresponded with the results found with stimuli in Italian rather than stimuli in English, supporting the explanation that differences in language could not completely account for differences in results between Experiment 1 and Experiment 3.

Previous studies with atDCS over the left DLPFC have found selective modulations of the false alarm rate, supporting the current finding that offline tDCS over the DLPFC led to increased false alarms. For example, Zwissler and colleagues (2014) found that anodal tDCS over the region increased false alarms for pictures by increasing gist/blurred detail rather than verbatim memories, whereas cathodal tDCS reduced false alarms by inhibiting the processes that lead to imprecise memories. While it remains to be tested whether there was a higher level of neural noise in this experiment, the data do not suggest that the signal-to-noise ratio (Miniussi, Harris, & Ruzzoli, 2013) differed considerably from Experiment 1. Rather, the significant differences between low-

frequency and high-frequency items, with higher hits for high-frequency items, in both groups suggests that there was greater attention toward common rather than distinctive features of items, perhaps because there was only a small proportion of low-frequency, distinctive words at study. Thus, it seems that the semantic elaboration process was the same in Experiment 1 and Experiment 3. Perhaps the activity associated with the process led to a strong signal compared to noise in both experiments, explaining the relatively-strong effect of tDCS on the semantic network and false alarms. However, in Experiment 1, semantic elaboration of distinctive features led to a decrease in false alarms, and in Experiment 3, elaboration of common features led to an increase in false alarms, with atDCS strengthening these elaboration processes and associated effects.

However, it is a limitation that in the current study, atDCS effects over the DLPFC at retrieval were not examined. Javadi and Walsh (2011) found a trend toward improved verbal recognition after atDCS over the DLPFC at retrieval, although effects were stronger at encoding. In addition, Manenti and colleagues (2013) found improved verbal recall after bilateral atDCS to the DLPFC and parietal cortex. There may be a greater effect of atDCS over the left DLPFC at retrieval, especially since no effect of atDCS was found at retrieval for the VLPFC, suggesting that other regions such as the DLPFC may play a greater role. There is also evidence that the DLPFC interacts with the PPC at retrieval (Staresina & Davachi, 2006), and existing tDCS studies have shown that PPC activity is necessary for successful retrieval (Chen, Lo, Liu, & Cheng, 2016; Manenti, Tettamanti, Cotelli, Miniussi, & Cappa, 2010; Pergolizzi & Chua, 2015; Pisoni et al., 2015b).

Experiment 4: Replication of Experiment 1, atDCS over the VLPFC During Encoding

Method.

***Participants*.** Participants were 47 healthy younger adults (eight male; *M* = 21.29, *SD* = 2.46; range = 18-29) with normal-to-corrected vision, English as a native language, no history of neurological or psychiatric disorders, and no contraindications for tES as specified by the screening form (Antal et al., 2017). See below for details about sample size determination and exclusion. The groups did not differ in age $t(47) = 0.86$, $p = .393$ and included equal numbers of each gender (19 female for Sham; 17 female for Online tDCS). The participants in Online tDCS were similar in age (*M* = 21.61, *SD* = 2.44) to Sham (*M* = 21.00, *SD* = 2.48).

Sample size and exclusions. The aim was to recruit 20 participants per group, based on a power analysis using to detect a medium effect size found in Experiment 1 ($\alpha = 0.05$, $1-\beta = .95$). However, additional participants were recruited due to data loss on a secondary measure that is not reported here (EEG recording), and the addition of these participants did not significantly change the results. The group sizes became imbalanced due to data loss in the secondary measure, and data collection continued until complete data on the secondary measure were available for 40 participants. Outlier exclusion followed the same procedure as in Experiment 1. Data for memory performance were available for 59 participants (Sham *N* = 30, Online tDCS *N* = 29), but after exclusion for incomplete data (five participants) and outliers (five participants), the final sample size was 47. Participants were excluded for not returning for the second session (two in Sham and two in Online tDCS) or not completing the recognition test (one participant in Online tDCS could not complete due to construction in the building). In addition, outliers with values of two standard deviations beyond the mean on any dependent measure (except

response bias) were excluded (two in Sham and three in Online tDCS), leaving a final sample size of 49 (Online tDCS N = 23, Sham N = 26).

Experimental design. The method was identical to Experiment 1 with the following exceptions: only the Online Encoding group was examined for comparison with Sham, and there was an inter-trial interval of 2-4 s at test to accommodate collection of additional data (EEG) that were not related to the current experiment. In addition, the study was double-blind (see Appendix N for blinding procedure): neither the participant nor the experimenter was aware of the experimental condition. At the end of the session, participants completed a questionnaire about sensations felt during tDCS (Antal et al., 2017; see Appendix I) and awareness of the experimental condition ("real or placebo?"). Finally, the cathode was placed on the ipsilateral (left) shoulder instead of the contralateral (right) shoulder (see Figure 2.0.4). All other tDCS parameters were identical to Experiment 1. The data analysis procedure was identical to Experiment 1 in terms of analyses for pairwise comparisons. One-tailed independent t-tests were conducted for all dependent measures that were significantly affected by tDCS in Experiment 1: reaction time at encoding, recognition accuracy, proportion of false alarms, response bias, and average reaction time.

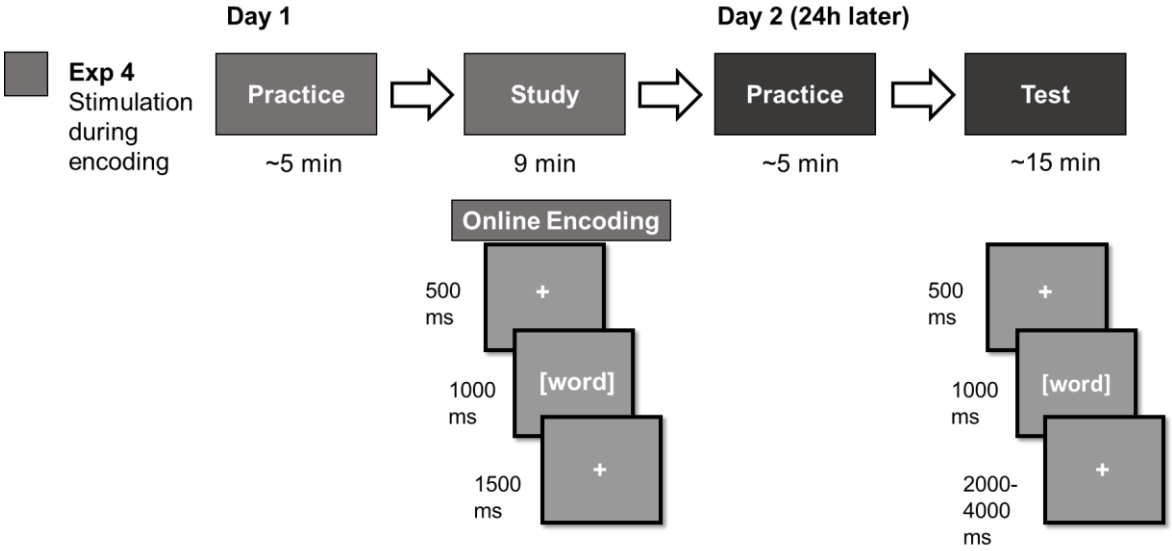

Figure 5.4.1. Procedure for Experiment 4.

Results. Participants tolerated the stimulation well (Questionnaire $N = 43$), with low ratings by the majority for sensations including burning ($N = 38$), pain ($N = 41$), and metallic taste ($N = 38$). Other reported sensations included a "white flash" and "tingliness". There were no significant differences between the groups in average rating for each sensation, ps>.350, except for burning, $p = .03$: the tDCS group had a higher rating for burning than the Sham group, likely because there were more participants in the Sham group who reported no burning at all. The frequency of each sensation is plotted in Appendix K. Blinding was successfully achieved: 95% of participants were oblivious to the condition, indicating that they believed the stimulation was real or could not guess whether real stimulation was delivered. Specifically, 78% of participants who completed the questionnaire expressed a belief that the stimulation was real.

Accuracy was significantly above Chance ($N = 26$) for Online tDCS $t(22) = 9.74$, $p<.001$ and Sham $t(25) = 12.43$, $p<.001$. The assumption of homogeneity of variances was met for all dependent measures of interest: Hits $F(1,47) = .88$; False Alarms $p = .354$; $F(1,47) = 1.11$, $p = .298$; recognition accuracy $F(1,47) = .53$, $p = .472$, average reaction time $F(1,47) = .15$, $p = .704$; RT for Hits $F(1,47) = .29$, $p = .595$; RT for False Alarms $F(1,47) = .17$, $p = .685$; and response bias $F(1,47) = .93$, $p = .340$.

There was no significant difference in reaction times at encoding $t(47) = 1.23$, $p = .226$; see Table 5.5.3. The difference in discrimination ability did not reach significance $t(47) = 1.30$, $p = .067$. The means were similar between Online tDCS ($M = 0.30$, $SD = 0.19$) and Sham ($M = 0.25$, $SD = 0.17$). There was a significant difference in the proportion of false alarms, $t(47) = -2.21$, $p = .016$, while means for proportion of hits were similar. There was also a significant difference in average reaction time at retrieval, $t(47) = 2.14$, $p = .019$. Reaction times for hits and false alarms separately are presented in Table 5.5.2. There was no significant difference in response bias, $t(47) = -1.55$, $p = .065$.

Discussion. The current experiment partially replicated Experiment 1, like Medvedeva and colleagues (2018; Experiment 4), with a significant effect of atDCS over the VLPFC on false recognition but not discrimination ability when atDCS was delivered during encoding. There was also a significant increase in average reaction times at retrieval but not encoding.

The aim of the experiment was to replicate the results of Experiment 1 with a larger sample size, and Experiment 4 was also more robust by including a double-blind design and measure of tDCS sensations and blinding success. The successful replication of the atDCS-induced reduction in false alarms and increase in retrieval reaction times is encouraging, suggesting that the results of Experiment 1 were not likely to be due to experimenter effects or Type I error. However, it is unclear why the effect on accuracy and encoding reaction times did not replicate. It is notable that Medvedeva and colleagues (2018; Experiment 4) did not report differences in reaction times at encoding or retrieval, and in their partial replication, they found differences in discrimination ability but not false alarms.

There were few methodological differences between Experiments 1 and 4, and it seems unlikely that minor changes in procedure such as EEG setup and a longer inter-trial interval would explain differences in results. It seems more likely that atDCS effects are sensitive to individual variability and baseline performance, which can increase with larger sample size, although the contribution of each individual score to the mean decreases. Moreover, there could be a different proportion of individuals for whom tDCS was not effective, either due to high or low baseline memory accuracy. Cesario (2014) suggests that replication success must be carefully interpreted in the context of the multiple factors and conditions that are necessary for the effect to emerge, and it is also important to consider that some of these conditions are unknown. However, a replication study is best conducted in the same laboratory as the original study since there is a higher likelihood of

replicating the original conditions, including those that are unknown but necessary for the effect.

An issue that emerged from Experiment 4 as well as Experiment 1 was the proximity of the anode electrode to the eye. Initially, the analysis of the sensations data suggests that strong current flow through the eye, which would be reflected by the emergence of phosphenes ("white flash" reported by participants), was not likely because only a handful of participants reported the white flash. However, future studies should address this issue by estimating the flow of current through the eye with a computational model (Bikson, Rahman, & Datta, 2012) and measuring the exact distance to the eye, which can vary depend on head size. Moreover, future studies could include a more explicit measure of phosphenes (e.g. did you see a spot of light?) and consider excluding participants who report strong sensations of phosphenes.

Experiment 5: atDCS over the VLPFC During Encoding in a False Memory Task

Overview. The DRM task is a false memory task that reliably elicits false recognition and is an established method of studying false recognition. It involves the presentation of lists of words, or associates, that are highly related with an unpresented theme (critical lure). The associates are selected so that they are likely to elicit the critical lure. For example, *mad, fear, hate,* and *rage* would be presented one at a time in a sequence, while the highly-associated critical lure, *anger*, would be presented at test. The strong association between *anger* and the presented words of the corresponding list (*mad, fear…*) could lead to false recognition of the critical lure. Once a set of lists is selected, some of those lists are presented in the study phase, whereas the rest are presented in the recognition phase along with the lists presented in the study phase. Studies have selected lists to present based on forward associative strength, which indicates the extent to which the associate is likely to elicit the theme or critical lure. At study, words are presented in order of highest to lowest association strength with the lure. Thus, words that are most

likely to activate the critical lure are presented first (*mad* and *fear* rather than *rage*). In the recognition test, some of the associates from the studied list, usually selected based on serial position in the list, are presented again along with their corresponding critical lures. In addition, words from the same serial positions in unstudied lists and their critical lures are presented.

Method.

Participants. Forty participants were recruited (18 females, 22 males; *M* age = 23, *SD* = 3.4, range 18-31), and the final sample size included 31 participants (16 in Online tDCS; 15 in Sham; see Exclusions below). Participants were randomly assigned to two groups: online tDCS or sham. The two groups did not differ significantly in age ($p = .902$). All participants spoke English as their native language, had normal or corrected-to-normal vision, and no recent history of major psychiatric or neurological disease.

All participants completed a screening questionnaire (Antal et al., 2017) and were excluded for any contraindications, including severe skin conditions, history of epilepsy, pregnancy, and head trauma. and gave written informed consent. Participants received £10 or course credits upon completion of the experiment. The study was conducted in accordance with the ethical procedures at Kingston University.

Exclusions. One participant took part in the study phase but did not return the following day for the test phase, which resulted in a sample of 39 participants (20 in the sham group, 19 in the online tDCS group). Outlier exclusion followed the same procedure as experiments in Chapter 5. Data from 3 participants in the tDCS group and 5 participants in the Sham group were identified as outliers and excluded.

Experimental design. Although the design was similar to Experiment 4, there were several key differences: An explicit false memory task was used to study the effect of atDCS on false recognition. Thus, an independent t-test conducted to compare Online tDCS and Sham in false alarms to lures. In addition, stimulus presentation times varied to

correspond to the task (Curran et al., 2000; Düzel et al., 1997). An additional self-paced task for a separate research question (see Chapter 6) followed recognition trials for old words, lasting at least 2000 ms. Thus, the duration of the encoding task and tDCS administration was longer (~20 min), but all other parameters were identical to Experiment 4 and similar to the previous experiments.

Procedure. Upon arrival to the lab, participants received the information sheet, screening form, and consent form to sign. Then, the experimenter applied the electrodes (see tDCS settings for more detail). Participants tried the stimulation for less than 30 s (to ensure that the stimulation was not uncomfortable) and gave verbal consent to continue with the experiment. Participants read the instructions, which the experimenter repeated verbally, and completed the practice phase. They were instructed to indicate whether each word was pleasant (by pressing the key A) or unpleasant (by pressing the key L) and to memorise the word. All participants reported being able to see the words and colour backgrounds presented on the screen. Once participants understood the task (either by asking additional questions or repeating the practice), the stimulation was started at the same time as the study task. During the breaks, the experimenter ensured that the stimulation was bearable for participants and that they understood the instructions.
At study, a fixation cross was presented for 500 ms, followed by the word 1200 ms and an inter-trial interval of 1500 ms. There were four breaks of 20 s each, and the study phase lasted 20 min at most, accounting for delays in stimulus presentation. The overall duration of the study phase was approximately 45 min, with 15 min for the completion of forms, 10 min for application of electrodes, and 20 min for the stimulation during the study task.

Participants returned for the test phase 24 h later. No electrodes were applied, and participants were given the instructions for the recognition and source memory tasks. Participants were instructed to discriminate between old and new items by pressing the keys A and L, depending on assignment. The response key was counterbalanced across

participants. At test, a fixation cross was presented for 500ms, followed by the word for at least 1000ms (self-paced). All trials included a 1000-ms inter-trial interval. The test phase could vary but lasted approximately 25 min. At the end of the test task, participants were given a tDCS sensations questionnaire (Antal et al., 2017) and were asked whether they received placebo or real stimulation.

Materials. A modified version of the DRM task was presented visually using MATLAB version 8.3.0 (Mathworks) and Cogent Toolbox version 1.32 (Cogent, www.vislab.ucl.ac.uk/Cogent/). There were 27 lists selected and modified from the DRM paradigm, resulting in 324 study words (Deese, 1959; Roediger & McDermott, 1995). The lists were selected to minimise repetition of words. Repeating words were replaced with a synonym that matched the original meaning, and care was taken to replace words that were in lower serial positions, being less likely to evoke the critical lure. Because the original lists included norms that were catered to an American population, these norms were adapted to British culture. In addition, the critical lures and three highest semantic associates from each list were extracted to be presented at the test phase only. The semantic associates were most closely associated with the critical lure and were likely to be evoked by other words in the list (Düzel et al., 1997; Curran et al., 2001). For example, *fear, hate,* and *rage* served as critical lures together with *anger* for the list beginning with *mad, temper,* and *fury*. The semantic associates were selected to serve as additional critical lures so that there would be a sufficient number of lures at test (108 instead of 27) to compare false alarms to lures and false alarms to new items. An additional set of 108 unrelated new words were selected from the MRC psycholinguistic database based on similar characteristics to the DRM lists (Coltheart, 1981). New words had frequency greater than 76, concreteness greater than 200, and word length between 4 and 8 letters (Curran et al., 2001).

The design was adapted from previous experiments with DRM lists and large trial numbers for lures (Düzel et al., 1997; Curran et al., 2001). They indicated using the highest semantic associates, the list words with the highest backward association strength, in positions 1-5 in the list (Roediger, Watson, McDermott, & Gallo, 2001). Because the word in position 1 is most likely to evoke the critical lure and words from positions 1,8, and 10 are usually used, or words from the first 6 positions (Roediger & McDermott, 1995). Thus, old words from positions 1, 5, 8, and 10 were used at test. In addition to the critical lure, the lures were words from positions 2, 3, and 4 with the highest backward association strength to the critical lure (except for the word in position 1).

Thus, at study, 324 words were presented: each list was presented sequentially according to highest to lowest backward association strength (Roediger, Watson, McDermott, & Gallo, 2001). At test, 324 words were presented: 108 study words, 108 lures, and 108 unrelated new items. Although the items were presented in random order, the test presentation ensured that there were 4 lures, 4 studied items, and 4 new items for every subset of 12 trials. This was designed to minimise response bias (Curran et al., 2001).

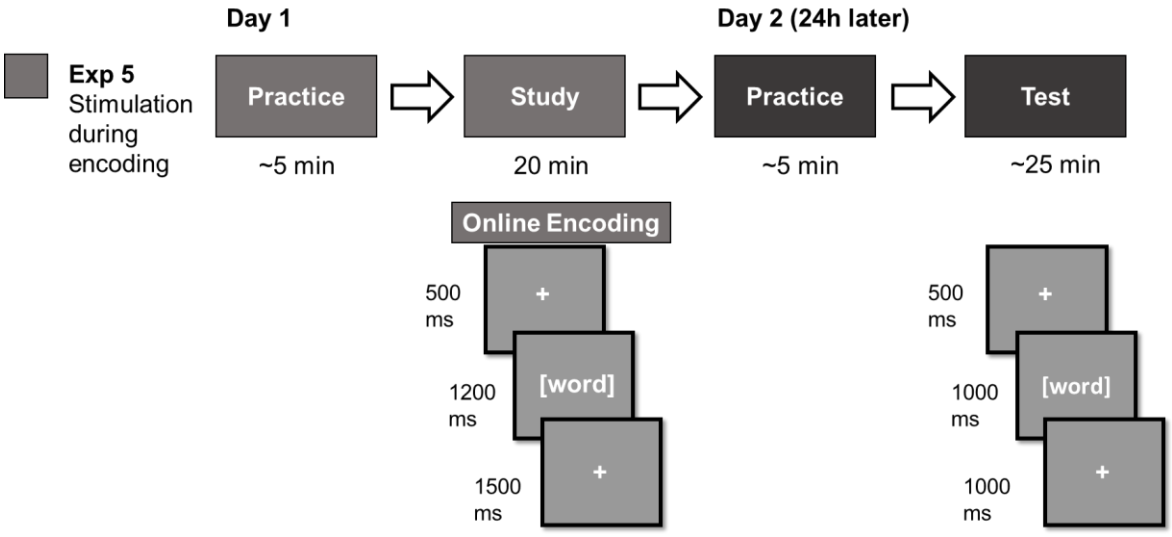

Figure 5.5.1. Procedure for Experiment 5.

Data analysis. All independent t-tests were one-tailed, with the prediction that the Online tDCS group would have increased accuracy and reaction time and decreased false alarms to new items and lures. Online tDCS and Sham were compared in discrimination ability, response bias, average reaction time, and false alarms to new items and lures and associated reaction times.

Results. Participants did not report any adverse sensations, and sensations did not differ between participants in the Sham and tDCS group, *p*s > .224The frequency of each sensation reported is plotted in Appendix O. The majority of participants believed that they received real stimulation. The assumption of homogeneity of variances was met for all dependent measures. Levene's test was not significant for reaction times at encoding, $F(1,29) = 1.18$, $p = .287$, and accuracy $F(1,60) = 1.05$, $p = .309$.

Accuracy was significantly above Chance ($N = 16$) for Online tDCS $t(15) = 12.49$, $p<.001$ and Sham $t(14) = 9.44$, $p<.001$. Equal variances were not assumed for Online tDCS $F(1,30) = 27.23$, $p<.001$ or Sham $F(1,29) = 23.69$, $p<.001$.

There was no significant difference in reaction time at encoding between Online tDCS ($M = 904.64$, $SD = 176.36$) and Sham ($M = 909.02$, $SD = 327.40$), $t(47) = 1.23$, $p = .226$. There was no significant difference in reaction times at encoding, $t(29) = 0.05$, $p = .963$. There were no significant differences in discrimination ability $t(27) = 0.04$, $p = .965$, response bias $t(60) = -0.54$, $p = .590$, or average reaction time $t(27) = -0.60$, $p = .554$. There were also no significant differences in proportion of false alarms $t(27) = 0.73$, $p = .469$ or hits $t(27) = 1.13$, $p = .271$. There were also no significant differences between the groups in proportion of false alarms to lures $t(20) = -1.28$, $p = .106$, although false alarms to lures were numerically higher in Online tDCS compared to Sham (see Figure 5.5.2), and there was a marginally significant increase in reaction times for Online tDCS $t(29) = -1.72$, $p = .048$.

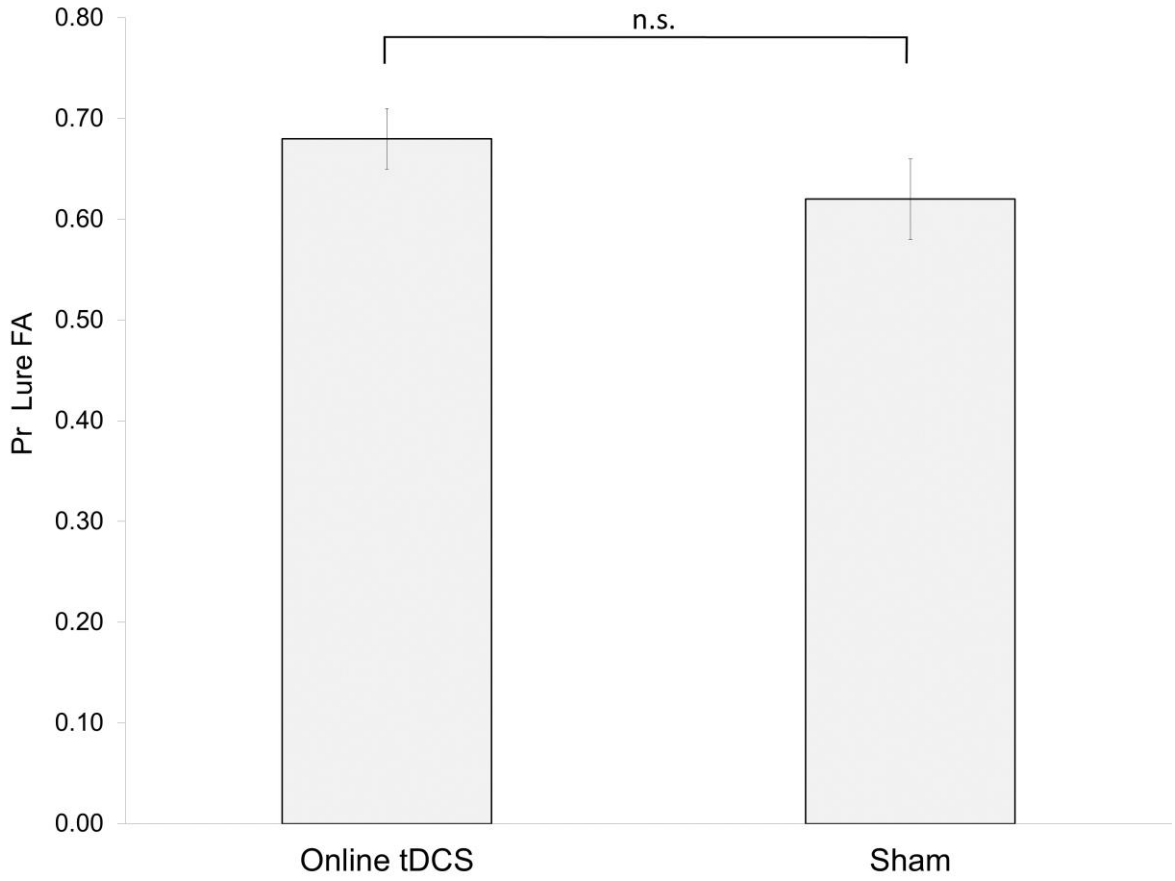

Figure 5.5.2. Proportion of false alarms to lures for each group.

Table 5.5.1

Means for accuracy measures across Experiments 3-5

	Online tDCS		Sham	
	M	*SD*	*M*	*SD*
Experiment 3 ***N***	**25**		**23**	
Pr discrimination	0.09	(0.11)	0.16	(0.18)
Br response bias	0.66	(0.12)	0.56	(0.17)
Pr hits	0.69	(0.11)	0.63	(0.16)
Pr false alarms	0.59	(0.12)	0.47	(0.18)
Experiment 4 ***N***	**23**		**26**	
Pr discrimination	0.31	(0.19)	0.24	(0.17)
Br response bias	0.64	(0.14)	0.70	(0.15)
Pr hits	0.74	(0.12)	0.78	(0.11)
Pr false alarms	0.43	(0.14)	0.54	(0.18)
Experiment 5 ***N***	**16**		**15**	
Pr discrimination	0.35	(0.15)	0.34	(0.16)
Br response bias	0.66	(0.15)	0.64	(0.17)
Pr hits	0.79	(0.09)	0.77	(0.11)
Pr false alarms	0.44	(0.16)	0.43	(0.16)

Note: Means and standard deviations are shown for average reaction time, reaction time for hits, and reaction time for false alarms for each experiment. Sample sizes (N) are also shown for each experiment. *The Online tDCS condition refers to atDCS delivered online encoding over the VLPFC.*

Table 5.5.2

Reaction times at retrieval for Online tDCS and Sham across Experiments 3-5

	Online tDCS		Sham	
	M	*SD*	*M*	*SD*
Experiment 3 ***N***	**25**		**23**	
Average RT	484.00	(82.58)	535.72	(156.16)
RT Hits	490.18	(79.85)	532.52	(142.72)
RT FA	477.82	(86.10)	538.91	(171.43)
Experiment 4 ***N***	**23**		**26**	
Average RT	914.80	(246.69)	757.34	(266.63)
RT Hits	877.48	(212.93)	739.06	(232.36)
RT FA	938.84	(272.72)	775.62	(303.14)
Experiment 5 ***N***	**16**		**15**	
Average RT	1238.78	(402.41)	1188.78	(280.34)
RT Hits	999.97	(259.24)	880.02	(146.43)
RT FA	1115.50	(376.01)	983.54	(184.73)

Note: *Means and standard deviations are shown for average reaction time, reaction time for hits, and reaction time for false alarms for each experiment. Sample sizes (N*) are also shown for each experiment. *The Online tDCS condition refers to atDCS delivered online encoding over the VLPFC.*

Table 5.5.3

Reaction times during administration (encoding) across Experiments 3-5

	Online tDCS		Sham	
	M	*SD*	*M*	*SD*
Experiment 3	725.49	(68.18)	742.36	(96.62)
Experiment 4	838.8	(172.38)	787.51	(118.09)
Experiment 5	904.64	(176.36)	909.02	(327.40)

Note: Means and standard deviations are shown for average reaction time, reaction time for hits, and reaction time for false alarms for each experiment. Sample sizes (N) are also shown for each experiment. *The Online tDCS condition refers to atDCS delivered online encoding over the VLPFC.*

Discussion. Experiment 5 showed no differences between atDCS and Sham in false alarms for new items or lures, failing to replicate the results of Experiments 1 and 4. There was also no significant difference in accuracy. It is unclear why there was no effect of atDCS in this experiment, although the trend toward higher false alarms for lures in the atDCS group suggests that the effect of atDCS could resemble that of Experiment 3.

Díez and colleagues (2017) examined the effects of atDCS over the left ATL on false memory and found a reduction in false alarms for the DRM task but not categorically-related items, suggesting that there could be distinct cognitive mechanisms for processing categorical vs associative similarity. The tasks in Experiments 1-4 could resemble categorically-related rather than associatively-related lists, since items could be related based on category (i.e. animals) rather than a common association (i.e. anger).

However, in the case of the VLPFC, the false alarm reduction could occur for categorical but not DRM lists. Previous research suggests that the VLPFC processes semantic features of individual items and also binds adjacent items, thus engaging in item-specific and relational encoding. In addition, the VLPFC clusters items over time, possibly interacting with the hippocampus to bind items in context and order (Dubrow & Davachi, 2016). It is possible that the VLPFC was engaging in greater relational encoding because while the items were likely to be high in frequency and share common features, the common association emerged as items were presented sequentially in a list rather than as items were presented individually. In other words, the common association only emerged after *fast, current, rapid,* and *stream* were presented rather than a common feature that could be instantly encoded for members of the same category (*cat*, *dog*, and *mouse* are animals, and this category readily comes to mind). Future research is needed to understand whether relational encoding and temporal clustering occur in the VLPFC during the DRM task and can be modulated by atDCS. Finally, there is a possibility that there was a higher level of neural noise in this experiment compared to previous experiments because of

activation of semantic lures during encoding, including processing for items that were mentally but not physically present. In addition, VLPFC neurons could be more attentive to the order of the items since there was a common association across groups of items. Finally, the background changed colour, perhaps engaging neuron populations involved in perceptual discrimination. Although VLPFC neurons may not be so attentive to perceptual cues as DLPFC or PPC neurons (Bartolomeo, Thiebaut De Schotten, & Chica, 2012; Nee & Jonides, 2009), they are associated with object recognition (Chan, 2013) and could have been processing multiple semantic and perceptual features during the task, increasing neural noise even if the semantic features were processed to a greater extent.

Exploratory Correlations

To investigate tDCS further and examine whether tDCS affected low and high performers differently, low performers and high performers in Sham and Online VLPFC tDCS were paired for each experiment (Experiments 1, 3, 4, and 5) under the assumption that Online tDCS low and high performers would have similar baseline performance to low and high performers in Sham, respectively. Specifically, performers in the Online tDCS and Sham groups were sorted from lowest to highest and then paired. In cases of unequal group sizes, the highest performers in the unbalanced group (group with greater number of participants) were removed, so sample sizes were made equal to enable comparison between groups. Gains in performance due to tDCS were defined for recognition accuracy as the difference in discrimination ability between Sham and Online tDCS (DI tDCS – DI sham), while reductions in false alarm rate due to tDCS were defined as the difference in proportion of false alarms between Sham and Online tDCS (FA Sham – FA tDCS). The data did not meet the assumptions for a simple regression, including normality of residuals and homoscedastity, so exploratory correlations were conducted using Sham score as a predictor, representing the baseline score, and gains in recognition accuracy and reductions in false alarm rate due to tDCS as outcome variables. Because

significant differences between groups were present for false alarms to lures but not new items, false alarm rate of Experiment 5 were divided into two datasets: false alarms to new items, comparable to previous experiments (Experiment 5), and false alarms to lures (Experiment 5 Lure).

The correlations revealed positive correlations between baseline false alarm rate and reduction in false alarm rate that were consistent across experiments (except non-significant for Experiment 5), with greatest tDCS-induced reductions in false alarms predicted for lowest performers who had the highest baseline false alarms. In contrast, the correlation between baseline recognition and tDCS gains was not consistent across experiments: Experiments 1 and 3 as well as false lure recognition in Experiment 5 showed significant negative correlations, with the prediction that tDCS gains would be greater for lower baseline scores, while Experiments 4 and 5 showed positive correlations, with the prediction that tDCS gains would be greater for higher performers.

Table 5.6.1.

Correlations between baseline score and tDCS gains for accuracy and false alarms for each experiment

	Exp 1	Exp 3	Exp 4	Exp 5	Exp 5 Lure
Accuracy	-.95**	-.96**	.83**	.72**	-.55*
False alarms	.94**	.91**	.59**	.39	.72**

Note: *$p < .05$. **$p < .01$.*** p<.001.

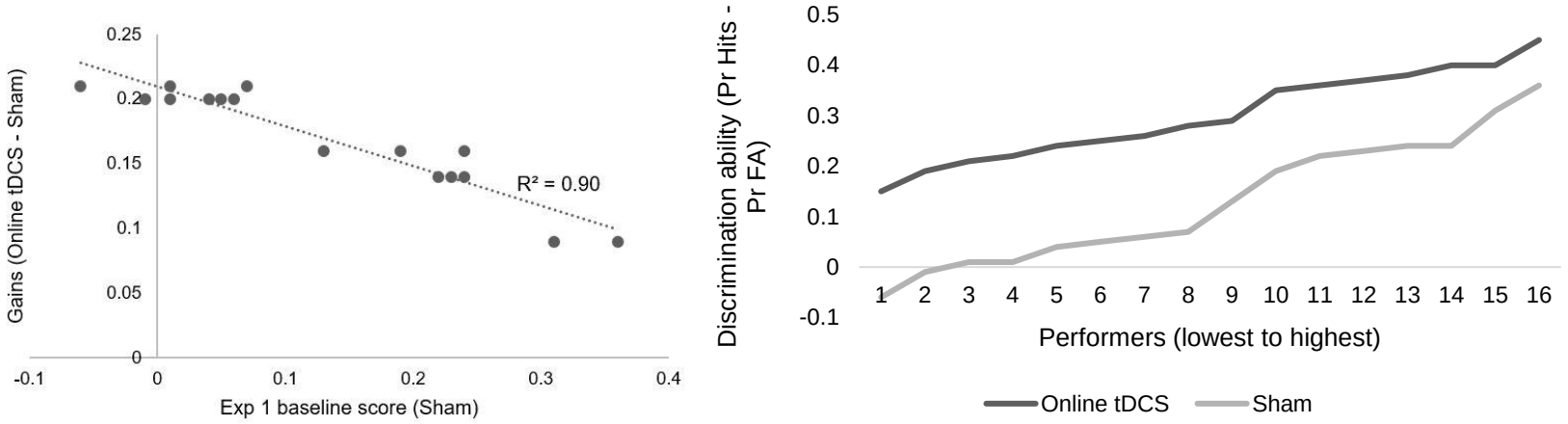

Figure 5.6.1. Experiment 1 tDCS gains in DI (left panel) as a function of Sham DI score and DI (right panel) from lowest to highest performers.

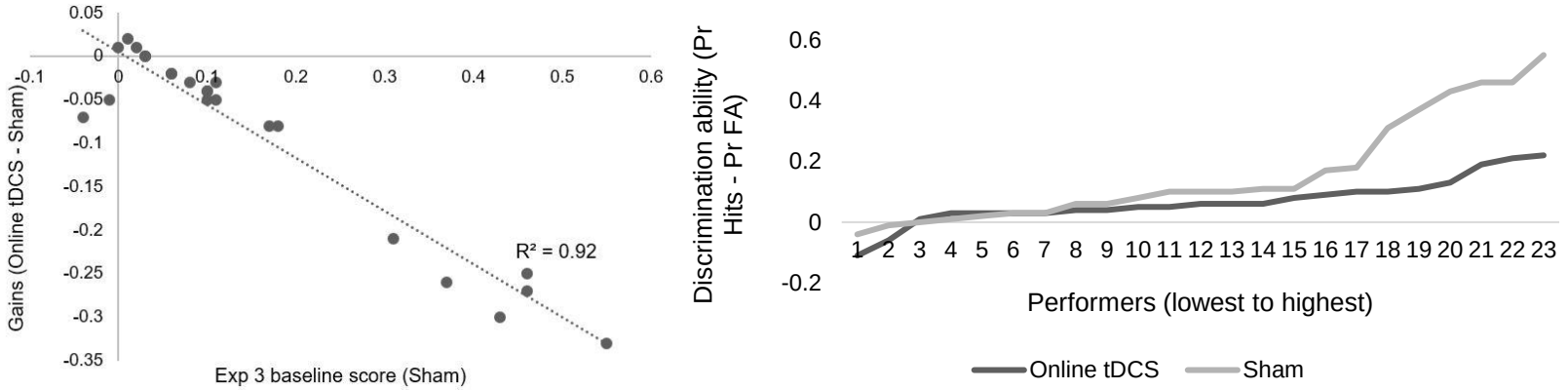

Figure 5.6.2. Experiment 3 tDCS gains in DI (left panel) as a function of Sham DI score and DI (right panel) from lowest to highest performers.

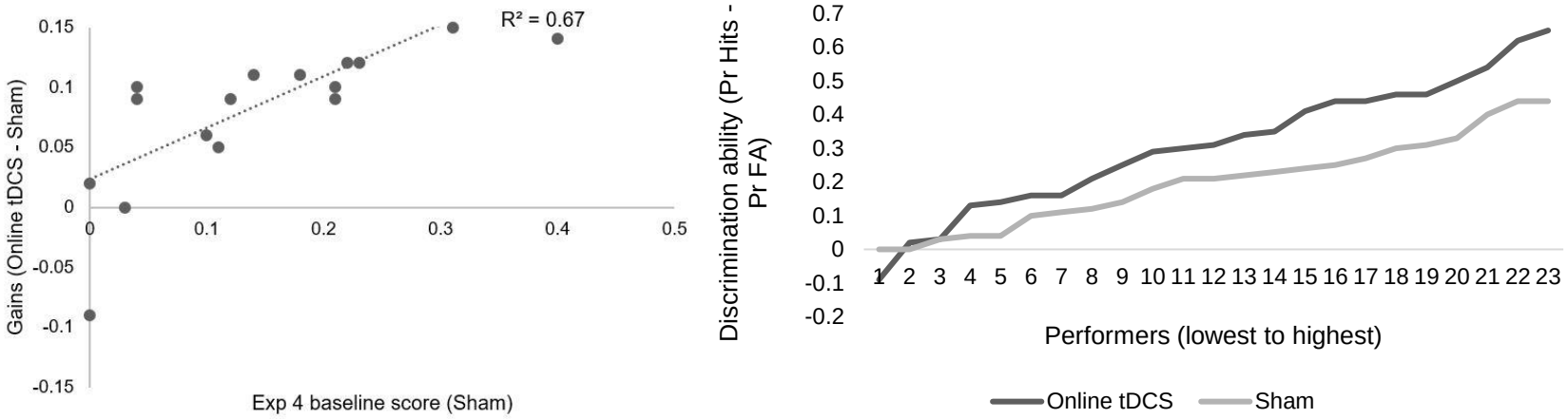

Figure 5.6.3. Experiment 4 tDCS gains in DI (left panel) as a function of Sham DI score and DI (right panel) from lowest to highest performers.

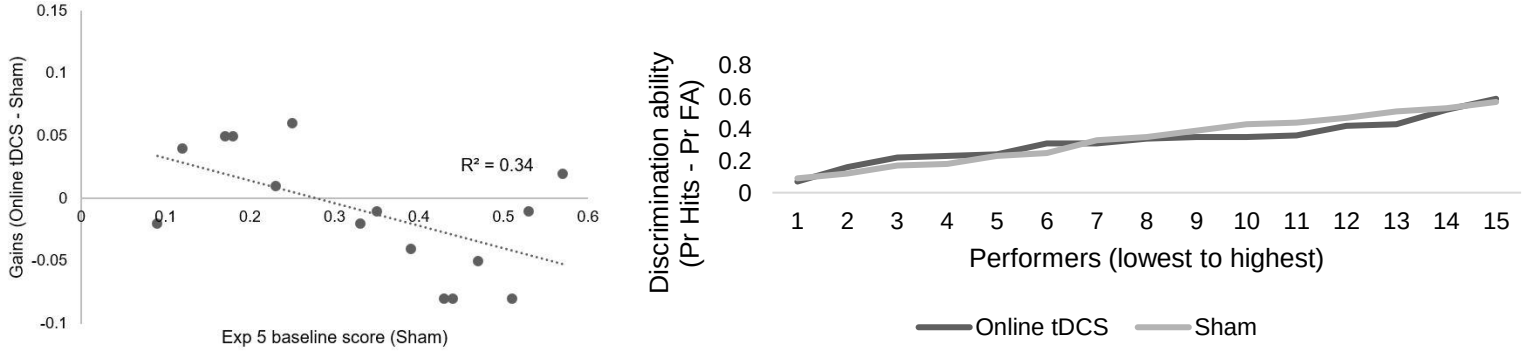

Figure 5.6.4. Experiment 5 tDCS gains in DI (left panel) as a function of Sham DI score and DI (right panel) from lowest to highest performers.

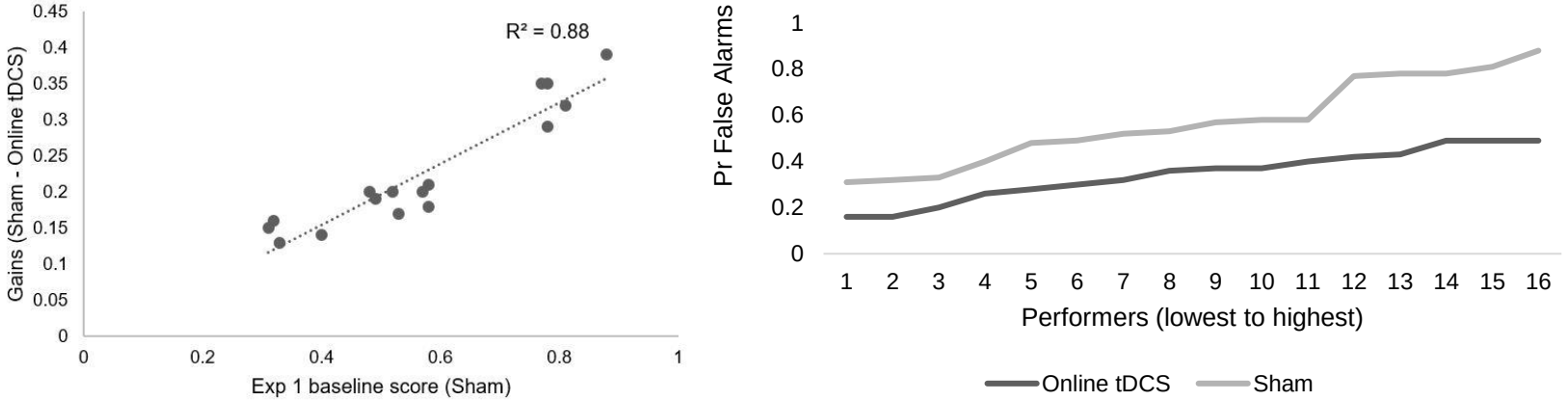

Figure 5.6.5. Experiment 1 tDCS reduction in Pr FA (left panel) as a function of Sham FA and Pr FA (right panel) from lowest to highest performers.

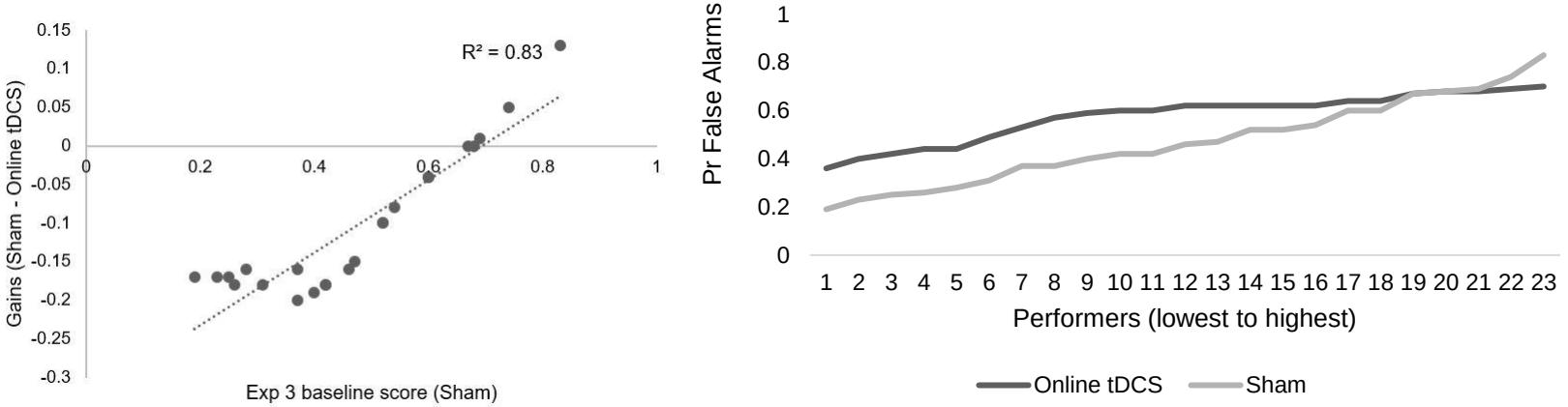

Figure 5.6.6. Experiment 3 tDCS reduction in Pr FA (left panel) as a function of Sham FA and Pr FA (right panel) from lowest to highest performers.

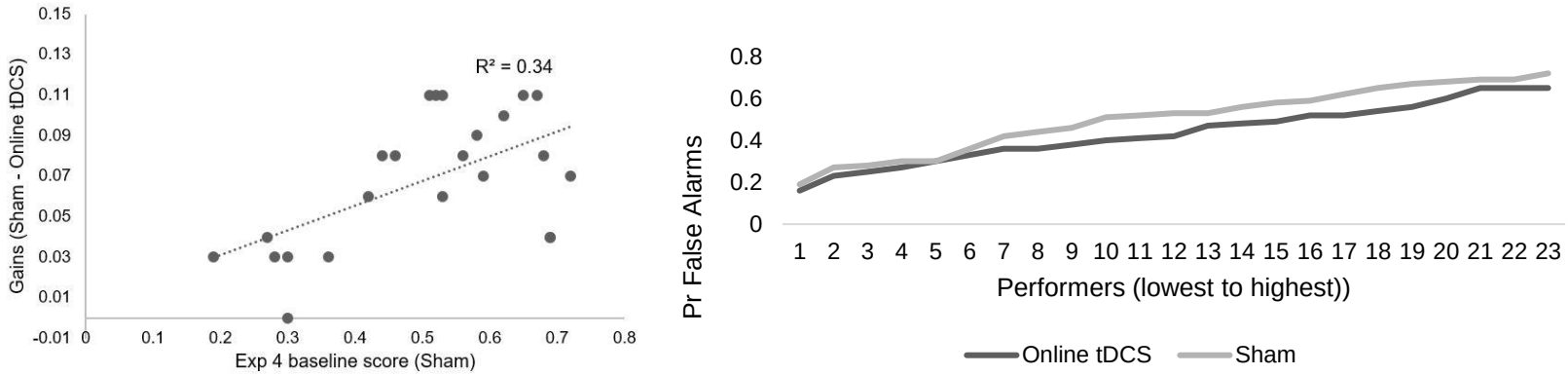

Figure 5.6.7. Experiment 4 tDCS reduction in Pr FA (left panel) as a function of Sham FA and Pr FA (right panel) from lowest to highest performers.

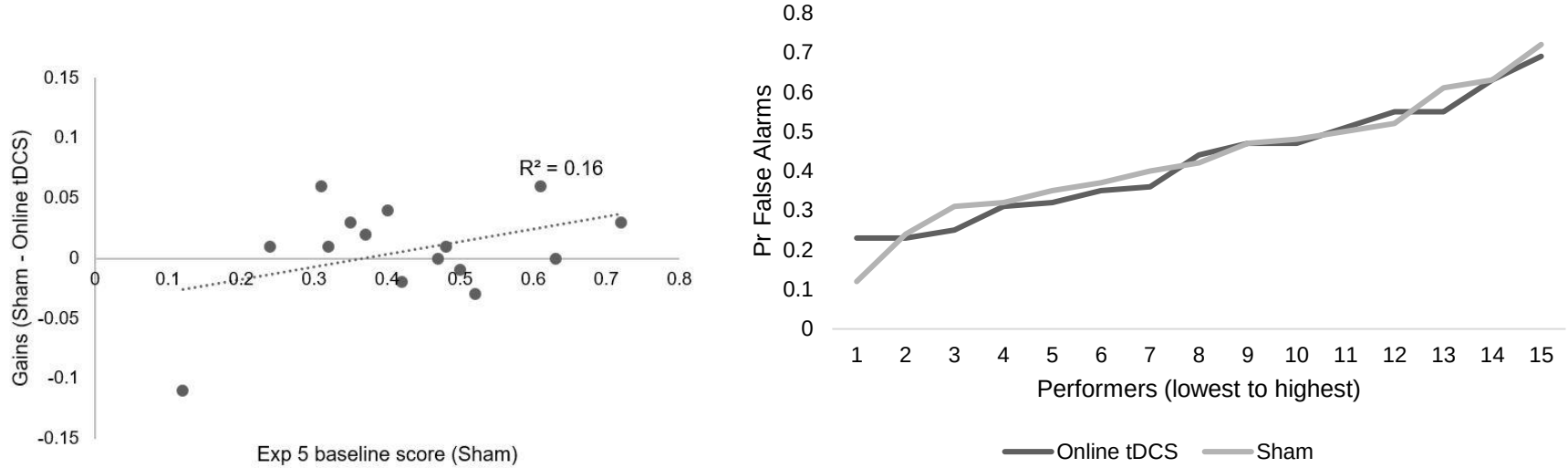

Figure 5.6.8. Experiment 5 tDCS reduction in Pr FA (left panel) as a function of Sham FA and Pr FA (right panel) from lowest to highest performers.

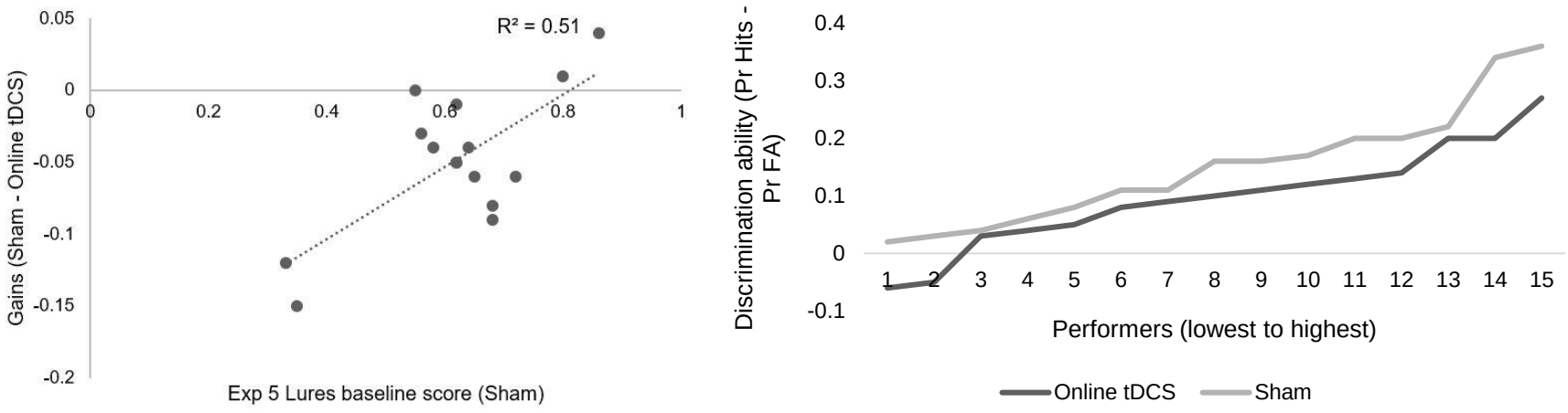

Figure 5.6.9. Experiment 5 Lure tDCS reduction in Pr FA (left panel) as a function of Sham FA and Pr FA (right panel) from lowest to highest performers.

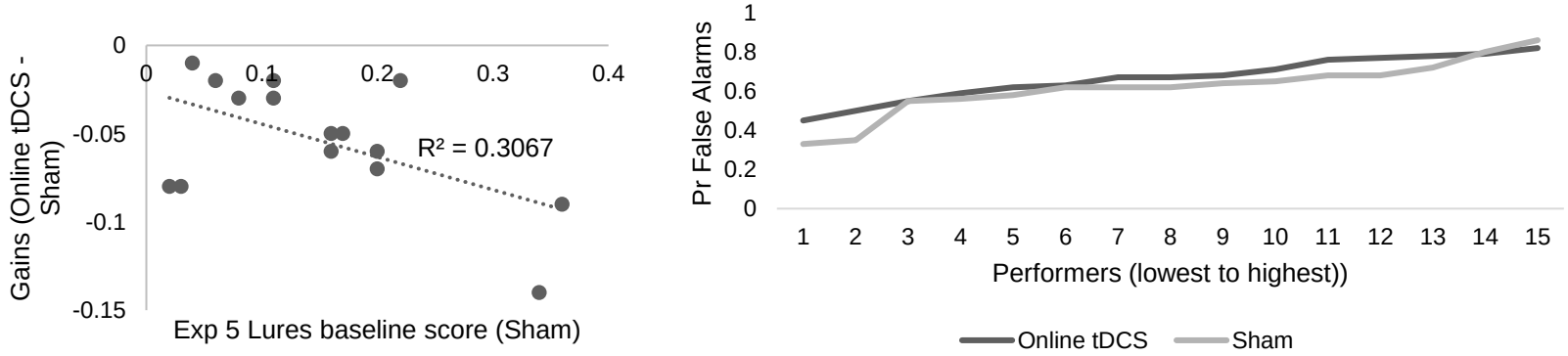

Figure 5.6.10. Experiment 5 Lure tDCS gains in DI (left panel) as a function of Sham DI score and DI (right panel) from lowest to highest performers.

Discussion. The current exploratory analysis paired participants in the Online Encoding VLPFC tDCS and Sham groups across experiments based on performance from lowest to highest, and then exploratory correlations were conducted with difference between Sham and tDCS in false alarm rate and accuracy (gains due to tDCS) as the outcome variables. The analysis found consistent positive correlations between baseline false alarm rate and tDCS-induced reduction in false alarms, and all correlations were significant except for Experiment 5, reflecting that atDCS had a greater effect of lower than higher performers. However, the correlations between baseline recognition accuracy and tDCS gains in accuracy were less consistent, with negative correlations for Experiments 1, 3, and 5 Lure, and positive correlations for Experiments 4 and 5. The inconsistency in correlations may help to explain why Experiments 4 and 5 did not replicate the significant effect of atDCS on accuracy. The negative correlations reflect that atDCS had a greater effect for lower than higher performers: participants with lower baseline performance would have greater increases in performance after atDCS than participants with higher baseline performance. However, the positive correlations reflect a greater increase in accuracy for higher performers, and the reason for the reversal of the relationship between Experiments 1, 3, and 5 Lure and Experiments 4 and 5 is unclear. atDCS could exert effects for higher performers if performance is not at ceiling and there is a possibility of additional improvement. However, it is important to note that performance was variable, with unequal numbers of low and high performers within small sample sizes. Future studies should consider when atDCS is more beneficial for higher or lower performers by sampling from populations with more similar cognitive characteristics and implementing crossover designs, taking care to recruit a large sample size with more equal numbers of low- and high-performers.

Previous studies have found differences in tDCS effects between low and high performers, generally showing greater tDCS effects for participants with low compared to

high baseline scores in episodic memory (Habich, Klöppel, Abdulkadir, Scheller, Nissen, & Peter, 2017); working memory (Heinen, Sagliano, Candini, Husain, Cappelletti, & Zokaei, 2016); visual short-term memory (Hsu, Tseng, Liang, Cheng, & Juan, 2014; Tseng et al., 2012); and visual discrimination (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Learmonth, Thut, Benwell, & Harvey, 2015).

For example, Habich and colleagues (2017) found no overall effect of atDCS over the DLPFC on episodic memory but significant moderation of atDCS gains by baseline retrieval accuracy, with greater gains for lower than higher performers. Hsu and colleagues (2015) found that participants with lower alpha power before stimulus presentation showed enhanced alpha power and visual short-term memory performance after atDCS over the parietal cortex, while participants with higher alpha power showed no differences in alpha power or cognitive performance.

Benwell and colleagues (2015) found that improved visual discrimination sensitivity in low performers when delivered at 2 mA and in high performers when delivered at 1 mA, although atDCS effects were weak when the groups were collapsed. They suggested that the level of baseline neural activation, particularly of task-relevant neurons, modulated tDCS effects, which in turn increased or decreased beneficial noise. For participants with high baseline performance and perhaps higher task-related neural activation, a weaker dose of tDCS could be necessary for the induced neural noise to benefit performance. For low performers who could have lower general activation, tDCS at a higher dose could increase activation, including task-related activity.

Although the experiments in the current analysis did not vary current strength, future directions could compare the effects of high (2 mA) and low (1 mA) tDCS dose However, the positive relationship between baseline performance and accuracy in Experiments 4 and 5 suggests that other factors could be involved. Experiment 5 and Experiment 5 lure used the same current strength and duration, yet the relationships with

accuracy were reversed. However, Experiment 5 implemented a different recognition task than other experiments, which could lead to slightly different patterns of neural engagement and task-related activation. Experiment 4 followed the same procedure as Experiment 1 but showed a reversed relationship with accuracy, so it is unclear what factors were driving the reversed effect. Future studies could clarify this by repeating the analysis in a similar set of experiments with a cross-sectional design.

The experiments included in the current analysis involved a parallel rather than crossover design and no baseline measure was available from participants in each group, so the Sham group served as the baseline measure for the atDCS group. By assuming that low and high performers in the tDCS group would have similar baseline performance to the lowest and highest performers in the Sham group, the analysis enabled an estimate of individual differences in atDCS-induced cognitive enhancement.

Meta-Analysis II

Data analysis. A random-effects meta-analysis on accuracy, proportion of false alarms, and average reaction times was conducted using the studies included in this chapter. The dependent measures were selected based on the results that were significant across multiple experiments. In addition, another study conducted in the same lab was included (Medvedeva et al., 2018; Experiment 4) to increase the sample size and reliability of the meta-analysis. Thus, the final sample size included five independent sample studies. To eliminate the variability due to changes in stimuli, an additional meta-analysis was conducted on a subset of studies ($k = 3$) that included the same experimental procedure and stimuli (Experiments 1 and 4; Medvedeva et al., 2018 Experiment 4).

Table 5.7.1

Overview of studies

Study	**Exp**	**Total sample size**	**Age**	**Design** (active/ control)	**Random**	**Blind**	**Control**	**Montage Polarity**	**Anode || Cathode**	**Duration (min)**	**Current Density (mA/cm^2)**	**Phase**	**Memory task**
Chapter 5	1	32	Y	Parallel (16/16)	Yes	SB	Sham	Unilateral atDCS	F7 || RS	9	0.06	During encoding	Intentional encoding Recognition
Chapter 5	3	48	Y	Parallel (25/23)	Yes	SB	Sham	Unilateral atDCS	F7 || RS	9	0.06	During encoding	Intentional encoding Recognition
Chapter 5	4	149	Y	Parallel (23/26)	Yes	DB	Sham	Unilateral atDCS	F7 || RS	9	0.06	During encoding	Intentional encoding Recognition
Chapter 5	5	31	Y	Parallel (16/15)	Yes	DB	Sham	Unilateral atDCS	F7 || LS	20	0.06	During encoding	Intentional encoding Recognition
Medvedeva et al., 2018	4	22	O	Parallel (11/11)	Yes	SB	Sham	Unilateral atDCS	F7 || LS	9	0.06	During encoding	Intentional encoding Recognition

Note: Y = younger adults; O = older adults; SB = single-blind; DB = double-blind; F7 = VLPFC; RS = Right Shoulder; LS = Left Shoulder. In summary, all included experiments included an examination of online encoding atDCS over the VLPFC for at least 9 min with a standard recognition task (except Experiment 5, which implemented a false memory task).

Results. Effect sizes for each study and measure are shown in Figure 5.7.7. As expected, the accuracy effect sizes for Experiments 1 and 3 were larger than for Experiments 4 and 5, reflecting the pattern of significance. For Experiment 4 (Medvedeva et al., 2018), there was a moderately strong but non-significant effect. Nonetheless, only the effect sizes for Experiment 1 were consistent across dependent measures.

Accuracy. Accordingly, there was a weak, non-significant effect of tDCS on recognition accuracy, $z = 1.33$, $p = .182$, in the positive direction $g = 0.46$, 95% Cl[-0.21, 1.13]. There was a significant proportion of heterogeneity $Q(4) = 20.44$, $p<.001$, and there was a trend toward significant funnel plot asymmetry that was indicative of publication bias $b = 9.57$, 95% Cl [-0.37, 19.51], $z = 1.89$, $p = .06$.

For the subsample $k = 3$, there was a significant positive effect of tDCS on recognition accuracy, $g = 0.91$, 95% Cl [0.23, 1.59], $z = 2.63$, $p = .009$. There was a trend toward significant heterogeneity $Q(2) = 5.95$, $p = .05$, but there was no indication of publication bias $b = 6.12$, 95% Cl [-4.11, 16.34], $z = 1.17$, $p = .241$.

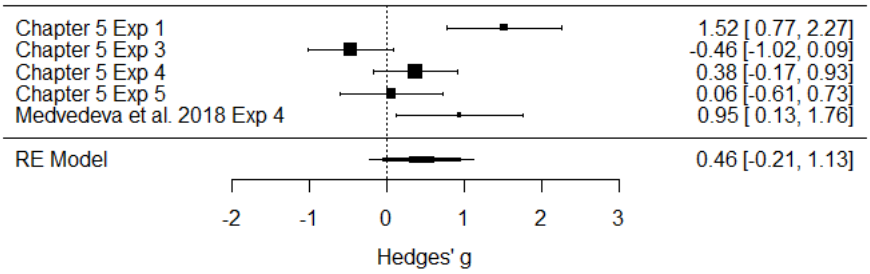

Figure 5.7.1. Forest plot showing effect sizes for accuracy and overall effect size when all studies are included.

Note: Although the proportion of false alarms to lures in Experiment 5 was not included in the analysis, the effect size was larger but also negative and non-significant compared to the index used (false alarms to new items), $g = -0.39$, 95% Cl[-1.06, 0.29], indicating that atDCS in Experiment 5 led to a non-significant increase in false alarms to lures.

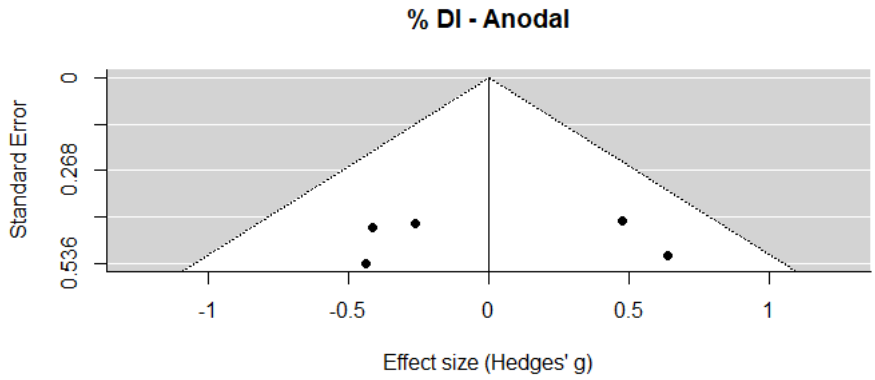

Figure 5.7.2. Funnel plot asymmetry for accuracy when all studies are included.

False alarms. The overall effect was weak (*g* = -0.33, 95% Cl[-1.05, 0.40]) and non-significant, *z* = -0.89, *p* = .371, although it was in the expected negative direction. There was also a significant proportion of heterogeneity *Q*(4) = 25.58, *p*<.001. There was no significant publication bias, as indicated in the test of funnel plot asymmetry, *b* = -8.11, 95% Cl[-24.08, 7.85], *z* = -1.0, *p* = .319. Figure 5.7.4 displays the funnel plot.

For the subsample, here was a significant negative effect *g* = -0.85, *z* = -3.13, *p* = .002, 95% Cl[-1.38, -0.32], indicating that tDCS significantly lowered false recognition. In addition, the proportion of heterogeneity was not significant *Q*(2) = 3.64, *p* = 0.17. There was no significant publication bias, as indicated in the test of funnel plot asymmetry, *b* = -1.50, 95% Cl[-16.75, 13.75], *z* = -0.19, *p* = .847.

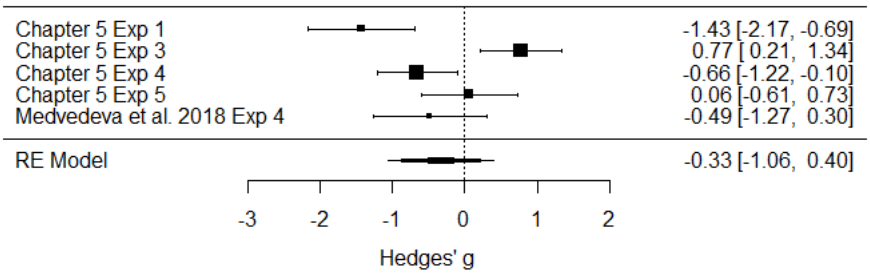

Figure 5.7.3. Forest plot showing effect sizes for proportion of false alarms and overall effect size when all studies are included.

Note: Although the proportion of false alarms to lures in Experiment 5 was not included in the analysis, the effect size was larger but also positive and non-significant compared to the index used (false alarms to new items), g = 0.46, 95% Cl[-0.22, 1.14], indicating that atDCS in Experiment 5 led to a non-significant increase in false alarms to lures.

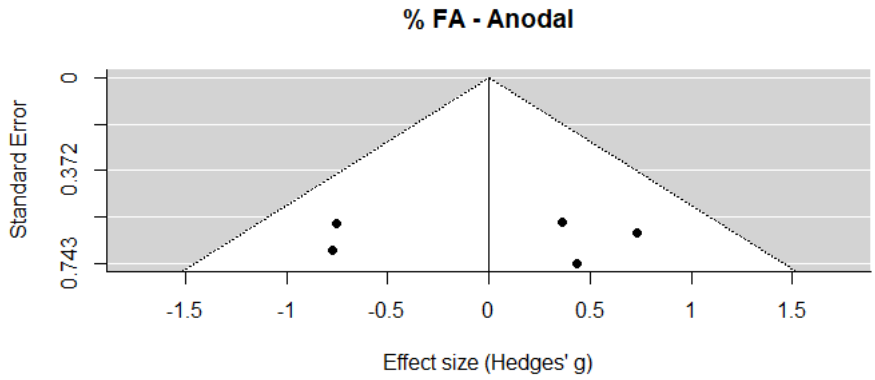

Figure 5.7.4. Funnel plot asymmetry for proportion of false alarms when all studies are included.

Average reaction times. There was a non-significant positive effect g = 0.36, 95% Cl [-0.13, 0.86], z = 1.43, p = .152 and significant heterogeneity $Q(4)$ = 12.32, p = .02. There was no significant publication bias, b = 5.48, 95% Cl [-5.53, 16.48], z = 0.98, p = .329.

For the subsample, there was a significant positive effect g = 0.72, 95% Cl [0.34, 1.10], z = 3.71, p<.001, indicating that atDCS increased reaction times for hits and false alarms. There was no indication of publication bias b = 1.14, 95% Cl [-6.57, 8.86], z = 0.29, p = .771.

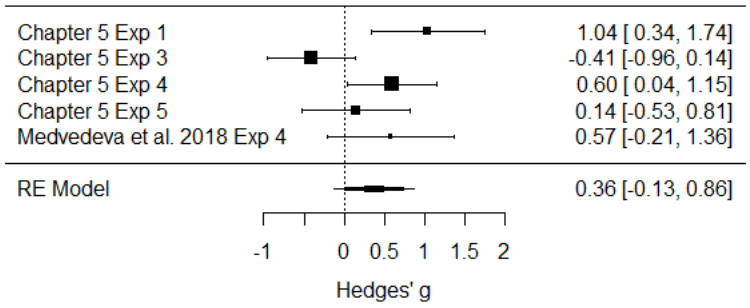

Figure 5.7.5. Forest plot showing effect sizes for average reaction time and overall effect size when all studies are included.

Note: Although the proportion of false alarms to lures in Experiment 5 was not included in the analysis, the effect size was larger but also positive and non-significant compared to the index used (false alarms to new items), g = 0.58, 95% Cl[-0.10, 1.26], indicating that atDCS in Experiment 5 led to a non-significant increase in false alarms to lures.

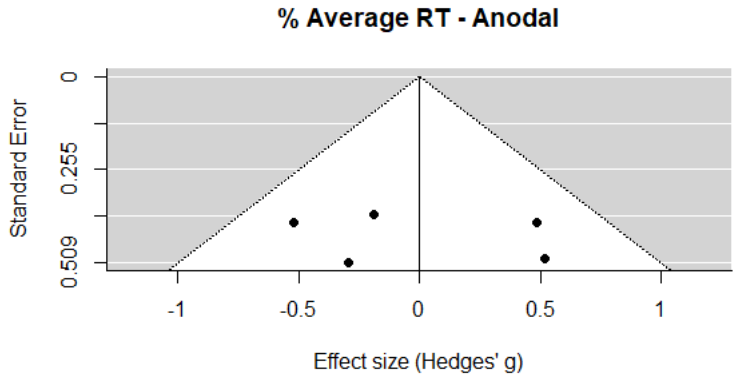

Figure 5.7.6. Funnel plot asymmetry for average reaction time when all studies are included.

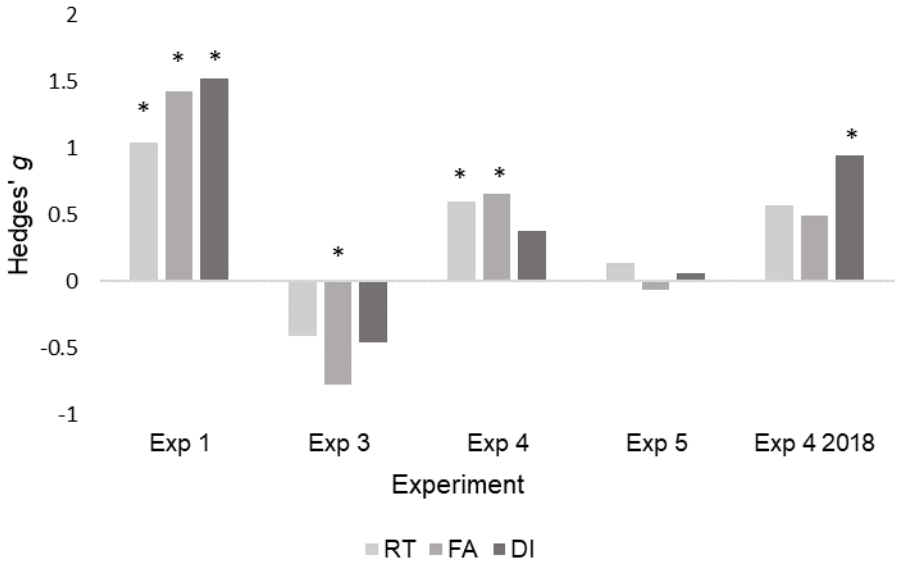

Figure 5.7.7. Effect sizes (Hedges' *g*) across experiments and measures.

Note, RT = average reaction time, FA = proportion of false alarms, DI = discrimination ability, the measure of accuracy. * denotes a significant effect size where the confidence interval does not include zero. Exp 4 2018 refers to Medvedeva et al., 2018 Experiment 4. The sign for false alarms was reversed for readability, so increases in effect sizes for false alarms reflect decreases in false recognition as a result of tDCS.

Discussion. The meta-analysis showed a significant overall effect of atDCS on discrimination ability, proportion of false alarms, and average reaction time when two replications in the same lab (Experiment 4, and Medvedeva et al., 2018; Experiment 4) were combined with the original experiment that found the effects (Experiment 1). However, although individual effects were found for at least one measure in nearly every experiment, no significant effects were found in the meta-analysis that included all five studies.

The sample size was the most crucial limitation of the study, with only five studies and small sample sizes within some of the included studies (Experiment 1; Experiment 4, Medvedeva et al., 2018) and future studies in NIBS should take care to pool together a greater number of studies that include systematic replication. While Higgins and Green

(2008) suggest 10 studies, Fu and colleagues (2011) suggest that with moderate-large sample sizes in each, six studies would be sufficient for a single continuous variable, and subgroups should include at least four studies, but a greater number of studies would increase the relevance and generalisability of clinical applications. Price and Hamilton (2015) criticised a meta-analysis by Horvath and colleagues (2015) for conducting multiple meta-analyses on small sub-groups (3-5) rather than on all the included studies, commenting that the conducted meta-analyses were too underpowered to yield meaningful results.

Nonetheless, a random-effects model was conducted so that results could be at least partially generalised to a broader population. Although a fixed-effects model would have provided information about effects within the conducted studies, an examination of the effect sizes across studies clearly shows that the effect of tDCS on discrimination ability *and* false alarms in the successful replications (Experiment 4, Medvedeva et al., 2018 and Experiment 4, current chapter, respectively) was weaker, nearly half of the effect sizes in Experiment 1. Thus, the current study suggests that atDCS effects may not be consistently strong within this investigation as well as investigations in other labs with different samples.

Vacas and colleagues (2018) also conducted a random-effects meta-analysis on a small total sample size of studies (N = 4) and compared results with a meta-analysis on a subset of studies (N = 2) with more homogeneous methods. They compared effects of tDCS (N = 2) and rTMS (N = 2) on dementia outcomes and found a significant effect only in the subset of studies that examined rTMS effects, concluding that there are promising directions for future clinical testing with rTMS. Inagawa and colleagues (2018) conducted a fixed-effects meta-analysis on eight studies with five and three in the subgroups for different measures, and they found no significant effects on the measures, but they were

able to compare effect sizes across studies and make hypotheses about the mechanisms and effects of tDCS.

Compared to previous meta-analyses with low sample sizes, an advantage of the current meta-analysis was the inclusion of studies that were conducted in the same lab and followed nearly identical technical and experimental parameters (Experiments 1 and 4 and Experiment 4; Medvedeva et al., 2018). The other included studies (Experiments 3 and 5) varied in relatively-minor ways, although the duration of atDCS administration was longer for Experiment 5. Although heterogeneity was significant for the total sample ($k = 5$), reflecting variability in effect sizes, heterogeneity was not significant for the sub-sample. In addition, it is possible that this heterogeneity can be attributed to fluctuations of tDCS that may be random or affected by individual differences or conditions that are not yet identifiable. For example, the exploratory correlational analysis showed that tDCS effects may be greater for low performers than high performers. Future studies can further investigate these individual differences (Ammann, Lindquist, & Celnik, 2017), including measuring GABA and glutamate concentration with proton spectroscopy (Filmer, Ehrhardt, Bollmann, Mattingley, & Dux, 2019).

Although the results should be interpreted with caution given methodological limitations, they suggest that there is a relatively-consistent but subtle effect of atDCS that is present in younger and older adults. While this effect can be useful for revealing the importance of a region to a specific cognitive function, showing clearly that across all studies with the same recognition test and stimuli (Experiments 1-4; Experiment 4 in Medvedeva et al., 2018), tDCS over the VLPFC leads to significant changes in memory performance, applying tDCS to cognitive theories may be more complex, as illustrated and discussed in Experiment 5 and Chapter 6. In addition, given the current assessment of the effect, it may be difficult to understand the mechanisms of tDCS based on cognitive data alone, since the effect could fluctuate due to factors that are not manipulated by the

experimenter. Future studies can consider using biomarkers such as BOLD signal in conjunction with behavioural data, although this too may not allow for a straightforward interpretation (Baudewig, Nitsche, Paulus, and Frahm, 2001).

Figure 5.7.7 is illustrative of a statistical phenomenon known as the "winner's curse", in which the discovery of a significant effect in a small-sample study (usually one of the first to examine the effect) is "cursed" by an inflated effect size that cannot be easily replicated in other studies (Button et al., 2013; Medina & Cason, 2017). Under-powered studies can only find large but not medium or small effects, and random error can lead to finding an effect that is larger (e.g. $d = 1.70$) than the true effect (e.g. $d = 0.90$) and significant because in a small sample, the true effect would not cross significance threshold (Button et al., 2013). The winner's curse can occur when multiple underpowered studies are investigating an effect for the first time; because of random error and sampling variation, one of the studies will find the significant but exaggerated effect and be published (Héroux, Loo, Taylor, & Gandevia, 2017). Thus, historically, the first studies to examine an effect would find large effect sizes, while subsequent studies could find smaller effects sizes or not replicate the effect at all.

General Discussion

The first systematic investigation of different timings of atDCS administration on episodic memory was conducted through three experiments: atDCS was delivered over the DLPFC at encoding and over the VLPFC at encoding and retrieval. Included in the investigation was the first systematic comparison of offline and online effects of atDCS, and online and offline tDCS were compared over the VLPFC and DLPFC. The investigation also included a direct replication of the significant condition in Experiment 1 (Online tDCS over the VLPFC), and although the effect was reversed from the original experiment, the findings provide robust evidence for the role of the VLPFC in episodic memory by demonstrating that tDCS over the VLPFC at encoding modulated memory

performance, significantly increasing performance (Experiments 1 and 4) or significantly decreasing performance (Experiment 3). Finally, Despite the small sample size, an exploratory meta-analysis was conducted to illuminate the effects of tDCS. In three direct replications using the same experimental procedure, there was a significant effect of tDCS. It is notable, however, that the tDCS modulation for each study varied. In Experiment 1, there was a significant effect on recognition accuracy *and* false alarms. In Experiments 3 and 4, however, there was a significant effect on false alarms but not recognition accuracy. The aim of this chapter was to closely examine the atDCS effects found by calculating an overall effect size. The chapter continued to address the need for evaluating tDCS as a research tool and understanding the decrease in false alarms following tDCS over the VLPFC.

The findings demonstrated that there was a significant effect of online tDCS over the VLPFC at encoding but not retrieval: in Experiment 1, atDCS improved recognition accuracy by lowering the proportion of false alarms, while in Experiment 2, atDCS impaired recognition by increasing false alarms. However, there were no effects of offline atDCS over the VLPFC at encoding or retrieval. In addition, there was a significant but weaker effect of offline but not online tDCS over the DLPFC at encoding: atDCS over the DLPFC led to worse recognition, and there was a trend toward increased false alarms in this group. In all significant effects, atDCS seemed to selectively affect false alarms, with hits remaining unaffected.

Thus, the results confirm the role of the VLPFC in episodic memory. For the first time in tDCS research, the causal relationship between the VLPFC and semantic item encoding is established. Although a functional connection between the VLPFC and memory has been established before, the results add to the handful of tDCS studies that examined the VLPFC in episodic memory and extend the results of Medvedeva and colleagues (2018; Experiment 3) in particular.

However, the results also raise doubt about the reliability of tDCS as a research tool. When larger sample sizes were used, the expected effect was absent, and when there were slight differences in verbal stimuli (language), the effect was reversed. The results lend support to the observation that there is a risk of finding spurious effects in studies with small sample sizes, especially when tDCS exerts a subtle effect and is sensitive to individual differences. Although it is unlikely that the effect in Experiment 1 was spurious because the effect size was so large, there is a possibility that the effect is bound to the specific conditions of the experiment and these conditions were only partly replicated in Experiments 3 and 4. Thus, the effect of tDCS could be sensitive to characteristics of the population (Experiments 3 and 4), verbal stimuli (Experiments 3 and 5), and stimulus presentation times (Experiment 4). Although samples in all experiments seemed to include a homogeneous group of students with similar ages and cognitive performance, the distribution of low and high performers could have been different. Baseline differences in memory function could predict the magnitude of tDCS effects, as suggested by a preliminary comparison of low and high performers in the Sham and Online VLPFC tDCS groups. The correlations between tDCS gains and performers (low to high) in the Online suggested that tDCS led to the greatest increase in accuracy for low performers, but only to an extent. The lower gains and higher performance for the lowest performers in Experiments 4 and 5 suggest that performance may have been too high for tDCS modulation or modulated by another factor (i.e. deeper encoding). It is interesting to note that the expected negative correlation was present for false lure but not new word recognition in Experiment 5, indicating that the false recognition effect in Experiments 1 and 3 may resemble that of false memory experiments in which the lure induces false recognition through semantic similarity at study.

An argument could be made that the stimuli significantly differed in Experiment 3 because of language differences and in Experiment 5 because of semantic similarity.

However, even with the interpretation that other word characteristics such as phonetics could have affected word processing in Experiment 3, there is little evidence to suggest that *semantic* processing differed.

In all experiments, the high proportion of false alarms to new items suggested that the stimuli were semantically similar and could have elicited false alarms in the same way as a false memory task. Thus, the use of semantically-related lists in Experiment 5 should not have prevented an effect of tDCS. The interpretations for the findings of Experiment 5 are discussed further in Chapter 6, but taken together, the results of the systematic investigation suggest that tDCS effects on episodic memory may be generally weak. There is a possibility that tDCS modulates a linguistic or short-term memory process that is conducive to long-term memory performance but is not predictive of successful recollection. This account is in line with previous research that found facilitation in language tasks following atDCS to the VLPFC.

It is important to note that a systematic data analysis procedure was applied to each experiment, increasing the similarity between analyses as much as possible. It is also notable that there was a partial replication of the effect of tDCS in the same lab (Medvedeva et al., 2018; Experiment 4) with older adults: Medvedeva and colleagues found a significant effect of tDCS on discrimination ability but not proportion of false alarms. Thus, in multiple direct and conceptual comparisons, the effect of tDCS did not remain consistent, suggesting that the heterogeneity in the tDCS literature may not be entirely due to heterogeneity in methods.

Chapter 6: Using atDCS to Address Research Questions: Identifying Cognitive Mechanisms of atDCS Effects on False Recognition

Abstract

Previous experiments have found a selective modulation of false recognition as a result of experimental manipulations (i.e. item-specific encoding) or neuromodulation to the VLPFC. The VLPFC is a key region in episodic memory and plays a causal role. The specific role of the VLPFC is still unknown, but it is clear that stimulating the VLPFC with NIBS leads to cognitive effects, including changes in language and memory performance. The current experiment investigated the cognitive mechanisms whereby tDCS led to a decrease in false alarms. Specifically, did tDCS increase the distinctiveness of items? The experiment investigated tDCS modulations of item-specific vs relational processing leading to the distinctiveness heuristic. While undergoing stimulation, participants completed a modified version of the DRM task in which they memorised semantically-related lists of words. Then they completed a recognition test and source memory tests that indirectly measured the extent of item-specific and relational processing at encoding. There were no significant differences between the groups in any dependent measure, but the findings suggested that in this experiment tDCS impaired item-specific encoding and subsequent source memory. In conclusion, the effects of tDCS could have been obscured by deeper encoding and higher recognition, and tDCS may have been ineffective due to greater temporal clustering of semantically-similar words, a default strategy in the VLPFC.

Introduction

False memory can be a dangerous phenomenon in everyday life, affecting the results of court cases based on eyewitness testimony and harming the quality of life of those who are more vulnerable to it, such as individuals with PTSD and memory disorders (Goodman, Magnussen, Andersson, Lokken, & Moestue, 2007). Older adults in particular

are more susceptible to false recognition because of poorer memory monitoring, and individuals with early-stage dementia can present with false recognition as one of the symptoms (Fairfield & Mammarella, 2009; Mitchell, Hunt, & Schmitt, 1986; Souchay, Isingrini, & Gill, 2002). Thus, it is crucial for episodic memory research to identify ways to reduce false recognition, whether behaviourally through experimental manipulations, or neurologically through NIBS. Although previous research (Chapter 5) has shown the possibility of modulating false recognition with tDCS, it remains unclear how and when a reduction of false recognition can occur. tDCS researchers have investigated such modulations using paradigms designed to elicit false recognition, such as the Deese-Roediger-McDermott (DRM) task.

Why false memories occur. There are multiple theories for why the false memory effect occurs, including the activation monitoring account, source monitoring framework, and fuzzy trace theory. The activation monitoring account (Roediger, Watson, McDermott, & Gallo, 2001; Hunt & Smith, 2014) states that at encoding, related information is activated in addition to the information contained in the word (e.g. meaning). Particularly in the presence of a common theme in a related list, his activation can spread throughout the semantic system and create implicit associative responses, including unpresented concepts, like schema processing. If the theme in a related list is strongly activated, it can even take on the features of list items and become part of the memory trace.

The source monitoring framework suggests that false memories arise because of errors in monitoring source memory. Misattribution is part of a source monitoring error in which participants remember something about an event but mistake the source of the memory, for example (in a reality monitoring error) whether the event was internal or external. In the DRM paradigm, this could be when a lure is activated mentally, but participants thought it was actually presented on screen. Thus, they mistake the thought for a studied word. Whereas participants may remember the presentation of words on screen

and the activation of lures mentally, they may mistake the source of the word (on screen or mentally), which is an error of monitoring rather than recollection.

Fuzzy trace theory proposes the formation of gist memories, which include general, conceptual information about the episode, rather than verbatim memories for specific features and unique details. Fuzzy trace theory proposes that words are encoded as gist memories, which include general, conceptual information rather than specific features and details (verbatim memory). Thus, participants memorize less details about individual items and more generally about the study episode (conceptual rather than specific features). Gist-based memory is incorrectly recognising a similar but not identical item, such as a synonym of a studied word, a similar abstract shape, a picture of the same object with a verbal label (Guerin et al., 2012). Research suggests that it occurs when people remember the general information, like the category of an object, but not specific details of the study event (Guerin et al., 2012). Thus, gist vs verbatim processing can lead to false memories because a gist representation can be facilitated by high semantic relatedness between items (especially between list items and the critical item). Participants may not pay attention to specific details of words and later respond based on gist information, using common attributes of the words and mistaking similar words for presented words because of the absence of specific information.

For example, Gray and colleagues (2015) administered atDCS to the DLPFC immediately after encoding and found modulations of source accuracy in a criterial recollection task by Gallo (2006, 2010, 2013). In the criterial recollection task, words in black font were followed by the same item presented as a picture and/or word in red font; some items were only associated with one modality (red font or picture) while others were associated with both (presented as picture and red font). All items were presented twice, and this task required that participants rely on memory for specific details rather than simply familiarity. For items presented in both formats, participants were asked in one test

to indicate whether items had been presented as red words (font test), and in another test they were asked to indicate whether items had been presented as pictures (picture test). For items presented only in one format, participants were asked to indicate whether items had been presented in red font, and they were instructed that recollecting items as pictures meant that they had not been presented in red font. They expected DLPFC activity in retrieval monitoring (using distinctive recollection for pictures) for this test, and in turn they expected a benefit of tDCS for performance. The distinctiveness heuristic was replicated with higher performance on the picture and exclusion than font test, with no difference between picture and exclusion. In addition, false alarms (mistaking items studied as pictures for items studied as words) were higher for the font test than either other test, and false alarms were lower for critical lures but not new items in the exclusion test. Stimulation on both DLPFC hemispheres but not the parietal site increased performance on the font test but not the other tests. This increase in performance was driven by an increase in hits rather than a decrease in false alarms. Gray and colleagues concluded that atDCS increased source accuracy by improving a selective search for target information rather than reducing source monitoring errors.

Roediger and colleagues (2001) found that there is no correlation between true and false memory, because greater recall does not lead to greater priming of the critical item. When younger adults, healthy older adults, and Alzheimer's disease adults are compared, the groups have intact activation processes but have impaired source monitoring, as due to impaired frontal lobe functioning. They suggest that gist theory can help explain the negative correlation between true and false recognition because an over-reliance on verbatim memory would lead to fewer false alarms but also fewer hits. Wong and colleagues (2012) also suspected that participants relied on gist-based similarity or familiarity in word recognition. They found that older adults had higher false alarms and rated greater confidence in source memory errors than younger adults (Wong et al., 2012).

Behavioural manipulations of false memory have established explanations and theories for why false memories occur and how they can be reduced. One theory that could apply to the effect of VLPFC tDCS on false recognition is the distinctiveness heuristic. Studies have frequently found differences between item-specific encoding, the processing of each item individually, and relational encoding, the processing of items in relation to each other: item-specific encoding reduces false recognition compared to relational encoding by enhancing the distinctiveness of each item. Enhancing distinctiveness reduces false recognition, in turn, by enabling participants to recognise that the unstudied items lacked a sense of recollection, specifically associated memories or episodic details. The distinctiveness account may be particularly relevant because the VLPFC is thought to be more active in item-specific encoding, whereas relational encoding may selectively engage the DLPFC.

Distinctiveness heuristic. The distinctive encoding theory (Hunt & Smith, 2014) posits that there is a benefit of processing differences among items in context of similarity, such as similar semantic context (e.g. processing individual words in themed lists or lists that are similar; item specific task that encourages processing item-specific meaning like pleasantness rating, on categorised list). The distinctiveness heuristic (Israel & Schacter, 1997; Schacter, Norman, & Koutsaal, 1998; Schacter, Israel, & Racine, 1999) suggests contributions at retrieval, arguing that strategic monitoring is increased when there is an expectation for high-quality recollection for previously-presented items, and the absence of unique, item-specific details for an item is diagnostic of the item being new. The distinctiveness heuristic is a monitoring mechanism in which participants rely on expected unique, item-specific details (distinctive information) upon seeing an item to decide whether the item was previously-presented or is new. It is a retrieval strategy in which the absence of memory for expected distinctiveness is a sign of the event not occurring (Hege & Dodson, 2004). It is important to consider distinctive processing at study, and the item-

specific details participants memorised, to consider how they monitor for information of a similar quality at test. In the distinctiveness heuristic, when people expect to remember specific/vivid details of a study episode, they can use this information to respond to a recognition test. If there is an absence of expected distinctive information, as in a new item, people can use this to correctly reject the item as new (Huff, Bodner, & Fawcett, 2015). The distinctiveness heuristic account theorizes that the effects are due to monitoring at test in which vivid details associated with the item show that it was studied, whereas the absence provides evidence that it was not studied.

In Koutsaal and Schacter's (1997) study, participants were presented with pictures in specific categories at study and then different pictures in the same categories at test. They still had high false alarm rates to lures. Koutsaal and Schacter (1997) suggested that false alarm rate is decreased only when (in addition to encoding distinctive information) participants have the cue to use distinctive information at test. For example, seeing distinctive, unrelated pictures at study will activate the distinctiveness heuristic. In a study by Schacter and colleagues (1999), participants studied half the DRM lists with pictures (the word below) and the other half with just the word, and false recognition was low across all lists because of the strategy used.

In addition, Gallo and colleagues (2004, 2006, 2007) found that when presenting coloured pictures and red words at study, based on word cues (in white) participants could better remember which words were studied as pictures as red words. While hits stayed the same in both conditions, false recognition for all lures was lower for pictures than for words (Gallo et al., 2007). It is important to note that even with higher false recognition rate for words, the false alarm rate is much lower than for true recognition, unlike expected for the DRM paradigm. Thus, there may still have been a distinctiveness heuristic effect for words.

Similarly, participants had reduced false recognition in the DRM after "say" than "hear" encoding, but only in a between-subjects design. When participants were asked to say the words out loud rather than hearing them, they were less likely to falsely recognise semantically related items (Dodson & Schacter, 2001). Dodson and Schacter suggested that they used the distinctiveness heuristic at test, trying to recollect whether they had said each item out loud. Saying words at study, like studying pictures, gave participants a reason to use the distinctiveness heuristic.

The distinctiveness heuristic appears to reduce false alarms for lures/similar related items in pictures and words, but in pictures to a greater extent than in words (Dodson & Schacter, 2002). Dodson and Schacter (2002) concluded that participants expected distinctive detail in pictures but not words. Interestingly, there was reduced false recognition for pictures compared to words only in a between-subjects design, not in a within-subjects design (Schacter, Israel, & Racine, 1999; Dodson & Schacter, 2002). Thus, the distinctiveness heuristic was activated when it could be reliably and accurately used.

In Schacter and colleagues' experiment (Schacter et al., 2001; Experiment 2), participants saw concepts as words or pictures and received instructions for a standard or meaning-based recognition test (Brainerd & Reyna, 1998). In the meaning instructions, they were instructed to indicate that items were "old" if they were previously-presented or fit the concept/meaning of one of the previously-presented words. Participants were instructed to accept all the items with the same meaning as the list themes and words. They found that recognition was higher for pictures than words in the standard instructions condition, whereas there was a smaller difference between word and picture recognition in the meaning test. This is indicative of the distinctiveness heuristic, that participants activate under standard but not meaning instructions because for meaning instructions item-specific details are not diagnostic of the information required.

Aims. Previous studies have established that the VLPFC is a critical region for memory formation and possibly false recognition, although few studies have investigated the latter role explicitly. Thus, this study aims to investigate the role of the VLPFC in reducing false recognition and clarify the cognitive mechanisms of this effect. The aim of this experiment was to clarify the modulation of VLPFC tDCS on false recognition and enable a better understanding of the cognitive mechanisms of the effect. Specifically, the study investigated the effect of VLPFC tDCS on false recognition and item-specific encoding during the DRM task. Item-specific and relational encoding have been manipulated in different ways, usually in between-subjects designs. For example, item-specific encoding has been elicited by asking participants to indicate the pleasantness of a word, as conducted in the tDCS experiments of Chapter 5. The distinctiveness effect also occurs when pictures are presented or when words are presented in colour compared to words in black. In turn, the results show increased false recognition for the words in black compared to the pictures or the words in colour. False recognition was measured in a recognition test, and item-specific encoding was measured with a source memory task following each recognition trial that presented a studied item. The Item source memory task tested recollection for the colour of backgrounds on which words were presented at study, following previous studies that measured the distinctiveness effect and other studies that identified a strong relationship between item-specific encoding and memory for colour (Cruse & Wilding, 2009; MacLeod & Donaldson, 2017; Wilding & Rugg, 1996). If participants engaged in item-specific encoding at study, they should recollect more item-specific details and perform better on the item source memory task. In contrast, the Relational source task tested the order for the semantically-related items presented within a list. If relational encoding occurred, participants should create associations between items within the same DRM list and recollect the order of a subsequent item. It was expected that tDCS would reduce false recognition in the DRM task by increasing memory for

distinctive, item-specific details compared to relational information. When delivered over the VLPFC, atDCS should lead to lower false alarms for new items compared to the Sham condition, and the reduction in false alarms should be accompanied by evidence of item-specific encoding, as reflected in greater source memory for item-specific details. The study could contribute to the distinctiveness account and enhance understanding of tDCS effects and VLPFC processes. In turn, the findings could be applied to further developing false memory interventions using behavioural and neurological means.

Method

Participants. Information about participants is detailed in Experiment 5 (Chapter 5). In addition, all participants reported no colour blindness that interfered with their ability to see the colour backgrounds presented on the screen.

Experimental design. Stimulation groups, procedure, and materials were identical to Experiment 5 (Chapter 5). In addition, participants completed Item-Specific and Relational source tasks at tests. For half of the previously-presented ("old") words, participants were asked to indicate which colour background had been presented (blue or orange; Item-Specific source test), and for the other half, participants were asked the word that had been presented immediately after the current one (Relational source test). Words at study were presented on one of two different colour backgrounds: bright orange or dark blue. The brightness contrast was an additional way of drawing attention to the different colours, since participants were not explicitly instructed to attend to the colours. For the source task, they were instructed to select Q or P, depending on whether the correct response was presented on the left or right of the screen, respectively. At test, a fixation cross was presented for 500ms, followed by the word for at least 1000ms (self-paced). For all old words, regardless of the participant's response, the source task was be presented. In the source task, a picture of a keyboard with the response options for the source task (Q & O) highlighted was presented for 1000 ms, followed by the word and the answer choices

for at least 1000 ms (self-paced). Finally, a picture of a keyboard with the highlighted response options for the recognition test (A & L) was presented for 1000 ms.

Data analysis. A two-way ANOVA was conducted using group (sham, atDCS) as the between-subject factor and the source test (item-specific, relational) as the within-subject factor on source memory hits to identify the effect of tDCS on item-specific and relational processing. Significant effects were followed up with Bonferroni post-hoc tests (two-tailed).

In addition, an exploratory analysis was conducted to compare Sham and Online tDCS in recognition accuracy for participants who performed better in the Item-Specific source test than the Relational Test. Participants were divided into Item-Specific and Relational groups according to their source memory scores where there was a clear bias toward one or the other (e.g. 0.58 vs 0.54). Specifically, participants with more than 4 points difference between item specific and relational source accuracy were categorised into one of the two groups. An additional group emerged, 'both', in which participants had similar scores for item-specific and relational source accuracy. Once participants were divided into the groups, a two-way ANOVA was conducted using group as between-subject factor and encoding type (item-specific, relational, both) as the within-subject factor on discrimination ability.

Results

The assumption of homogeneity of variances was violated for the two-way ANOVA $F(3,58) = 4.95$, $p = .004$, so the significance criterion was adjusted to .025 to adjust for the violation and possibility of increased Type-I error (Haase & Ellis, 1987).

There was not a significant effect of stimulation group $F\ (1,58) = 5.04$, $p = .029$, $\eta_p^2 = .080$, source test $F(1,58) = 1.72$, $p = .194$, $\eta_p^2 = .029$, or a group x source test interaction $F(1,58) = .235$, $p = .629$, $\eta_p^2 = .004$. Source accuracy was only numerically higher for Sham ($M = 0.52$, $SD = 0.06$) than Online tDCS ($M = 0.48$, $SD = 0.09$), both for Relational

and Item-Specific tests. In addition, there was no significant difference between the groups (Sham *M* = 1551.91, SD = 587.04; tDCS *M* = 1511.56, *SD* = 640.80) in reaction time for correct source judgements $t(60) = 0.26$, $p = .797$.

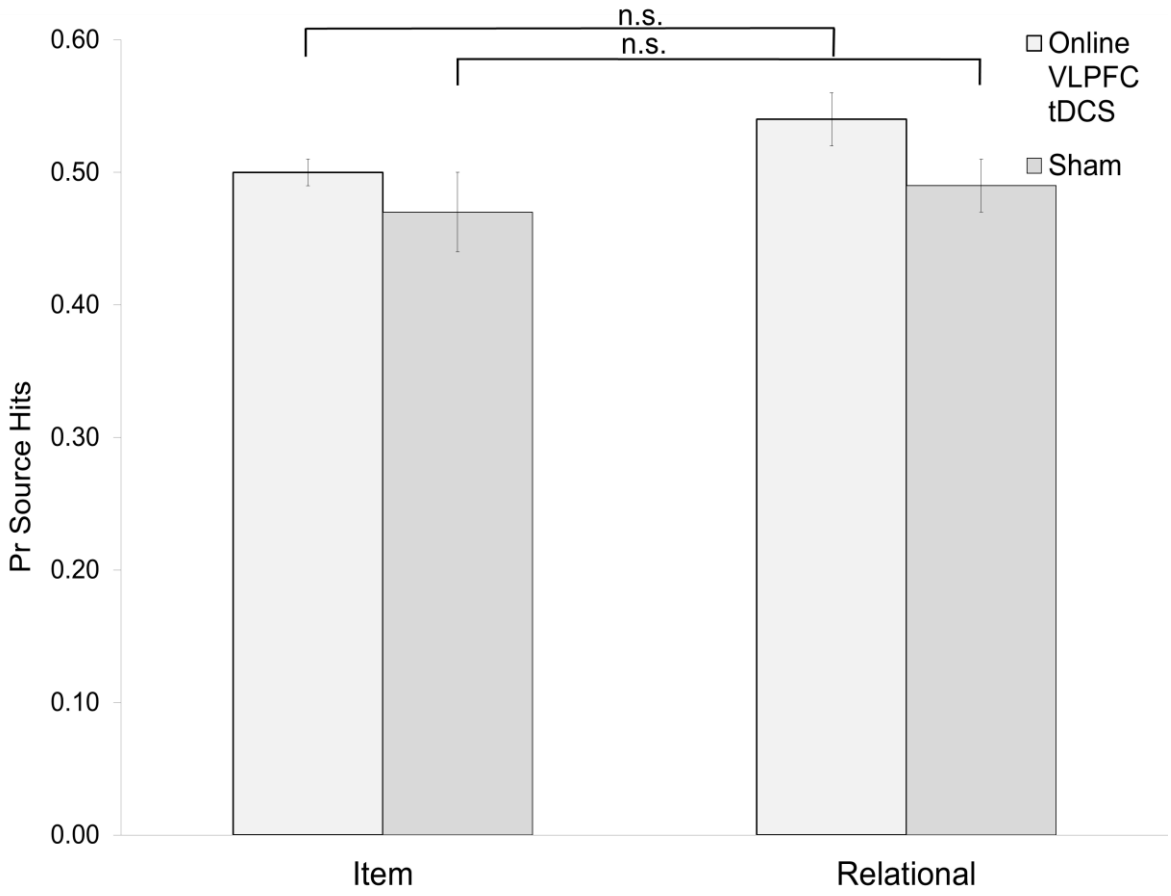

Figure 6.3.1. Proportion of correct source judgements for each source test across experimental groups.

Note: Item and Relational refer to item-specific and relational source tests, respectively.

Although there was no significant difference in source accuracy between the groups, an exploratory analysis was conducted to determine whether atDCS effects were specific to a subset of participants that showed greater item-specific encoding, as indicated by higher item-specific source accuracy compared to relational source accuracy.

First, participants were divided into item-specific and relational groups according to their source memory scores where there was a clear bias toward one or the other (e.g. 0.58 vs 0.54). Specifically, participants with more than 4 points difference between item specific and relational source accuracy were categorised into one of the two groups.

Participants who could not be categorised into item-specific or relational groups were excluded for the analysis.

The item-specific group (N = 4 for sham; N = 5 for tDCS) had significantly higher hits for item-specific source accuracy (M = 0.56, SD = 0.07) than the relational group (M = 0.44, SD = 0.08), $t(22) = 3.66$, $p = .001$. Similarly, the relational group (N = 7 for sham; N = 8 for atDCS) had a higher proportion of hits for the relational task (M = 0.56, SD = 0.08) than the item-specific group (M = 0.44, SD = 0.08), $t(22) = 3.54$, $p = .002$. Once participants were divided into these groups, a two-way ANOVA was conducted using group as between-subject factor and encoding type (item-specific, relational, both) as the within-subject factor on discrimination ability.

There was no significant main effect of group, $F(1,20) = 0.49$, $p = .493$, $\eta_p^2 = .024$, or encoding, $F(1,20) = 0.05$, $p = .833$, $\eta_p^2 = .002$, on source accuracy, although the interaction effect approached significance, $F(1,20) = 3.41$, $p = .080$, $\eta_p^2 = .146$. Pairwise comparisons showed significantly higher discrimination ability for Sham (M = 0.42, SD = 0.11) compared to Online tDCS (M = 0.27, SD = 0.07) when considering only the item-specific group $t(7) = 2.52$, $p = .040$. However, there were no significant differences between Sham and tDCS in the relational group (M = 0.37, SD = 0.17; M = 0.30, SD = 0.15, respectively), $t(13) = 0.82$, $p = .428$.

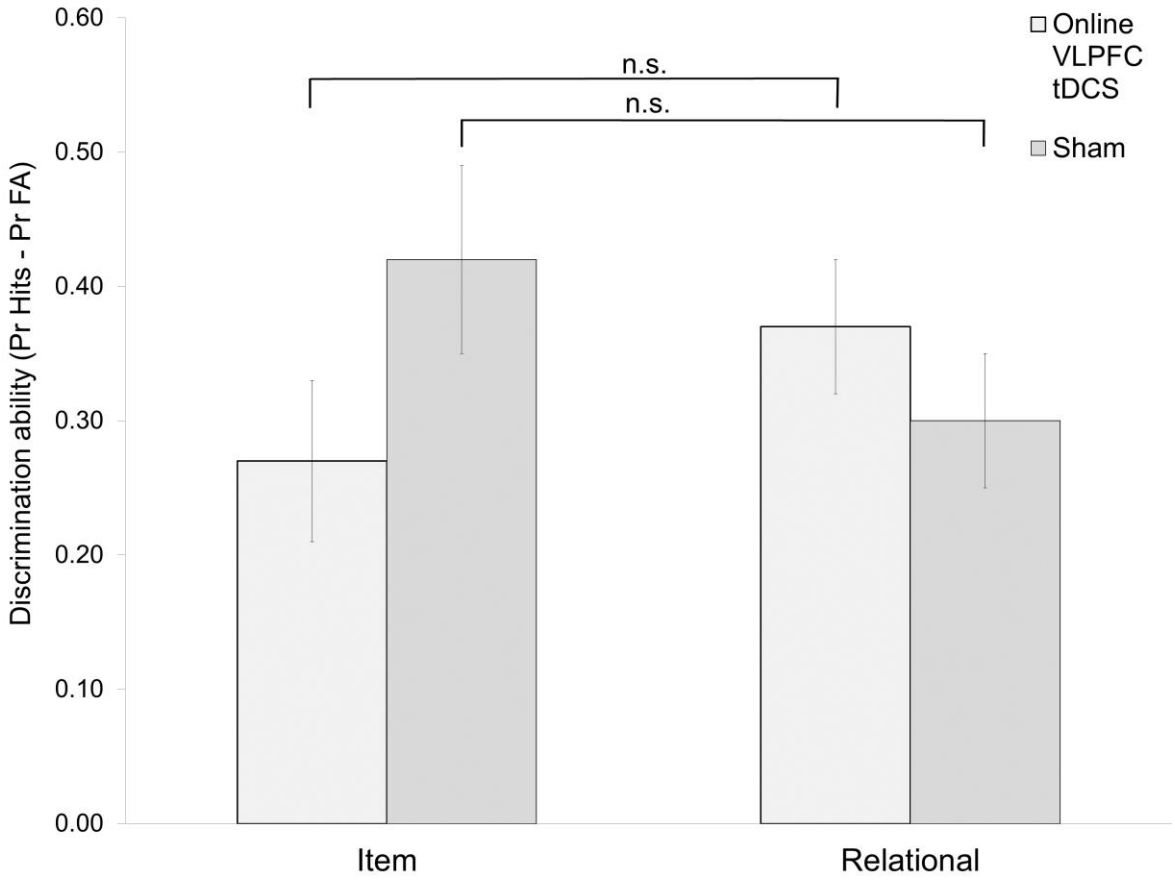

Figure 6.3.2. Discrimination ability across item-specific and relational groups and experimental groups.

Note: Item and Relational groups reflect participants who showed greater source accuracy for item-specific and relational source tests, respectively. These participants may have engaged in greater item-specific or relational encoding that led to changes in discrimination ability.

Discussion

There was no evidence that the distinctiveness effect was greater in the tDCS group, as reflected in the non-significant effect of tDCS on false alarms for lures or source accuracy for the item-specific test. However, the exploratory analysis on individuals with a bias toward item-specific encoding suggested that greater item-specific encoding was associated with higher false alarms following tDCS but not Sham. These results suggest that when delivered in item-specific encoding, tDCS may have led to distinctive representations of semantically-related but unpresented words that were activated at study.

Overall, tDCS may have served as a distraction and disruption more than a facilitatory mechanism, and the task may have engaged increased semantic and temporal clustering in the VLPFC compared to the previous task. In fact, the Sham group seemed to exhibit the usual pattern of decreased false alarms following item-specific encoding. A second exploratory analysis included the individuals who engaged in greater relational encoding, and there were no differences between atDCS and Sham in false alarms. However, a comparison between the Sham groups in each analysis confirmed that an increase in item-specific encoding led to fewer false alarms than an increase in relational encoding. Considering the role of the VLPFC in item encoding and associative encoding separately, the findings suggest that perhaps the VLPFC was not effective at regulating competing processes (item encoding and associative encoding). Specifically, the VLPFC appears to be active in temporal over semantic clustering during recall tasks (temporal relational encoding), whereas in recognition tasks, the VLPFC appears to link each item to a unique semantic representation that becomes distinct at retrieval (item-specific encoding and distinctiveness effect). Perhaps the VLPFC was engaging in these processes simultaneously, and the processes were competing, causing interference. This account would explain the increase in false alarms for the individuals in the item-specific encoding subset of the atDCS group, and the increase in false alarms and associated explanation would replicate that of Experiment 3 in Chapter 5.

The VLPFC is associated with true and false recognition, and while the VLPFC is active during semantic or phonological interference, the VLPFC may not be the source of interference resolution (Atkins & Reuter-Lorenz, 2011). The VLPFC has been associated with semantic elaboration and selection between semantically-similar competing responses (particularly in a *post-semantic retrieval process*). Semantic interference increases when participants must generate corresponding verbs for nouns with multiple vs few associated verbs (e.g. *ball* vs *scissors*) and temporal interference increases when the working memory

test item was presented not on the current trial but on the trial immediately before. VLPFC activity is correlated to increased interference in these tasks, as measured with an index comparing reaction times for correct responses between trials with high interference and trials with no interference (Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009). The VLPFC may modulate cognitive control to resolve interference, as evident by the activation of additional regions (including DLPFC) during greater selection demands (Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009). While the left VLPFC showed correlations that increased with interference, it did not show differential activation for correct rejections and false alarms to lures, in contrast to the left DLPFC which may engage in post-retrieval monitoring in the presence of interference in the left VLPFC to lower false recognition. The left parahippocampal gyrus was the only region in the medial temporal lobe with differential activity for true and false recognition. Participants completed a short-term DRM task in which they saw four semantically-related items presented simultaneously for 1200 ms, followed by a distractor math question and then a test item that was part of the presented set or new (unrelated or related). Semantic interference was indexed by comparing reaction times for correct rejections between related and unrelated lures. VLPFC activation was not simply associated with semantic familiarity (increased activation to targets as well as lures); rather, the increased activation was selective to related lures, including correct rejections and false alarms (Atkins & Reuter-Lorenz, 2011).

Kim and Cabeza (2006) presented semantically-related lists to participants and found subsequent memory effects for true and false recognition in the left VLPFC and visual areas in the occipital lobe. They found selective effects for true recognition in the left parahippocampal cortex and other medial temporal lobe regions as well as the occipital pole. They suggested that visual areas in the early time window were associated with true recognition only, whereas late visual areas were implicated in true and false recognition. In

addition, they found a weak but significant correlation between hits and false alarms, suggesting that greater elaboration contributed to true and false recognition. They found activation in the anterior VLPFC (BA 45) that is associated with semantic processing and a posterior area (BA 6) that is associated with working memory (maintenance of category information). Although the increased false alarm rate associated with elaboration was in line with theories of false memories (spreading activation, fuzzy trace, gist memory), the degree of semantic elaboration was unclear. The medial temporal lobe was implicated as a region selectively involved in declarative but not unconscious memory. The critical lures were not consciously experienced, so there was no memory trace associated with them. Although the critical lures could be activated at encoding and form part of the memory, the authors suggest that the categorical memory task did not elicit false memory as strongly as the DRM task (although there was a 49% false alarm rate). The false alarm rate was comparable to the DRM task, but there were more trials with semantically-related lures, so the false alarm rate was not due to the presence of a few critical lures that were strongly activated at encoding. Notably, the hippocampus was only associated with true recognition and confident responses, reflecting the selective role in recollection but not familiarity. The PFC is associated with a work in progress and manipulating memory traces, whereas the MTL generates the true memory traces. They suggested that because early visual areas would capture raw sensory representations, they would likely be associated with true recognition (bottom-up), whereas late visual areas could be modulated by the PFC (top-down), and they could form integrations with stored sensory representations, leading to false and true memory. Thus, the reactivation of elaborative representations in late visual areas could lead to false recognition.

However, Stark, Okado, and Loftus (2010) found activity in the right hippocampus and left parahippocampal cortex that was similarly associated with true and false recognition, perhaps because the false memories were elaborate and richer in detail.

Participants were shown images and then told corresponding narratives, and part of these narratives were incorrect. Then participants completed a surprise recognition test and source memory task, indicating whether the description was presented in both modalities, only visually, or only audibly. Consistent with sensory reactivation, hits but not correct rejections or false alarms were associated with greater visual cortex activity in early and late regions. However, only activity in early, posterior visual regions was associated with true memory, whereas posterior regions were active at true and false memories. It is notable that the auditory cortex was reactivated for all items with a corresponding narrative, regardless of whether participants judged that the trace was presented visually or audibly. Frontal regions were associated with hits and false alarms, with different subregions for each. The authors suggested that there were greater post-retrieval monitoring processes for hits and there were domain-general, effortful processes for correct rejections. Alternatively, there was a distinctiveness effect at the time of the correct rejection, and participants recalled the true memory trace to reject the current item (recall-to-reject).

It is interesting to note that in Experiment 1 (Chapter 5) in which there was a significant effect of atDCS on accuracy, there was a relatively high false alarm rate that was comparable to the hit rate, suggesting strong semantic similarity within the word set. However, the key distinction with Chapter 6 in which there was no atDCS effect may be the order of the word presentation. While the semantically-similar words were presented in a random order for each participant in Experiments 1 and 2, the words in Experiment 5 were presented in a consistent order of strongest to weakest association strength to a critical lure. The left VLPFC has a role in temporal clustering. Thus, false memories would be more likely when the semantically-related words are presented in order, as in the DRM task, than if they are scattered throughout the experiment (Experiment 1).

Evrard, Gilet, Colombel, Dufermont, and Corson (2016) showed that ordering DRM lists based on ascending forward association strength led to increased critical lure generation in patients with Alzheimer's Disease compared to healthy older or younger adults. Patients with Alzheimer's Disease show an intact recency effect in serial recall and phonological loop in working memory, but long-term memory is impaired, as evident in the worse primacy effect. They suggested that patients with AD could show comparable performance to healthy controls on descending forward association strength (FAS) lists because of forgetting the first words in the list that most strongly evoke the critical lure. In contrast, ascending FAS led to increased activation of the critical lure, and because of the unimpaired recency effect, patients were more likely to recall the most recent and most strongly associated words to the critical lure. Thus, they were more likely to make the associations leading to the activation of the critical lure.

McEvoy, Nelson, and Komatsu (1999) found that the strength of connections within the list predicted false recall, whereas the density of the connections was associated with correct recall. On the other hand, increasing the strength and density of connections increased the likelihood of false recognition. Specifically, strength of the connections was manipulated by varying the association between each list item and the critical lure (evoking false recall/recognition), whereas density was manipulated by maintaining constant item-lure strength and varying association strength between the items within the list, increasing the likelihood of each list item activating the others (generating retrieval cues as in cued recall). In the first experiment, two sets of lists were presented: strong and weak, with the strong lists being likely to evoke the critical lure and the weak lists being unlikely to evoke the critical lure. This was based on association strength (proportion of participants who named an associate in response to a cue word). In subsequent experiments, these sets were used while also considering the likelihood of each word evoking the other as an associate (association of words through norms). Even DRM lists

with low backward association strength (association strength from presented words to the critical lure) and controlled FAS led to false recognition (Cadavid & Beato, 2017). BAS and FAS may both be important in predicting false memory, but BAS may be even more important.

Some studies have found that associations at encoding and test predict false memory, but Dewhurst, Bould, Knott, and Thorley (2009) found that in categorical and DRM false memory tasks, activations at study but not test predicted false memory. Coane and McBride (2007) found that increasing the number of studied items sequentially presented at test (0, 6, or 12) led to increased false recognition, suggesting contributions of encoding and retrieval semantic processing to false recognition. Initially, there were no differences in false recognition between the number of studied items at test. However, after items were presented in a random vs blocked order (lowering rates of false recognition) and nonstudied lists were included (to test whether semantic processes leading to false memory were specific to retrieval). False recognition was higher in studied lists, although there was a false recognition effect for studied and non-studied lists: six and 12 studied items presented at test led to higher false recognition than zero studied items, although there was no difference between the two conditions (6 and 12 studied items).

Tussing and Greene (1997) found lower false recognition for incidental encoding and random presentation compared to intentional encoding and blocked presentation. However, shallow vs deep processing and repetition (three times) did not affect false recognition. On the other hand, Dewhurst and Anderson (1999) did not find any differences between blocked and random presentation. McEvoy, Nelson, and Komatsu (1999) also found no effects of varying list presentation randomly or in order of ascending or descending strength on false recall or recognition.

When participants were asked to silently read or generate associates out loud, false recognition was higher after generation of associates (Dewhurst, Bould, Knott, & Thorley,

2009). Blocked lists led to higher true and false recognition specifically for 'remember' vs 'know' responses compared to the random lists, partially explaining the discrepancy between the results of Tussing and Greene (1997) and Dewhurst and Anderson (1999). When presenting blocked lists at encoding, including different numbers of studied items (zero, three, or six) at test did not lead to differences in false recognition or false recall. In general, false recognition was higher for DRM task than categorized lists with lists of high-frequency exemplars sorted by category, possibly due to greater backward association strength.

The distinctiveness heuristic could have been tested with tDCS by comparing effects between words and pictures, in a between-subjects and within-subjects design. However, the VLPFC may not respond to perceptual semantic cues, unlike the DLPFC (Gray et al., 2015). The VLPFC is sensitive to *semantic* rather than perceptual information, and there is a possibility that participants would have benefitted from distinctive semantic information instead of colour backgrounds. False memories can be avoided by including distinctive information at study that is not present in new words at test (e.g. colour), and distinctive semantic information can be included through infrequent words or unusual combinations of words in fragments or sentences. The distinctiveness effect could occur in Experiment 1 (Chapter 5) but not the current experiment because the semantically-similar words were presented in a random order and intermixed with infrequent, distinctive words. In contrast, the current experiment included semantically-related words in order from strongest to weakest association with a theme, and this temporal proximity could have been beneficial in memorisation through temporal clustering in the VLPFC. However, the temporal proximity could have increased interference because the words were adjacent in time *and* similar in semantics.

There were no significant differences between the groups in recognition or source accuracy. Thus, the tDCS effect from Experiment 1 was not replicated in this experiment

and the hypotheses about the mechanisms of tDCS were not supported. Specifically, item-specific encoding was not greater in the tDCS group, and this is to be expected given that there was no decrease in false alarms following tDCS. It is important to note that performance in this experiment was generally higher than in the previous experiments, specifically in hits rather than false alarms. Specifically, participants in the Sham group had higher performance than sham groups in previous experiments, whereas performance in the atDCS group was similar to Experiments 1 and 4. The facilitation of temporal and semantic clustering due to presentation of semantically-related words sequentially could have led to deeper encoding and greater semantic elaboration, in turn increasing the amount of information encoded and strengthening the memory trace (Hunt & Einstein, 1981). Thus, there could be a higher degree of relational encoding than in previous experiments. Perhaps there was an effect of atDCS that was not evident in group differences because of higher performance in the Sham group. Because of the possible confound created by relational encoding, the task implemented may not be optimal to examine the mechanisms whereby tDCS improves recognition memory. The DRM task may encourage deeper encoding than standard tasks, it may not be optimal to observe tDCS effects.

A limitation was that the task was substantially different from the previous experiment, although it was necessary to include a task that elicited a high proportion of false alarms. In addition, perhaps the perceptual cues (colours) did not enhance distinctiveness of the words because they were not semantic; the VLPFC could respond more to cues that include distinctive semantic features, such as bizarreness or low word frequency. The DLPFC was not examined as a comparison site (online encoding), although it could have played a greater role in this experiment than in the previous experiment because of its importance for relational encoding. Future work may examine the possibility that relational encoding impedes tDCS effects over the VLPFC by

comparing tDCS effects on relational and item-specific encoding separately through a between-subjects design. However, the current study and previous experiments (Experiment 3, Chapter 5) suggest that VLPFC activity may be more beneficial for semantic elaboration in item-specific but not relational encoding because of interference caused by semantic similarity in relational encoding.

Chapter 7: Using rTMS to Address Research Questions: Identifying verbal episodic processes and associated time windows in the VLPFC

Abstract

The DLPFC has been a widely-used target for applying tDCS and addressing research questions, but it may not be the optimal target because of its secondary role in episodic memory. However, applying tDCS over more optimal sites such as the VLPFC may not yield consistent effects either. This could be due to the specific timing of stimulation or general lack of reliability of tDCS as a research tool. Investigating encoding processes at more fine-grained time intervals may be important for understanding the effects of tDCS and identifying the role of the VLPFC, which may vary over time and across tasks. The current study compared the effects of rTMS on memory impairment when delivered during or after the presentation of each word: rTMS was delivered at 1100 ms or 1000 ms with respect to word onset or at 0 ms or 100 ms with respect to word offset. There was a significant impairment only for the offset condition when rTMS was delivered at 100 ms post-stimulus offset (1100 ms post-stimulus onset for a 1000-ms word). A comparison with previous rTMS studies suggests that there are two dissociable processes in the VLPFC: online processing, which involves semantic elaboration, and offline processing, which involves binding of item features to temporal context with the hippocampus. The findings suggest that tDCS may modulate online processing, a longer process that is susceptible to individual differences compared to offline processing. Thus, previous tDCS effects over the VLPFC may be limited and inconsistent because of individual and task-related differences in semantic elaboration and a lack of direct effects over the offline binding process that may determine successful memory formation.

Introduction

The DLPFC has become a predominant target for development of memory treatments through NIBS, but recent findings (Chapter 5) suggest that the VLPFC may be

a more viable target. The VLPFC has been established as an essential region for verbal encoding processes through findings in fMRI, tDCS, and TMS research. Experiment 1 demonstrated that the VLPFC is more functionally active at encoding than retrieval, and Experiment 3 demonstrated that the VLPFC is more critical to encoding than the DLPFC, in line with a previous TMS study comparing the VLPFC and DLPFC (Galli, Feurra, Pavone, Sirota, & Rossi, 2017). Although there is an abundance of correlational evidence linking the VLPFC to specific functions, including information maintenance and controlled retrieval, the contribution of the VLPFC to episodic memory formation remains unclear. Like tDCS, TMS can be a powerful tool for establishing causality between a region and a specific function.

TMS has been used to identify the contributions of processes in the VLPFC and DLPFC to memory formation, supporting the greater role of the VLPFC compared to the DLPFC at encoding. For example, Lee, Blumenfeld, and D'Esposito (2013) delivered theta-burst TMS over the DLPFC (-43, 35, 30 MNI; F3) and VLPFC (-53, 28, 12 MNI; Wagner et al., 1998) during a visual implicit memory task. TMS over the VLPFC worsened accuracy between "remember", "know" and "guess" responses with a graded decrease, while there was a slight increase for "familiar" items. while TMS over the DLPFC led to improved accuracy in "guess" responses and for implicit memory responses generally. The authors concluded that memory processes associated with the DLPFC interfered with implicit memory, while interfering with the VLPFC reflected impairment of both explicit and implicit memory processes. Blumenfeld, Lee, and D'Esposito (2014) applied a similar design (two groups; DLPFC and VLPFC) to an intentional verbal encoding task (concrete or abstract semantic judgement for nouns). They administered trains of 3 pulses per 200 ms at 50 Hz to two groups of participants (VLPFC and DLPFC), and each group also received vertex stimulation. They noted that accuracy on encoding and recognition judgements decreased following TMS to the VLPFC, whereas accuracy

increased numerically but not statistically following TMS to the DLPFC. The findings suggested that semantic processes in the VLPFC may have been more crucial to memory formation than those in the DLPFC.

In contrast to tDCS, TMS can identify the functional importance of activation at a specific time. Overall, TMS has higher temporal *and* spatial focality than tDCS and can target a region with a similar level of precision as fMRI and with similar temporal precision as EEG. Thus, researchers have begun to target processes at the same coordinates found in fMRI studies and at specific time windows that correspond to subsequent memory effects in EEG studies. However, the time windows in EEG studies can be broad, and coordinates in fMRI studies can vary. Thus, a continued investigation of time of rTMS administration on episodic memory is warranted, especially for the VLPFC. Multiple studies have targeted the DLPFC and have examined time windows of critical DLPFC activity for memory function. It seems that important processes in verbal encoding occur after the word is presented, in addition to crucial processes before and during the word.

For example, Hawco and colleagues (2017) delivered TMS over the DLPFC during an associative pictorial encoding task at various times after stimulus onset (200, 600, or 1000 ms). When measured with fMRI, the DLPFC showed decreased activity at 200 ms post-stimulus for unrelated pairs and at 1000 ms post-stimulus for related pairs. There were marginally significant modulations of cued recall performance, higher performance for related pairs after 600 ms post-stimulus TMS and worse performance for related pairs after 1000 ms post-stimulus TMS. They concluded that the DLPFC modulates visual activity within certain time windows. They suggested that the DLPFC initiates memory strategies while the VLPFC executes them, so VLPFC activity would be prolonged or suppressed by the DLPFC depending on whether strategies would be useful.

However, few other studies have previously examined later stages of encoding, specifically encoding processes that follow the disappearance of the item from view. Even

fewer studies have investigated the exact timings of these processes in the VLPFC. The majority of studies over the VLPFC have investigated disruptions to online processing and identified functions related to language and semantics.

Grafman and colleagues (1994) delivered rTMS to various frontal (F7 & F8), temporal, parietal, and occipital regions. They found that immediate recall for a 12-word list decreased after stimulation to the left and right VLPFC (F7 and F8) at 0 and 250 ms after word onset (but not 1000 ms after). In addition, rTMS to the left mid-temporal cortex (T5) and VLPFC at 500 ms post-stimulus onset led to decreased recall. The control condition was no TMS, including noise resembling that of the TMS condition, and only 0 and 250 ms conditions were administered for the right hemisphere. An exploratory analysis showed that the primacy effect (recall of serial positions 1 and 2) was diminished for the left mid-temporal site at 0 and 250 ms, and for the left VLPFC at 0 and 500 ms. Words were presented for 500 ms. While it is surprising that there was an effect at word onset but not word offset, there is a possibility that the immediate recall task relied more on short-term memory and any long-term memory processes were not engaged. Thus, there may have been a greater reliance on online semantic processing rather than offset-related processing. The primacy effect may be more indicative of long-term memory, so a long-term memory process could have been engaged and disrupted by rTMS at the offset of the word (500 ms). In addition, participants were asked to read the words but not to memorise them, perhaps leading to faster processing for semantic information.

There have also been specific dissociations between the anterior and posterior VLPFC for semantic and phonological processing, respectively, during word presentation. Köhler and colleagues (2004) delivered stimulation 200-800 ms post-stimulus onset to the left and right VLPFC and a left parietal control site. They found higher recognition accuracy, specifically hits, after left PFC stimulation compared to the other two sites. In addition, they found that reaction times were slower at encoding for the left PFC site, and

accuracy for semantic decisions (abstract or concrete) was marginally higher. Similarly, Kahn and colleagues (2005) disrupted VLPFC performance on a phonological episodic memory task with single-pulse TMS at 200-600 ms with respect to word onset. They used BA 44/9 as the stimulation site, with fMRI-guided MNI coordinates including 36, 15, 27 and 48, 12, 30, corresponding to the posterior part of the VLPFC. They found facilitation of encoding performance after disruption to the right VLPFC, specifically at 340 and 380 ms post-stimulus, whereas stimulating the left VLPFC led to worse performance, particularly in high confidence recognition at 380 ms post-stimulus for unfamiliar words. They concluded that subsequent memory for familiar English words was impaired after TMS to the left VLPFC, specifically recognition confidence. Their results confirm the role of the left VLPFC in encoding and provide support for the specific role of the posterior VLPFC in phonological processing between 300 and 400 ms.

To the author's knowledge, only two studies have explicitly examined post-stimulus processing in the VLPFC, and there remains a lack of understanding about the importance of processing after the offset of a word. Machizawa and colleagues (2010) found that interrupting activity in the VLPFC at three post-stimulus time intervals at encoding led to the same magnitude of recognition impairment. However, Galli and colleagues (2017) found that recognition was only impaired during the first 100 ms after word offset.

Machizawa and colleagues (2010) administered TMS to the left and right anterior VLPFC at 50, 450, or 850 ms post-stimulus offset and found that subsequent recognition was worse at both hemispheres relative to vertex and no-TMS. They administered two pulses of TMS separated by 40 ms over coordinates from Köhler and colleagues (2004): -48, 35, 5 (Talairach). They found that TMS over any site increased reaction times and decreased accuracy on living/non-living judgements at study, but this was due to TMS and not specific to the left VLPFC. In addition, there were differences in reaction times and

accuracy between TMS over the vertex and no TMS. However, reaction times and accuracy at test were not affected by TMS alone. There were significant differences between TMS over the left VLPFC and TMS over the vertex, with fewer hits and response bias reflecting the pattern of fewer responses to studied items (selecting "old"). However, there was no significant difference in effects between the left and right VLPFC: discrimination accuracy was worse following TMS to both hemispheres, regardless of the time of stimulation or confidence. They suggested that rTMS disrupted the use of semantic elaboration in facilitating memory formation, which led to less detailed semantic representations and greater difficulty in retrieval.

Galli and colleagues (2017) delivered rTMS over the VLPFC (F7 in 10-20 EEG system) and DLPFC (F3) during word onset and after word offset and found an impairment in recognition accuracy after VLPFC but not DLPFC stimulation. Specifically, 20Hz pulses were delivered over 500 ms at various points (six conditions) with respect to the word onset and offset: 500 ms after word onset, immediately at word offset, or 100-400 ms after word offset. The greatest disruption was found 0 and 100 ms after the offset of the word. There appeared to be a graded effect such that performance was worse than baseline after TMS at the onset of the word, even worse at the offset, and lowest of all the conditions at 100 ms after offset. At longer times (200 ms and longer) following word offset, there was no reliable pattern, although performance was generally less affected. The disruption was evident for most of the 12 subjects, whereas for the DLPFC the effects were subtler and mixed, between enhancement and impairment. There was a slight enhancement for only three subjects in the VLPFC group, whereas four subjects had a strong enhancement and two had a slight enhancement in the DLPFC group. Galli and colleagues concluded that encoding processes at the offset of the word may be just as important as those at the onset of the word, and these offset-related processes may involve

interactions between the VLPFC and the hippocampus in binding semantic features and contextual details to form a single memory trace (Dubrow & Davachi, 2016).

Although only a few studies in neuroimaging have examined offset-related processes in the VLPFC, they suggest that the VLPFC may be active before (Ben-Yakov & Dudai, 2011) and during (Dubrow & Davachi, 2016) the offset of a word, perhaps in interactions with the hippocampus to bind item-specific details to a spatiotemporal context. Specifically, the VLPFC may be active at boundaries between distinct events (Ezzyat & Davachi, 2011; Dubrow & Davachi, 2016). Specifically, Ezzyat and Davachi found activation in the left VLPFC during verbal transitions in a narrative that cued a boundary ("A while later" compared to "A moment later"), and this activation predicted successful recall for the information presented after the boundary, suggesting that the VLPFC may be associated with binding information between distinct contexts rather than within contexts. Similarly, Dubrow and Davachi (2016) found greater activation of the left VLPFC and hippocampus during gaps between transitions to a different context (from faces and judging their likability to objects and judging their commonality) compared to gaps between items in the same context (transitions between faces). Since activation in the VLPFC predicted subsequent serial recall, the processes in the left VLPFC at the offset of a word cannot be attributed to task-switching or other domain general processes. Taken together, the studies suggest that the VLPFC plays an important role during the offset interval between stimuli, particularly when those stimuli are in distinct semantic or verbally-distinguishable contexts. It is important to characterize the time course of memory formation at encoding, the importance of processes in the VLPFC during and after the word's presentation to learn more about the role of the VLPFC, specifically when it is engaged and what processes it is involved in. This could help with developing memory treatment aimed at the VLPFC at a certain time. It is also important to characterize when the VLPFC is active to understand its specific role and interaction with

other brain regions. In this way, a better understanding will be gained of the different contributions of prefrontal regions, and in the context of what is already known about medial temporal regions. Finally, researchers have recently hypothesised that episodic memory formation depends on a distributed network of regions, and this study will help to confirm the extent to which the VLPFC is necessary rather than simply active in memory formation. tDCS and EEG studies revealed that processes at encoding are important for retrieval (cortical reinstatement theory), and this study provides support to the theory by specifying when these critical processes occur. The focality of TMS in time and space allows for an extension of the tDCS and EEG findings, characterising the time course of memory formation in a specific region such as the VLPFC.

The current study aims to replicate and advance the findings of Galli and colleagues (2017) in identifying the critical time window for memory formation in the VLPFC. In addition, the study aims to extend the findings of Experiment 1 by looking at effects of specific times of stimulation administration on recognition. Specifically, the study will compare the effects of varying post-stimulus timings of rTMS on recognition impairment. It was expected that the impairment would be greater in the intervals following word offset, replicating the findings of Galli and colleagues (2017). In addition, the findings will help to understand the recognition-dependent process that occurs in the VLPFC and in turn, how this VLPFC process interacts with hippocampal processes that occur at similar times.

Method

Participants. Twenty-four young adults (14 female) completed the experiment (*M* age = 20.42, *SD* = 2.92, range = 18-29), but the final sample size included eighteen participants (see Exclusions below). Participants received 20-pound vouchers or course credits for participation. Ten additional participants were recruited but did not start the experiment because they were unable to tolerate the stimulation at 90% active motor

threshold (rTMS protocol is described below). These participants were compensated with five-pound vouchers or partial course credits. All recruited participants were healthy right-handed Native English speakers between 18 and 30 years old without current or past neurological or psychiatric diseases, and they had normal-to-corrected vision. Participants were appropriately screened for risk (Rossi, 2009) and excluded for any metal implants, pregnancy, syncope, and history of seizures. Participants completed all stimulation conditions, and conditions were counterbalanced across participants. All participants provided informed consent before starting the experiment, and the study was conducted in accordance with ethical approval from University of Roehampton.

Exclusions. For five participants, the maximum stimulation intensity became intolerable at the 90% threshold level, and the intensity was lowered to 85% of their active motor threshold. Although the results of the analyses did not significantly with or without these participants, as an additional control for methodological rigour, the data for these participants were excluded from final analyses. Data for the 1100 Offset condition were removed from three participants due to technical issues with the TMS coil.

Outliers were defined as any extreme values beyond two standard deviations of the mean. On this basis, one outlier was excluded for extreme values on all measures. There were two extreme values for hits, but these outliers did not affect discrimination index, so they were kept. Thus, the final sample size included 18 participants for all conditions except for the 1100 Offset condition, which included 17 participants.

Experimental design. Participants received stimulation in six different conditions, depending on the time of administration and word duration (See Figure 7.2.1). There were two control conditions and four experimental conditions, counterbalanced with six different orders (i.e. No TMS, VLPFC, Vertex). The VLPFC conditions were always presented together so that the coil would remain in a stable position over the VLPFC. However, the order of the four VLPFC conditions was randomised for each participant.

In one control condition (No TMS), no rTMS was delivered, and in the second control condition (Vertex), rTMS was delivered at 1000 ms post-stimulus onset, at word offset, over the vertex. In the experimental conditions, rTMS was delivered over the VLPFC at varying times with respect to word duration. In the Offset conditions, rTMS was delivered at the offset of the word, whereas in the Onset conditions, rTMS was delivered before the offset of the words. rTMS was administered with respect to several different word durations. In the 1000 Offset condition, rTMS was delivered at the offset of a word lasting 1000 ms, whereas in the 1100 Offset condition, rTMS was delivered at the offset of a 1100-ms word. In the 1000 Online and 1100 Online conditions, rTMS was delivered at 1000 and 1100 ms with respect to word onset, with words lasting 1200 and 1300 ms, respectively. Thus, there were four experimental conditions: 1000 Offset, 1100 Offset, 1000 Onset, and 1100 Offset.

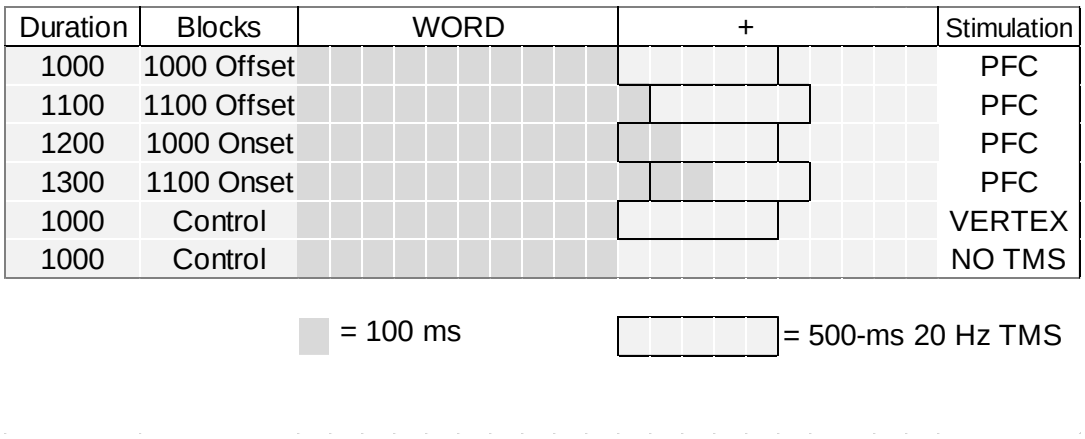

Figure 7.2.1. Stimulation conditions, including word duration and rTMS administration. The 500-ms trains of rTMS started at the offset of a word lasting 1000 or 1100 ms (1000 Offset and 1100 Offset, respectively) or at 1000 or 1100 ms after word onset for a 1200-ms and 1300-ms word, respectively. Vertex stimulation started at the offset of the word and served as a control condition for non-specific stimulation effects, and a no-TMS condition was included in which no rTMS was delivered.

Materials. Stimuli were 318 seven-letter English words (mean word frequency = 24.86, *SD* = 36.11; Kučera and Francis 1967) randomly selected from the MRC

Psycholinguistic Database (Coltheart, 1981). See Appendix M (Table M1) for the selected words and associated frequencies. For each participant, 180 words from the pool were randomly assigned to the study phase ("old" words), and 108 words were assigned to the test phase ("new" words). The study words were randomly ordered in six blocks of 30 words each. At test, the 30 study words were randomly ordered within the same blocks in addition to 18 unpresented words. The new, unpresented words were randomly selected from the test list and ordered into different blocks. Thirty additional words from the pool were selected to form practice lists for the tasks. 20 words were presented at the practice for the study task, and those 20 words were presented again with 10 new words during the practice for the test task. At study and test, words were presented in white uppercase Helvetica on a black background. At a viewing distance of approximately 71 cm, words subtended a visual angle of 1° vertically, and 5° horizontally. Stimuli were presented in MATLAB version 9.0 (Mathworks) and Cogent Toolbox version 1.32 (Cogent, www.vislab.ucl.ac.uk/Cogent/). Data analyses were conducted in SPSS version 24 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY).

Procedure. The experiment included an intentional deep encoding task at study, and participants were instructed to indicate whether each word was "pleasant" or "unpleasant" and memorise the word. Participants selected "pleasant" or "unpleasant" with the A and L keys, respectively. The hand assigned to each judgement was not counterbalanced since responses at encoding were not of interest. The words were presented in six consecutive blocks with 30 words in each block, corresponding to the six stimulation conditions (rTMS protocol is described below). Participants received self-paced breaks between each block.

Each block corresponded to a different rTMS condition. At the study phase, a fixation was presented for 1000 ms, followed by the word and inter-trial interval which

varied depending on the condition. The inter-trial interval varied depending on the condition so that the duration of the trial was consistently 5600 ms.

Thus, in the 1000 Offset condition, the word was presented for 1000 ms, followed by an rTMS train at word offset, and finally an inter-trial interval of 3600 ms in which a fixation cross was presented. In the 1100 Offset condition, the word was presented for 1100 ms, followed by an rTMS train at word offset, and an inter-trial interval of 3500 ms. In the 1000 Onset condition, the word was presented for 1200 and the inter-trial fixation cross was presented for 3400 ms. In the 1100 Onset condition, the word was presented for 1300 ms and the inter-trial interval was 3300 ms. No TMS and Vertex conditions included a word duration of 1000 ms and an inter-trial interval of 3600 ms; in the Vertex condition, rTMS was delivered at word offset.

TMS procedures. Repetitive TMS was delivered through a figure-of-eight, 70-mm Magstim coil that was placed tangentially at a 45-degree angle to the scalp. TMS was delivered over the VLPFC at a site corresponding to F9, the inferior frontal gyrus: -52, 45, 10 in MNI coordinates. The location of the vertex corresponded to the centre of the head (Cz). Both locations are shown in Figure 7.2.2. High-frequency rTMS trains were delivered at 20 Hz with 5 s between successive trains, in line with safety considerations.

Active motor threshold was determined by delivering single pulses to the left motor cortex and carefully examining involuntary motor responses in the contralateral hand. The intensity was adjusted for each participant to 90% of active motor threshold. Individuals who did not show a visible motor response in the right hand were asked for any sensation of reflex in the right arm or other muscles on the right side of the body. Participants experienced several trains of rTMS in an estimate of the stimulation site before continuing with the experiment to ensure that the stimulation was comfortable. Ten participants could not tolerate the stimulation and did not complete the experiment.

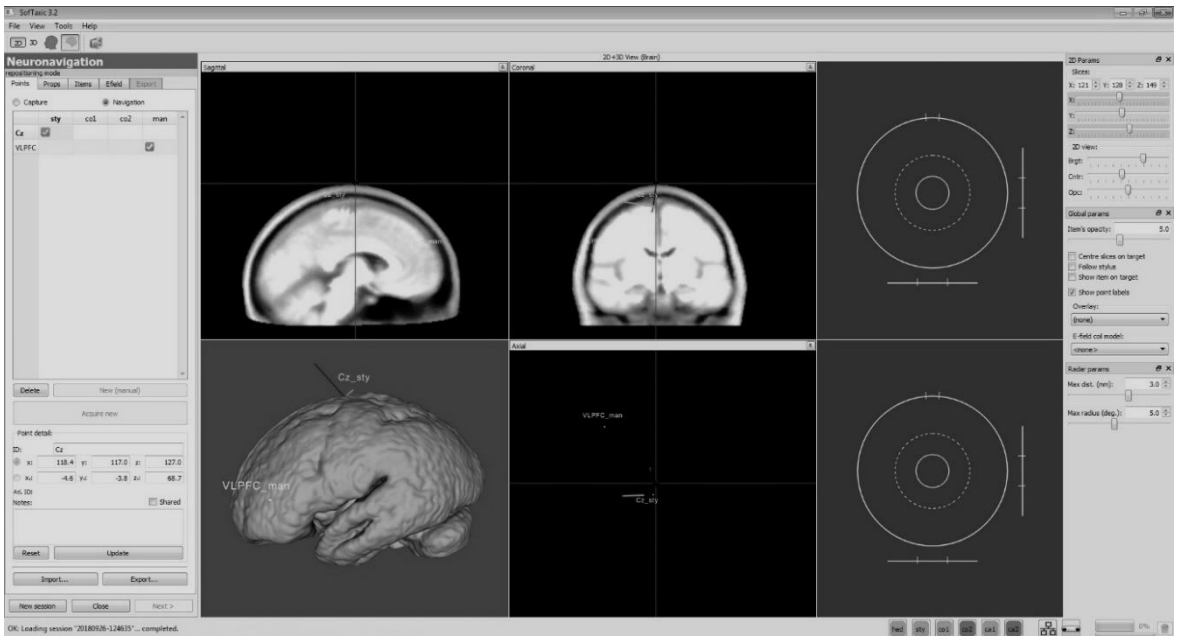

Figure 7.2.2. Neuronavigation system with VLPFC and Vertex (Cz) as stimulation targets.

Data analysis. Because there were no significant differences in any measure (*p*s>.085, Vertex and No TMS conditions were averaged to form one control group (Control). There was no significant difference between No TMS (M = 908.47, SD = 311.96) and Vertex (M = 932.32, SD = 390.45) in encoding reaction times $t(17) = -0.41$, $p = .691$, the two conditions were collapsed into one control condition. There was not a significant difference between the Vertex and No TMS conditions in accuracy $t(17) = 1.83$, $p = .085$ or average reaction time $t(17) = 0.35$, $p = .733$. There was also no difference between Vertex (M = 756.35, SD = 80.01) and No TMS (M = 731.39, SD = 97.67) in reaction times for hits $t(17) = 1.53$, $p = .145$. There was no difference between Vertex (M = 721.45, SD = 255.50) and No TMS (M = 683.80, SD = 375.71) in reaction times for false alarms $t(14) = 0.38$, $p = .712$. Note: the degrees of freedom changed for false alarms because for three participants, there were no false alarms in the No TMS and Vertex conditions. Thus, the two conditions were collapsed into one Control condition.

A repeated-measures ANOVA was conducted on reaction times at encoding, followed by two-tailed pairwise comparisons between each VLPFC group and the Control. In addition, repeated-measures ANOVAs were conducted for recognition accuracy,

proportion of hits, and proportion of false alarms and associated reaction times: average reaction times, reaction times for hits, and reaction times for false alarms. Significant interactions were followed up with two-tailed pairwise comparisons between each VLPFC group and Control. For all pairwise comparisons, the significance criterion was adjusted to $\alpha = .013$ (Bonferroni correction) for multiple comparisons.

Results

Participant sensations. Participants who completed the experiment ($N = 25$) did not report any adverse effects and reported only low scores when averaged across all sensations ($M = 0.88$, $SD = 0.78$). There were also low levels of general discomfort ($M = 1.38$, $SD = 0.97$), pain ($M = 1.13$, $SD = 1.03$), and burning ($M = 0.13$, $SD = 0.34$). Figure 7.3.1 shows the distribution of sensations as a function of each level (none, mild, moderate, strong). See Appendix Q for the frequency distribution of each sensation.

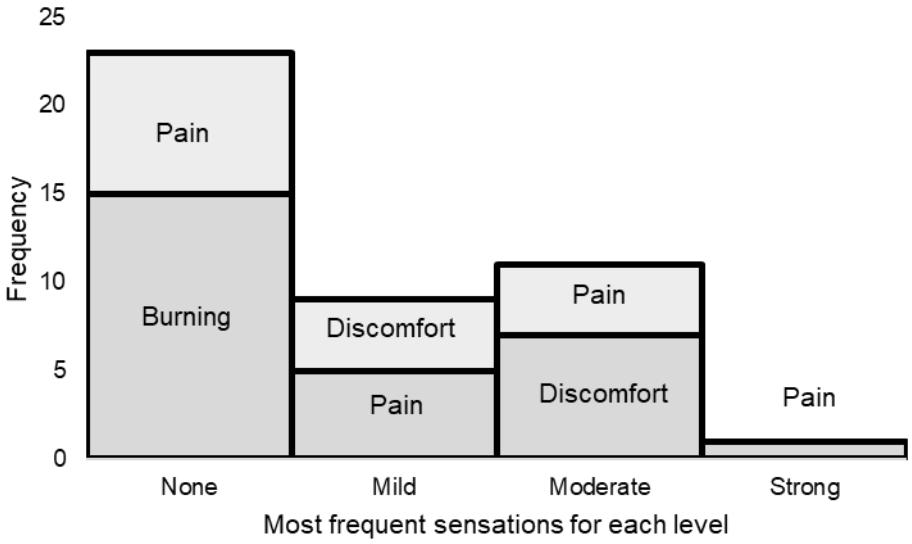

Figure 7.3.1. The sensation that was most frequently reported for each response level. Note: Response levels were: None, Mild, Moderate, and Strong. Most frequent sensations are in dark grey, and the second most frequent sensations are in light grey. When participants reported strong levels of sensations, only pain was reported as the associated sensation.

TMS effects at encoding. Reaction times were examined to ensure that differences at retrieval were not related to differences at encoding. Mauchly's test of sphericity was significant $\chi^2(9) = 56.99$, $p<.001$, indicating that the assumption of sphericity was violated. Thus, Greenhouse-Geisser-corrected values were implemented $\varepsilon = .386$. The repeated-measures ANOVA on encoding reaction times revealed no significant difference between the conditions $F(1.54, 24.23) = 0.03$, $p = .998$, $\eta^2_p = .002$. Planned pairwise comparisons between each experimental group and control revealed no significant differences between Control and 1000 Offset $t(17) = 0.19$, $p = .850$; 1100 Offset $t(17) = 0.23$, $p = .820$; 1000 Onset $t(17) = 0.12$, $p = .909$; or 1100 Onset $t(17) = 0.12$, $p = .903$.

TMS effects at retrieval. Mauchly's test confirmed that the assumption of sphericity was met for accuracy, $\chi^2(9) = 9.77$, $p = .373$, and reaction times for hits, $\chi^2(9) = 11.96$, $p = .219$, but not average reaction time $\chi^2(9) = 54.74$, $p<.001$ or reaction times for false alarms $\chi^2(9) = 68.33$, $p<.001$. Thus, Greenhouse-Geisser-corrected values were implemented for average reaction time $\varepsilon = .413$ and reaction times for false alarms $\varepsilon = .387$.

There was no significant difference between the conditions in average reaction time, $F(1.65, 23.11) = 1.54$, $p = .235$, $\eta^2_p = .099$, or reaction times for false alarms, $F(1.55, 21.66) = 1.57$, $p = .230$, $\eta^2_p = .101$. However, there was a significant difference in reaction times for hits $F(4,56) = 2.71$, $p = .039$, $\eta^2_p = .162$. Pairwise comparisons revealed no significant differences in reaction times for hits between Control and 1000 Offset $t(17) = -1.59$, $p = .130$; 1100 Offset $t(17) = 1.30$, $p = .213$; 1000 Onset $t(17) = 1.48$, $p = .158$; or 1100 Onset $t(17) = 0.80$, $p = .433$.

There was a significant difference in discrimination ability accuracy between the conditions $F(4,64) = 3.25$, $p = .017$, $\eta^2_p = .169$ (see Figure 7.3.2). Planned pairwise comparisons revealed a significant difference between the 1100 Offset condition and Control $t(16) = 4.44$, $p<.001$. Thus, recognition accuracy was significantly lower when

TMS was delivered at the offset of a 1100-ms word (M = 0.44, SD = 0.23) compared to Control (M = 0.56, SD = 0.21). There was a trend toward significant impairment in the 1000 Onset condition $t(17) = 2.18$, $p = .044$, but it did not reach significance after the Bonferroni correction. There were no significant differences between Control and 1000 Offset $t(17) = -0.56$, $p = .653$ or between Control and 1100 Onset $t(17) = -0.30$, $p = .769$. Figure 7.3.3 shows that the impairment for the 1100 Offset condition was relatively consistent across participants, whereas in the 1000 Offset condition, the rTMS-induced impairment was less consistent (see Figure 7.3.4). Individual differences in rTMS effects on recognition accuracy for the combined offset (effect of rTMS averaged across 1000 Offset and 1100 Offset, following Galli, Feurra, Pavone, Sirota, & Rossi, 2017) and onset condition (1000 Onset) are shown in Appendix S. There were no significant differences in proportion of hits $F(4,64) = 0.98$, $p = .428$ or false alarms $F(4,64) = 2.14$, $p = .086$, indicating that the difference in recognition accuracy was not specific to a response type.

Table 7.3.1

Means for accuracy and reaction times at retrieval for each condition

Stimulation	DI *M* *SD*	Hits *M* *SD*	FA *M* *SD*
At word offset (1000 ms word)	0.53 (0.20)	0.78 (0.17)	0.25 (0.14)
	690.50 (214.50)	711.58 (87.35)	669.41 (462.50)
At word offset (1100 ms word)	0.46 (0.20)	0.74 (0.11)	0.28 (0.14)
	813.66 (119.74)	765.05 (94.02)	862.26 (185.78)
1000 ms after word onset (1200	0.48 (0.20)	0.74 (0.16)	0.26 (0.12)
ms word)	674.22 (271.14)	774.14 (102.09)	574.31 (586.43)
1100 after word onset (1300 ms	0.54 (0.24)	0.77 (0.16)	0.24 (0.15)
word)	747.67 (137.28)	755.84 (71.64)	739.51 (280.26)
Vertex	0.60 (0.22)	0.79 (0.14)	0.19 (0.15)
	740.05 (134.26)	757.89 (82.20)	712.27 (253.45)
No TMS	0.50 (0.25)	0.77 (0.16)	0.27 (0.16)
	720.11 (220.99)	727.84 (99.48)	701.38 (378.97)

Note. Associated reaction times are reported below means, including average reaction times below DI for each condition. DI = discrimination index, and FA = proportion of false alarms.

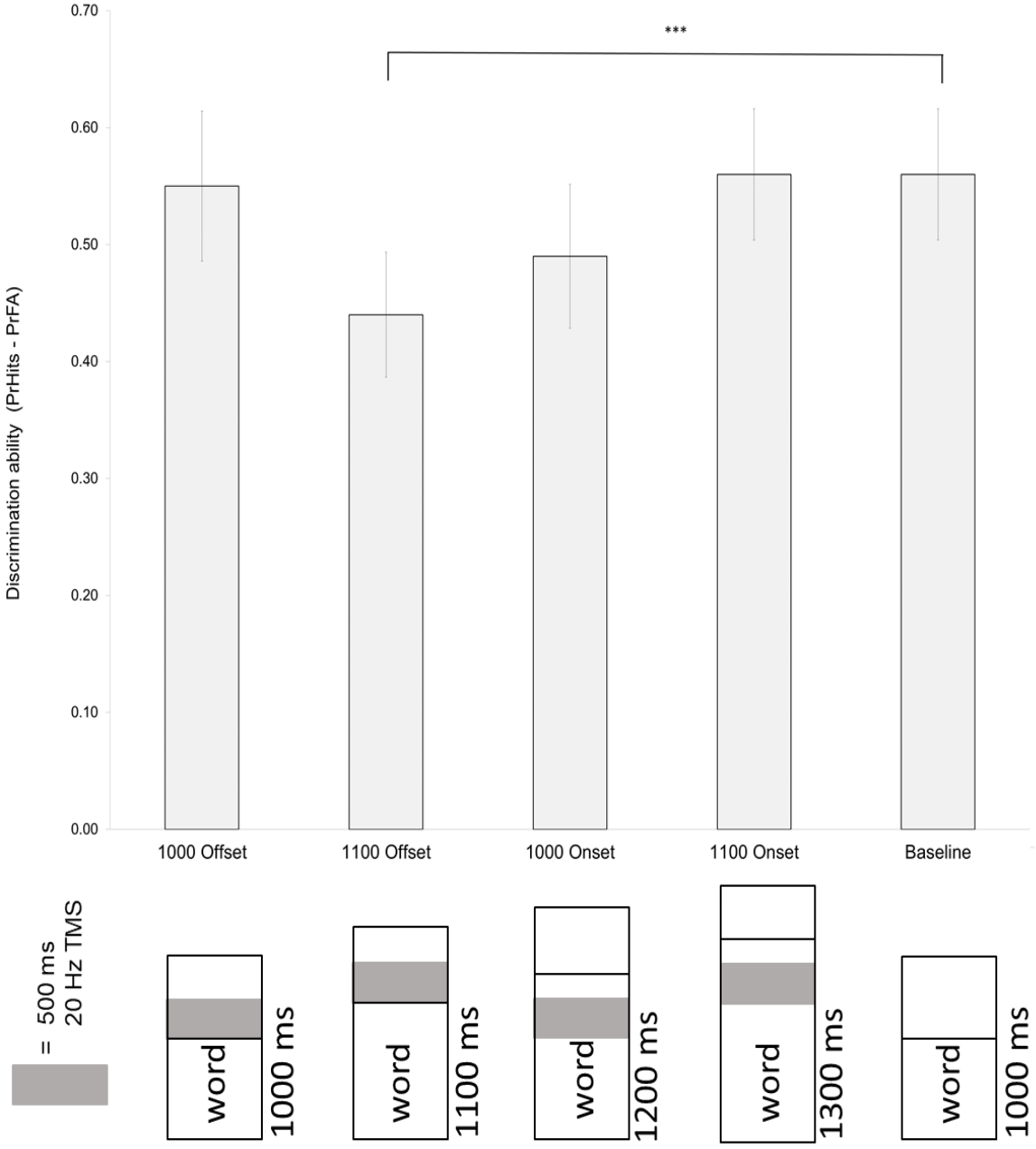

Figure 7.3.2. Discrimination ability across stimulation conditions that varied in rTMS onset, word duration, and inter-trial interval.

The condition is listed along with the duration of the word. For the first two conditions, rTMS was delivered at the offset of the word. For the last two conditions, rTMS was delivered 100 ms before the offset of the word. rTMS only impaired recognition accuracy in the 1100 Offset condition, interfering with the first 500 ms of the post-stimulus interval for words presented for 1100 ms.

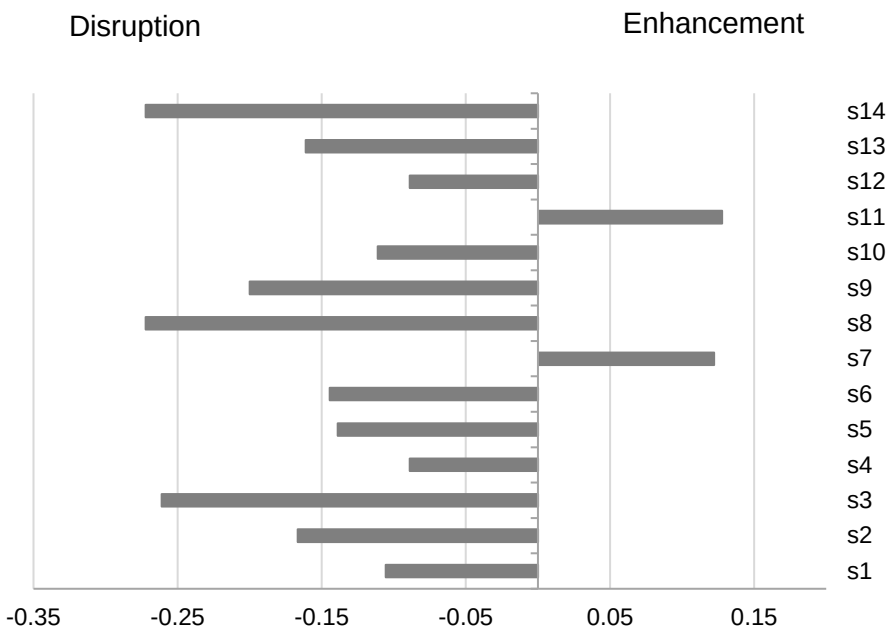

Figure 7.3.3. Individual differences in rTMS disruption of recognition accuracy at the offset of a 1100 ms-word.

For each participant, the figure shows the difference in discrimination ability between baseline and the 1100 Offset condition, where significant differences emerged. Negative values on the left hand panel show a disruption, whereas positive values show an enhancement. The disruption was clear for all except two participants.

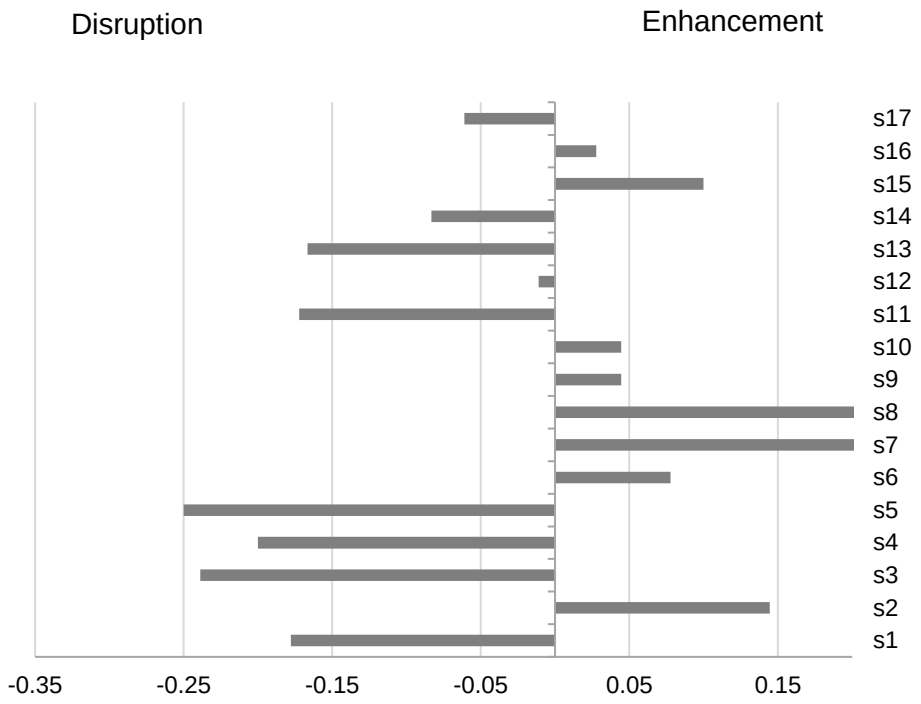

Figure 7.3.4. Individual differences in rTMS disruption of recognition accuracy at the offset of a 1000-ms word.

For each participant, the figure shows the difference in discrimination ability between baseline and the 1000 Offset condition, where there were no significant differences. Negative values on the left hand panel show a disruption, whereas positive values show an enhancement. The disruption was clear for all except two participants.

Discussion

The current study examined the effects of different timings of rTMS administration on episodic recognition. There were significant impairments in recognition when rTMS was delivered at the offset of a 1100-ms word, and there was a trend toward significant impairment when rTMS was delivered at 1000 ms post-stimulus onset for a 1200-ms word. There was no significant decrease in accuracy when rTMS was delivered at the offset of a 1000-ms word or 1100 ms post-stimulus onset for a word lasting 1300 ms.

The findings partially support those of Galli and colleagues (2017), who found that rTMS at 1000 ms and 1100 ms post-stimulus onset for a 1000-ms word impaired subsequent recognition. The time window of 1100 ms post-stimulus onset appears to be important, since an effect was found for the current study and Galli and colleagues (2017). The trend toward significance for the 1000 ms post-stimulus onset condition in the current study may overlap with the effect at 1000 ms post-stimulus onset (Galli, Feurra, Pavone, Sirota, & Rossi, 2017), highlighting 1000 ms post-stimulus onset as another critical time window. However, an impairment at 1000 ms post-stimulus onset was less consistent across participants than the impairment at the offset of a 1100-ms word, as evident from Figure 7.3.4, which shows individual differences in rTMS impairment at this time window. The key difference between the current study and the study by Galli and colleagues (2017) was the use of an intentional vs incidental task, which could lead to differences in processing times at encoding. While reaction times for encoding judgements did not appear to differ, it is likely that processing in the incidental task was complete shortly after the judgement, while in intentional encoding, semantic elaboration processes continued. Support for the idea that processing is longer for greater semantic elaboration arises from a comparison of reaction times between deep and shallow encoding (Galli, Feurra, Pavone, Sirota, & Rossi, 2017; Innocenti et al., 2010), indicating that perhaps greater semantic elaboration and thus longer processing is required to make a judgement. In addition, in Experiment 1 of Chapter 5, longer reaction times at encoding were found during the atDCS Online Encoding condition, which was likely to involve greater semantic elaboration. However, support for the idea that processing can be longer in intentional encoding and that processing can continue after a semantic judgement is available in findings from EEG, which show the time course of memory processes. Previous studies show that processing can be longer for intentional than incidental encoding, especially when processing time is compared between memory tasks and language tasks. Visual recognition of the word may

occur within 500 ms, while a semantic judgement may occur within 1000 ms, and processing in memory-related regions can continue up to 1500 ms.

Mainy and colleagues (2007) found differences in HFA increases when presenting words, nonwords, consonant strings, and unreadable symbols. The HFA is thought to reflect the same neural activation as the BOLD signal in fMRI studies (Conner, Ellmore, Pieters, DiSano, & Tandon, 2011). They found gamma increases for all tasks in the word form area of the fusiform gyrus at 200 ms post-stimulus onset, with increased activation for words and nonwords compared to consonants and symbols. Gamma activity peaked in the superior temporal gyrus, anterior VLPFC, and posterior VLPFC at 400 ms post-stimulus onset. There was an overlapping pattern of activation in the VLPFC for phonological and semantic processing in the posterior and anterior VLPFC, respectively. Continuous gamma activity in the DLPFC was found simultaneously with deactivation in the VLPFC at 500 ms post-stimulus onset, possibly reflecting domain-general selective attention and engagement of a semantic buffer, respectively. Generally, there was the expected increase in HFA (gamma) and decrease in LFA (alpha and beta). In all conditions, there were sharp increases within 400 ms in the bilateral DLPFC, and the activation decreased depending on processing (returning to baseline at similar rates when reaction times were controlled for). Overall, there were strong differences between semantic and phonological processing and smaller differences between semantic and visual and between phonological and visual. For most patients, there was a consistently large difference between semantic and visual processing in the VLPFC, although the difference between semantic and phonological processing was less consistent, perhaps because of the differences in VLPFC electrode position. In the VLPFC, there was selective gamma activation at 400 ms post-stimulus onset for phonological compared to visual processing, with gradual decrease over 1500 ms. Gamma changes in semantic processing were not consistent across patients, but for one patient, semantic processing peaked at 400

ms with no corresponding activity for visual or phonological processing. The Talairach coordinates for this site were -50,23,11, similar to the coordinates used to locate the anterior VLPFC. For consonant strings, gamma activation in the VLPFC peaked at 500 ms and then gradually decreasing over 500 ms. It is notable that during passive reading, the left VLPFC peaks at nearly the same time as visual areas (130 vs 140 ms post-stimulus onset; fusiform gyrus/visual word form area) after the occipital gyrus (115 ms). There was increased power in the IFG compared to nonwords and faces within the 300-ms stimulus onset window. This pattern suggests that in visual word recognition, phonological and semantic processes begin early after perception (Cornelissen et al., 2009).

Burke and colleagues (2014) examined subsequent memory effects for high frequency (gamma; 44-100 Hz) EEG activity at specific times and regions during the presentation of each 1600-ms word. They found post-stimulus onset activity in primary visual and fusiform areas (0-500) and activation in the left ventrolateral temporal cortex (VLTC) and bilateral hippocampus (400-900 ms). In the later time window (800-1300 ms post-stimulus onset), the medial temporal lobes and visual cortices deactivated, while the left VLPFC and posterior parietal cortex activated and the left VLTC continued to be active until 100 ms post-stimulus offset. After stimulus offset, neocortical activation gradually decreased and only the VLTC remained active, with sustained activation until subsequent item presentation. The visual and fusiform cortices peaked at 500 ms together with the left parahippocampal area, followed by a peak in the left hippocampus (700 ms) and peaks in the left PPC and VLPFC at 1000 ms. The VLTC peaked shortly after, and the left PPC, VLPFC, VLTC, and hippocampus showed patterns toward another peak within 500 ms post-stimulus offset. Specifically, the left hippocampus showed sustained activity for the entire post-stimulus offset window, and the left VLTC showed a similar pattern of activation. Notably, VLPFC activity from 800-1700 ms predicted subsequent recollection, whereas activity in the post-stimulus offset cluster (1600-2100 ms) was weaker and

showed high-frequency activity decreases. Peak activation in the early cluster (posterior visual and medial temporal lobe regions) occurred at 500 ms post-stimulus onset, whereas peak activation in the late cluster (left IFG, PPC, and VLTC) occurred at 1100 ms post-stimulus onset. The VLPFC may exert top-down control over the left VLTC and PPC to modulate semantic and attentional processing, supporting the findings of previous studies that the VLPFC plays a role in control over encoding and regions associated with mnemonic information and attention (posterior areas).

Similarly, Long and Kahana (2015) found HFA increases predictive of successful recollection in the left VLPFC, left IT, and bilateral hippocampus. They used a similar task including the presentation of high-frequency nouns for 1600 ms and delayed free recall. They examined temporal clustering specifically and found early and late peaks in the VLPFC (~500 ms and 1000 ms post-stimulus onset) and hippocampus (~750 and 1300 ms post-stimulus onset), but there were differences in median peak between the VLPFC (600-700 ms) and hippocampus (900-1000 ms) but not the left IT (500-600 ms). It is interesting to note that clustering-related HFA was not found in the left VLPFC when pre-stimulus and post-stimulus activity were compared, but there was significantly greater post-stimulus HFA in the hippocampus, reflecting binding. Furthermore, there was a correlation between temporal clustering and hippocampal HFA in the peak time window (1300-1400 ms) that was most consistent across individuals. Thus, HFA was greater for temporally-clustered and recollected items compared to items that were recalled but not clustered. This indicates that late HFA hippocampal activity predicts clustering and associated recall. They suggested that the early HFA activity in the VLPFC reflected the retrieval of stored representations and associations to be bound in the hippocampus. Thus, the VLPFC engaged in item-memory processes (semantic, elaborative encoding; selection of item representations and semantic associations; controlled retrieval) that were necessary for item-context binding in the hippocampus, and VLPFC activation over time and interaction

with the hippocampus could determine successful item-context binding (including temporal or spatial context). It is interesting that they found that theta and gamma power predictive of recall in the VLPFC and hippocampus, but only gamma power predicted successful clustering. Although theta may be associated with hippocampal activation, temporal context and context manipulation, and long-term potentiation, theta-specific power changes in temporal clustering may have been obscured due to the general pattern of higher HFA and lower LFA in the subsequent memory effect. Contextual binding may involve theta-gamma coupling, and in line with context reinstatement theory, there could be an association between HFA and encoding-retrieval neural similarity.

Burke and colleagues (2013) compared post-stimulus onset changes in theta and gamma that predicted successful recall during the presentation of 1600-ms words (encoding). They found that larger increases in gamma and decreases in theta predicted successful recall. Although there were increases in gamma in the early time window (0-1000 ms post-stimulus onset) in the left VLPFC, only increases in the later time window (500-1500 ms post-stimulus onset) predicted successful recollection. The changes in theta did not appear to reach the VLPFC, and increases in surrounding regions did not predict successful recall. However, increases and decreases in theta synchrony predicted. Decreased intra-lobe theta synchrony in the frontal lobes accompanied the subsequent memory effect for the 1000-ms post-stimulus-onset time window at encoding. Notably, subsequent memory effects in the early time window (0-1000 ms) were accompanied by weak increases in theta synchrony, while strong decreases in theta synchrony were visible in the late time window (750-1750 ms post-stimulus onset). The early time window was accompanied by increases in theta synchrony that weakly but reliably predicted successful memory, while the late time window was accompanied by decreases in gamma connectivity that were not predictive of successful memory. The left PFC was the major region of theta synchrony in the network of regions associated with verbal encoding.

Overall, subsequent memory involved theta synchrony in posterior areas during the early time window, followed by strong theta synchrony selective to the left PFC, and lastly asynchronous LFA and HFA beginning in posterior areas and spreading to the left PFC.

Limitations and future directions. There were several methodological limitations of the study. There was no direct measure of the process in which participants were engaging. Future studies should include a task that measures the extent of binding, for example presenting sentences one word at a time or testing serial recall or recognition for order. In addition, it remains unclear whether rTMS at offset disrupted working memory in addition to long-term memory. The idea that the offset process reflects a transfer from working memory to long-term memory could be investigated by measuring working memory for half the items presented in the rTMS disruption condition and testing the remaining half with a long-term recognition test. Finally, there was a limited range of rTMS times of administration with respect to different word durations. The account that episodic binding depends on the termination of online processing and word offset should be tested with longer word durations (e.g. rTMS delivered at offset of a 1200-ms word). Furthermore, the distinction between online semantic processing and memory-specific offset processing should be further clarified with comparisons of rTMS disruption of language-focused and memory-focused tasks within the same experiment.

Conclusion. Galli and colleagues (2017) found memory impairments as a result of disruptions to online (1000 ms post-stimulus onset) and offline (100 ms post-stimulus offset) processing for incidental encoding of a 1000-ms word. Similarly, the current study found memory impairments after disruptions to online (1000 ms post-stimulus onset for a 1200-ms word) and offline (at the offset of a 1100-ms word) for intentional encoding. The use of different word durations permits the clarification of time-dependent vs offset-dependent processes, and the lack of effect for 1100 ms post-stimulus onset suggests that the process at 1100 ms is time- and offset-dependent and can last up to 100 ms. Thus,

disrupting activity between 0 and 100 ms post-stimulus offset for a word lasting 1100 ms should lead to a memory impairment (e.g. rTMS at the offset of a 1300-ms word, or rTMS 100-ms post-stimulus offset for a 1100-ms word). The current study seemed to suggest that rTMS disrupted an encoding process that began after 1000 ms but is also dependent on offset, supporting both explanations proposed by Galli and colleagues (2017). In line with previous intracranial EEG studies, the VLPFC may deactivate shortly after the offset, which may explain why previous fMRI studies did not find VLPFC activation in the post-stimulus time window (Ben-Yakov & Dudai, 2011). The left VLPFC appears to be engaged throughout the onset and offset period, as suggested by the current study and previous intracranial EEG studies showing multiple HFA peaks. Specifically, the left VLPFC could be engaged at early item identification, semantic elaboration at the middle time window, and selection of features for binding at the offset of the word. Thus, the current study proposed that at incidental encoding, semantic processing terminates quickly and leads to offset-dependent binding processes between the VLPFC and the hippocampus. On the other hand, at intentional encoding, online processing may continue up to 1000 ms, and interruption of this process leads to disruption of the memory trace. After online processing is complete (by 1100 ms), binding may be triggered by the offset of the item and occur through theta-gamma oscillations that represent interactions between the hippocampus and left VLPFC.

Chapter 8: General Discussion

Overview

The general discussion reviews the aims and major findings of the thesis: a meta-analysis and systematic review introduced the state of the field and important issues and questions; a set of five experiments and a meta-analysis specific to those experiments examined the effects of atDCS on episodic recognition when delivered over the VLPFC; and a final experiment investigated the nature of encoding processes in the VLPFC that could have been modulated by tDCS. Together, the findings address the aim of the thesis to uncover and explain the effects of neuromodulation on memory formation. In addition, the findings fit with contemporary theories of memory including the HERA model of lateralised function; levels of processing framework; cortical reinstatement theory; and prefrontal-hippocampal interactions via synchronised oscillations.

A revised model of function in the VLPFC is proposed, including a timeline of how the VLPFC interacts with other regions in memory processes across time. The VLPFC may engage in online and offline processes related to semantic elaboration and item-context binding, with the online process occurring during word presentation until 1100 ms in intentional encoding and the offset-dependent offline process occurring for 100 ms after the termination of online processes at 1100 ms. In turn, at retrieval the elaborative trace could be reactivated with corresponding sensory representations and the VLPFC could engage in controlled retrieval of the task-relevant representation from one or more options maintained in working memory.

A revised model of tDCS and TMS mechanisms is proposed, including how the mechanisms at the cellular level affect the network level. tDCS may affect semantic processing and binding through synaptic connections and gamma oscillations. TMS effects may not be as straightforward as evident from the literature, with TMS leading to memory impairment regardless of the parameters and task. TMS can lead to memory impairment or

facilitation depending on specific parameters (e.g. repetitive or single-pulse) and interaction with individual differences including anatomy and baseline neural activation. Low-frequency rTMS has been successful in facilitating neural function in animal studies (Huang et al., 2017), and an application to investigating memory function in the VLPFC is proposed. Future studies should examine the effects of inhibitory rTMS on the left VLPFC and could target the prefrontal-hippocampal pathway with optogenetic rTMS (Barnett, Perry, Dalrymple-Alford, & Parr-Brownlie, 2018;.Opris, 2017), increasing excitation in the excitatory pathways with continuous theta burst stimulation and inhibiting pathological synaptic activity through low-frequency rTMS in patients with Alzheimer's Disease.

Methodological limitations and future directions are discussed, including the lack of imaging data and the need for an examination of biomarkers following neuromodulation. In conclusion, the thesis provides a robust examination of atDCS effects over the VLPFC with a broader understanding of neuromodulation and the processes leading to memory formation. Moreover, these considerations can inform the application of atDCS to other higher-order cognitive functions including selective attention, language, and decision-making.

A Review of the Findings

Several important findings were unfolded through four chapters: Chapter 4 (systematic review and meta-analysis), Chapter 5 (five systematic experiments investigating the effects of tDCS timings of administration and a meta-analysis on the experiments within), Chapter 6 (Cognitive-theoretical explanations for effects found in Chapter 3), and Chapter 7 (Cognitive-neurobiological account of episodic processes in the VLPFC). Together, these experiments add vital information to the tDCS and episodic memory fields in terms of resolving methodological concerns, updating theories and models, and advancing the development of memory treatments. In addition, these

experiments developed an understanding of the VLPFC as an essential region in episodic memory and clarified the time course of encoding processes in the VLPFC.

The primary meta-analysis in Chapter 4 (atDCS vs sham in hits) revealed effects of anodal tDCS in both directions (impairments and enhancements) that were close to zero. Although the significant heterogeneity in atDCS effects on proportion of hits could be partially explained by retrieval task and stimulation duration, much of the heterogeneity remained unexplained, suggesting that a larger number of more systematic investigations must be included in a future meta-analysis to enable conclusions about tDCS effects. In addition, a secondary meta-analysis was conducted on the effects of multiple sessions of atDCS on memory accuracy in a small sample size ($k = 2$) and found significant positive effects. The finding suggested that future tDCS studies and meta-analyses should focus on the effects of atDCS at learning through multiple sessions of atDCS administration. Finally, the primary meta-analysis revealed publication bias in anodal tDCS effects on accuracy, suggesting a need for more unbiased, systematic, and rigorous research and a better understanding of tDCS as a research tool.

Chapter 5 also addressed the understanding of tDCS as a research tool by systematically examining the effect of timings of atDCS administration on episodic recognition when tDCS was delivered over the DLPFC (the predominant stimulation site in tDCS research) and the VLPFC (an under-represented and under-explored stimulation site). Experiments 1 and 2 demonstrated that when tDCS was delivered online and offline at encoding and retrieval over the VLPFC, only online encoding tDCS led to an effect on recognition performance. Specifically, online tDCS led to a decrease in the false alarm rate, whereas other tDCS groups showed high false alarm rates that reflected high semantic similarity and possibly interference. Moreover, Chapter 5 addressed some of the concerns of Chapter 4 in terms of methodological rigour, systematicity, and good research practice by conducting three systematic experiments to identify *when* tDCS can be effective and

replicating the effective condition in two experiments. The main findings included a significant but subtle enhancement of memory when tDCS was delivered *online encoding* over the VLPFC but not the DLPFC. No other timings of administration led to tDCS effects over the VLPFC. A closer examination of the significant effect showed that tDCS modulated the proportion of false alarms but not hits, leading to a decrease in false memory. The findings suggested that tDCS may lead to an increase in the distinctiveness of memorised items, leading to the distinctiveness effect at test: participants are able to better recognise the new words because unpresented words lack a distinctive memory trace. A successful replication was found in the same lab using the same stimuli, and an unsuccessful replication was found in a different lab using the same stimuli but translated into a different language. These results suggest that language may be an important factor for verbal memory replications, since the characteristics of the words within the stimulus set must be similar across experiments. In addition, the results highlight the importance of stimuli as parameters of tDCS-memory research: task and stimuli should be as consistent as possible between experiments, as evident from inconsistencies in previous work (Boggio et al., 2009; Chi, Fregni, & Snyder, 2010). Specifically, Experiments 1 and 3 revealed seemingly conflicting effects of online encoding over the VLPFC when delivered in an English-speaking sample and a Russian-speaking sample, respectively. However, the findings were reconciled by the hypothesis that the VLPFC engages in multiple different functions at encoding, and one of those functions is resolving semantic and phonological interference. The presence of semantic interference could have been resolved by the anterior VLPFC, and this possibly occurred in Experiment 1, as reflected in the generally high false alarm rate (representing semantic interference) but significantly lower false alarm rate in the VLPFC online encoding group. However, additional phonological interference could have engaged the posterior VLPFC and led to competing activation between the anterior and posterior VLPFC. Perhaps because of the large electrode size,

atDCS increased neuronal excitability in the posterior and anterior VLPFC in Experiment 1, but only the anterior VLPFC was active. Anterior VLPFC tDCS led to a state-dependent behavioural modulation, while the relatively-inactive posterior VLPFC did not interact with tDCS. Thus, in support of previous work, VLPFC activation does not always correlate with successful cognitive performance and subsequent recollection. Nonetheless, Experiments 1 and 3 provide support for the critical role of the VLPFC at encoding: an effect in both studies suggests that the VLPFC was actively engaged, and this engagement led to modulations of recognition accuracy. In addition, Experiment 3 demonstrated that offline encoding tDCS over the DLPFC led to the same impairment as online encoding tDCS over the VLPFC. This finding suggests that the DLPFC may play an indirect role in semantic encoding through interactions with the VLPFC. The DLPFC may not be involved directly, since there was no effect of online encoding tDCS on recognition. While the DLPFC may be engaged at encoding in control processes related to intentional encoding and may mediate functional connectivity with the VLPFC, perhaps this role is not as critical to memory formation as the role of the VLPFC. In fact, taken together with evidence from older adults, the study suggests that the DLPFC may serve as a compensatory mechanism for dysfunctional memory in other regions of the brain. Anodal tDCS can increase bilateral DLPFC activation, the neural signature for memory-related compensatory mechanisms, in older adults when delivered online (Di Rosa et al., 2019). While studies have implicated the VLPFC as a compensatory region as well, rTMS studies of VLPFC disruption demonstrate that the VLPFC may be necessary to memory formation in younger as well as older adults (Galli, Feurra, Pavone, Sirota, & Rossi, 2017).

Chapter 6 investigated the cognitive mechanisms whereby online encoding tDCS over the VLPFC lowered false recognition. Online encoding tDCS was delivered over the VLPFC during a false memory task (DRM), and engagement in item-specific vs relational encoding was measured, and no effect of tDCS was found on either of two false alarm

measures (new and lure). Specifically, Chapter 6 investigated the cognitive mechanisms of the tDCS effect found in the VLPFC using a false memory task by measuring the extent to which participants were creating associations between items (relational encoding) vs engaging distinctive, item-specific encoding. The results indicated that there were no differences between online encoding atDCS over the VLPFC and Sham in false alarms to new items or semantically-related distractors. However, an exploratory analysis comparing atDCS and sham including only the individuals who engaged in greater item-specific encoding found significantly more false alarms for atDCS compared to Sham.

Chapter 7 further examined encoding processes in the VLPFC by temporarily disrupting VLPFC encoding activity with rTMS. In addition, Chapter 7 aimed to identify the function in the VLPFC and associated time window that was crucial to memory formation. High-frequency rTMS was used to disrupt VLPFC function at different times with respect to stimulus onset and offset, and disruptive effects were found at specific times: at the offset of a 1100-ms word and 1000 post-stimulus onset. Thus, the results partially replicated and extended the findings of previous research that found critical memory-related VLPFC activity after 1000 ms post-stimulus onset and at the offset of a word (Burke et al., 2014; Galli, Feurra, Pavone, Sirota, & Rossi, 2017). The findings shed light on the multiple processes in which the VLPFC is differentially engaged during different tasks (working memory vs long-term intentional memory) and contribute to updating the model of memory formation in the VLPFC over time. Like Chapter 5 and Chapter 6, Chapter 7 provided evidence that the VLPFC engages in multiple different functions at different times, depending on the task. Thus, tDCS modulations and VLPFC processes depend on the nature of the encoding task. At working memory or incidental learning, the VLPFC appears to be engaged in more general semantic processing, while at intentional learning, the VLPFC may engage in contextual binding of items and their features and temporal binding of sequential items together with the hippocampus. The

findings suggested that there may be a time-dependent process and an offset-dependent process. At 1000 ms post-stimulus onset, the VLPFC may continue combining features of the item from the semantic network (i.e. meaning) that were activated in an earlier time window (400 ms post-stimulus onset), and at approximately 100 ms later, the VLPFC may exert top-down control over the hippocampus (which may already be active) to bind items and context. 1100 ms post-stimulus onset could be the impo7tant time interval irrespective of incidental or intentional encoding. The results of Chapter 7 suggest that the recognition impairment at the offset of a 1000-ms word in Galli and colleagues (2017) reflected a continuation of onset-based processing, whereas the disruption of the VLPFC at the offset of a 1100-ms word reflected the disruption of a process that was dependent on offset and time. Some studies have suggested that the VLPFC becomes active before the hippocampus and serves as an episodic buffer between short-term and long-term memory as it relays semantic information to the hippocampus. However, other studies have proposed that the VLPFC becomes active after the hippocampus and is engaged in control processes to mediate hippocampal binding of the information. Perhaps without top-down control by the VLPFC, the hippocampus would not bind the semantic features with the item appropriately, and the item would not be recollected as a distinct, episodic event. The VLPFC and hippocampus may be engaged in a particularly important process at the offset of an event, which could be considered a boundary between the current and subsequent item. This interaction could start at the offset of a word and continue for 100 ms after offset. Thus, Chapter 7 supports the observation that the VLPFC is engaged throughout the onset time window, initially generating semantic representations for the items and later modulating attentional and semantic processes and engaging in binding-related interactions with the hippocampus; these latter processes would be vital to encoding. Perhaps at 1000 ms, the VLPFC is at its peak activation in control processes during intentional encoding. Disrupting activity at this time window could be detrimental to some individuals but not

others because the critical time window is at 1100 ms post-stimulus onset, right before the VLPFC deactivates. Although hippocampal activation peaks well before this time window, VLPFC could exert control over the hippocampus and deactivate when this regulation is no longer needed. Thus, the VLPFC seems vital to the regulation of functions in other regions, such as attention in the PPC and language in the VLTL. In addition, the VLPFC appears to engage in particularly important processes with the hippocampus that may initiate *after* peak activation (in which the VLPFC may be mediating attention and language, which is associated with greater activation). As the VLPFC becomes less active, the memory transfers to the hippocampus and cannot be disrupted. Disrupting the VLPFC within 100 ms post-stimulus offset or 1100 ms post-stimulus onset would interfere with these processes.

In sum, the results demonstrate that while TMS remains a valuable tool for identifying the processes and neural generators of successful recollection, atDCS may not be the most effective tool for investigating episodic memory. The results reveal key aspects of conducting research with tDCS and TMS in terms of the advantages, limitations, and mechanisms of action. In addition, the results further an understanding of the temporal dynamics of episodic memory in the prefrontal cortex. Finally, the thesis continues to bridge the gap in the field between an understanding of neuromodulation and the cognitive mechanisms of its effects on behaviour.

Theoretical Contributions

The thesis addresses major cognitive and neurobiological theories of learning and memory, providing support for existing theories of episodic processes including encoding, storage, retrieval, and consolidation. Specifically, encoding includes perceptual, attentional, and elaborative processes, and storage may include a transfer from working memory to long-term memory. Retrieval involves a reinstatement of activity at encoding, including sensory representations of the event.

The DLPFC is engaged in the attentional processes at encoding, engaging top-down control over perception, while the VLPFC appears to be engaged in elaborative processes with control exerted over attention and language. The DLPFC and VLPFC interact with each other and with regions in the medial temporal lobe, including the hippocampus. The interaction of the PFC and the hippocampus leads to successful encoding and consolidation. Specifically, the VLPFC may be engaged in semantic elaboration, the transfer to long-term memory, and temporal associations between distinct items. Synapses can be strengthened between VLPFC neurons associated with the item's identity and pre-existing representations for the item. The VLPFC appears to be modality-independent in semantic elaboration, responding to auditory, verbal, and visual objects. In addition, the VLPFC may engage in material-independent control processes such as information maintenance, especially at retrieval. The elaborative processing in the VLPFC could lead to true and false memories, leading to a reinstatement of the semantic and sensory elaboration at retrieval as language and sensory areas are recruited. Thus, the VLPFC function informs theories of false memory that specify an activation of unpresented associations through elaboration.

In addition, the thesis supports hemisphere-specific models of the PFC that are based on the memory process (encoding or retrieval) and the nature of the material (verbal or non-verbal). Specifically, the left hemisphere may be preferentially engaged in encoding of verbal material, whereas the right hemisphere may be preferentially engaged for retrieval of non-verbal material (Opitz, Mecklinger, & Friederici, 2000; Nyberg, Cabeza, & Tulving, 1996; Wagner, Poldrack, Eldridge, Desmond, Glover, & Gabrieli, 1998). The thesis supports that the left hemisphere, specifically the VLPFC, may be critical for memory formation by contributing to semantic verbal processing at encoding. While the disruption of this process would not lead to clear memory impairments, it could weaken the strength of the memory. On the other hand, the VLPFC resembles other regions that

may involve more categorical rather than literal processing, and in certain cases (e.g. false memory paradigms), inhibition could be helpful.

The comparison of online and offline VLPFC processing suggests that semantic elaboration may not be the critical feature for memory formation; rather, the selection of item features for item-context binding in the hippocampus may be the necessary process, and this process occurs rapidly within 100 ms. Thus, the process may be easily modulated by temporally-specific rTMS but not tDCS, which exerts modulations over time. Together with evidence in other domains (working memory), the thesis proposes that the involvement of each hemisphere may be more graded, with the left hemisphere being more engaged with *semantic* material and more crucial to memory formation, although it may also be engaged for non-verbal material and at retrieval. Specifically, the thesis proposes that although the VLPFC is critical for linguistic processes, it may also be associated with material-independent elaboration (e.g. names and faces) and regulation of other regions (top-down control over emotion, language, attention).

The study found that offline processing (post-stimulus offset) contributed more to memory formation than online processing (during word presentation), also supported by previous rTMS studies that found no effects of online disruption. While this online processing may contribute to a stronger memory trace, it may not be necessary for successful memory formation. Thus, the online rather than offline processing could be modulated by tDCS because semantic elaboration is longer and occurs continuously throughout item presentation. An argument could be made that presenting words for longer at encoding with a more complicated task would lead to even greater modulations since tDCS functions across time. However, because the modulation is subtle, there would be no additional benefit of tDCS after processing reached maximal efficiency as suggested by Experiment 5 in Chapter 5, in which deeper encoding led to higher performance overall but no tDCS effects.

In this thesis, item memory was the focus of investigation rather than spatial or temporal components of episodic memory or autonoetic consciousness. However, the thesis provides support to existing work that has examined temporal, spatial, and semantic clustering in the VLPFC and DLPFC. The thesis advances these findings by identifying the critical time points for memory formation on a timescale of hundreds of milliseconds and providing evidence to support the existence of multiple roles in the VLPFC that lead to memory formation, whether directly or indirectly. In addition, language and consciousness are closely linked, so verbal memory was an ideal starting point of investigation. It can be assumed that autonoetic consciousness was engaged at least to some extent, although future studies can examine this issue in more detail by recording a participant's experience at encoding and asking the participant to recollect his or her engagement in the task (thoughts, feelings, actions) in addition to task-related information.

The thesis provides evidence of a function-process mapping across time, with the VLPFC shifting functions flexibly in response to varying task demands and time scales. Specifically, an updated model of the VLPFC is proposed in which the time course of memory processes and VLPFC-specific functions changes across tasks (intentional or incidental), depth of processing (shallow vs deep), and number of items (item or associative encoding). The activity and interactions that predict successful memory encoding can be mapped (Chapter 7), while other interactions can occur that do not predict encoding success (e.g. control processes that are active in accurate and false memory judgements). Future work should develop predictions about VLPFC interactions at retrieval that contribute to accurate memory judgements.

It is important to note that the early processes may overlap between intentional and incidental encoding, and the incidental encoding processes may have even stronger overlap with working memory processes. Specifically, VLPFC activation during working memory tasks resembles activation at incidental encoding tasks and at retrieval. The work posits

that verbal memory encoding predominantly involves interactions between areas specialising in perception (visual fusiform area), attention (left posterior parietal cortex), language (left VLTC), memory (hippocampus), and control (VLPFC). For example, at -750 to -250 ms pre-stimulus onset, the posterior inferior temporal region may be engaged in preparatory processes for intentional encoding (Burke et al., 2014). This pattern of activation is not visible in incidental encoding.

False Memory and Interference

Five experiments were conducted on the effect of atDCS on the VLPFC during semantic encoding. While the thesis could have benefitted from an examination of the neurobiological effects of tDCS, examining the conditions of the behavioural modulation could provide insight for an interpretation on both the cognitive and neurobiological level. The reduction in false alarms was evident in only one experiment and not the replication, was nearly identical except for larger sample size and longer inter-trial interval. However, the other two experiments differed in stimuli: Experiment 3 included a direct translation of the Experiment 1 word set in Russian, and Experiment 5 involved a set of semantically-related words adapted from the DRM false memory paradigm. The reversed effects in Experiment 3 (increased false alarms) and Experiment 4 (increased false alarms to lures) suggest that the stimuli influenced encoding processes in the VLPFC.

The thesis supports the theory that different tasks may rely on anatomically and functionally distinct processes. For example, shallow encoding could engage the posterior VLPFC, whereas deep encoding could engage the anterior VLPFC. Intentional and incidental encoding could engage the VLPFC, but with different degrees of activation and different time courses of activation. These tasks could lead to differences in neural activation, as evident in the effect of tDCS on intentional vs incidental tasks.

The thesis completes the picture of effects of neuromodulation over the VLPFC at every stage of encoding, suggesting that tDCS modulated ongoing semantic processing

during word presentation, whereas rTMS disrupted the essential offline process for memory formation: episodic binding with the hippocampus. Specifically, tDCS may have led to continuous subthreshold activation of VLPFC neurons, increasing their response to further input and enhancing their readiness to form synaptic connections that represent object features and underlie semantic associations that become long-term episodic traces. rTMS research demonstrated that disrupting this online process may not impair memory formation, but interrupting the subsequent process (perhaps feature selection for item-context binding in the hippocampus) disrupts memory. Thus, the VLPFC may be only partially relevant initially for object identification and elaborative processing through top-down control over attention (together with the DLPFC) and language, whereas the most critical role of the VLPFC arises later after the word is removed from the screen.

The effects of tDCS under different task conditions reveals important findings in VLPFC function and tDCS research. The reversed effects of tDCS in Experiments 3 (Chapter 5) and Chapter 6 indicate that increased elaboration facilitated by tDCS may have led to increased false memory, in line with existing theories and understanding of VLPFC activation during interference. Specifically, the greater role of the VLPFC in temporal compared to semantic clustering suggests that in Experiment 5, the order of the words in terms of association strength led to greater interference because of temporal proximity and semantic association. Thus, the VLPFC neurons could have formed multiple synaptic connections, including distinctive features for individual items but also equally strong associations with neighbouring units. At test, these connections could be reactivated and the VLPFC be forced to select between the competing representations. While the VLPFC is active during interference, the DLPFC may be the region associated with resolving the interference through cognitive control. The mechanisms of action for rTMS may be clearer, since multiple bursts of excitatory, high-frequency rTMS led to overactivation of the region and a subsequent inhibitory period that only lasted for the duration of the bursts.

Neural Activity in the PFC

Pre-stimulus onset, multiple regions, including the hippocampus and VLPFC, are engaged in preparatory processes such as anticipatory firing. These processes occur at the network level with synaptic changes in neuron populations. At perception, the PFC interacts with the posterior sensory areas to exert top-down control over perception through attention. Specifically, the PFC biases attention toward goal-relevant stimuli and achieves this through NMDA receptors. A feedback loop occurs whereby the PFC receives NMDA-receptor signals from the posterior parietal cortex and then biases posterior parietal cortex neuron firing so that glutamate binding occurs and leads to greater storage for the attended information (Raffone, Murre, & Wolters, 2003). Neurons in the VLPFC are differentially activated by different stimuli including vocalizations and faces (Romanski & Diehl, 2011), specifically learned rather than random vocalizations (Hage & Nieder, 2015). Specifically, there may be a graded pattern of material-specific function in the VLPFC: abstract vs literal representations can be spread from the mid-VLPFC to the anterior VLPFC (Blumenfeld & Ranganath, 2017).

At perception, PFC control neurons can exert top-down control on the firing rate of neuron populations in the posterior sensory areas that respond to input through NMDA synapses, which can increase the signal-to-noise ratio for the input selected by the PFC through glutamate binding for attended items (5-50 ms post-stimulus onset) and lead to greater storage. Being voltage-dependent, the signals generated by NMDA receptor activity are selectively activated in the presence of sensory input. Otherwise, as in the absence of NMDA receptors or the presence of NMDA antagonists, the spontaneous activity of unrelated neurons can spread through the PFC-posterior cortex feedback loop, leading to overactivity in the circuit and possibly unreliable sensory representations (hallucinations) and lower maintenance capacity (symptoms of schizophrenia).

In working memory after stimulus offset, sensory representations may be maintained through bidirectional pathways between the PFC and posterior sensory areas, and features of the item can be integrated through simultaneous synaptic firing and strengthening, and distinctions between objects is possible through inhibition of similar but irrelevant synapses. NMDA synapses are active during this process, particularly in biased attentional competition between sensory representations of items (Snyder, Banich, & Munakata, 2011).

At retrieval, VLPFC processes of selection may occur through inhibition, in which large neuron populations of competing representations inhibit each other, and the remaining strongest representation can be selected (Snyder, Banich, & Munakata, 2011). NMDA receptors can play a role in competitive inhibition through voltage-dependency processes: as part of the gain-control effect, they can increase the target signal and decrease noise by biasing inhibitory interneurons (Phillips & Silverstein, 2003). While NMDA receptors are present in all cortical regions but show increased densities in the hippocampus and PFC, and NMDA-receptor synapses can occur with pyramidal as well as inhibitory interneuron cells (Philips & Silverstein, 2003). In turn, NMDA receptors can affect selection and goal-relevant information maintenance within the visual working memory network.

The weaker representations may be activated more slowly and only reach the threshold for responding after more time to activate or increased activation (Snyder, Banich, & Munakata, 2011; for example, continuous activation of the entire network through stimulation). Continuous network stimulation can lead to an increase in signal-to-noise ratio by distinguishing better between strong and weak activations (Snyder, Banich, & Munakata, 2011). In line with this, GABA agonists can facilitate selection by increasing the activity of GABAergic interneurons that inhibit competing responses (Snyder, Banich, & Munakata, 2011). On the other hand, natural GABA antagonists such as anxiety can

lead to worse selection. It is important to note that selection is distinct from controlled retrieval, and effects on selection do not affect retrieval (Snyder, Banich, & Munakata, 2011). Thus, the VLPFC can be active at encoding in semantic selection processes that do not predict successful retrieval. For example, in generating verbs, the strength of synaptic connections between nouns and associated verbs determines the response in language tasks (Snyder, Banich, & Munakata, 2011). In addition, if the VLPFC fails in verbal selection or retrieval, other regions such as the pre-supplementary motor area (pre-SMA) can succeed in controlling these processes with top-down regulation (Snyder, Banich, & Munakata, 2011).

Limitations

A limitation of the experiments was the absence of a serial recall measure. The VLPFC may contribute to memory formation by temporally clustering serially-presented items, and tDCS may contribute to improvement in this process. In addition, there were several methodological limitations of this thesis that could be addressed in future studies: neuroimaging, computational modelling, and measuring biological markers were not conducted and would have been valuable for interpreting the results.

Simultaneous EEG recording at tDCS would help to elucidate the effects of tDCS on online processing as visible in spectral power. Specifically, tDCS cognitive and neurobiological effects could be tested in epilepsy patients using intracranial EEG. Existing studies have safely examined tDCS effects in epilepsy patients with implanted electrodes and simultaneously measured intracranial EEG. Lafon and colleagues (2017) measured transcranial alternating current stimulation (tACS)-induced entrainment during sleep in epilepsy patients with intracranial EEG with and found no effects of 0.75-1 Hz tACS over the left frontal and occipital poles on spindle activity and theta power during sleep. They were able to measure broadband frequency changes during stimulation. Opitz and colleagues (2016) successfully applied offline tACS for 2 min (5 x 5 cm^2 electrodes on

left and right temple with 1 Hz alternating current at 1 mA) in human epilepsy patients while recording intracranial EEG. In addition, studies have begun to examine biophysical markers of TES effects to account for factors involving skull conductance and changes in the electrical field based on region. Logothetis, Kayser, and Oeltermann (2007) investigated the measurement of electric field potentials and neuronal spiking activity (biomarkers of baseline neural activation) and found differences based on the neural process and the magnitude of the source signal rather than conductance of the neural tissue. In addition, they found small effects as a result of oscillatory stimulation but that slow oscillations spread over greater cortical distances than faster, high-frequency waves such as gamma. They suggested that slow oscillations involve large populations of neurons, compared to fast oscillations which could include concentrated clusters. Thus, neuromodulation could influence the continuous activity and neural state that is dependent on the task. Opitz and colleagues (2016) investigated this further by examining changes in the electrical field induced by tACS and found similar subtle effects, with no changes in phase shifts as a result of tACS. They found that it was important to account for differences in field strength that could be due to variation in skull thickness and head size.

Conclusions

Together, the results from the chapters point to the importance of task during episodic memory and tDCS research. While the VLPFC appears to be engaged in important roles in a variety of tasks (i.e. intentional *and* incidental, deep a*nd* shallow), the processes and associated timelines may differ based on task. Specifically, the VLPFC appears to be engaged in semantic processing early after the onset of a word in intentional and incidental tasks, but while this online processing may continue for longer in incidental tasks, intentional tasks may engage control processes before or during the offset of a word, and in both intentional and incidental tasks, binding could occur between 1000 and 1100 ms post-stimulus onset depending on the offset of the word, the amount of information

processed, and individual differences. In sum, online processing appears to continue until the offset of a word in incidental and intentional encoding. Selectively for intentional encoding, control processes on attention and language could peak at 1000 ms post-stimulus onset independent of the onset. In intentional and incidental encoding, binding processes be contingent on offset and occur within 100 ms after.

There appear to be multiple roles of the VLPFC *and* DLPFC, which could explain inconsistent findings of neuromodulation over the DLPFC. It is important to target the right process, which may depend on the task and whether the task elicits multiple processes simultaneously. For example, Chapter 6 suggests that item-specific and relational encoding could occur simultaneously, and effects of neuromodulation could be difficult to interpret because the target process is not isolated. The same logic for EEG experiments should be applied to NIBS experiments: one process should be isolated as much as possible at a specific point in time, particularly for rTMS effects that have high temporal specificity.

In addition, the findings provide a basis for standardisation of tDCS parameters in adjacent fields (working memory and language) that require further investigation of tDCS effects. The parameters from Experiment 1 have been replicated and modified across experiments, and the variations in findings demonstrate the importance of each parameter for studies over the VLPFC: 1) intentional, item-specific semantic task 2) online administration, with tDCS covering the entire duration of the task and 3) tDCS stimulation duration of at least ten min. Additional considerations specific for verbal experiments include consistent stimulus material that is matched in phonological and semantic characteristics. The replication of an effect in another paper may require implementing the same stimuli and instructions. The instructions may be critical to the success of a manipulation, and the results of another study could be replicated if the same materials are implemented. Thus, future research with tDCS should take care to follow more

standardised procedures to maximise an examination of neuromodulation. Moreover, certain parameters of tDCS should be standardised for all experiments on humans, regardless of the specific cognitive function or the neural measure implemented, for example delivering atDCS at 2 mA for 5 x 7 cm electrodes and adjusting the current strength for smaller electrodes to maintain the same current density.

tDCS may have greater relevance in research, particularly with biomarkers from neurobiology and neuroimaging that can reveal its subtle effects. The current work investigated the reliability of tDCS as a research tool and in the process established the reliability of a common assessment (recognition test) used to measure tDCS effects and changes in memory performance. The main findings were that atDCS showed subtle effects under certain conditions, but even when these conditions were replicated closely, the magnitude of the effect weakened. However, differences in atDCS effects across studies cannot be attributed to differences in language or flaws in the assessment of effects with a recognition test. Generalizability theory was applied for possibly the first time in episodic memory research to show that the recognition test was reliable in Russian and English (Experiment 3, Chapter 5). Moreover, Generalizability theory can be applied to any area of Psychology to measure the reliability of other cognitive tests (e.g. child creativity; Radzi, Nor, & Matore, 2018) and identify sources of error in measurement including time of day (Wong et al., 2018).

It remains unclear whether the enhancing effects of atDCS over the VLPFC in long-term verbal memory will be found in other laboratories, since there was a reversed effect when atDCS effects were examined with Russian speakers in a different lab. However, parameters were found that can enhance memory performance or at least show changes that are indicative of brain-behaviour relationships when the experimental design and parameters are similar.

tDCS appears to be advantageous for establishing causality between a cognitive function and activity in a certain region: after atDCS may indirectly increase neuron excitability and neural noise, the enhancement *or* impairment of cognitive performance is indicative of the necessary role of the stimulation site to the function. Paired with rTMS, tDCS can also be a valuable tool for exploring effects of cortical inhibition vs excitation. In line with previous research, tDCS can be applied before or after rTMS to measure interactions of weak offline vs online effects (tDCS) with strong effects (rTMS). Currently, tDCS and TMS are used separately in episodic memory research to provide corroborating, causal evidence about the role of different regions to different phases, including the VLPFC in encoding and PPC in retrieval. There could be further benefits to implementing tDCS and TMS together, as evident in the motor and visual domains (Antal, Kincses, Nitsche, & Paulus, 2003a; Antal, Kincses, Nitsche, & Paulus, 2003b; Cambieri, Scelzo, Voti, Priori, Accornero, & Inghilleri, 2012).

Further testing is needed to uncover how the facilitatory effects of atDCS can be translated to clinical outcomes for patients, particularly across multiple sessions, and whether the effects are long-lasting like previous studies that have found enhancement in cognition nearly a month later. Future research can consider examining the applicability of the current findings to clinical research by using structural MRI scans and neuronavigation systems to localise the stimulation site in each individual. Combining this approach with smaller electrodes or HD-tDCS to increase focality can lead to more consistent beneficial outcomes because of increased precision. The current work suggests that individual differences are an important consideration and atDCS may exert larger effects for individuals with weaker baseline memory performance (Exploratory Correlations, Chapter 5), including older adults and patients with mild cognitive impairment. Studies can also focus on effects at the neuron level in humans by measuring neurochemical changes in GABA and glutamate with proton spectroscopy (Patel, Romanzetti, Pellicano, Nitsche,

Reetz, & Binkofski, 2019) to better understand the mechanisms of tDCS effects, which can help in developing more effective treatments.

As a clinical tool, tDCS may be potentially applied to more malleable aspects of memory such as learning in multiple sessions. This proposal is supported by a growing number of multiple-session studies on learning that show subtle facilitatory effects of atDCS across sessions. In addition, recent meta-analysis (Simonsmeier et al., 2018) supported the role of atDCS and other non-invasive stimulation methods in enhancing learning. Generalizability theory can also be applied to testing tDCS in clinical populations by removing error due to individual differences including type of lesion, level of impairment, or progression of disorder (Medvedev, Theadom, Barker-Collo, Feigin, & BIONIC Research Group; Siegert, Medvedev, & Turner-Stokes, 2018). However, unless tDCS can overcome issues of non-linearity, transience, and variability in effects as evident in research, pharmacological treatments and invasive brain stimulation may remain the most promising avenues for clinical testing with the aim of application to patients. TMS can also be a promising avenue for clinical research if inhibitory pathways can be stimulated in a way that leads to beneficial neurophysiological or cognitive outcomes or if excitatory pathways can be targeted specifically without the collateral stimulation of inhibitory pathways.

Studying episodic memory is extremely relevant to a variety of domains: diagnosing and treating patients; developing neuropsychological measures; and designing tests for educational settings and students with learning disabilities. If informed by current memory research, the work of these domains could be greatly improved. Memory is a critical concern for domains in which lives are at stake, such as medicine and skilled labour including flight. There is a possibility that neuromodulation could also improve the lives of healthy younger and older adults by facilitating learning with a variety of verbal material: medical knowledge, foreign language vocabulary, job-related protocols, and

acting scripts. Although such a far-reaching application requires further research, it is not far from sight. New means of increasing synaptic plasticity must be developed, particularly to reduce costly errors in fields such as medicine and to improve the quality of life for older adults and patients. Thus, future research should continue developing atDCS and rTMS as tools for cognitive and clinical settings whilst taking into account the scope and limitations of each.

References

Abel, T., & Lattal, K. M. (2001). Molecular mechanisms of memory acquisition, consolidation and retrieval. *Current Opinion in Neurobiology, 11*, 180-187.

Achim, A. M., & Lepage, M. (2005). Dorsolateral prefrontal cortex involvement in memory post-retrieval monitoring revealed in both item and associative recognition tests. *Neuroimage, 24*, 1113-1121.

Addis, D. R., & McAndrews, M. P. (2006). Prefrontal and hippocampal contributions to the generation and binding of semantic associations during successful encoding. *Neuroimage, 33*, 1194-1206.

Amassian, V. E., Cracco, R. Q., Maccabee, P. J., Cracco, J. B., Rudell, A., & Eberle, L. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 74*, 458-462.

Amassian, V. E., Eberle, L., Maccabee, P. J., & Cracco, R. Q. (1992). Modelling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: the significance of fiber bending in excitation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 85*, 291-301.

Ammann, C., Lindquist, M. A., & Celnik, P. A. (2017). Response variability of different anodal transcranial direct current stimulation intensities across multiple sessions. *Brain Stimulation, 10*, 757-763.

Ambrus, G. G., Al-Moyed, H., Chaieb, L., Sarp, L., Antal, A., & Paulus, W. (2012). The fade-in–short stimulation–fade out approach to sham tDCS–reliable at 1 mA for naive and experienced subjects, but not investigators. *Brain Stimulation, 5*, 499-504.

Anderson, B. S., Kavanagh, K., Borckardt, J. J., Nahas, Z. H., Kose, S., Lisanby, S. H., ... & George, M. S. (2009). Decreasing procedural pain over time of left prefrontal rTMS for

depression: initial results from the open-label phase of a multisite trial (OPT-TMS). *Brain Stimulation, 2,* 88-92.

Anderson, M. C., & Weaver, C. (2009). Inhibitory control over action and memory. *The New Encyclopedia of Neuroscience*, 153-163.

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., ... & Fregni, F. (2017). Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology, 128*, 1774-1809.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003a). Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. *Neuropsychologia, 41*, 1802-1807.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003b). Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Experimental Brain Research, 150*, 375-378.

Antal, A., Kincses, T. Z., Nitsche, M. A., Bartfai, O., & Paulus, W. (2004). Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Investigative Ophthalmology & Visual Science, 45*, 702-707.

Antal, A., Nitsche, M. A., Kincses, T. Z., Kruse, W., Hoffmann, K. P., & Paulus, W. (2004a). Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. *European Journal of Neuroscience, 19*, 2888-2892.

Antal, A., Nitsche, M. A., Kruse, W., Kincses, T. Z., Hoffmann, K. P., & Paulus, W. (2004b). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of Cognitive Neuroscience, 16,* 521-527.

Antal, A., Nitsche, M. A., & Paulus, W. (2001). External modulation of visual perception in humans. *Neuroreport, 12*, 3553-3555.

Antal, A., Nitsche, M. A., & Paulus, W. (2006). Transcranial direct current stimulation and the visual cortex. *Brain Research Bulletin, 68,* 459-463.

Antal, A., & Paulus, W. (2011). A case of refractory orofacial pain treated by transcranial direct current stimulation applied over hand motor area in combination with NMDA agonist drug intake. *Brain Stimulation, 4,* 117-121.

Antal, A., Paulus, W., & Nitsche, M. A. (2009). Principle and mechanisms of transcranial direct current stimulation (tDCS). *Journal of Pain Management, 2,* 249-258.

Antal, A., Polanía, R., Schmidt-Samoa, C., Dechent, P., & Paulus, W. (2011). Transcranial direct current stimulation over the primary motor cortex during fMRI. *Neuroimage, 55,* 590-596.

Antal, A., Varga, E. T., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2004). Oscillatory brain activity and transcranial direct current stimulation in humans. *Neuroreport, 15,* 1307-1310.

Anwyl, R. (1999). Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Research Reviews, 29,* 83-120.

Atallah, B. V., and Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron, 62,* 566–577. doi: 10.1016/j.neuron.2009.04.027

Atilgan, H. (2013). Sample Size for Estimation of G and Phi Coefficients in Generalizability Theory. *Eurasian Journal of Educational Research, 51,* 215-227.

Atkins, A. S., & Reuter-Lorenz, P. A. (2011). Neural mechanisms of semantic interference and false recognition in short-term memory. *Neuroimage, 56,* 1726-1734.

Baddeley, A. D. (2001). Is working memory still working?. *American Psychologist, 56,* 851.

Baddeley, A. (2003). Working memory: looking back and looking forward. *Nature Reviews Neuroscience, 4,* 829-839.

Baddeley, A. D., & Patterson, K. (1971). The relation between long-term and short-term memory. *British Medical Bulletin, 27,* 237-242.

Baddeley, A. D., Thomson, N., & Buchanan, M. (1975). Word length and the structure of short-term memory. *Journal of Verbal Learning and Verbal Behavior, 14,* 575-589.

Badre, D. (2008). Cognitive control, hierarchy, and the rostro–caudal organization of the frontal lobes. *Trends in Cognitive Sciences, 12,* 193-200.

Badre, D., & Wagner, A.D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia, 45,* 2883-2901.

Balconi, M. (2013). Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques. *Neuroscience Bulletin, 29,* 381-389.

Balconi, M., & Ferrari, C. (2012). Emotional memory retrieval. rTMS stimulation on left DLPFC increases the positive memories. *Brain Imaging and Behavior, 6,* 454-461.

Balzarotti, S., & Colombo, B. (2016). Effects of unilateral transcranial direct current stimulation of left prefrontal cortex on processing and memory of emotional visual stimuli. *PloS One, 11,* e0159555.

Banerjee, J., Sorrell, M. E., Celnik, P. A., & Pelled, G. (2017). Immediate effects of repetitive magnetic stimulation on single cortical pyramidal neurons. *PloS One, 12,* e0170528.

Barnett, S. C., Perry, B. A. L., Dalrymple-Alford, J. C., & Parr-Brownlie, L. C. (2018). Optogenetic stimulation: Understanding memory and treating deficits. *Hippocampus, 28,* 457-470.

Bartrés-Faz, D., Rossi, S., & Pascual-Leone, A. (2016). Editorial: NIBS and plasticity changes in aging. *Frontiers in Aging Neuroscience, 8,* 96.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of Physiology, 591,* 1987-2000.

Baudewig, J., Nitsche, M. A., Paulus, W., & Frahm, J. (2001). Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. *Magnetic Resonance in Medicine, 45,* 196-201.

Bauer, J., Magg, S., & Wermter, S. (2015). Attention modeled as information in learning multisensory integration. *Neural Networks, 65,* 44-52.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *The Lancet, 325,* 1106-1107.

Barsalou, L. W. (2003). Situated simulation in the human conceptual system. *Language and Cognitive Processes, 18,* 513-562.

Barsalou, L. W. (2008). Grounded cognition. *Annual Reviews in Psychology, 59,* 617-645.

Bartolomeo, P., Thiebaut De Schotten, M., & Chica, A. B. (2012). Brain networks of visuospatial attention and their disruption in visual neglect. *Frontiers in Human Neuroscience, 6,* 110.

Bastin, C., & Van der Linden, M. (2005). Memory for temporal context: Effects of ageing, encoding instructions, and retrieval strategies. *Memory, 13,* 95-109.

Bennabi, D., Pedron, S., Haffen, E., Monnin, J., Peterschmitt, Y., & Van Waes, V. (2014). Transcranial direct current stimulation for memory enhancement: from clinical research to animal models. *Frontiers in Systems Neuroscience, 8,* 159.

Benwell, C. S., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: evidence from biparietal tDCS influence on lateralized attention bias. *Cortex, 69,* 152-165.

Ben-Yakov, A., & Dudai, Y. (2011). Constructing realistic engrams: poststimulus activity of hippocampus and dorsal striatum predicts subsequent episodic memory. *Journal of Neuroscience, 31,* 9032-9042.

Berryhill, M. E., & Jones, K. T. (2012). tDCS selectively improves working memory in older adults with more education. *Neuroscience Letters, 521,* 148-151.

Berryhill, M. E., Peterson, D. J., Jones, K. T., & Stephens, J. A. (2014). Hits and misses: leveraging tDCS to advance cognitive research. *Frontiers in Psychology, 5,* 800.

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., & Jefferys, J. G. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *The Journal of Physiology, 557,* 175-190.

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., ... & Brunoni, A. R. (2016). Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimulation, 9,* 641-661.

Bikson, M., Rahman, A., & Datta, A. (2012). Computational models of transcranial direct current stimulation. *Clinical EEG and Neuroscience, 43,* 176-183.

Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends in Cognitive Sciences, 15,* 527-536.

Bindman, L. J., Lippold, O. C. J., & Redfearn, J. W. Tc. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *The Journal of Physiology, 172,* 369-382.

Bjork, R. A., & Whitten, W. B. (1974). Recency-sensitive retrieval processes in long-term free recall. *Cognitive Psychology, 6,* 173-189.

Bloch, R., & Norman, G. (2012). Generalizability theory for the perplexed: a practical introduction and guide: AMEE Guide No. 68. *Medical Teacher, 34,* 960-992.

Blumenfeld, R. S., Lee, T. G., & D'Esposito, M. (2014). The effects of lateral prefrontal transcranial magnetic stimulation on item memory encoding. *Neuropsychologia, 53,* 197-202.

Blumenfeld, R. S., & Ranganath, C. (2006). Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *Journal of Neuroscience, 26*, 916-925.

Blumenfeld, R. S., & Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *The Neuroscientist, 13*, 280-291.

Blumenfeld, R. S., & Ranganath, C. (2017). Prefrontal cortex and human memory: An integrated account from the cognitive neuroscience of working and long-term memory. In J.H. Byrne, *Learning and memory: a comprehensive reference* (pp. 275-293). Amsterdam: Academic Press.

Bocchio, M., Nabavi, S., & Capogna, M. (2017). Synaptic plasticity, engrams, and network oscillations in amygdala circuits for storage and retrieval of emotional memories. *Neuron, 94,* 731-743.

Boggio, P. S., Fregni, F., Valasek, C., Ellwood, S., Chi, R., Gallate, J., ... & Snyder, A. (2009). Temporal lobe cortical electrical stimulation during the encoding and retrieval phase reduces false memories. *PloS one, 4,* e4959.

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology, 11*, 249-254.

Bohning, D. E., Shastri, A., Wassermann, E. M., Ziemann, U., Lorberbaum, J. P., Nahas, Z., ... & George, M. S. (2000). BOLD-f MRI response to single-pulse transcranial magnetic stimulation (TMS). *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine, 11*, 569-574.

Bonaiuto, J. J., & Bestmann, S. (2015). Understanding the nonlinear physiological and behavioral effects of tDCS through computational neurostimulation. In S. Bestmann,

Progress in brain research: Computational neurostimulation (Vol. 222, pp. 75-103). Amsterdam: Elsevier.

Borenstein, M., Hedges, L. V., Higgins, P. T., & Rothstein, H. R. (2009). *Introduction to meta-analysis*. Chichester: John Wiley & Sons, Ltd.

Botzung, A., Denkova, E., & Manning, L. (2008). Experiencing past and future personal events: Functional neuroimaging evidence on the neural bases of mental time travel. *Brain and Cognition, 66*, 202-212.

Bradshaw, G. L., & Anderson, J. R. (1982). Elaborative encoding as an explanation of levels of processing. *Journal of Verbal Learning and Verbal Behavior, 21*, 165-174.

Brainerd, C. J., & Reyna, V. F. (1998). When things that never happened are easier to remember than things that did. *Psychological Science, 9*, 484-489.

Brem, A. K., Ran, K., & Pascual-Leone, A. (2013). Learning and memory. *Handbook of Clinical Neurology, 116*, 693-737.

Broadbent, D. E. (1957). A mechanical model for human attention and immediate memory. *Psychological Review, 64*, 205-215. doi: http://dx.doi.org/10.1037/h0047313

Brown, J., Lewis, V. J., & Monk, A. F. (1977). Memorability, word frequency and negative recognition. *The Quarterly Journal of Experimental Psychology, 29*, 461-473.

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with NIBS of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain and Cognition, 86*, 1-9.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Wagner, A. D., & Rosen, B. R. (1998). Functional–anatomic study of episodic retrieval using fMRI: I. Retrieval effort versus retrieval success. *Neuroimage, 7*, 151-162.

Burke, J. F., Long, N. M., Zaghloul, K. A., Sharan, A. D., Sperling, M. R., & Kahana, M. J. (2014). Human intracranial high-frequency activity maps episodic memory formation in space and time. *Neuroimage, 85*, 834-843.

Burke, J. F., Zaghloul, K. A., Jacobs, J., Williams, R. B., Sperling, M. R., Sharan, A. D., & Kahana, M. J. (2013). Synchronous and asynchronous theta and gamma activity during episodic memory formation. *Journal of Neuroscience, 33,* 292-304.

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14,* 365-376.

Burgess, N., & Hitch, G. (2005). Computational models of working memory: putting long-term memory into context. *Trends in Cognitive Sciences, 9,* 535-541.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychology and Aging, 17,* 85-100.

Cabeza, R., Prince, S. E., Daselaar, S. M., Greenberg, D. L., Budde, M., Dolcos, F., ... & Rubin, D. C. (2004). Brain activity during episodic retrieval of autobiographical and laboratory events: an fMRI study using a novel photo paradigm. *Journal of Cognitive Neuroscience, 16,* 1583-1594.

Cadavid, S., & Beato, M. S. (2017). False recognition in DRM lists with low association: A normative study. *Psicologica: International Journal of Methodology and Experimental Psychology, 38,* 133-147.

Cambieri, C., Scelzo, E., Voti, P. L., Priori, A., Accornero, N., & Inghilleri, M. (2012). Transcranial direct current stimulation modulates motor responses evoked by repetitive transcranial magnetic stimulation. *Neuroscience Letters, 522,* 167-171.

Cantone, M., Di Pino, G., Capone, F., Piombo, M., Chiarello, D., Cheeran, B., ... & Di Lazzaro, V. (2014). The contribution of transcranial magnetic stimulation in the diagnosis and in the management of dementia. *Clinical Neurophysiology, 125,* 1509-1532.

Centeno, M., Thompson, P. J., Koepp, M. J., Helmstaedter, C., & Duncan, J. S. (2010). Memory in frontal lobe epilepsy. *Epilepsy Research, 91,* 123-132.

Cesario, J. (2014). Priming, replication, and the hardest science. *Perspectives on Psychological Science, 9*, 40-48.

Cheke, L. G., & Clayton, N. S. (2013). Do different tests of episodic memory produce consistent results in human adults?. *Learning & Memory, 20,* 491-498.

Cheke, L. G., & Clayton, N. S. (2015). The six blind men and the elephant: Are episodic memory tasks tests of different things or different tests of the same thing?. *Journal of Experimental Child Psychology, 137,* 164-171.

Chen, H. Y., Gilmore, A. W., Nelson, S. M., & McDermott, K. B. (2017). Are there multiple kinds of episodic memory? An fMRI investigation comparing autobiographical and recognition memory tasks. *Journal of Neuroscience,* 1534-16.

Chen, N. F., Lo, C. M., Liu, T. L., & Cheng, S. K. (2016). Source memory performance is modulated by transcranial direct current stimulation over the left posterior parietal cortex. *NeuroImage, 139,* 462-469.

Chi, R. P., Fregni, F., & Snyder, A. W. (2010). Visual memory improved by NIBS. *Brain Research, 1353,* 168-175.

Clark D., & Wagner, A.D. (2003). Assembling and encoding word representations: fMRI subsequent memory effects implicate a role for phonological control. *Neuropsychologia, 41,* 304–317.

Classen, J., Liepert, J., Wise, S. P., Hallett, M., & Cohen, L. G. (1998). Rapid plasticity of human cortical movement representation induced by practice. *Journal of Neurophysiology, 79,* 1117-1123.

Coane, J. H., McBride, D. M., Raulerson III, B. A., & Jordan, J. S. (2007). False memory in a short-term memory task. *Experimental Psychology, 54,* 62-70.

Cohen, G. (2008). The study of everyday memory. In G. Cohen & M.A. Conway (Eds.), *Memory in the real world* (3rd ed, pp. 1-20). Hove, England: Psychology Press.

Cohen, M. E., & Carr, W. (1975). *Facial recognition and the von Restorff effect. Bulletin of the Psychonomic Society, 6,* 383-384.

Coltheart, M. (1981). The MRC psycholinguistic database. *The Quarterly Journal of Experimental Psychology Section A, 33,* 497-505.

Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in HM. *Seminars in Neurology, 4,* 249-259.

Coussens, C. M., Kerr, D. S., & Abraham, W. C. (1997). Glucocorticoid receptor activation lowers the threshold for NMDA-receptor-dependent homosynaptic long-term depression in the hippocampus through activation of voltage-dependent calcium channels. *Journal of Neurophysiology, 78,* 1-9.

Cowan, N. (1984). On short and long auditory stores. *Psychological Bulletin, 96,* 341.

Cowan, N. (1995). *Oxford psychology series, No. 26. Attention and memory: An integrated framework.* New York, NY, US: Oxford University Press.

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society of London B, 302,* 341-359.

Craik, F. I., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior, 11,* 671-684.

Craik, F. I., & Tulving, E. (1975). Depth of processing and the retention of words in episodic memory. *Journal of Experimental Psychology: General, 104,* 268-294.

Craik, F. I., & Rose, N. S. (2012). Memory encoding and aging: a neurocognitive perspective. *Neuroscience & Biobehavioral Reviews, 36,* 1729-1739.

Cronbach, L. J. (1967). *The dependability of behavioral measurements: Multifacet studies of generalizability.* Stanford, CA: Stanford University Press.

Cruse, D., & Wilding, E. L. (2009). Prefrontal cortex contributions to episodic retrieval monitoring and evaluation. *Neuropsychologia, 47,* 2779-2789.

Curran, T. (2000). Brain potentials of recollection and familiarity. *Memory and Cognition, 28,* 923-938.

Curran, T., Schacter, D. L., Johnson, M. K., & Spinks, R. (2001). Brain potentials reflect behavioral differences in true and false recognition. *Journal of Cognitive Neuroscience, 13,* 201-216.

Dark, V. J., & Loftus, G. R. (1976). The role of rehearsal in long-term memory performance. *Journal of Memory and Language, 15,* 479.

Das, S., Holland, P., Frens, M. A., & Donchin, O. (2016). Impact of transcranial direct current stimulation (tDCS) on neuronal functions. *Frontiers in Neuroscience, 10,* 550.

Daselaar, S. M., Veltman, D. J., Rombouts, S. A., Raaijmakers, J. G., & Jonker, C. (2003). Deep processing activates the medial temporal lobe in young but not in old adults. *Neurobiology of Aging, 24,* 1005-1011.

DaSilva, A. F., Volz, M. S., Bikson, M., & Fregni, F. (2011). Electrode positioning and montage in transcranial direct current stimulation. *JoVE (Journal of Visualized Experiments), 51,* e2744.

Davis, M. (2011). NMDA receptors and fear extinction: implications for cognitive behavioral therapy. *Dialogues in Clinical Neuroscience, 13,* 463-474.

Davis, N. J., & Koningsbruggen, M. V. (2013). "Non-invasive" brain stimulation is not non-invasive. *Frontiers in Systems Neuroscience, 7,* 76.

Day, B. L., Thompson, P. D., Dick, J. P., Nakashima, K., & Marsden, C. D. (1987). Different sites of action of electrical and magnetic stimulation of the human brain. *Neuroscience Letters, 75,* 101-106.

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimulation, 9,* 501-517.

Deese, J. (1959). On the prediction of occurrence of particular verbal intrusions in immediate recall. *Journal of Experimental Psychology, 58,* 17-22. doi: http://dx.doi.org/10.1037/h0046671

De Lara, G. A. D., Knechtges, P. N., Paulus, W., & Antal, A. (2017). Anodal tDCS over the left DLPFC did not affect the encoding and retrieval of verbal declarative information. *Frontiers in Neuroscience, 11,* 452.

Del Caño, G.G. (2004). Human brain, lateral view. Retrieved from https://www.flickr.com/photos/euskalanato/1971828859

Dewhurst, S. A., & Anderson, S. J. (1999). Effects of exact and category repetition in true and false recognition memory. *Memory & Cognition, 27,* 665-673.

Dewhurst, S. A., Bould, E., Knott, L. M., & Thorley, C. (2009). The roles of encoding and retrieval processes in associative and categorical memory illusions. *Journal of Memory and Language, 60,* 154-164.

Díez, E., Gómez-Ariza, C. J., Díez-Álamo, A. M., Alonso, M. A., & Fernandez, A. (2017). Encoding/retrieval dissociation of false recognition with transcranial direct current stimulation (tDCS) of the left temporal lobe. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 10,* 372.

Di Lazzaro, V., Dileone, M., Capone, F., Pellegrino, G., Ranieri, F., Musumeci, G., ... & Fregni, F. (2014). Immediate and late modulation of interhemipheric imbalance with bilateral transcranial direct current stimulation in acute stroke. *Brain Stimulation, 7,* 841-848.

Di Rosa, E., Brigadoi, S., Mapelli, D., Cutini, S., Tarantino, V., Dell'Acqua, R., ... & Vallesi, A. (2019). Behavioral and hemodynamic effects of prefrontal anodal stimulation in healthy older adults: A simultaneous tDCS-fNIRS study. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 12,* 472.

Dodson, C. S., & Schacter, D. L. (2001). "If I had said it I would have remembered it: Reducing false memories with a distinctiveness heuristic. *Psychonomic Bulletin & Review, 8,* 155-161.

Dodson, C. S., & Schacter, D. L. (2002). When false recognition meets metacognition: The distinctiveness heuristic. *Journal of Memory and Language, 46,* 782-803.

Droege, Paula. (2013). Memory and consciousness. *Philosophia Scientiæ, 17, 171-193.*

DuBrow, S., & Davachi, L. (2016). Temporal binding within and across events. *Neurobiology of Learning and Memory, 134,* 107-114.

Duncan, N. W., Wiebking, C., & Northoff, G. (2014). Associations of regional GABA and glutamate with intrinsic and extrinsic neural activity in humans—a review of multimodal imaging studies. *Neuroscience & Biobehavioral Reviews, 47,* 36-52.

Düzel, E., Yonelinas, A. P., Mangun, G. R., Heinze, H. J., & Tulving, E. (1997). Event-related brain potential correlates of two states of conscious awareness in memory. *Proceedings of the National Academy of Sciences, 94,* 5973-5978.

Eichenbaum, H. (2016). Still searching for the engram. *Learning & Behavior, 44,* 209-222.

Ekuni, R., Vaz, L. J., & Bueno, O. F. A. (2011). Levels of processing: The evolution of a framework. *Psychology & Neuroscience, 4,* 333-339.

Einstein, G. O., & McDaniel, M. A. (1987). Distinctiveness and the mnemonic benefits of bizarre imagery. In M. A. McDaniel & M. Pressley (Eds.), *Imagery and related mnemonic processes* (pp. 78-102). New York, NY: Springer.

Elder, W., & Miles, A. (1902). Meeting IV.—January 15, 1902: A Case of Tumour of the Left Prefrontal Lobe Removed by Operation. *Transactions of Medico-Chirurgical Society of Edinburgh, 21,* 81-92.

Elmer, S., Burkard, M., Renz, B., Meyer, M., & Jancke, L. (2009). Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. *Behavioral and Brain Functions, 5, 29.*

Epstein, C. M., Sekino, M., Yamaguchi, K., Kamiya, S., & Ueno, S. (2002). Asymmetries of prefrontal cortex in human episodic memory: effects of transcranial magnetic stimulation on learning abstract patterns. *Neuroscience Letters, 320*, 5-8.

Erk, S., Spottke, A., Meisen, A., Wagner, M., Walter, H., & Jessen, F. (2011). Evidence of neuronal compensation during episodic memory in subjective memory impairment. *Archives of General Psychiatry, 68*, 845-852.

Ester, E. F., Sprague, T. C., & Serences, J. T. (2015). Parietal and frontal cortex encode stimulus-specific mnemonic representations during visual working memory. *Neuron, 87*, 893-905.

Evrard, C., Gilet, A. L., Colombel, F., Dufermont, E., & Corson, Y. (2018). Now you make false memories; now you do not: the order of presentation of words in DRM lists influences the production of the critical lure in Alzheimer's disease. *Psychological Research, 82*, 429-438.

Eysenck, M.W., & Keane, M.T. (2010). *Cognitive Psychology: A Student's Handbook* (6th ed;pp. 205-323). East Sussex, England: Psychology Press.

Ezzyat, Y., & Davachi, L. (2011). What constitutes an episode in episodic memory?. *Psychological Science, 22*, 243-252.

Farrell, S. (2012). Temporal clustering and sequencing in short-term memory and episodic memory. *Psychological Review, 119*, 223-271. doi: http://dx.doi.org/10.1037/a0027371

Fairfield, B., & Mammarella, N. (2009). The role of cognitive operations in reality monitoring: a study with healthy older adults and Alzheimer's-type dementia. *The Journal of General Psychology, 136*, 21-40.

Filmer, H. L., Dux, P. E., & Mattingley, J. B. (2014). Applications of transcranial direct current stimulation for understanding brain function. *Trends in Neurosciences, 37*, 742-753.

Filmer, H. L., Ehrhardt, S. E., Bollmann, S., Mattingley, J. B., & Dux, P. E. (2019). Accounting for individual differences in the response to tDCS with baseline levels of neurochemical excitability. *Cortex, 115,* 324-334.

Fletcher, P. C., & Henson, R. N. A. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain, 124,* 849-881.

Fletcher, P. C., Shallice, T., & Dolan, R. J. (2000). "Sculpting the response space"—an account of left prefrontal activation at encoding. *Neuroimage, 12,* 404-417.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain: a Journal of Neurology, 12,* 1249-1256.

Flöel, A., Poeppel, D., Buffalo, E. A., Braun, A., Wu, C. W. H., Seo, H. J., ... & Cohen, L. G. (2004). Prefrontal cortex asymmetry for memory encoding of words and abstract shapes. *Cerebral Cortex, 14*, 404-409.

Foerde, K., Knowlton, B. J., & Poldrack, R. A. (2006). Modulation of competing memory systems by distraction. *Proceedings of the National Academy of Sciences, 103,* 11778-11783.

Foerster, A., Schmitz, J. M., Nouri, S., & Claus, D. (1997). Safety of rapid-rate transcranial magnetic stimulation: heart rate and blood pressure changes. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 104,* 207-212.

Ford, J. H., & Kensinger, E. A. (2017). Age-by-Emotion Interactions in Memory Retrieval Processes: An Event-Related Potential Study. *The Journals of Gerontology: Series B, 00,* gbx098. doi: https://doi.org/10.1093/geronb/gbx098.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience, 6*, 119-130.

Franzen, M. D., & Wilhelm, K. L. (1996). Conceptual foundations of ecological validity in neuropsychological assessment. In R. J. Sbordone & C. J. Long (Eds.), *Ecological*

validity of neuropsychological testing (pp. 91-112). Delray Beach, FL, England: Gr Press/St Lucie Press, Inc.

Fregni, F., Boggio, P. S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., ... & Pascual-Leone, A. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental Brain Research, 166,* 23-30.

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008a). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. *Journal of Clinical Psychiatry, 69,* 32-40.

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A., Nitsche, M. A., ... & Boggio, P. S. (2008b). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite, 51,* 34-41.

Fricke, K., Seeber, A. A., Thirugnanasambandam, N., Paulus, W., Nitsche, M. A., & Rothwell, J. C. (2010). Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation (tDCS) of the human motor cortex. *American Journal of Physiology-Heart and Circulatory Physiology.*

Fu, R., Gartlehner, G., Grant, M., Shamliyan, T., Sedrakyan, A., Wilt, T. J., ... & Santaguida, P. (2011). Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *Journal of Clinical Epidemiology, 64,* 1187-1197.

Fujii, S., Jia, Y., Yang, A., & Sumikawa, K. (2000). Nicotine reverses GABAergic inhibition of long-term potentiation induction in the hippocampal CA1 region. *Brain Research, 863,* 259-265.

Fuster, J. M. (1973). Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *Journal of Neurophysiology, 36,* 61-78.

Fuster, J.M. (2001). Prefrontal cortex. In N.J. Smelser & P.B. Baltes (Eds.), *International Encyclopedia of the Social & Behavioral Sciences* (pp. 11969-11976). Oxford, England: Elsevier Science Ltd.

Gagnon, G., Schneider, C., Grondin, S., & Blanchet, S. (2011). Enhancement of episodic memory in young and healthy adults: a paired-pulse TMS study on encoding and retrieval performance. *Neuroscience Letters, 488*, 138-142.

Gaiarsa, J. L., Caillard, O., & Ben-Ari, Y. (2002). Long-term plasticity at GABAergic and glycinergic synapses: mechanisms and functional significance. *Trends in Neurosciences, 25*, 564-570.

Gallo, D. (2013). *Associative illusions of memory: False memory research in DRM and related tasks.* New York, NY: Psychology Press.

Gallo, D. A., Bell, D. M., Beier, J. S., & Schacter, D. L. (2006). Two types of recollection-based monitoring in younger and older adults: Recall-to-reject and the distinctiveness heuristic. *Memory, 14*, 730-741.

Gallo, D. A., Cotel, S. C., Moore, C. D., & Schacter, D. L. (2007). Aging can spare recollection-based retrieval monitoring: The importance of event distinctiveness. *Psychology and Aging, 22*, 209-213.

Gallo, D. A., Weiss, J. A., & Schacter, D. L. (2004). Reducing false recognition with criterial recollection tests: Distinctiveness heuristic versus criterion shifts. *Journal of Memory and Language, 51*, 473-493.

Galli, G. (2014). What makes deeply encoded items memorable? Insights into the levels of processing framework from neuroimaging and neuromodulation. *Frontiers in Psychiatry, 5*, 61.

Galli, G., Feurra, M., Pavone, E. F., Sirota, M., & Rossi, S. (2017). Dynamic changes in prefrontal cortex involvement during verbal episodic memory formation. *Biological Psychology, 125*, 36-44.

Galli, G., Vadillo, M. A., Sirota, M., Feurra, M., & Medvedeva, A. (2018). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) on episodic memory. *Brain Stimulation, 12,* 231-241.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117,* 845-850.

Gavett, B. E., & Horwitz, J. E. (2011). Immediate list recall as a measure of short-term episodic memory: Insights from the serial position effect and item response theory. *Archives of Clinical Neuropsychology, 27,* 125-135.

Gaynor, A. M., & Chua, E. F. (2016). tDCS over the prefrontal cortex alters objective but not subjective encoding. *Cognitive Neuroscience, 8,* 156-161.

Geraci, L., McDaniel, M. A., Miller, T. M., & Hughes, M. L. (2013). The bizarreness effect: evidence for the critical influence of retrieval processes. *Memory & Cognition, 41,* 1228-1237.

Gerwig, M., Kastrup, O., Meyer, B. U., & Niehaus, L. (2003). Evaluation of cortical excitability by motor and phosphene thresholds in transcranial magnetic stimulation. *Journal of the Neurological Sciences, 215,* 75-78.

Glanzer, M., & Cunitz, A. R. (1966). Two storage mechanisms in free recall. *Journal of Verbal Learning and Verbal Behavior, 5,* 351-360.

Golestanirad, L., Izquierdo, A. P., Graham, S. J., Mosig, J. R., & Pollo, C. (2012). Effect of realistic modeling of deep brain stimulation on the prediction of volume of activated tissue. *Progress in Electromagnetics Research, 126,* 1-16.

Goodman, G.S., Magnussen, S., Andersson, T.E., Lokken, L., & Moestue, A.G. (2007). Memory illusions and false memories in the real world. In S. Magnussen & T. Helstrup, *Everyday memory*. Hove, England: Taylor and Francis.

Gordon, A. M., Rissman, J., Kiani, R., & Wagner, A. D. (2013). Cortical reinstatement mediates the relationship between content-specific encoding activity and subsequent recollection decisions. *Cerebral Cortex, 24,* 3350-3364.

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience, 25,* 8010-8016.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., ... & Haxby, J. V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience, 14,* 1450-1462.

Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *Journal of Neuroscience, 23,* 986-993.

Graf, P., Shimamura, A. P., & Squire, L. R. (1985). Priming across modalities and priming across category levels: Extending the domain of preserved function in amnesia. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 11,* 386-396. doi: http://dx.doi.org/10.1037/0278-7393.11.2.386

Grafman, J., Pascual-Leone, A., Alway, D., Nichelli, P., Gomez-Tortosa, E., & Hallett, M. (1994). Induction of a recall deficit by rapid-rate transcranial magnetic stimulation. *Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience, 5,* 1157-1160.

Gray, S. J., Brookshire, G., Casasanto, D., & Gallo, D. A. (2015). Electrically stimulating prefrontal cortex at retrieval improves recollection accuracy. *Cortex, 73,* 188-194.

Gualtierotti, T., & Paterson, A. S. (1954). Electrical stimulation of the unexposed cerebral cortex. *The Journal of Physiology, 125,* 278-291.

Guerin, S. A., Robbins, C. A., Gilmore, A. W., & Schacter, D. L. (2012). Retrieval failure contributes to gist-based false recognition. *Journal of Memory and Language, 66,* 68-78.

Guo, H., Zhang, Z., Da, S., Sheng, X., & Zhang, X. (2018). High-definition transcranial direct current stimulation (HD-tDCS) of left dorsolateral prefrontal cortex affects performance in Balloon Analogue Risk Task (BART). *Brain and Behavior, 8,* e00884.

Haase, R. F., & Ellis, M. V. (1987). Multivariate analysis of variance. *Journal of Counseling Psychology, 34,* 404-413.

Habich, A., Klöppel, S., Abdulkadir, A., Scheller, E., Nissen, C., & Peter, J. (2017). Anodal tDCS enhances verbal episodic memory in initially low performers. *Frontiers in Human Neuroscience, 11,* 542. doi: 10.3389/fnhum.2017.00542

Hales, J. B., & Brewer, J. B. (2011). The timing of associative memory formation: frontal lobe and anterior medial temporal lobe activity at associative binding predicts memory. *Journal of Neurophysiology, 105,* 1454-1463.

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature, 406,* 147.

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron, 55,* 187-199.

Hamada, M., & Rothwell, J. (2015). *Introduction to Nonconvulsive Brain Stimulation: Focus on Transcranial Magnetic Stimulation* (pp. 149-164).

Hammer, A., Mohammadi, B., Schmicker, M., Saliger, S., & Münte, T. F. (2011). Errorless and errorful learning modulated by transcranial direct current stimulation. *BMC Neuroscience, 12,* 72.

Harris, J. A., Clifford, C. W., & Miniussi, C. (2008). The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation?. *Journal of Cognitive Neuroscience, 20,* 734-740.

Hasselmo, M. E. (2011). Behavioral dynamics of episodic memory. In *How we remember: brain mechanisms of episodic memory* (pp. 1-30). Boston, MA: MIT press.

Hawco, C., Armony, J. L., Daskalakis, Z. J., Berlim, M. T., Chakravarty, M. M., Pike, G. B., & Lepage, M. (2017). Differing time of onset of concurrent TMS-fMRI during associative memory encoding: a measure of dynamic connectivity. *Frontiers in Human Neuroscience, 11*, 404.

Hawco, C., Berlim, M. T., & Lepage, M. (2013). The dorsolateral prefrontal cortex plays a role in self-initiated elaborative cognitive processing during episodic memory encoding: rTMS evidence. *PLoS One, 8,* e73789.

Hayes, S. M., Nadel, L., & Ryan, L. (2007). The effect of scene context on episodic object recognition: parahippocampal cortex mediates memory encoding and retrieval success. *Hippocampus, 17,* 873-889.

Hebb, D. O. (1949). *The organization of behavior; a neuropsychological theory.* Oxford, England: Wiley.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis.* London: Academic Press, Inc.

Hege, A. C., & Dodson, C. S. (2004). Why distinctive information reduces false memories: evidence for both impoverished relational-encoding and distinctiveness heuristic accounts. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 30, 787-795.

Heimrath, K., Sandmann, P., Becke, A., Müller, N. G., & Zaehle, T. (2012). Behavioral and electrophysiological effects of transcranial direct current stimulation of the parietal cortex in a visuo-spatial working memory task. *Frontiers in Psychiatry, 3*, 56.

Heinen, K., Sagliano, L., Candini, M., Husain, M., Cappelletti, M., & Zokaei, N. (2016). Cathodal transcranial direct current stimulation over posterior parietal cortex enhances distinct aspects of visual working memory. *Neuropsychologia, 87,* 35-42.

Heise, K. F., Niehoff, M., Feldheim, J. F., Liuzzi, G., Gerloff, C., & Hummel, F. C. (2014). Differential behavioral and physiological effects of anodal transcranial direct current

stimulation in healthy adults of younger and older age. *Frontiers in Aging Neuroscience, 6,* 146.

Helfrich, R. F., Huang, M., Wilson, G., & Knight, R. T. (2017). Prefrontal cortex modulates posterior alpha oscillations during top-down guided visual perception. *Proceedings of the National Academy of Sciences*, *114*, 9457-9462.

Hernandez, M. T., Sauerwein, H. C., Jambaqué, I., de Guise, E., Lussier, F., Lortie, A., ... & Lassonde, M. (2003). Attention, memory, and behavioral adjustment in children with frontal lobe epilepsy. *Epilepsy & Behavior, 4*, 522-536.

Héroux, M. E., Loo, C. K., Taylor, J. L., & Gandevia, S. C. (2017). Questionable science and reproducibility in electrical brain stimulation research. *PloS One, 12,* e0175635.

Higgins, J. P. , & Green, S. (Eds.). (2008). *Cochrane handbook for systematic reviews of interventions.* Chichester, UK: The Cochrane Collaboration, John Wiley & Sons.

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

Hindy, N. C., Hamilton, R., Houghtling, A. S., H Branch Coslett, M. D., & Thompson-Schill, S. L. (2009). Computer-mouse tracking reveals TMS disruptions of prefrontal function during semantic retrieval. *Journal of Neurophysiology*, *102*, 3405-3413.

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: a systematic review. *Neuropsychologia*, *66,* 213-236.

Hoy, K. E., Emonson, M. R., Arnold, S. L., Thomson, R. H., Daskalakis, Z. J., & Fitzgerald, P. B. (2013). Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. *Neuropsychologia*, *51,* 1777-1784.

Hsu, T. Y., Tseng, P., Liang, W. K., Cheng, S. K., & Juan, C. H. (2014). Transcranial direct current stimulation over right posterior parietal cortex changes prestimulus alpha oscillation in visual short-term memory task. *Neuroimage, 98,* 306-313.

Huang, Y. Z., Chen, R. S., Rothwell, J. C., & Wen, H. Y. (2007). The after-effect of human theta burst stimulation is NMDA receptor dependent. *Clinical Neurophysiology, 118,* 1028-1032.

Huang, Z., Tan, T., Du, Y., Chen, L., Fu, M., Yu, Y., ... & Dong, Z. (2017). Low-Frequency Repetitive Transcranial Magnetic Stimulation Ameliorates Cognitive Function and Synaptic Plasticity in APP23/PS45 Mouse Model of Alzheimer's Disease. *Frontiers in Aging Neuroscience, 9,* 292.

Huff, M. J., & Bodner, G. E. (2013). When does memory monitoring succeed versus fail? Comparing item-specific and relational encoding in the DRM paradigm. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 39,* 1246-1256.

Huff, M. J., Bodner, G. E., & Fawcett, J. M. (2015). Effects of distinctive encoding on correct and false memory: A meta-analytic review of costs and benefits and their origins in the DRM paradigm. *Psychonomic Bulletin & Review, 22,* 349-365.

Hunt, R. R., & Einstein, G. O. (1981). Relational and item-specific information in memory. *Journal of Verbal Learning and Verbal Behavior, 20,* 497-514.

Hunt, R. R., & Smith, R. E. (2014). How distinctive processing enhances hits and reduces false alarms. *Journal of Memory and Language, 75,* 45-57.

Hutchinson, J. B., Uncapher, M. R., Weiner, K. S., Bressler, D. W., Silver, M. A., Preston, A. R., & Wagner, A. D. (2012). Functional heterogeneity in posterior parietal cortex across attention and episodic memory retrieval. *Cerebral Cortex, 24,* 49-66.

Inagawa, T., Narita, Z., Sugawara, N., Maruo, K., Stickley, A., Yokoi, Y., & Sumiyoshi, T. (2018). A meta-analysis of the effect of multisession transcranial direct current

stimulation on cognition in dementia and mild cognitive impairment. *Clinical EEG and Neuroscience,* 1550059418800889.

Innocenti, I., Cappa, S. F., Feurra, M., Giovannelli, F., Santarnecchi, E., Bianco, G., ... & Rossi, S. (2013). TMS interference with primacy and recency mechanisms reveals bimodal episodic encoding in the human brain. *Journal of Cognitive Neuroscience, 25*, 109-116.

Innocenti, I., Giovannelli, F., Cincotta, M., Feurra, M., Polizzotto, N. R., Bianco, G., ... & Rossi, S. (2010). Event-related rTMS at encoding affects differently deep and shallow memory traces. *Neuroimage, 53*, 325-330.

Irish, M., Hornberger, M., Lah, S., Miller, L., Pengas, G., Nestor, P. J., ... & Piguet, O. (2011). Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease. *Neuropsychologia, 49*, 2694-2702.

Irish, M., Lawlor, B. A., O'Mara, S. M., & Coen, R. F. (2011). Impaired capacity for autonoetic reliving during autobiographical event recall in mild Alzheimer's disease. *Cortex, 47*, 236–249.

Israel, L., & Schacter, D. L. (1997). Pictorial encoding reduces false recognition of semantic associates. *Psychonomic Bulletin & Review, 4*, 577-581.

Jacobson, L., Goren, N., Lavidor, M., and Levy, D. A. (2012). Oppositional transcranial direct current stimulation (tDCS) of attention during encoding modulates episodic memory. *Brain Res*earch, *1439*, 66–72. doi: 10.1016/j.brainres.2011.12.036

Jasper, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology, 10,* 370-375.

Javadi, A. H., Brunec, I. K., Walsh, V., Penny, W. D., & Spiers, H. J. (2014). Transcranial electrical brain stimulation modulates neuronal tuning curves in perception of numerosity and duration. *NeuroImage, 102,* 451-457.

Javadi, A. H., & Cheng, P. (2013). Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. *Brain Stimulation, 6,* 668-674.

Javadi, A. H., & Walsh, V. (2012). Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. *Brain Stimulation, 5,* 231-241.

Jeong, W., Chung, C. K., & Kim, J. S. (2015). Episodic memory in aspects of large-scale brain networks. *Frontiers in Human Neuroscience, 9,* 454.

Jiang, Y., & Kanwisher, N. (2003). Common neural substrates for response selection across modalities and mapping paradigms. *Journal of Cognitive Neuroscience, 15,* 1080-1094.

Johnson, M. K. (2005). The relation between source memory and episodic memory: Comment on Siedlecki et al. (2005). *Psychology and Aging, 20,* 529-531. doi: http://dx.doi.org/10.1037/0882-7974.20.3.529

Johnson, J. D., McDuff, S. G., Rugg, M. D., & Norman, K. A. (2009). Recollection, familiarity, and cortical reinstatement: a multivoxel pattern analysis. *Neuron, 63,* 697-708.

Jones, K. T., Gözenman, F., & Berryhill, M. E. (2014). Enhanced long-term memory encoding after parietal neurostimulation. *Experimental Brain Research, 232,* 4043-4054.

Kadosh, R. C., Levy, N., O'Shea, J., Shea, N., & Savulescu, J. (2012). The neuroethics of NIBS. *Current Biology, 22,* R108-R111.

Kahn, I., Pascual-Leone, A., Theoret, H., Fregni, F., Clark, D., & Wagner, A. D. (2005). Transient disruption of ventrolateral prefrontal cortex during verbal encoding affects subsequent memory performance. *Journal of Neurophysiology, 94,* 688-698.

Kalat, J. (2016). Nerve cells and nerve impulses. *Biological psychology* (pp. 26-50). Belmont: Wadsworth, Cengage Learning.

Kapogiannis, D., & Wassermann, E. M. (2008). Transcranial magnetic stimulation in clinical pharmacology. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents), 8*, 234-240.

Karlsgodt, K. H., Shirinyan, D., van Erp, T. G., Cohen, M. S., & Cannon, T. D. (2005). Hippocampal activations during encoding and retrieval in a verbal working memory paradigm. *Neuroimage, 25,* 1224-1231.

Kennerley, S. W., & Wallis, J. D. (2009). Reward-dependent modulation of working memory in lateral prefrontal cortex. *Journal of Neuroscience, 29*, 3259-3270.

Kerr, N. L. (1998). HARKing: Hypothesizing after the results are known. *Personality and Social Psychology Review, 2,* 196-217.

Kirchhoff, B. A., Wagner, A. D., Maril, A., & Stern, C. E. (2000). Prefrontal–temporal circuitry for episodic encoding and subsequent memory. *Journal of Neuroscience, 20*, 6173-6180.

Kirsner, K. (1973). An analysis of the visual component in recognition memory for verbal stimuli. *Memory & Cognition, 1,* 449-453.

Kim, H., & Cabeza, R. (2006). Differential contributions of prefrontal, medial temporal, and sensory-perceptual regions to true and false memory formation. *Cerebral Cortex, 17,* 2143-2150.

Kim, G. W., Chung, Y. C., Yang, J. C., Chung, G. H., Park, T. J., & Jeong, G. W. (2015). Neuroanatomical mechanism on the effect of distraction in working memory maintenance in patients with schizophrenia. *The Journal of Neuropsychiatry and Clinical Neurosciences, 27*, e1-e9.

Kim, K., Ekstrom, A. D., & Tandon, N. (2016). A network approach for modulating memory processes via direct and indirect brain stimulation: toward a causal approach for the neural basis of memory. *Neurobiology of Learning and Memory, 134,* 162-177.

Kincses, T. Z., Antal, A., Nitsche, M. A., Bártfai, O., & Paulus, W. (2004). Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia, 42,* 113-117.

King, J. A., Hartley, T., Spiers, H. J., Maguire, E. A., & Burgess, N. (2005). Anterior prefrontal involvement in episodic retrieval reflects contextual interference. *Neuroimage, 28,* 256-267.

Kirwan, C. B., Wixted, J. T., & Squire, L. R. (2008). Activity in the medial temporal lobe predicts memory strength, whereas activity in the prefrontal cortex predicts recollection. *Journal of Neuroscience, 28,* 10541-10548.

Klaus, J., & Schutter, D. J. (2018). Putting focus on transcranial direct current stimulation in language production studies. *PloS one, 13,* e0202730.

Klem, G. H., Lüders, H. O., Jasper, H. H., & Elger, C. (1999). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology, 52,* 3-6.

Klirova, M., Novak, T., Kopecek, M., Mohr, P., & Strunzova, V. (2008). Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode during pregnancy. *Neuro Endocrinology Letters, 29,* 69-70.

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine, 58,* 208-213.

Kobayashi, S. (2009). Reward neurophysiology and primate cerebral cortex. In L.R. Squire, *Encyclopedia of Neuroscience.* (pp. 325-333). London, England: Academic Press.

Köhler, S., Black, S. E., Sinden, M., Szekely, C., Kidron, D., Parker, J. L., ... & Bronskill, M. J. (1998). Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: an MR volumetry study in Alzheimer's disease. *Neuropsychologia, 36,* 901-914.

Köhler, S., Paus, T., Buckner, R. L., & Milner, B. (2004). Effects of left inferior prefrontal stimulation on episodic memory formation: a two-stage fMRI—rTMS study. *Journal of Cognitive Neuroscience, 16,* 178-188.

Kolb, B., Nonneman, A. J., & Singh, R. K. (1974). Double dissociation of spatial impairments and perseveration following selective prefrontal lesions in rats. *Journal of Comparative and Physiological Psychology, 87,* 772-780.

Koutstaal, W., & Schacter, D. L. (1997). Gist-based false recognition of pictures in older and younger adults. *Journal of Memory & Language, 37,* 555-583.

Kučera, H., & Francis, W. N. (1967). *Computational analysis of present-day American English.* Providence, RI: Brown University Press.

Kühn, A. A., & Huebl, J. (2011). Safety of transcranial magnetic stimulation for the newer generation of deep brain stimulators. *Parkinsonism & Related Disorders, 17,* 647-648.

Kuo, M. F., & Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clinical EEG and Neuroscience, 43,* 192-199.

Kučera H., Francis W.N. (1967). *Computational analysis of present-day American English.* Providence, RI: Brown University Press.

Kvavilashvili, L., & Ellis, J. (2004). Ecological validity and twenty years of real-life/laboratory controversy in memory research: A critical (and historical) review. *History and Philosophy of Psychology, 6,* 59-80.

Lafon, B., Henin, S., Huang, Y., Friedman, D., Melloni, L., Thesen, T., ... & Liu, A. A. (2017). Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. *Nature Communications, 8,* 1199.

Lafontaine, M. P., Théoret, H., Gosselin, F., & Lippé, S. (2013). Transcranial direct current stimulation of the dorsolateral prefrontal cortex modulates repetition suppression to unfamiliar faces: an ERP study. *PloS one, 8,* e81721.

Lally, N., Nord, C. L., Walsh, V., & Roiser, J. P. (2013). Does excitatory fronto-extracerebral tDCS lead to improved working memory performance?. *F1000Research, 2,* 219-219.

Lashley, K. S. (1950). In search of the engram. In Society for Experimental Biology, *Physiological mechanisms in animal behavior. (Society's Symposium IV.)* (pp. 454-482). Oxford, England: Academic Press.

Leach, R. C., McCurdy, M. P., Trumbo, M. C., Matzen, L. E., & Leshikar, E. D. (2018). Differential age effects of transcranial direct current stimulation on associative memory. *The Journals of Gerontology: Series B, gby003.* doi: https://doi.org/10.1093/geronb/gby003

Learmonth, G., Thut, G., Benwell, C. S., & Harvey, M. (2015). The implications of state-dependent tDCS effects in aging: behavioural response is determined by baseline performance. *Neuropsychologia, 74*, 108-119.

Lechner, H. A., Squire, L. R., & Byrne, J. H. (1999). 100 years of consolidation—remembering Müller and Pilzecker. *Learning & Memory, 6*, 77-87.

Lee, T. G., Blumenfeld, R. S., & d'Esposito, M. (2013). Disruption of dorsolateral but not ventrolateral prefrontal cortex improves unconscious perceptual memories. *Journal of Neuroscience, 33,* 13233-13237.

Lepage, M., Hawco, C., & Bodnar, M. (2015). Relational Memory as a Possible Neurocognitive Marker of Schizophrenia. *JAMA Psychiatry, 72*, 946-947.

Leshikar, E. D., Leach, R. C., McCurdy, M. P., Trumbo, M. C., Sklenar, A. M., Frankenstein, A. N., & Matzen, L. E. (2017). Transcranial direct current stimulation of dorsolateral prefrontal cortex during encoding improves recall but not recognition memory. *Neuropsychologia, 106,* 390-397.

Lian, J., Bikson, M., Sciortino, C., Stacey, W. C., & Durand, D. M. (2003). Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro. The *Journal of Physiology, 547,* 427-434.

Liang, P., Wang, Z., Yang, Y., Jia, X., & Li, K. (2011). Functional disconnection and compensation in mild cognitive impairment: evidence from DLPFC connectivity using resting-state fMRI. *PloS one, 6*, e22153.

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain, 125*, 2238-2247.

Linden, A. (2018, July). Publication bias and questionable research practices in meta-analysis: a simulation study. In M. Pelton (Chair), *History and philosophy of psychology*. Symposium conducted at the meeting of Psychology Postgraduate Affairs Group, Huddersfield, England.

Linden, D. E. (2007). The working memory networks of the human brain. *The Neuroscientist, 13*, 257-267.

Linden, A, & Hönnekopp, J. (2017, July). *Heterogeneity in meta-analyses: Implications for cumulative knowledge in psychology*. Poster session presented at the meeting of Psychology Postgraduate Affairs Group, Newcastle, England.

Ljubisavljevic, M., Maxood, K., Bjekic, J., Oommen, J., & Nagelkerke, N. (2016). Long-term effects of repeated prefrontal cortex transcranial direct current stimulation (tDCS) on food craving in normal and overweight young adults. *Brain Stimulation, 9*, 826-833.

Lockhart, R. S., & Craik, F. I. (1990). Levels of processing: A retrospective commentary on a framework for memory research. *Canadian Journal of Psychology/Revue Canadienne de Psychologie, 44*, 87-112.

Logothetis, N. K., Kayser, C., & Oeltermann, A. (2007). In vivo measurement of cortical impedance spectrum in monkeys: implications for signal propagation. *Neuron, 55*, 809-823.

London, R. E., & Slagter, H. A. (2015). Effects of transcranial direct current stimulation over left dorsolateral pFC on the attentional blink depend on individual baseline performance. *Journal of Cognitive Neuroscience, 27*, 2382-2393.

Long, N. M., & Kahana, M. J. (2015). Successful memory formation is driven by contextual encoding in the core memory network. *NeuroImage, 119*, 332-337.

Lu, Y., Wang, C., Chen, C., & Xue, G. (2015). Spatiotemporal neural pattern similarity supports episodic memory. *Current Biology, 25*, 780-785.

Lyashevskaya, O. N., & Sharov, S. A. (2009). Dictionary of word frequency of the modern Russian language (on the materials of the National corpus of the Russian language). Moscow, Russia: Azbukovnik.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288,* 1835-1838.

Machizawa, M. G., Kalla, R., Walsh, V., & Otten, L. J. (2010). The time course of ventrolateral prefrontal cortex involvement in memory formation. *Journal of Neurophysiology, 103,* 1569-1579.

MacLeod, C. A., & Donaldson, D. I. (2017). Investigating the Functional Utility of the Left Parietal ERP Old/New Effect: Brain Activity Predicts within But Not between Participant Variance in Episodic Recollection. *Frontiers in Human Neuroscience, 11*, 580.

Macmillan, M., & Lena, M. L. (2010). Rehabilitating Phineas Gage. *Neuropsychological Rehabilitation, 20*, 641-658.

Malmberg, K. J., Steyvers, M., Stephens, J. D., & Shiffrin, R. M. (2002). Feature frequency effects in recognition memory. *Memory & Cognition, 30*, 607-613.

Mainy, N., Jung, J., Baciu, M., Kahane, P., Schoendorff, B., Minotti, L., ... & Lachaux, J. P. (2008). Cortical dynamics of word recognition. *Human Brain Mapping, 29,* 1215-1230.

Manenti, R., Brambilla, M., Petesi, M., Ferrari, C., & Cotelli, M. (2013). Enhancing verbal episodic memory in older and young subjects after NIBS. *Frontiers in Aging Neuroscience, 5,* 49.

Manenti, R., Cotelli, M., Calabria, M., Maioli, C., & Miniussi, C. (2010). The role of the dorsolateral prefrontal cortex in retrieval from long-term memory depends on strategies: a repetitive transcranial magnetic stimulation study. *Neuroscience, 166,* 501-507.

Manenti, R., Cotelli, M., & Miniussi, C. (2011). Successful physiological aging and episodic memory: a brain stimulation study. *Behavioural Brain Research, 216,* 153-158.

Manenti, R., Cotelli, M., Robertson, I. H., & Miniussi, C. (2012). Transcranial brain stimulation studies of episodic memory in young adults, elderly adults and individuals with memory dysfunction: a review. *Brain Stimulation, 5,* 103-109.

Manenti, R., Sandrini, M., Gobbi, E., Cobelli, C., Brambilla, M., Binetti, G., & Cotelli, M. (2017). Strengthening of existing episodic memories through non-invasive stimulation of prefrontal cortex in older adults with subjective memory complaints. *Frontiers in Aging Neuroscience, 9,* 401.

Manenti, R., Tettamanti, M., Cotelli, M., Miniussi, C. S. F. C., & Cappa, S. F. (2010). The neural bases of word encoding and retrieval: a fMRI-guided transcranial magnetic stimulation study. *Brain Topography, 22,* 318-332.

Manns, J. R., Hopkins, R. O., & Squire, L. R. (2003). Semantic memory and the human hippocampus. *Neuron, 38,* 127-133.

Manuel, A. L., & Schnider, A. (2016). Effect of prefrontal and parietal tDCS on learning and recognition of verbal and non-verbal material. *Clinical Neurophysiology, 127*, 2592-2598.

Marián, M., Szőllősi, Á., & Racsmány, M. (2018). Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex impairs long-term retention of reencountered memories. *Cortex, 108,* 80-91.

Markowitsch, H. J. (1995). Which brain regions are critically involved in the retrieval of old episodic memory?. *Brain Research Reviews, 21*, 117-127.

Marshall, L., Mölle, M., Siebner, H. R., & Born, J. (2005). Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. *BMC Neuroscience, 6,* 23.

Mattson, M. P. (2008). Glutamate and neurotrophic factors in neuronal plasticity and disease. *Annals of the New York Academy of Sciences, 1144*, 97-112.

Matzen, L. E., Trumbo, M. C., Leach, R. C., & Leshikar, E. D. (2015). Effects of NIBS on associative memory. *Brain Research, 1624,* 286-296.

Mayer, M. L., Westbrook, G. L., & Guthrie, P. B. (1984). Voltage-dependent block by Mg 2+ of NMDA responses in spinal cord neurones. *Nature, 309*, 261-263.

Mayford, M., Siegelbaum, S. A., & Kandel, E. R. (2012). Synapses and memory storage. *Cold Spring Harbor Perspectives in Biology, 4,* a005751.

Mccabe, D. P., Presmanes, A. G., Robertson, C. L., & Smith, A. D. (2004). Item-specific processing reduces false memories. *Psychonomic Bulletin & Review, 11*, 1074-1079.

McDaniel, M. A., DeLosh, E. L., & Merritt, P. S. (2000). Order information and retrieval distinctiveness: Recall of common versus bizarre material. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 26,* 1045-1056.

Medina, J., & Cason, S. (2017). No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. *Cortex, 94,* 131-141.

Medvedeva, A., Materassi, M., Neacsu, V., Beresford-Webb, J., Hussin, A., Khan, N., ... & Galli, G. (2018). Effects of anodal transcranial direct current stimulation over the ventrolateral prefrontal cortex on episodic memory formation and retrieval. *Cerebral Cortex, 29,* 657-665.

Medvedev, O. N., Krägeloh, C. U., Narayanan, A., & Siegert, R. J. (2017). Measuring mindfulness: applying generalizability theory to distinguish between state and trait. *Mindfulness, 8,* 1036-1046.

Medvedev, O. N., Theadom, A., Barker-Collo, S., & Feigin, V. (2018). Distinguishing between enduring and dynamic concussion symptoms: applying Generalisability Theory to the Rivermead Post Concussion Symptoms Questionnaire (RPQ). *PeerJ, 6,* e5676.

Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., ... & Flöel, A. (2012). Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. *Journal of Neuroscience, 32,* 1859-1866.

Meinzer, M., Jähnigen, S., Copland, D. A., Darkow, R., Grittner, U., Avirame, K., ... & Flöel, A. (2014). Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex, 50,* 137-147.

Meredith, R. M., Floyer-Lea, A. M., & Paulsen, O. (2003). Maturation of long-term potentiation induction rules in rodent hippocampus: role of GABAergic inhibition. *Journal of Neuroscience, 23,* 11142-11146.

Merton, P. A., Morton, H. B., Hill, D. K., & Marsden, C. D. (1982). Scope of a technique for electrical stimulation of human brain, spinal cord, and muscle. *The Lancet, 320,* 597-600.

McEvoy, C. L., Nelson, D. L., & Komatsu, T. (1999). What is the connection between true and false memories? The differential roles of interitem associations in recall and

recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 25,* 1177-1194. doi: http://dx.doi.org/10.1037/0278-7393.25.5.1177.

Miller, E. K. (2000). The prefrontal cortex: no simple matter. *Neuroimage, 11,* 447-450.

Milham, M. P., Banich, M. T., & Barad, V. (2003). Competition for priority in processing increases prefrontal cortex's involvement in top-down control: an event-related fMRI study of the stroop task. *Cognitive Brain Research, 17,* 212-222.

Milner, B., Petrides, M., & Smith, M. L. (1985). Frontal lobes and the temporal organization of memory. *Human Neurobiology, 4,* 137-142.

Minarik, T., Berger, B., Althaus, L., Bader, V., Biebl, B., Brotzeller, F., ... & Leitner, M. (2016). The importance of sample size for reproducibility of tDCS effects. *Frontiers in Human Neuroscience, 10,* 453.

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., ... & Walsh, V. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimulation, 1,* 326-336.

Miniussi, C., Cappa, S. F., Sandrini, M., Rossini, P. M., & Rossi, S. (2003). The causal role of the prefrontal cortex in episodic memory as demonstrated with rTMS. In W. Paulus, F. Tergau, M.A. Nitsche, J.C. Rothwell, U. Ziemann, & M. Hallett (Eds.), *Supplements to clinical neurophysiology* (Vol. 56, pp. 312-320). Gottingen: Elsevier.

Miniussi, C., Harris, J. A., & Ruzzoli, M. (2013). Modelling NIBS in cognitive neuroscience. *Neuroscience & Biobehavioral Reviews, 37,* 1702-1712.

Miranda, P. C., Faria, P., & Hallett, M. (2009). What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS?. Clinical *Neurophysiology, 120,* 1183-1187.

Mitchell, D. B., Hunt, R. R., & Schmitt, F. A. (1986). The generation effect and reality monitoring: Evidence from dementia and normal aging. *Journal of Gerontology, 41,* 79-84.

Mitchell, K. J., & Johnson, M. K. (2009). Source monitoring 15 years later: what have we learned from fMRI about the neural mechanisms of source memory?. *Psychological Bulletin, 135,* 638-677.

Molholm, S., Ritter, W., Javitt, D. C., & Foxe, J. J. (2004). Multisensory visual–auditory object recognition in humans: a high-density electrical mapping study. *Cerebral Cortex, 14,* 452-465.

Moliadze, V., Antal, A., and Paulus, W. (2010). Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. *Clinical Neurophysiology, 121,* 2165–2171. doi: 10.1016/j.clinph.2010.04.033

Monchi, O., Taylor, J. G., & Dagher, A. (2000). A neural model of working memory processes in normal subjects, Parkinson's disease and schizophrenia for fMRI design and predictions. *Neural Networks, 13,* 953-973.

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated NIBS. *Brain Stimulation, 6,* 424-432.

Mordillo-Mateos, L., Turpin-Fenoll, L., Millán-Pascual, J., Núñez-Pérez, N., Panyavin, I., Gómez-Argüelles, J. M., ... & Oliviero, A. (2012). Effects of simultaneous bilateral tDCS of the human motor cortex. *Brain Stimulation, 5,* 214-222.

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic memory and beyond: the hippocampus and neocortex in transformation. *Annual Review of Psychology,* 67, 105-134.

Moscovitch, M., & Craik, F. I. (1976). Depth of processing, retrieval cues, and uniqueness of encoding as factors in recall. *Journal of Verbal Learning and Verbal Behavior, 15,* 447-458.

Moser, E. I., Kropff, E., & Moser, M. B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual Reviews in Neuroscience, 31*, 69-89.

Murray, L. J., & Ranganath, C. (2007). The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *Journal of Neuroscience, 27*, 5515-5522.

Murdock Jr, B. B. (1962). The serial position effect of free recall. *Journal of Experimental Psychology, 64*, 482.

Murphy, S. C., Palmer, L. M., Nyffeler, T., Müri, R. M., & Larkum, M. E. (2016). Transcranial magnetic stimulation (TMS) inhibits cortical dendrites. *Elife*, *5*, e13598.

Nabavi, S., Fox, R., Proulx, C. D., Lin, J. Y., Tsien, R. Y., & Malinow, R. (2014). Engineering a memory with LTD and LTP. *Nature*, *511*, 348.

Nagarajan, S. S., Durand, D. M., & Warman, E. N. (1993). Effects of induced electric fields on finite neuronal structures: a simulation study. *IEEE Transactions on Biomedical Engineering, 40*, 1175-1188.

Nakanishi, S. (1994). Metabotropic glutamate receptors: synaptic transmission, modulation, and plasticity. *Neuron, 13*, 1031-1037.

Naghavi, H. R., & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration?. *Consciousness and Cognition, 14*, 390-425.

Nasseri, P., Nitsche, M. A., & Ekhtiari, H. (2015). A framework for categorizing electrode montages in transcranial direct current stimulation. *Frontiers in Human Neuroscience*, *9*, 54.

Nee, D. E., & Jonides, J. (2009). Common and distinct neural correlates of perceptual and memorial selection. *Neuroimage*, *45*, 963-975.

Neill, D. B. (1976). Frontal-striatal control of behavioral inhibition in the rat. *Brain Research, 105*, 89-103.

Nelson, J. K., Reuter-Lorenz, P. A., Persson, J., Sylvester, C. Y. C., & Jonides, J. (2009). Mapping interference resolution across task domains: a shared control process in left inferior frontal gyrus. *Brain Research, 1256,* 92-100.

Nevler, N., & Ash, E. L. (2015). TMS as a tool for examining cognitive processing. *Current Neurology and Neuroscience Reports, 15*, 52.

Nikolin, S., Loo, C. K., Bai, S., Dokos, S., & Martin, D. M. (2015). Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning. *Neuroimage, 117,* 11-19.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., ... & Pascual-Leone, A. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimulation, 1,* 206-223.

Nitsche M. A., Fricke K., Henschke U., Schlitterlau A., Liebetanz D., Lang N., et al. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology, 553,* 293–30110.1113/jphysiol.2003.049916

Nitsche, M. A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004). Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology, 29,* 1573 - 1578.

Nitsche, M. A., Liebetanz, D., Schlitterlau, A., Henschke, U., Fricke, K., Frommann, K., ... & Tergau, F. (2004). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *European Journal of Neuroscience, 19,* 2720-2726.

Nitsche, M. A., Nitsche, M. S., Klein, C. C., Tergau, F., Rothwell, J. C., & Paulus, W. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clinical Neurophysiology, 114*, 600-604.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology, 527*, 633-639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*, 1899-1901.

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation–update 2011. *Restorative Neurology and Neuroscience, 29*, 463-492.

Nitsche, M. A., Roth, A., Kuo, M. F., Fischer, A. K., Liebetanz, D., Lang, N., ... & Paulus, W. (2007). Timing-dependent modulation of associative plasticity by general network excitability in the human motor cortex. *Journal of Neuroscience, 27*, 3807-3812.

Nitsche, M. A., Seeber, A., Frommann, K., Klein, C. C., Rochford, C., Nitsche, M. S., ... & Paulus, W. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *The Journal of Physiology, 568*, 291-303.

Nitsche, M. A., Polanía, R., & Kuo, M. (2015). Transcranial direct current stimulation: modulation of brain pathways and clinical applications. In I. M. Reti (Ed.), *Brain stimulation: methodologies and interventions* (pp. 233-254). Hoboken, NJ: Wiley-Blackwell.

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *Journal of Cognitive Neuroscience, 15*, 619-626.

Nixon, P., Lazarova, J., Hodinott-Hill, I., Gough, P., & Passingham, R. (2004). The inferior frontal gyrus and phonological processing: an investigation using rTMS. Jo*urnal of Cognitive Neuroscience, 16*, 289-300.

Norris, D. (2017). Short-term memory and long-term memory are still different. *Psychological Bulletin, 143,* 992-1009. doi: http://dx.doi.org/10.1037/bul0000108

Nonneman, A. J., Voigt, J., & Kolb, B. E. (1974). Comparisons of behavioral effects of hippocampal and prefrontal cortex lesions in the rat. *Journal of Comparative and Physiological Psychology, 87,* 249-260.

Norman, K. A., & O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning-systems approach. *Psychological Review, 110,* 611-646. doi: http://dx.doi.org/10.1037/0033-295X.110.4.611

Nozari, N., Mirman, D., & Thompson-Schill, S. L. (2016). The ventrolateral prefrontal cortex facilitates processing of sentential context to locate referents. *Brain and Language, 157,* 1-13.

Nozari, N., & Thompson-Schill, S.L. (2015). Left ventrolateral prefrontal cortex in processing of words and sentences. In G. Hickok & S.L. Small (Eds.), *Neurobiology of language* (pp. 569-584). London, England: Academic Press.

Nyberg, L., Cabeza, R., & Tulving, E. (1996). PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review, 3,* 135-148.

Purves, D., Augustine, G.J., Fitzpatrick, D., Katz, L.C., LaMantia, A.S., McNamara, J., & Williams, S.M. (Eds.). (2004). *Neuroscience* (3rd ed.). Sunderlamd, MA: Sinauer Associates.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences, 9,* 242-249.

Oh, S. H., Lee, J. G., Na, S. J., Park, J. H., Choi, Y. C., & Kim, W. J. (2003). Prediction of early clinical severity and extent of neuronal damage in anterior-circulation infarction using the initial serum neuron-specific enolase level. *Archives of Neurology, 60,* 37-41.

Opitz, B., Mecklinger, A., & Friederici, A. D. (2000). Functional asymmetry of human prefrontal cortex: encoding and retrieval of verbally and nonverbally coded information. *Learning & Memory, 7*, 85-96.

Opris, I. (2017). Electrical stimulation for modification of memory and cognition. In A. Majid (Ed.), *Electroceuticals* (pp. 283-316). Cham: Springer.

O'Reilly, R. C. (2010). The what and how of prefrontal cortical organization. *Trends in Neurosciences, 33*, 355-361.

O'Reilly, R. C., & Rudy, J. W. (2001). Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. *Psychological Review, 108*, 311-345. doi: http://dx.doi.org/10.1037/0033-295X.108.2.311

O'Shea, J., & Walsh, V. (2007). Transcranial magnetic stimulation. *Current Biology, 17*, R196-R199.

Otten, L. J., Henson, R. N., & Rugg, M. D. (2001). Depth of processing effects on neural correlates of memory encoding: relationship between findings from across-and within-task comparisons. *Brain, 124*, 399-412.

Otten, L. J., & Rugg, M. D. (2001). When more means less: neural activity related to unsuccessful memory encoding. *Current Biology, 11*, 1528-1530.

Pace-Schott, E.F. (2011). The neurobiology of dreaming. In M.H. Kryger, T. Roth, & W.C. Dement, *Principles and Practice of Sleep Medicine.* (5th ed., pp. 563-575). Philadelphia, PA: Elsevier Inc.

Paller, K. A. (2009). Memory consolidation: systems. *Encyclopedia of Neuroscience, 1*, 741-749.

Parazzini, M., Rossi, E., Rossi, L., Priori, A., & Ravazzani, P. (2013). Numerical estimation of the current density in the heart during transcranial direct current stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 6*, 457-458.

Parkin, B. L., Ekhtiari, H., & Walsh, V. F. (2015). Non-invasive human brain stimulation in cognitive neuroscience: a primer. *Neuron, 87,* 932-945.

Patel, H. J., Romanzetti, S., Pellicano, A., Nitsche, M. A., Reetz, K., & Binkofski, F. (2019). Proton Magnetic Resonance Spectroscopy of the motor cortex reveals long term GABA change following anodal Transcranial Direct Current Stimulation. *Scientific Reports, 9,* 2807.

Pelletier, S. J., & Cicchetti, F. (2015). Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. *International Journal of Neuropsychopharmacology, 18,* pyu047.

Penney, C. G. (1989). Modality effects and the structure of short-term verbal memory. *Memory & Cognition, 17,* 398-422.

Penfield, W. (1938). The cerebral cortex in man: I. The cerebral cortex and consciousness. *Archives of Neurology & Psychiatry, 40*, 417-442.

Penfield, W., & Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Archives of Neurology & Psychiatry, 79*, 475-497.

Penolazzi, B., Di Domenico, A., Marzoli, D., Mammarella, N., Fairfield, B., Franciotti, R., ... & Tommasi, L. (2010). Effects of transcranial direct current stimulation on episodic memory related to emotional visual stimuli. *PloS One, 5*, e10623.

Penolazzi, B., Stramaccia, D. F., Braga, M., Mondini, S., & Galfano, G. (2014). Human memory retrieval and inhibitory control in the brain: beyond correlational evidence. *Journal of Neuroscience, 34,* 6606-6610.

Pergolizzi, D., & Chua, E. F. (2015). Transcranial direct current stimulation (tDCS) of the parietal cortex leads to increased false recognition. *Neuropsychologia, 66,* 88-98.

Pessoa, L., & Engelmann, J. B. (2010). Embedding reward signals into perception and cognition. *Frontiers in Neuroscience, 4,* 17.

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioral and Brain Sciences, 26,* 65-82.

Pisoni, A., Papagno, C., & Cattaneo, Z. (2012). Neural correlates of the semantic interference effect: new evidence from transcranial direct current stimulation. *Neuroscience, 223,* 56-67.

Pisoni, A., Turi, Z., Raithel, A., Ambrus, G. G., Alekseichuk, I., Schacht, A., ... & Antal, A. (2015a). Separating recognition processes of declarative memory via anodal tDCS: boosting old item recognition by temporal and new item detection by parietal stimulation. *PloS One, 10,* e0123085.

Pisoni, A., Vernice, M., Iasevoli, L., Cattaneo, Z., & Papagno, C. (2015b). Guess who? Investigating the proper name processing network by means of tDCS. *Neuropsychologia, 66,* 267-278.

Poghosyan, V., & Ioannides, A. A. (2008). Attention modulates earliest responses in the primary auditory and visual cortices. *Neuron, 58,* 802-813.

Polanía, R., Nitsche, M. A., & Ruff, C. (2018). Studying and modifying brain function with NIBS. *Nature Neuroscience, 21,* 174.

Prehn, K., & Flöel, A. (2015). Potentials and limits to enhance cognitive functions in healthy and pathological aging by tDCS. *Frontiers in Cellular Neuroscience, 9,* 355.

Prehn, K., Stengl, H., Grittner, U., Kosiolek, R., Ölschläger, A., Weidemann, A., & Flöel, A. (2017). Effects of anodal transcranial direct current stimulation and serotonergic enhancement on memory performance in young and older adults. *Neuropsychopharmacology, 42,* 551-561.

Price, A. R., & Hamilton, R. H. (2015). A re-evaluation of the cognitive effects from single-session transcranial direct current stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8,* 663-665.

Preston, A. R., & Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. *Current Biology, 23,* R764-R773.

Price, A. R., & Hamilton, R. H. (2015). A re-evaluation of the cognitive effects from single-session transcranial direct current stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8*, 663-665.

Priori, A., Berardelli, A., Rona, S., Accornero, N., & Manfredi, M. (1998). Polarization of the human motor cortex through the scalp. *Neuroreport, 9,* 2257-2260.

Purpura, D.P. and McMurtry, J.G. (1965) lntracellular activities and evoked potential changes during polarization of motor cortex. *Journal of Neurophysiology, 28,* 166-185.

Radzi, N. M. M., Nor, M. M., & Matore, M. E. E. M. (2018). Using Generalizability Theory in the Development of Performance Assessment of the Cognitive Domain of Children. *Advanced Science Letters, 24*, 5297-5301.

Raffone, A., Murre, J. M., & Wolters, G. (2003). NMDA synapses can bias competition between object representations and mediate attentional selection. *Behavioral and Brain Sciences, 26*, 100-101.

Rajah, M. N., & D'esposito, M. (2005). Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain, 128,* 1964-1983.

Rami, L., Gironell, A., Kulisevsky, J., Garcıa-Sánchez, C., Berthier, M., & Estevez-Gonzalez, A. (2003). Effects of repetitive transcranial magnetic stimulation on memory subtypes: a controlled study. *Neuropsychologia, 41,* 1877-1883.

Reinhart, R. M., Cosman, J. D., Fukuda, K., & Woodman, G. F. (2017). Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. *Attention, Perception, & Psychophysics*, *79,* 3-23.

Reisberg, D. (2016). *Cognition: Exploring the science of the mind* (6th ed., pp. 333-339). New York: W. W. Norton & Company.

Reti, I. M., & Chang, A. D. (2015). Introduction to brain stimulation. In I. M. Reti (Ed.), *Brain stimulation: methodologies and interventions* (pp. 1-12). Hoboken, NJ: Wiley-Blackwell.

Riege, W. H., Metter, E. J., & Hanson, W. R. (1980). Verbal and nonverbal recognition memory in aphasic and nonaphasic stroke patients. *Brain and Language, 10,* 60-70.

Roediger, H. L., & McDermott, K. B. (1995). Creating false memories: Remembering words not presented in lists. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21*, 803-814.

Roediger, H. L., Watson, J. M., McDermott, K. B., & Gallo, D. A. (2001). Factors that determine false recall: A multiple regression analysis. *Psychonomic Bulletin & Review, 8,* 385-407.

Romanski, L. M., & Diehl, M. M. (2011). Neurons responsive to face-view in the primate ventrolateral prefrontal cortex. *Neuroscience, 189,* 223-235.

Rosenkilde, C. E., Bauer, R. H., & Fuster, J. M. (1981). Single cell activity in ventral prefrontal cortex of behaving monkeys. *Brain Research,* 209, 375-394.

Rosenkranz, K., Nitsche, M. A., Tergau, F., & Paulus, W. (2000). Diminution of training-induced transient motor cortex plasticity by weak transcranial direct current stimulation in the human. *Neuroscience Letters, 296,* 61-63.

Rosenmund, C.., Feltz, A., & Westbrook, G. L. (1995). Calcium-dependent inactivation of synaptic NMDA receptors in hippocampal neurons. *Journal of Neurophysiology, 73,* 427-430.

Rossi, S. (2009). Safety of TMS Consensus Group: safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120,* 2008-2039.

Rossi, S., Cappa, S. F., Babiloni, C., Pasqualetti, P., Miniussi, C., Carducci, F., ... & Rossini, P. M. (2001). Prefontal cortex in long-term memory: an "interference" approach using magnetic stimulation. *Nature Neuroscience, 4*, 948-952.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: An update. *Clinical Neurophysiology, 122*, 1686. doi: http://dx.doi.org/10.1016/j.clinph.2010.12.037

Rossi, S., Innocenti, I., Polizzotto, N. R., Feurra, M., De Capua, A., Ulivelli, M., ... & Cappa, S. F. (2010). Temporal dynamics of memory trace formation in the human prefrontal cortex. *Cerebral Cortex, 21*, 368-373.

Rugg, M. D., Johnson, J. D., Park, H., & Uncapher, M. R. (2008). Encoding-retrieval overlap in human episodic memory: a functional neuroimaging perspective. *Progress in Brain Research, 169*, 339-352.

Rugg, M.D., Johnson, J.D., & Uncapher, M.R. (2015). Encoding and retrieval in episodic memory. In D.R. Addis, M. Barense, & A. Duarte (Eds.), *The wiley handbook on the cognitive neuroscience of memory* (pp. 84-107). Chichester, England: John Wiley & Sons, Ltd.

Ruohonen, J., & Karhu, J. (2012). tDCS possibly stimulates glial cells. *Clinical Neurophysiology, 123*, 2006-2009.

Ruzzoli, M., Marzi, C. A., & Miniussi, C. (2010). The neural mechanisms of the effects of transcranial magnetic stimulation on perception. *American Journal of Physiology-Heart and Circulatory Physiology, 103*, 2982-2989.

Sallet, J., Mars, R., Quilodran, R., Procyk, E., Petrides, M., & Rushworth, M. (2011). Neuroanatomical basis of motivational and cognitive control: a focus on the medial and lateral prefrontal cortex. *Neural basis of motivational and cognitive control*, 5-20.

Sams, M., Hari, R., Rif, J., & Knuutila, J. (1993). The human auditory sensory memory trace persists about 10 sec: neuromagnetic evidence. *Journal of Cognitive Neuroscience, 5*, 363-370.

Sandrini, M., Cappa, S. F., Rossi, S., Rossini, P. M., & Miniussi, C. (2003). The role of prefrontal cortex in verbal episodic memory: rTMS evidence. *Journal of Cognitive Neuroscience, 15*, 855-861.

Sandrini, M., Rossini, P. M., & Miniussi, C. (2008). Lateralized contribution of prefrontal cortex in controlling task-irrelevant information during verbal and spatial working memory tasks: rTMS evidence. *Neuropsychologia, 46*, 2056-2063.

Sandrini, M., Brambilla, M., Manenti, R., Rosini, S., Cohen, L. G., & Cotelli, M. (2014). Noninvasive stimulation of prefrontal cortex strengthens existing episodic memories and reduces forgetting in the elderly. *Frontiers in Aging Neuroscience, 6*, 289.

Sandrini, M., Manenti, R., Brambilla, M., Cobelli, C., Cohen, L. G., & Cotelli, M. (2016). Older adults get episodic memory boosting from noninvasive stimulation of prefrontal cortex during learning. *Neurobiology of Aging, 39*, 210-216.

Sandrini, M., Censor, N., Mishoe, J., & Cohen, L. G. (2013). Causal role of prefrontal cortex in strengthening of episodic memories through reconsolidation. *Current Biology, 23*, 2181-2184.

Santarnecchi, E., Feurra, M., Galli, G., Rossi, A., & Rossi, S. (2013). Overclock your brain for gaming? Ethical, social and health care risks. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 6*, 713-714.

Saturnino, G. B., Antunes, A., & Thielscher, A. (2015). On the importance of electrode parameters for shaping electric field patterns generated by tDCS. *Neuroimage, 120*, 25-35.

Schacter, D. L., Cendan, D. L., Dodson, C. S., & Clifford, E. R. (2001). Retrieval conditions and false recognition: Testing the distinctiveness heuristic. *Psychonomic Bulletin & Review, 8,* 827-833.

Schacter, D. L., Israel, L., & Racine, C. (1999). Suppressing false recognition in younger and older adults: The distinctiveness heuristic. *Journal of Memory and Language, 40,* 1-24.

Schacter, D. L., Norman, K. A., & Koutstaal, W. (1998). The cognitive neuroscience of constructive memory. *Annual Review of Psychology, 49,* 289-318.

Schmolck, H., Qureshi, S.U., & Schulz, P.E. (2011). Neuropsychiatry and behavioral neurology. In L.A. Rolak (Ed.), *Neurology Secrets.* (5th ed., pp. 247-260). Philadelphia, PA: Mosby Elsevier.

Sehm, B., Kipping, J. A., Schäfer, A., Villringer, A., & Ragert, P. (2013). A comparison between uni-and bilateral tDCS effects on functional connectivity of the human motor cortex. *Frontiers in Human Neuroscience, 7,* 183.

Siebner, H. R., Lang, N., Rizzo, V., Nitsche, M. A., Paulus, W., Lemon, R. N., & Rothwell, J. C. (2004). Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *Journal of Neuroscience, 24,* 3379-3385.

Siegert, R. J., Medvedev, O., & Turner-Stokes, L. (2018). Dimensionality and scaling properties of the Patient Categorisation Tool in patients with complex rehabilitation needs following acquired brain injury. *Journal of Rehabilitation Medicine, 50,* 435-443.

Silas, J., & Brandt, K. R. (2016). Frontal transcranial direct current stimulation (tDCS) abolishes list-method directed forgetting. *Neuroscience Letters, 616,* 166-169.

Simonsmeier, B. A., Grabner, R. H., Hein, J., Krenz, U., & Schneider, M. (2018). Electrical brain stimulation (tES) improves learning more than performance: a meta-analysis. *Neuroscience & Biobehavioral Reviews, 84,* 171-181.

Silvanto, J., & Muggleton, N. G. (2008). Testing the validity of the TMS state-dependency approach: targeting functionally distinct motion-selective neural populations in visual areas V1/V2 and V5/MT+. *Neuroimage, 40,* 1841-1848.

Silvanto, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2007). Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. *European Journal of Neuroscience, 25,* 1874-1881.

Silvanto, J., & Pascual-Leone, A. (2008). State-dependency of transcranial magnetic stimulation. *Brain Topography, 21*, 1.

Simmons, J. P., Nelson, L. D., & Simonsohn, U. (2011). False-positive psychology: Undisclosed flexibility in data collection and analysis allows presenting anything as significant. P*sychological Science, 22,* 1359-1366.

Shastri, L. (2002). Episodic memory and cortico–hippocampal interactions. *Trends in Cognitive Sciences, 6,* 162-168.

Shenoy, S., Bose, A., Chhabra, H., Dinakaran, D., Agarwal, S. M., Shivakumar, V., ... & Venkatasubramanian, G. (2015). Transcranial direct current stimulation (tDCS) for auditory verbal hallucinations in schizophrenia during pregnancy: a case report. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 8,* 163-164.

Shiffrin, R. M. (1975). Short-term store: The basis for a memory system. *Cognitive Theory, 1*, 193-218.

Shiffrin, R. M., & Atkinson, R. C. (1969). Storage and retrieval processes in long-term memory. *Psychological Review, 76,* 179-193. doi: http://dx.doi.org/10.1037/h0027277

Smirni, D., Turriziani, P., Mangano, G. R., Cipolotti, L., & Oliveri, M. (2015). Modulating memory performance in healthy subjects with transcranial direct current stimulation over the right dorsolateral prefrontal cortex. *PloS One, 10,* e0144838.

Smith, M. C., Bentin, S., & Spalek, T. M. (2001). Attention constraints of semantic activation during visual word recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 27,* 1289-1298.

Snodgrass, J. G., & Corwin, J. (1988). Pragmatics of measuring recognition memory: applications to dementia and amnesia. *Journal of Experimental Psychology: General, 117,* 34-50.

Snyder, H. R., Banich, M. T., & Munakata, Y. (2011). Choosing our words: retrieval and selection processes recruit shared neural substrates in left ventrolateral prefrontal cortex. *Journal of Cognitive Neuroscience, 23,* 3470-3482.

Sohn, M. H., Goode, A., Stenger, V. A., Carter, C. S., & Anderson, J. R. (2003). Competition and representation during memory retrieval: Roles of the prefrontal cortex and the posterior parietal cortex. *Proceedings of the National Academy of Sciences, 100,* 7412-7417.

Solé-Padullés, C., Bartres-Faz, D., Junqué, C., Clemente, I. C., Molinuevo, J. L., Bargalló, N., ... & Valls-Solé, J. (2005). Repetitive transcranial magnetic stimulation effects on brain function and cognition among elders with memory dysfunction. A randomized sham-controlled study. *Cerebral Cortex, 16,* 1487-1493.

Souchay, C., Isingrini, M., & Gil, R. (2002). Alzheimer's disease and feeling-of-knowing in episodic memory. *Neuropsychologia, 40,* 2386-2396.

Souza, M. J., Donohue, S. E., & Bunge, S. A. (2009). Controlled retrieval and selection of action-relevant knowledge mediated by partially overlapping regions in left ventrolateral prefrontal cortex. *Neuroimage, 46,* 299-307.

Spaniol, J., Davidson, P. S., Kim, A. S., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia, 47,* 1765-1779.

Spataro, P., Mulligan, N. W., Bechi Gabrielli, G., & Rossi-Arnaud, C. (2017). Divided attention enhances explicit but not implicit conceptual memory: an item-specific account of the attentional boost effect. *Memory, 25,* 170-175.

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature, 437,* 1272-1278.

Sturm, V. E., Haase, C. M., & Levenson, R. W. (2016). Emotional dysfunction in psychopathology and neuropathology: neural and genetic pathways. In T. Lehner, B. L. Miller, & M. W. State, *Genomics, circuits, and pathways in clinical neuropsychiatry* (pp. 345-364). London: Academic Press.

Squire, L. R. (1982). The neuropsychology of human memory. *Annual Review of Neuroscience, 5,* 241-273.

Squire, L. R. & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology, 5,* 169–177.

Squire, L. R. & Kandel, E. R. (1999) *Memory: from mind to molecules*. New York: W. H. Freedman & Co.

Sreeraj, V. S., Bose, A., Shanbhag, V., Narayanaswamy, J. C., Venkatasubramanian, G., & Benegal, V. (2016). Monotherapy with tDCS for treatment of depressive episode during pregnancy: a case report. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 9,* 457-458.

Stagg, C. J., Bachtiar, V., Amadi, U., Gudberg, C. A., Ilie, A. S., Sampaio-Baptista, C., ... & Near, J. (2014). Local GABA concentration is related to network-level resting functional connectivity. *Elife, 3,* e01465.

Stagg, C. J., Bachtiar, V., & Johansen-Berg, H. (2011). The role of GABA in human motor learning. *Current Biology, 21*, 480-484.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., ... & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters

by transcranial stimulation. *Journal of Neuroscience, 29,* 5202-5206. Doi: 10.1523/JNEUROSCI.4432-08.2009

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17,* 37-53.

Staresina, B. P., Gray, J. C., & Davachi, L. (2008). Event congruency enhances episodic memory encoding through semantic elaboration and relational binding. *Cerebral Cortex, 19,* 1198-1207.

Stark, C. E., Okado, Y., & Loftus, E. F. (2010). Imaging the reconstruction of true and false memories using sensory reactivation and the misinformation paradigms. *Learning & Memory, 17,* 485-488.

Stuss, D. T., Alexander, M. P., Palumbo, C. L., Buckle, L., Sayer, L., & Pogue, J. (1994). Organizational strategies with unilateral or bilateral frontal lobe injury in word learning tasks. *Neuropsychology, 8,* 355-373. doi: http://dx.doi.org/10.1037/0894-4105.8.3.355

Suddendorf, T., & Corballis, M. C. (1997). Mental time travel and the evolution of the human mind. *Genetic Social and General Psychology Monographs, 123,* 133–167.

Summers, J. J., Kang, N., & Cauraugh, J. H. (2016). Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta-analysis. *Ageing Research Reviews, 25,* 42-54.

Szczepanski, S. M., & Knight, R. T. (2014). Insights into human behavior from lesions to the prefrontal cortex. *Neuron, 83,* 1002-1018.

Takahashi, E., Ohki, K., & Kim, D. S. (2007). Diffusion tensor studies dissociated two fronto-temporal pathways in the human memory system. *Neuroimage, 34,* 827-838.

Talsma, L. J., Kroese, H. A., & Slagter, H. A. (2017). Boosting cognition: effects of multiple-session transcranial direct current stimulation on working memory. *Journal of Cognitive Neuroscience, 29,* 755-768.

Téllez-Alanís, B., & Cansino, S. (2004). Incidental and intentional encoding in young and elderly adults. *Neuroreport, 15,* 1819-1823.

Teo, F., Hoy, K. E., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Investigating the role of current strength in tDCS modulation of working memory performance in healthy controls. *Frontiers in Psychiatry*, *2*, 45.

Tranchina, D., & Nicholson, C. (1986). A model for the polarization of neurons by extrinsically applied electric fields. *Biophysical Journal, 50,* 1139-1156.

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Frontiers in Neuroscience*, *11*, 641.

Thompson-Schill, S. L., Jonides, J., Marshuetz, C., Smith, E. E., D'Esposito, M., Kan, I. P., ... & Swick, D. (2002). Effects of frontal lobe damage on interference effects in working memory. *Cognitive, Affective, & Behavioral Neuroscience, 2,* 109-120.

Tseng, P., Hsu, T. Y., Chang, C. F., Tzeng, O. J., Hung, D. L., Muggleton, N. G., ... & Juan, C. H. (2012). Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *Journal of Neuroscience, 32,* 10554-10561.

Tsuchida, A., & Fellows, L. K. (2009). Lesion evidence that two distinct regions within prefrontal cortex are critical for n-back performance in humans. *Journal of Cognitive Neuroscience, 21*, 2263-2275.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson, Organization of memory. Oxford, England: Academic Press.

Tulving, E. (1984). Precis of elements of episodic memory. *Behavioral and Brain Sciences*, *7*, 223-238.

Tulving, E. (1998). Brain/mind correlates of human memory. In M. Sabourin, F. Craik, & M. Robert (Eds.), *Advances in psychological science, Vol. 2. Biological and cognitive*

aspects (pp. 441-460). Hove, England: Psychology Press/Erlbaum (UK) Taylor & Francis.

Tulving, E. (2002a). Chronesthesia: Conscious awareness of subjective time. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 311-325). New York, NY, US: Oxford University Press. doi: http://dx.doi.org/10.1093/acprof: oso/9780195134971.003.0020

Tulving, E. (2002b). Episodic memory: from mind to brain. *Annual Review of Psychology, 53*, 1-25.

Tulving, E. (2005). Episodic memory and autonoesis: uniquely human?. In H.S. Terrace & J. Metcalfe (Eds.), *The missing link in cognition: origins of self-reflective consciousness* (pp. 3-56). New York, NY: Oxford University Press.

Turriziani, P., Smirni, D., Zappalà, G., Mangano, G.R., Oliveri, M., & Cipolotti, L. (2012). Enhancing memory performance with rTMS in healthy subjects and individuals with Mild Cognitive Impairment: the role of the right dorsolateral prefrontal cortex. *Frontiers in Human Neuroscience, 6*, 62.

Tussing, A. A., & Greene, R. L. (1997). False recognition of associates: How robust is the effect?. *Psychonomic Bulletin & Review, 4*, 572-576.

Uncapher, M. R., Boyd-Meredith, J. T., Chow, T. E., Rissman, J., & Wagner, A. D. (2015). Goal-directed modulation of neural memory patterns: Implications for fMRI-based memory detection. *Journal of Neuroscience, 35*, 8531-8545.

Ullman, M. T. (2015). The declarative/procedural model: a neurobiological model of language learning, knowledge, and use. In G. Hickok & S.L. Small (Eds.), *Neurobiology of language* (pp. 953-968). London, UK: Academic Press.

Ursino, M., Cuppini, C., & Magosso, E. (2010). A computational model of the lexical-semantic system based on a grounded cognition approach. *Frontiers in Psychology, 1*, 221.

Vacas, S.M., Stella, F., Loureiro, J.C., do Couto, F.S., Oliveira-Maia, A.J. &, Forlenza, O.V. (2018). Noninvasive brain stimulation for behavioural and psychological symptoms of dementia: A systematic review and meta-analysis. *International Journal of Geriatric Psychiatry.* doi: https://doi.org/10.1002/gps.5003

Vanderhasselt, M. A., De Raedt, R., Baeken, C., Leyman, L., Clerinx, P., & D'haenen, H. (2007). The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes. *Brain Research, 1137,* 111-116.

Vandermeeren, Y., Jamart, J., & Ossemann, M. (2010). Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. *BMC Neuroscience, 11,* 38.

Van Horn, J. D., Irimia, A., Torgerson, C. M., Chambers, M. C., Kikinis, R., & Toga, A. W. (2012). Mapping connectivity damage in the case of Phineas Gage. *PloS One, 7,* e37454.

Vannorsdall, T. D., van Steenburgh, J. J., Schretlen, D. J., Jayatillake, R., Skolasky, R. L., & Gordon, B. (2016). Reproducibility of tDCS results in a randomized trial: failure to replicate findings of tDCS-induced enhancement of verbal fluency. *Cognitive and Behavioral Neurology, 29,* 11-17.

Veltman, D. J., Rombouts, S. A., & Dolan, R. J. (2003). Maintenance versus manipulation in verbal working memory revisited: an fMRI study. *Neuroimage, 18,* 247-256.

Vidal-Piñeiro, D., Martin-Trias, P., Arenaza-Urquijo, E. M., Sala-Llonch, R., Clemente, I. C., Mena-Sánchez, I., ... & Bartrés-Faz, D. (2014). Task-dependent activity and connectivity predict episodic memory network-based responses to brain stimulation in healthy aging. *Brain Stimulation, 7,* 287-296.

Vigod, S., Dennis, C. L., Daskalakis, Z., Murphy, K., Ray, J., Oberlander, T., ... & Blumberger, D. (2014). Transcranial direct current stimulation (tDCS) for treatment of

major depression during pregnancy: study protocol for a pilot randomized controlled trial. *Trials, 15,* 366.

Vilberg, K. L., & Rugg, M. D. (2012). The neural correlates of recollection: transient versus sustained FMRI effects. *Journal of Neuroscience, 32,* 15679-15687.

Wagner, A. D., Poldrack, R. A., Eldridge, L. L., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport, 9,* 3711-3717.

Westwood, S. J., & Romani, C. (2017). Transcranial direct current stimulation (tDCS) modulation of picture naming and word reading: A meta-analysis of single session tDCS applied to healthy participants. *Neuropsychologia, 104*, 234-249.

Westwood, S. J., & Romani, C. (2018). Null Effects on Working Memory and Verbal Fluency Tasks When Applying Anodal tDCS to the Inferior Frontal Gyrus of Healthy Participants. Frontiers in Neuroscience, 12, 166.

Wais, P. E., Kim, O. Y., & Gazzaley, A. (2012). Distractibility during episodic retrieval is exacerbated by perturbation of left ventrolateral prefrontal cortex. *Cerebral Cortex, 22,* 717-724.

Walsh, V. Q. (2013). Ethics and social risks in brain stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 6,* 715-717.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1*, 73-80.

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia, 37,* 125-136.

Wang, S. H., de Oliveira Alvares, L., & Nader, K. (2009). Cellular and systems mechanisms of memory strength as a constraint on auditory fear reconsolidation. *Nature Neuroscience, 12,* 905-912.

Waddill, P. J., & McDaniel, M. A. (1998). Distinctiveness effects in recall. *Memory & Cognition, 26,* 108-120.

Watier, N., & Collin, C. (2012). The effects of distinctiveness on memory and metamemory for face–name associations. *Memory, 20,* 73-88.

Wheeler, M. A., Stuss, D. T., & Tulving, E. (1997). Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychological Bulletin, 121,* 331-354.

Whitehouse, P. J. (1981). Imagery and verbal encoding in left and right hemisphere damaged patients. *Brain and Language, 14,* 315-332.

Wilding, E. L., & Rugg, M. D. (1996). An event-related potential study of recognition memory with and without retrieval of source. *Brain, 119,* 889-905.

Williams, H.L., Conway, M.A., & Cohen, G. (2008). Autobiographical memory. In G. Cohen & M.A. Conway (Eds.), *Memory in the real world* (3rd ed, pp. 21-90). Hove, England: Psychology Press.

Willis, M. L., Murphy, J. M., Ridley, N. J., & Vercammen, A. (2015). Anodal tDCS targeting the right orbitofrontal cortex enhances facial expression recognition. *Social Cognitive and Affective Neuroscience, 10,* 1677-1683.

Wimber, M., Heinze, H. J., & Richardson-Klavehn, A. (2010). Distinct frontoparietal networks set the stage for later perceptual identification priming and episodic recognition memory. *Journal of Neuroscience, 30,* 13272-13280.

Windey, B., Gevers, W., & Cleeremans, A. (2013). Subjective visibility depends on level of processing. *Cognition, 129,* 404-409.

Winograd, E. (1981). Elaboration and distinctiveness in memory for faces. *Journal of Experimental Psychology: Human Learning and Memory, 7,* 181-190.

Wollen, K. A., & Cox, S. D. (1981). Sentence cuing and the effectiveness of bizarre imagery. *Journal of Experimental Psychology: Human Learning and Memory, 7,* 386-392.

Wolters, G., & Raffone, A. (2008). Coherence and recurrency: Maintenance, control and integration in working memory. *Cognitive Processing, 9,* 1-17.

Wong, J. T., Cramer, S. J., & Gallo, D. A. (2012). Age-related reduction of the confidence–accuracy relationship in episodic memory: Effects of recollection quality and retrieval monitoring. *Psychology and Aging*, *27*, 1053-1065.

Wong, L. Y., Gray, S. J., & Gallo, D. A. (2018). Does tDCS over prefrontal cortex improve episodic memory retrieval? Potential importance of time of day. *Cognitive Neuroscience, 9,* 167-180.

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., ... & Knotkova, H. (2016). A technical guide to tDCS, and related NIBS tools. *Clinical Neurophysiology, 127*, 1031-1048.

Wu, S., Wang, H., Chen, C., Zou, J., Huang, H., Li, P., ... & Pandit, S. (2017). Task performance modulates functional connectivity involving the dorsolateral prefrontal cortex in patients with schizophrenia. *Frontiers in Psychology, 8,* 56.

Xia, G., Gajwani, P., Muzina, D. J., Kemp, D. E., Gao, K., Ganocy, S. J., & Calabrese, J. R. (2008). Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. *International Journal of Neuropsychopharmacology, 11*, 119-130.

Zich, C., Harty, S., Kranczioch, C., Mansfield, K. L., Sella, F., Debener, S., & Kadosh, R. C. (2017). Modulating hemispheric lateralization by brain stimulation yields gain in mental and physical activity. *Scientific Reports, 7,* 13430.

Zimmer, H., & Steiner, A. (2003). Colour specificity in episodic and in perceptual object recognition with enhanced colour impact. *European Journal of Cognitive Psychology, 15*, 349-370.

Zwaan, R. A. (1996). Processing narrative time shifts. Journal of Experimental Psychology: *Learning, Memory, and Cognition, 22*, 1196.

Zwissler, B., Sperber, C., Aigeldinger, S., Schindler, S., Kissler, J., & Plewnia, C. (2014). Shaping memory accuracy by left prefrontal transcranial direct current stimulation. *Journal of Neuroscience, 34*, 4022-4026.

APPENDIX A

Information sheet for Experiments 1-2 and 4-5

Note: Minor changes were made between experiments, including data withdrawal date. For Experiment 3, the information sheet included nearly identical information in Russian and was in line with ethical guidelines at Moscow Higher Research University.

Investigation of memory functions through Transcranial Electrical Stimulation

Healthy young adults between the ages of 18 and 30 are invited to take part in studies which form part of a research programme investigating patterns of activity in the brain that are linked to mental functions such as attention, language and memory. The research aims to uncover new information about how these functions work and how they are organized in the brain using a technique named Transcranial Electrical Stimulation. This is an entirely safe technique that does not induce pain or side effects.

You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without having to give a reason and without penalties. Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish.

You will be invited to attend our laboratory at a mutually convenient time. On arrival at the laboratory you will be given information about the study, and you will have the chance to ask the experimenter any question about the study and to discuss any concern. If you agree to take part in the study, you would then sit in front of the computer screen and perform one or more psychological tasks giving judgements with the keyboard. The specific task(s) you are asked to do would differ depending on the exact study you are part of, but would involve doing things reading and memorizing words and deciding what they mean, deciding which of a series of pictures was presented in an earlier part of the study, and so on. During this, we would place two electrodes on your scalp to stimulate your brain. Especially at the very beginning, the stimulation may induce a minor discomfort and tingling sensation. This is supposed to last only for a few seconds. The stimulation would last twenty min. During this time, you would be in continuous contact with the investigator, and would be given regular rest breaks. The electrodes would be removed at the end of the experiment. There is no risk involved in this brain stimulation technique. All proposals for research using human subjects are reviewed by an ethics committee before they can proceed.

Data Protection Act, 1998: This Act requires that the reasons and methods for the above research must be explained to you. In consenting to participate in the study, you are stating that you have no objection to personal data relating to yourself (as defined by the Data Protection Act, 1998), being used for this research. The personal information that you give would be used for the above study only and it would not be used for any other purpose. In the reporting of the project, no information will be released which will enable to reader to identify who the respondent was. Your personal information would be kept for up to ten years, and then would be confidentially destroyed. You have a legal right to view your personal information stored with us. You have the right to withdraw your data from the study up until **30th June 2018**, if you wish to do so for any reason.

Person who should be contacted for further information:

Dr Giulia Galli
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Kingston University

Penrhyn Road
Kingston Upon Thames
Surrey KT1 2EE
Email: g.galli@kingston.ac.uk
Telephone: 020 8417 9000

APPENDIX B

Informed consent form for Experiments 1-2 and 4-5

Note: Minor changes were made between experiments, including project title and data withdrawal date. For Experiment 3, the consent form included nearly identical information in Russian and was in line with ethical guidelines at Moscow Higher Research University. Contraindications for tDCS are in items 12 and 13.

Project Title: _____

1 I have read the information sheet about this study
YES/NO

2 I have had an opportunity to ask questions and discuss this study
YES/NO

3 I have received satisfactory answers to all your questions
YES/NO

4 I have received enough information about this study
YES/NO

6 I understand that I am free to withdraw from this study

*At any time
YES/NO
*Without giving a reason for withdrawing
YES/NO

7 I understand that I can withdraw my data from the study
YES/NO
up until June 30th, 2018

8 I understand that all information obtained will be confidential
YES/NO

9 I agree that research data gathered for the study may be published
YES/NO
provided that I cannot be identified as a subject

10 Contact information has been provided should I (a) wish to seek

YES/NO
further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.

11 I agree to take part in this study
YES/NO

12 I have a personal or family history of epileptic fits or seizures
YES/NO

13 I could be pregnant
YES/NO/NA

Signed_____
Date_____

Name of volunteer (block letters)_____

Name of Investigator_____

Signature of Investigator_____

APPENDIX C

Information sheet for Chapter 7

STUDY INFORMATION SHEET

This study investigates how your brain forms new memories using Transcranial Magnetic Stimulation (TMS). TMS is a safe and non-invasive technique of brain stimulation that involves the application of transient magnetic fields on your scalp. This leads to temporary changes in the excitability of neurons which in turn alter brain functions in a temporary and reversible way. During the administration of TMS you will hear a sound connected to the administration of the TMS pulse. You may also feel some discomfort on your skin and painful sensations at the same time. The study will take place in the TMS laboratory of the Department of Psychology (Cognitive Labs: 2nd Floor Rm 2021 Parkstead House) and will involve 20 participants in total.

You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without having to give a reason and without penalties. Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish.

On arrival at the laboratory, the experimenter will first ask you to fill out a short questionnaire to assess whether you are eligible to take part in the study. This is because in some specific conditions TMS may induce side effects, and we want to make sure that this does not happen to you. You have completed this questionnaire already when you signed up to the study, we ask you to respond to the questions again now. Please reply to the questionnaire carefully and honestly. The experimenter will then identify the location on your scalp where the stimulation will be administered. This will take up to 45 min. You will then be seated and asked to perform a memory task while the stimulation occurs every 2 seconds or so. In this task, you will be asked to memorize single words or pairs of words. You will be asked to retrieve them. Altogether, the experiment is going to take two hours. You will be in continuous contact with the investigator, and will be given regular rest breaks. The task will last one hour approximately. Your personal information will be kept confidential, and only authorized people will have access to it for research purposes only.

Data Protection Act, 1998: This Act requires that the reasons and methods for the above research must be explained to you. In consenting to participate in the study, you are stating that you have no objection to personal data relating to yourself (as defined by the Data Protection Act, 1998), being used for this research. The personal information that you give would be used for the above study only and it would not be used for any other purpose. In the reporting of the project, no information will be released which will enable to reader to identify who the respondent was. Your personal information would be kept for up to ten years, and then would be confidentially destroyed. You have a legal right to view your personal information stored with us. You have the right to withdraw your data from the study at any time if you wish to do so for any reason, although your data may still be used in a collated form in scholarly publications or presentations.

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APPENDIX D

Informed consent form for Chapter 7

PARTICIPANT CONSENT FORM

University of Roehampton London

Participant Identification Number (ID Number):

|___|___|___| (to be filled in by the researcher)

Please note that this document must be given along with the Study Information Sheet

BACKGROUND INFORMATION

Title of Research Project: When are new memories formed in the brain? A NIBS study

Researchers: Dr Giorgio Fuggetta (lead, Department of Psychology Roehampton University), Dr Giulia Galli (Kingston University), Ms Angela Medvedeva (Kingston University) and Ms Rebecca Saw (Roehampton University).

Summary of details of participation: You are required to perform a memory task while we apply Transcranial Magnetic Stimulation on your scalp. This should take approximately 2 hours. For further information see Study Information Sheet.

CONSENT STATEMENT

-I have been given a full explanation by the investigator(s) of the nature, purpose, location and likely duration of the study and of what I will be expected to do.
-I have been given the opportunity to ask questions on all aspects of the study and have understood the advice and information given as a result.
-I have read and understood the Study Information Sheet provided.
-I have completed the TMS screening form accurately.
-I understand that the information I provide will be treated in confidence by the investigator and that my identity will be protected in the publication of any findings, and that data will be collected and processed in accordance with the Data Protection Act 1998 and with the University's Data Protection Policy.

-I agree to comply with instructions given to me during the study and to co-operate fully with the investigators.
-I am in between 18 and 30 years of age, and have no history of, and am taking no medication for, any psychiatric -disorders or diseases, or any neurological disorders or diseases.
-I agree to participate and am aware that I am free to withdraw at any point without giving a reason, although if I do so I understand that my data might still be used in a collated form.

Participant's Name and Surname (please print in capital letters):
|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Participant's signature:

_____

Date:| DD | MM | YYYY | **Date of Birth** (DoB):| DD | MM | YYYY |

Gender: **M** / **F / Other** (please circle as appropriate).

Please note: if you have a concern about any aspect of your participation or any other queries please raise this with the lead investigator. However if you would like to contact an independent party please contact the Head of Department.

Dr Giulia Galli, co-investigator E-mail: g.galli@kingston.ac.uk	Ms Angela Medvedeva Research assistant PhD student at Kingston University Collaborator on the project	Ms Rebecca Saw PhD student at the University of Roehampton Collaborator on the project

Lead investigator: Dr Giorgio Fuggetta, Department of Psychology, University of Roehampton, Whitelands College, Holybourne Avenue London SW15 4JD E-mail: giorgio.fuggetta@roehampton.ac.uk Telephone: 020 8392 3409	**Head of Department:** Dr Diane Bray, Department of Psychology, University of Roehampton, Whitelands College, Holybourne Avenue London SW15 4JD E-mail: d.bray@roehampton.ac.uk Telephone: 020 8392 3627

APPENDIX E

Instructions for study phase for Experiments 1-2 and 4-5 and Chapters 6-7

Note: The instructions for Experiment 3 were identical, following a direct translation to Russian.

INSTRUCTIONS

In this part of the experiment we ask you to perform very easy judgements on words that will appear quickly on the screen followed by a cross. You will have to judge whether the word refers to a pleasant or an unpleasant object. Try to be as spontaneous as possible. Keep in mind that there are no right or wrong answers. If you feel like you can't express a judgment, give the first answer that comes into your mind. Also try to memorize each word, because I will later ask you to recall some of them.

Please place your left index finger on the keyboard letter A and your right index finger on the keyboard letter L. If you think the word refers to a pleasant object press the A key (left index finger). If you think the word refers to an unpleasant object press the L key (right index finger). You can respond until the word is shown on the screen. There will be several breaks and opportunity to rest. Make sure that your fingers are always on the correct keyboard buttons, otherwise we won't be able to record your responses. If you take a break and move your hands away from the keyboard, always make sure you place your fingers back on the correct buttons when your start the experiment again.
Let's begin with a short practice. We can repeat the practice as many times as you like, until you feel confident with the task.

APPENDIX F

Instructions for the test phase for Experiments 1-2 and 4-5 and Chapter 7

Note: The instructions for Experiment 3 were identical, following a direct translation to Russian. Because the response key was counterbalanced, in each experiment, half the participants received the first set of instructions (L1), and the other half received the second set of instructions (R2). In L1, participants indicated that a word was previously-presented by pressing the A key with the left (L) hand, while in R2, they pressed the L key with the right (R) hand.

INSTRUCTIONS (L1)

Now we will test your memory for the words that you have seen in your previous phase.

You will see a lot of words appearing on the screen for a few seconds, one at the time. Some of these words will be new. Others will be words that you have seen in the previous phase. Your task will be to judge whether you have seen the word before or not.

Place your left index finger on the A key, and your right index finger on the L key. If you think you have seen the word before, press the A key with your LEFT index finger. If you think the word is new and was not among those you have seen in the previous phase, press the L key with your RIGHT index finger.

In this phase, it is even more important that you keep the finger on the correct buttons. If you take a break and move your hands away from the keyboard, always make sure you place your fingers back on the correct buttons when your start the experiment again. Please try to be as accurate as possible.

There will be several breaks and opportunity to rest. Let’s begin with a short practice. As for the previous phase, you can repeat the practice as many times as you like, until you feel confident with the task.

INSTRUCTIONS (R2)

Now we will test your memory for the words that you have seen in your previous phase.

You will see a lot of words appearing on the screen for a few seconds, one at the time. Some of these words will be new. Others will be words that you have seen in the previous phase. Your task will be to judge whether you have seen the word before or not.

Place your left index finger on the A key, and your right index finger on the L key. If you think you have seen the word before, press the L key with your RIGHT index finger. If you think the word is new and was not among those you have seen in the previous phase, press the A key with your LEFT index finger.

In this phase, it is even more important that you keep the finger on the correct buttons. You will see reminders on the screen to keep your fingers on the correct buttons. If you take a break and move your hands away from the keyboard, always make sure you place your fingers back on the correct buttons when your start the experiment again. Please try to be as accurate as possible.

There will be several breaks and opportunity to rest. Let’s begin with a short practice. As for the previous phase, you can repeat the practice as many times as you like, until you feel confident with the task.

APPENDIX G

Instructions for the test phase for Chapter 6

Note: The test instructions for Experiment 5 and Chapter 6 overlap, given that the experiments use the same sample but different indices of performance. The instructions for the source memory task discussed in Chapter 6 are in bold. The position of response options on the screen were randomised so that the correct answer sometimes appeared on the left side and other times on the right side. Thus, the response keys (Q and O) did not have to be counterbalanced.

INSTRUCTIONS (L1)

Now we will test your memory for the words that you have seen in your previous phase.

You will see a lot of words appearing on the screen for a few seconds, one at the time. Some of these words will be new. Others will be words that you have seen in the previous phase. Your task will be to judge whether you have seen the word before or not.

Place your left index finger on the A key, and your right index finger on the L key. If you think you have seen the word before, press the A key with your LEFT index finger. If you think the word is new and was not among those you have seen in the previous phase, press the L key with your RIGHT index finger.

Following some words, you will be asked to perform another task. This question is presented at random times, regardless of your response. You will be asked, "What colour was it presented on?" or "What word was after it?" If the question is presented after a word that you saw in the study phase, answer accordingly. If the question is presented for a word that do not remember seeing in the study phase, answer according to what makes most sense for that word (e.g. what background would fit best, or what word should follow it).

There will be two response options presented on the screen. Press Q to select the left option and O to select the right option.

In this phase, it is even more important that you keep the finger on the correct buttons. If you take a break and move your hands away from the keyboard, always make sure you place your fingers back on the correct buttons when your start the experiment again. Please try to be as accurate as possible.
There will be several breaks and opportunity to rest. Let's begin with a short practice. As for the previous phase, you can repeat the practice as many times as you like, until you feel confident with the task.

INSTRUCTIONS (R2)

Now we will test your memory for the words that you have seen in your previous phase.

You will see a lot of words appearing on the screen for a few seconds, one at the time. Some of these words will be new. Others will be words that you have seen in the previous phase. Your task will be to judge whether you have seen the word before or not.

Place your left index finger on the A key, and your right index finger on the L key. If you think you have seen the word before, press the L key with your RIGHT index finger. If you think the word is new and was not among those you have seen in the previous phase, press the A key with your LEFT index finger.

Following some words, you will be asked to perform another task. This question is presented at random times, regardless of your response. You will be asked, "What colour was it presented on?" or "What word was after it?" If the question is presented after a word that you saw in the study phase, answer accordingly. If the question is presented for a word that do not remember seeing in the study phase, answer according to what makes most sense for that word (e.g. what background would fit best, or what word should follow it).

There will be two response options presented on the screen. Press Q to select the left option and O to select the right option. You will see reminders on the screen of which key to press for which option.

In this phase, it is even more important that you keep the finger on the correct buttons. You will see reminders on the screen to keep your fingers on the correct buttons. If you take a break and move your hands away from the keyboard, always make sure you place your fingers back on the correct buttons when your start the experiment again. Please try to be as accurate as possible.

There will be several breaks and opportunity to rest. Let's begin with a short practice. As for the previous phase, you can repeat the practice as many times as you like, until you feel confident with the task.

APPENDIX H

Screening questionnaire for Experiments 4 and 5

Note: Screening questionnaire is reproduced from Antal and colleagues (2017).

SCREENING QUESTIONNAIRE FOR TRANSCRANIAL ELECTRICAL STIMULATION (TES)

YES NO

1 Do you have metal (except titanium) or electronic implants in the brain/skull (e.g., splinters, fragments, clips, cochlear implants, deep brain stimulation etc.)? If yes, please specify the type of metal and the location

_____

_____

2 Do you have metal or any electronic device at other sites in your body, such as a cardiac pacemaker or traumatic metallic residual fragments? If yes, please specify the device and the location

_____

3 Did you ever have surgical procedures involving your head or spinal cord? If yes, please specify the locations

_____

4 Have you ever had a head trauma followed by impairment of consciousness?

5 Do you have skin problems, such as dermatitis, psoriasis or eczema? If yes, please specify the location

_____

6 Do you have epilepsy or have you ever had convulsions, a seizure?

7 Did you ever have fainting spells or syncope?

8 Are you pregnant or is there any chance that you might be?

9 Are you taking any medications? If yes, please specify:

_____

10 Did you ever undergo transcranial electric or magnetic stimulation in the past? If yes, were there any adverse events? Please specify:

_____

An affirmative answer to one or more of questions do not represent an absolute contraindication to
TES, but the risk-benefit ratio should be carefully balanced by the Principal Investigator of the
research project or by the responsible (treating) physician.

Name _____ Surname _____

Date _____ Signature _____

APPENDIX I

Questionnaire of sensations and measure of blinding success for Experiments 4 and 5
Note: The questionnaire is reproduced from Antal and colleagues (2017). Blinding success is assessed with the question, "Do you believe that you received a real or placebo stimulation?"

Questionnaire of sensations related to transcranial electrical stimulation (TES)

(To be filled in by the participants and by the investigator)
Investigator:
Participant name/code:_____ **Date**: **/ / |**
Experiment/Treatment: _____
No stimulations experienced before ☐ **Experienced** ☐ # of **stimulations sessions before:**
…….
Type of electrical stimulation used here_____ **Intensity** ____mA (if known)
Electrodes dimension: anode (if known) ___*___ cathode (if known) ___*___ (shape _____)
other_____
Participant:
Did you experience any discomfort during the electrical stimulation? Please indicate the degree
of intensity of your discomfort according to the following scale:
- **None = I did not feel the sensation addressed**
- **Mild = I mildly felt the sensation addressed**
- **Moderate = I felt the sensation addressed**
- **Strong = I felt the sensation addressed to a considerable degree**

In the first stimulation block I felt (to be filled in by subject, if it is possible please separate the sensations with regard to the electrode positions):

None Mild Moderate Strong

Itching ☐ ☐ ☐ ☐

Pain ☐ ☐ ☐ ☐

Burning ☐ ☐ ☐ ☐

Warmth/Heat ☐ ☐ ☐ ☐

Metallic/Iron taste ☐ ☐ ☐ ☐

Fatigue/Decreased alertness☐ ☐ ☐ ☐

Other ☐ ☐ ☐ ☐

In case of perceived sensation, when did it begin*? (this part can be multiplied and completed for each sensation, e.g. one for pain, one for itching etc and could/should be modified according to the type of experiments)*

☐ At the beginning; ☐ At approximately in the middle; ☐ Towards the end of the

stimulation
Duration (multiple options allowed)
☐ Only initially ☐ It stopped in the middle of the block ☐ It stopped at the end of the
block
How much did these sensations affect your general state?
☐ Not at all ☐ Slightly ☐ Considerably ☐ Much ☐ Very much
Location of sensations:
☐ Diffuse ☐ localized ☐ close to the electrode, (which one?)_____; ☐ Other_____
If you would like to provide more details, please briefly describe the experimented sensations in
relation to the "Other" or "Fatigue" or ….. response:
In the second stimulation block
(if there is more than one condition, repeat the list above here based on the block numbers)
To be administered at the end of the entire experiment
Do you believe that you received a real or placebo stimulation?
In the first stimulation block/day/week: ☐ real ☐ placebo ☐ I don't know
In the second stimulation block/day/week: ☐ real ☐ placebo ☐ I don't know
Investigator*:*
Please report any adverse event/problem (typically skin irritation and redness – separately for
the electrodes -, headache, scalp pain, dizziness, or others, please specify) that occurred and rate
the event/problem on a scale from 0 to 3 as previously described.
_____
_____
_____
_____
_____
_____
Additional comments:
_____
_____
_____
_____
_____
___
A structured questionnaire on intensity and frequency of AEs increases safety, when transcranial electrical stimulation is used. It is a recommended procedure for publication of TES
experiments/trials.

APPENDIX J

Screening form for Chapter 7

Note: Screening form is reproduced from Rossi and colleagues (2009).

TMS SCREENING FORM (Rossi, Hallett, Rossini, & Pascual-Leone, 2011)

Please circle YES or NO as appropriate. Please ask the researcher to clarify any word you do not understand.

(1) Do you have epilepsy or have you ever had a convulsion or a seizure?	*YES*	*NO*
(2) Have you ever had a fainting spell or syncope?	*YES*	*NO*
(3) Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?	*YES*	*NO*
(4) Do you have any hearing problems or ringing in your ears?	*YES*	*NO*
(5) Do you have any cochlear implants?	*YES*	*NO*
(6) Are you pregnant or is there any chance that you might be?	*YES*	*NO*
(7) Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)?	*YES*	*NO*
(8) Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?	*YES*	*NO*
(9) Do you have a cardiac pacemaker or intracardiac lines?	*YES*	*NO*
(10) Do you have a medication infusion device?	*YES*	*NO*
(11) Do you suffer from chronic pain or do you have a low pain threshold?	*YES*	*NO*
(12) Are you taking any medications? (if yes, please list)	*YES*	*NO*
(13) Did you ever undergo TMS in the past? If yes, were there any problems?	*YES*	*NO*
(14) Did you ever undergo MRI in the past? If yes, were there any problems?	*YES*	*NO*

APPENDIX K

Verbal stimuli for Experiments 1-4

Table K1

English words with Russian equivalents and associated frequency and number of letters

English	Frequency	Letters	Russian	Frequency	Letters
ballerina	1	9	балерина	8.1	8
coyote	1	6	шакал	6.5	5
crocodile	1	9	крокодил	10.7	8
fireman	1	7	пожарный	24	8
panther	1	7	пантера	2.1	7
pheasant	1	8	фазан	1.8	5
butterfly	2	9	бабочка	21.3	7
drummer	2	7	ударник	4.5	7
gangster	2	8	бандит	42.8	6
peacock	2	7	павлин	2.4	6
spider	2	6	паук	9.9	4
pigeon	3	6	голубь	13.7	6
rooster	3	7	петух	16	5
butler	4	6	слуга	17.8	5
gardener	4	8	садовник	5.4	8
plumber	4	7	слесарь	9.3	7
nightingale	4	11	соловей	7.9	7
crane	5	5	журавль	5.2	7
decorator	5	9	маляр	2.7	5
fisherman	5	9	рыбак	21.9	5
kitten	5	6	котенок	14.5	7

photographer	5	12	фотограф	12.7	8
lecturer	6	8	лектор	3.9	6
oyster	6	6	устрица	3.6	7
tiger	7	5	тигр	15.2	4
butcher	8	7	мясник	3.1	6
hostess	8	7	хозяйка	54.2	7
turtle	8	6	черепаха	6.3	8
athlete	9	7	атлет	2.5	5
chef	9	4	повар	13.3	5
monkey	9	6	обезьяна	17.4	8
mouse	10	5	мышь	37	4
dentist	12	7	стоматолог	2.5	10
philosopher	16	11	философ	30.6	7
priest	16	6	священник	39.7	9
nurse	17	5	медсестра	16.1	9
seal	17	4	тюлень	2.6	6
merchant	20	8	купец	12.5	5
painter	21	7	художник	142.2	8
architect	22	9	архитектор	33.3	10
sheep	23	5	овца	17.5	4
witness	28	7	свидетель	55.7	9
clerk	34	5	секретарь	77	9
baker	36	5	пекарь	0.9	6
soldier	39	7	солдат	142.2	6
pope	40	4	поп	13.5	3
queen	41	5	королева	22.4	8

engineer	42	8	инженер	63.1	7
lawyer	43	6	юрист	20.8	5
snake	44	5	змея	20.5	4
detective	52	9	детектив	10.7	8
poet	99	4	поэт	155.1	4
acrobat	1	7	акробат	2.5	7
dinosaur	1	8	динозавр	3.1	8
dolphin	1	7	дельфин	7.6	7
frog	1	4	лягушка	10.5	7
grizzly	1	7	медведь	33.4	7
gymnast	1	7	гимнаст	1.6	7
mosquito	1	8	комар	15.2	5
moth	1	4	моль	5.2	4
octopus	1	7	осьминог	1.7	8
parrot	1	6	попугай	10	7
pharmacist	1	10	аптекарь	1.6	8
snail	1	5	улитка	3	6
accountant	2	10	бухгалтер	15.5	9
astronaut	2	9	космонавт	14.6	9
biologist	2	9	биолог	7.4	6
cockroach	2	9	таракан	10.3	7
guitarist	2	9	гитарист	2.8	8
postman	2	7	почтальон	4.9	9
wasp	2	4	оса	3.2	3
robin	2	5	снегирь	1.1	7
clown	3	5	клоун	13.9	5

shark	3	5	акула	9.3	5
swan	3	4	лебедь	14.9	6
gypsy	4	5	цыган	16.9	5
magician	4	8	маг	14.6	3
pilgrim	4	7	паломник	4.1	8
worm	4	4	червь	9.9	5
wolf	6	4	волк	36.1	4
dictator	7	8	диктатор	6.4	8
martyr	8	6	мученик	7.8	7
pig	8	3	свинья	23.1	6
duck	9	4	утка	13.1	4
journalist	10	10	журналист	97	9
psychologist	10	12	психолог	29.3	8
fox	13	3	лиса	8.7	4
politician	13	10	политик	45.5	7
lion	17	4	лев	64.3	3
knight	18	6	рыцарь	18.9	6
actor	24	5	актер	114.4	5
pilot	44	5	пилот	26.9	5
guard	48	5	сторож	14.4	6
dog	75	3	собака	132.2	6
doctor	100	6	доктор	143.1	6
helicopter	1	10	вертолет	38.7	8
horoscope	1	9	гороскоп	3.5	8
jeans	1	5	брюки	37.2	5
jumper	1	6	свитер	15	6

ketchup	1	7	кетчуп	1.5	6
robot	1	5	робот	8.7	5
notebook	2	8	блокнот	12.8	7
pyramid	2	7	пирамида	16	8
quiz	2	4	викторина	1.3	9
rooftop	2	7	крыша	85	5
shampoo	2	7	шампунь	6	7
volcano	2	7	вулкан	6	6
drone	3	5	шмель	3.5	5
kettle	3	6	чайник	21.5	6
keyboard	4	8	клавиатура	4.8	10
yacht	4	5	яхта	9.5	4
witch	5	5	ведьма	12.1	6
wrap	5	4	шарф	9.6	4
fingerprint	6	11	отпечаток	13.1	9
kidney	6	6	почка	16.2	5
graveyard	7	9	могила	50.9	6
riot	7	4	бунт	11.8	4
infection	8	9	инфекция	26	8
chocolate	9	9	шоколад	10.9	7
glove	9	5	перчатка	19.8	8
zoo	9	3	зоопарк	12.4	7
thumb	10	5	палец	219.1	5
juice	11	5	сок	35.8	3
bubble	12	6	пузырь	16.1	6
breeze	14	6	ветер	140.3	5

cafeteria	15	9	столовая	36.5	8
petition	15	8	петиция	1.1	7
jeep	16	4	джип	14.7	4
taxi	16	4	такси	30.6	5
flame	17	5	огонь	139.8	5
angel	18	5	ангел	32.4	5
candle	18	6	свеча	31.6	5
essay	19	5	эссе	5	4
jungle	20	6	джунгли	8.2	7
garage	21	6	гараж	26.6	5
monument	21	8	памятник	63.8	8
skirt	21	5	юбка	26.3	4
tsunami	21	7	цунами	1	6
exhibition	22	10	выставка	89.9	8
whisky	23	6	виски	14.2	5
storm	26	5	гроза	15.7	5
festival	27	8	праздник	115	8
prize	28	5	приз	22.4	4
wound	28	5	рана	29.4	4
fence	30	5	забор	48.3	5
network	30	7	сеть	105.5	4
root	30	4	корень	63.7	6
gallery	31	7	галерея	23.2	7
van	32	3	кузов	22.1	5
interview	34	9	интервью	44	8
ocean	34	5	океан	49.8	5

pencil	34	6	карандаш	46.6	8
bench	35	5	скамейка	29	8
stomach	37	7	живот	65.6	5
comedy	39	6	комедия	22.7	7
avenue	46	6	проспект	30.4	8
pocket	46	6	карман	120.5	6
ring	47	4	кольцо	59.5	6
breakfast	53	9	завтрак	28.3	7
lake	54	4	озеро	54.9	5
leg	58	3	нога	459.2	4
beach	61	5	пляж	25.4	4
dream	64	5	сон	152.7	3
traffic	68	7	проезд	15.7	6
rain	70	4	дождь	83.2	5
bottle	76	6	бутылка	117.1	7
knife	76	5	нож	66.6	3
neck	81	4	шея	85.3	3
window	119	6	окно	280.8	4
hotel	126	5	гостиница	68.9	9
letter	145	6	письмо	304.3	6
market	155	6	рынок	283.3	5
mailbox	1	7	почта	33	5
marathon	1	8	марафон	3	7
zombie	1	6	зомби	1.3	5
wrinkle	2	7	морщина	12.2	7
galaxy	3	6	галактика	12.5	9

lipstick	3	8	помада	9.1	6
napkin	3	6	салфетка	11.3	8
telescope	4	9	телескоп	3.8	8
treasure	4	8	сокровище	15.5	9
tribe	4	5	племя	23.1	5
itch	5	4	зуд	3.5	3
laundry	5	7	прачечная	3.4	9
passport	6	8	паспорт	49.6	7
signature	6	9	подпись	40.5	7
towel	6	5	полотенце	20.5	9
bargain	7	7	сделка	52.7	6
blossom	7	7	цветок	92.4	6
ink	7	3	чернила	10.5	7
postcard	7	8	открытка	18.9	8
knot	8	4	узел	48.6	4
lotion	8	6	лосьон	2.6	6
poison	10	6	яд	16.5	2
cliff	11	5	утес	6.3	4
doll	11	4	кукла	25.3	5
graduation	11	10	выпуск	62.5	6
sleeve	11	6	рукав	42.9	5
tear	11	4	слеза	114.2	5
canyon	12	6	ущелье	11.1	6
grill	12	5	решетка	29	7
toilet	13	6	туалет	35.1	6
auditorium	14	10	аудитория	31.9	9

bush	14	4	куст	60.9	4
picnic	15	6	пикник	4.1	6
gown	16	4	наряд	19.5	5
jaw	16	3	челюсть	17.1	7
lung	16	4	легкое	19.6	6
spray	16	5	струя	20.3	5
ticket	16	6	билет	75.4	5
kiss	17	4	поцелуй	21.1	7
airport	19	7	аэропорт	37.2	8
crown	19	5	корона	9.4	6
ham	19	3	ветчина	5	7
clock	20	5	часы	72.5	4
slide	20	5	каток	7.8	5
tent	20	4	палатка	29.1	7
jail	21	4	тюрьма	75.4	6
drug	24	4	лекарство	39.6	9
cocktail	25	8	коктейль	8.6	8
weekend	27	7	выходной	36	8
wedding	32	7	свадьба	39.6	7
gift	33	4	подарок	75.4	7
bus	34	3	автобус	64.8	7
tongue	35	6	язык	324.9	4
bomb	36	4	бомба	35.8	5
questionnaire	37	13	опросник	2.3	8
reception	38	9	приемная	14.7	8
drawing	40	7	рисунок	179.2	7

weapon	42	6	оружие	141.8	6
coat	43	4	пальто	48.6	6
brush	44	5	щетка	9.9	5
brain	45	5	мозг	84.5	4
birth	66	5	рождение	98.5	8
box	70	3	коробка	49	7
shelter	70	7	укрытие	8.3	7
wine	72	4	вино	80.9	4
park	94	4	парк	69.5	4
film	96	4	фильм	196.8	5
bridge	98	6	мост	65.4	4
hospital	110	8	больница	96.6	8

APPENDIX L

Verbal stimuli for Experiment 5 and Chapter 6

Table L1

DRM word lists presented at study and test

	List 1: anger	List 2: army	List 3: beautiful	List 4: bitter	List 5: black
Study 1	**furious**	**navy**	**ugly**	**sweet**	**white**
Study 2	**temper**	**Royal Air Force**	**homely**	**rice**	**night**
Study 3	**fury**	**draft**	**lovely**	**cold**	**funeral**
Study 4	**ire**	**military**	**nice**	**lemon**	**hue**
Study 5	**wrath**	**Marines**	**picture**	**angry**	**grief**
Study 6	**happy**	**march**	**lady**	**tough**	**blue**
Study 7	**fight**	**infantry**	**meadow**	**mad**	**death**
Study 8	**hatred**	**captain**	**snow**	**acid**	**ink**
Study 9	**mean**	**war**	**scene**	**almonds**	**bottom**
Study 10	**calm**	**uniform**	**music**	**herbs**	**coal**
Study 11	**emotion**	**pilot**	**day**	**grape**	**brown**
Study 12	**enrage**	**combat**	**gorgeous**	**fruit**	**grey**
Study 1	furious	navy	ugly	sweet	white
Study 2	temper	Royal Air Force	homely	rice	night
Study 5	wrath	Marines	picture	angry	grief
Study 7	fight	infantry	meadow	mad	death
Lure 1	anger	army	beautiful	bitter	black
Lure 2	fear	soldier	pretty	sour	dark
Lure 3	hate	United Kingdom	girls	taste	cat
Lure 4	rage	rifle	woman	chocolate	charred
New 1	algae	anchor	apartment	apple	apricot
New 2	cradle	desk	door	egg	envelope
New 3	nun	oak	oar	office	onion
New 4	rose	rug	sandal	seaweed	Secretary
	List 6: bread	List 7: butterfly	List 8: car	List 9: chair	List 10: citizen
Study 1	**butter**	**moth**	**truck**	**table**	**Great Britain**

Study 2	**rye**	**fly**	**vehicle**	**couch**	**nation**
Study 3	**jam**	**yellow**	**drive**	**desk**	**alien**
Study 4	**milk**	**net**	**jeep**	**recliner**	**people**
Study 5	**flour**	**flower**	**Vauxhall**	**sofa**	**vote**
Study 6	**jelly**	**bug**	**race**	**wood**	**me**
Study 7	**dough**	**cocoon**	**keys**	**cushion**	**patriot**
Study 8	**crust**	**summer**	**garage**	**swivel**	**flag**
Study 9	**slice**	**colour**	**highway**	**stool**	**foreigner**
Study 10	**wine**	**bee**	**sedan**	**sitting**	**France**
Study 11	**loaf**	**stomach**	**van**	**rocking**	**immigrant**
Study 12	**toast**	**worn**	**taxi**	**bench**	**member**
Study 1	butter	moth	truck	table	Great Britain
Study 2	rye	fly	vehicle	couch	nation
Study 5	flour	flower	Vauxhall	sofa	vote
Study 7	dough	cocoon	keys	cushion	patriot
Lure 1	bread	butterfly	car	chair	citizen
Lure 2	food	insect	bus	sit	man
Lure 3	eat	wing	tube	legs	person
Lure 4	sandwich	bird	automobile	seat	British
New 1	armour	atom	bean	bed	belly
New 2	evergreen	factory	fish	flea	flute
New 3	orange	ornament	padlock	pan	pants
New 4	seed	ship	shovel	snake	spinach
	List 11: city	List 12: cup	List 13: flag	List 14: health	List 15: foot
Study 1	**town**	**mug**	**banner**	**sickness**	**shoe**
Study 2	**streets**	**coaster**	**anthem**	**ill**	**sandals**
Study 3	**subway**	**lid**	**stripes**	**doctor**	**soccer**
Study 4	**country**	**handle**	**pole**	**service**	**yard**
Study 5	**New York**	**coffee**	**wave**	**strong**	**walk**
Study 6	**village**	**straw**	**raised**	**clinic**	**ankle**
Study 7	**metropolis**	**goblet**	**national**	**disorder**	**arm**

Study 8	**big**	**soup**	**checkered**	**body**	**boot**
Study 9	**Birmingham**	**stein**	**emblem**	**vigour**	**inch**
Study 10	**suburb**	**drink**	**sign**	**centre**	**sock**
Study 11	**county**	**plastic**	**freedom**	**pain**	**knee**
Study 12	**urban**	**sip**	**pendant**	**robust**	**mouth**
Study 1	town	mug	banner	sickness	shoe
Study 2	streets	coaster	anthem	ill	sandals
Study 5	New York	coffee	wave	strong	walk
Study 7	metropolis	goblet	national	disorder	arm
Lure 1	city	cup	flag	health	foot
Lure 2	crowded	saucer	Union Jack	good	hand
Lure 3	state	tea	symbol	happiness	toe
Lure 4	capital	measuring	cross	wealth	kick
New 1	boulder	bow	broom	bucket	cabbage
New 2	fort	frame	gown	hammer	heart
New 3	pearl	pepper	photograph	pickle	pie
New 4	sponge	submarine	tack	tape	tar
	List 16: high	List 17: king	List 18: mountain	List 19: rubber	List 20: shirt
Study 1	**low**	**queen**	**hill**	**elastic**	**blouse**
Study 2	**tower**	**George**	**top**	**ball**	**button**
Study 3	**jump**	**dictator**	**molehill**	**eraser**	**shorts**
Study 4	**above**	**palace**	**peak**	**springy**	**iron**
Study 5	**building**	**throne**	**plain**	**foam**	**polo**
Study 6	**noon**	**chess**	**glacier**	**galoshes**	**collar**
Study 7	**cliff**	**rule**	**goat**	**soles**	**vest**
Study 8	**sky**	**subjects**	**bike**	**latex**	**pocket**
Study 9	**over**	**monarch**	**climber**	**glue**	**jersey**
Study 10	**airplane**	**royal**	**range**	**flexible**	**belt**
Study 11	**dive**	**leader**	**steep**	**resilient**	**linen**
Study 12	**elevate**	**reign**	**ski**	**stretch**	**cuffs**
Study 1	low	queen	hill	elastic	blouse
Study 2	tower	George	top	ball	button
Study 5	building	throne	plain	foam	polo

Study 7	cliff	rule	goat	soles	vest
Lure 1	high	king	mountain	rubber	shirt
Lure 2	clouds	England	valley	bounce	sleeves
Lure 3	up	crown	climb	gloves	trousers
Lure 4	tall	prince	summit	tyre	tie
New 1	cafe	candy	canteen	cape	cart
New 2	honey	hospital	ice	jewel	lawn
New 3	pine	pond	pony	powder	princess
New 4	teacher	television	thorn	tooth	trailer
	List 21: sleep	List 22: wish	List 23: swift	List 24: smoke	List 25: soft
Study 1	**bed**	**want**	**fast**	**cigarette**	**hard**
Study 2	**dream**	**well**	**current**	**pollution**	**loud**
Study 3	**wake**	**think**	**rapid**	**ashes**	**cotton**
Study 4	**snooze**	**star**	**stream**	**cigar**	**fur**
Study 5	**blanket**	**bone**	**water**	**chimney**	**touch**
Study 6	**doze**	**ring**	**quick**	**fire**	**fluffy**
Study 7	**slumber**	**wash**	**Gulliver**	**tobacco**	**feather**
Study 8	**snore**	**thought**	**run**	**stink**	**furry**
Study 9	**nap**	**get**	**sure**	**pipe**	**downy**
Study 10	**peace**	**true**	**deer**	**lungs**	**kitten**
Study 11	**yawn**	**for**	**boat**	**flames**	**skin**
Study 12	**drowsy**	**money**	**author**	**stain**	**tender**
Study 1	bed	want	fast	cigarette	hard
Study 2	dream	well	current	pollution	loud
Study 5	blanket	bone	water	chimney	touch
Study 7	slumber	wash	Gulliver	tobacco	feather
Lure 1	sleep	wish	swift	smoke	soft
Lure 2	rest	fantasy	slow	puff	light
Lure 3	awake	desire	river	blaze	pillow
Lure 4	tired	hope	Jonathan	billows	plush
New 1	cent	chocolate	closet	cloth	cone
New 2	lever	library	marble	market	match
New 3	puddle	rabbi	ram	record	rectangle
New 4	umbrella	vase	vinegar	wick	Wolf

	List 26: thief	List 27: trash
Study 1	**steal**	**garbage**
Study 2	**cash**	**sewage**
Study 3	**cop**	**bag**
Study 4	**bad**	**junk**
Study 5	**rob**	**rubbish**
Study 6	**jail**	**sweep**
Study 7	**gun**	**scraps**
Study 8	**villain**	**pile**
Study 9	**crime**	**dump**
Study 10	**bank**	**landfill**
Study 11	**bandit**	**debris**
Study 12	**criminal**	**litter**
Study 1	steal	garbage
Study 2	cash	sewage
Study 5	rob	rubbish
Study 7	gun	scraps
Lure 1	thief	trash
Lure 2	robber	waste
Lure 3	crook	can
Lure 4	burglar	refuse
New 1	cork	cottage
New 2	minister	noodle
New 3	robin	rod
New 4	yolk	fan

Note: The title of each list is the critical lure evoked by Study 1-12 (Roediger, Watson, McDermott, & Gallo, 2001). The 12 words presented at study are shown in order, marked in bold and labelled Study 1-12. Each participant saw the words within each list in order from Study 1-12, although participants could see a different order of lists (i.e. List 1, List 4, and List 7). The study words presented at test are Study 1, Study 2, Study 5, and Study 7. The words that were not presented at study but are presented at test are Lure 1-4, which serve as the critical lures, and New 1-4, which are the unrelated new words.

Table L2

Adaptations to original DRM list words and reasons

List	Original list	Changed word	Reason
Citizen	country	nation	Repeated
Butterfly	Colour	Hue	Repeated
Bitter	Hard	Tough	Repeated (in list "sweet")
Flag	Stars	Cross	UK adaptation
Health	Hospital	Clinic	Repeated
Health	Disease	disorder	repeated
Beautiful	mountain	meadow	repeated
Shirt	Pants	trousers	UK adaptation
Wish	Dream	Fantasy	repeated
Swift	Car	Boat	repeated
Thief	Money	Cash	repeated
Car	Ford	Vauxhall	UK adaptation
Army	United States	United Kingdom	UK adaptation
Citizen	United States	Great Britain	UK adaptation
Citizen	American	British	UK adaptation

City	Chicago	Birmingham	UK adaptation
River	Mississippi	Thames	UK adaptation
Rubber	Tire	Tyre	UK adaptation
Flag	American	Union Jack	UK adaptation

APPENDIX M

Verbal stimuli for Chapter 7

Table M1

Words and associated frequency

Word	Freq[a]	Word	Freq[a]	Word	Freq[a]	Word	Freq[a]
admirer	3	grocery	9	pilgrim	4	arrival	23
apology	3	quartet	9	plumber	4	circuit	23
apparel	3	soloist	9	pronoun	4	crystal	23
armhole	3	balloon	10	rainbow	4	plaster	23
asphalt	3	costume	10	receipt	4	protest	23
autopsy	3	diagram	10	rubbish	4	academy	24
aviator	3	dialect	10	seminar	4	exhibit	25
blister	3	gazette	10	sparkle	4	fortune	25
cartoon	3	luggage	10	balcony	5	stadium	25
drinker	3	patriot	10	bicycle	5	horizon	27
emerald	3	perfume	10	borough	5	journey	28
equator	3	robbery	10	capsule	5	builder	29
esquire	3	sunrise	10	coroner	5	divorce	29
falsity	3	avocado	11	drizzle	5	blanket	30
fixture	3	poultry	11	dynasty	5	citizen	30
forearm	3	dentist	12	faction	5	network	30
fresnel	3	episode	12	hammock	5	suspect	30
gateway	3	harvest	12	laundry	5	counter	31
goddess	3	mineral	12	lullaby	5	finance	31
granite	3	outline	12	make-up	5	gallery	31
handbag	3	railway	12	martian	5	factory	32
handgun	3	alcohol	13	novelty	5	gesture	32
hygiene	3	antenna	13	oakwood	5	heading	32
insulin	3	compass	13	obesity	5	mistake	35
keyhole	3	elderly	13	prophet	5	revenue	35
linkage	3	grandma	13	proverb	5	routine	35
migrant	3	hormone	13	ranking	5	license	36
monarch	3	lantern	13	sandman	5	chicken	37
monitor	3	nursery	13	skyline	5	stomach	37
monsoon	3	pension	13	solvent	5	concert	39
nominee	3	posture	13	soybean	5	mystery	39
oratory	3	penalty	14	symptom	5	soldier	39
orchard	3	pianist	14	abdomen	6	storage	41
ottoman	3	sweater	14	actress	6	comment	42
pitfall	3	doorway	15	adviser	6	journal	42
pointer	3	essence	15	banquet	6	missile	48
portico	3	profile	15	contour	6	passage	49
printer	3	rancher	15	ecstasy	6	speaker	49
psychic	3	refusal	15	feather	6	expense	50
puncher	3	scholar	15	garment	6	bedroom	52
roaming	3	buffalo	16	monster	6	silence	52
rooster	3	channel	16	newborn	6	billion	62

rupture	3	cockpit	16	obelisk	6	library	62
seafood	3	glimpse	16	parkway	6	portion	62
showman	3	lecture	16	runaway	6	message	64
starter	3	miracle	16	soprano	6	fashion	69
stepson	3	payroll	16	surgery	6	shelter	70
stylist	3	pottery	16	analyst	7	brother	73
surname	3	cabinet	17	blossom	7	chapter	74
synonym	3	consent	17	chimney	7	faculty	74
acetone	4	embassy	17	coconut	7	address	77
auction	4	holiday	17	cypress	7	session	80
bandage	4	inquiry	17	dessert	7	captain	85
bathtub	4	battery	18	garbage	7	patient	86
convent	4	airport	19	gravity	7	product	87
curtail	4	caution	19	hallway	7	manager	88
doorman	4	cottage	19	peasant	7	failure	89
drywall	4	emperor	19	platoon	7	balance	90
entropy	4	servant	19	premise	7	kitchen	90
epitaph	4	impulse	20	refugee	7	project	93
eyebrow	4	mustard	20	revenge	7	officer	101
flannel	4	package	20	butcher	8	council	103
grammar	4	pioneer	20	caravan	8	machine	103
mammoth	4	sheriff	20	compost	8	station	105
marquis	4	painter	21	crusade	8	student	130
newsmen	4	protein	21	cushion	8	husband	131
outrage	4	summary	21	cyclist	8	meeting	159
overlap	4	insight	22	diamond	8	subject	161
fitness	8	shotgun	8	carrier	9	picture	162
hostess	8	spindle	8	ceramic	9	college	267
offense	8	athlete	9	cleaner	9	problem	313
recital	8	barrier	9	fighter	9	service	315

Note. [a]Freq. refers to frequency of usage in the English language (Kučera & Francis, 1972).

APPENDIX N

Blinding procedure

Single-blind: A single-blind design was implemented for Experiments 1-3. The experimenter was given codes by the supervisor that clearly specified the experimental condition but would remain ambiguous to the participant if seen (i.e. for Experiment 1, OnEn = Online Encoding tDCS, S = Sham, OfEn = Offline Encoding tDCS). The machine was placed out of participants' view so that they would not note any changes associated with stimulation termination.

Double-blind: A double-blind design was implemented for Experiments 4 and 5 and Chapter 6. The experimenter was given predefined codes by the supervisor, who did not collect any data, that corresponded to settings on the stimulator. The settings were associated with a specific experimental group (i.e. C = Online tDCS and D = Sham). If the experimenter became aware of the association between a code and experimental group during data collection, the supervisor was notified and made changes to the codes and stimulator settings accordingly. The stimulator was also placed in "Study" mode so that stimulation duration, the main difference between Sham and active tDCS, would not be visible on the screen.

APPENDIX O

Experiment 4 participant sensations

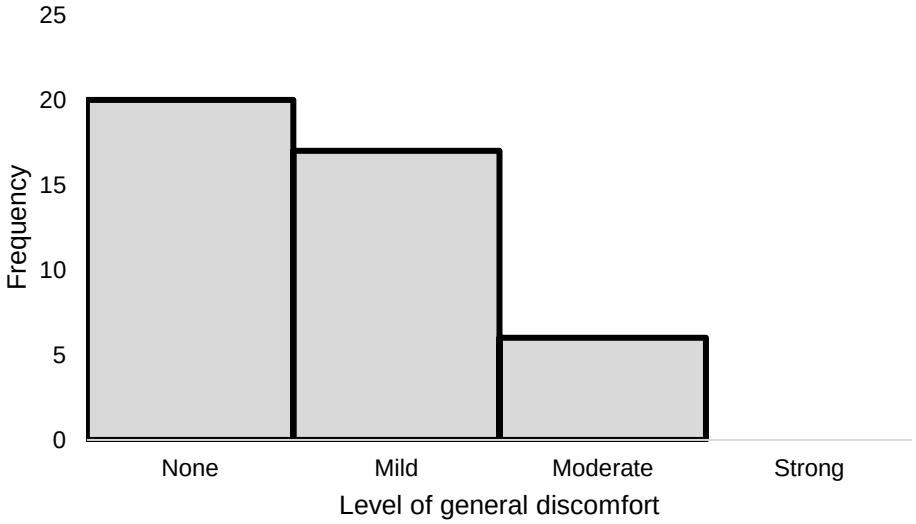


Figure N1. Frequency of general discomfort reported across levels (none, mild, moderate, strong).

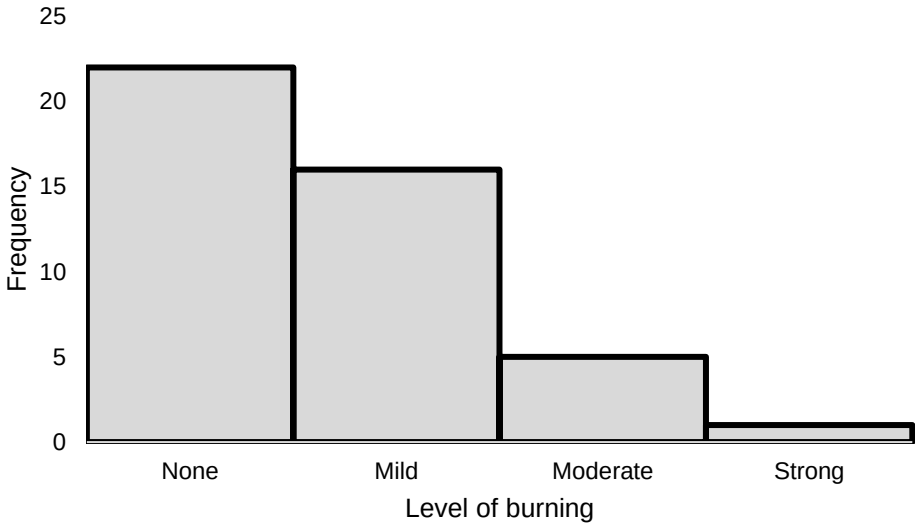


Figure N2. Frequency of burning sensations reported across levels (none, mild, moderate, strong).

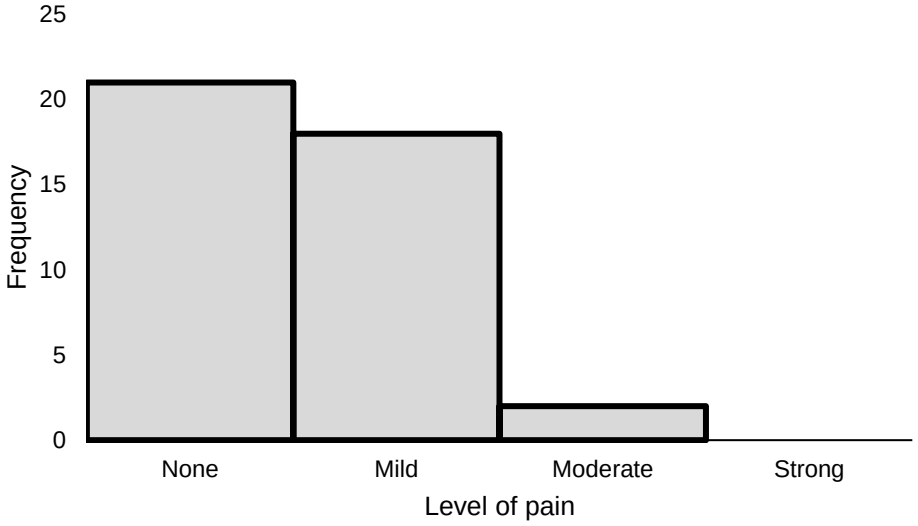


Figure N3. Frequency of pain reported across levels (none, mild, moderate, strong).

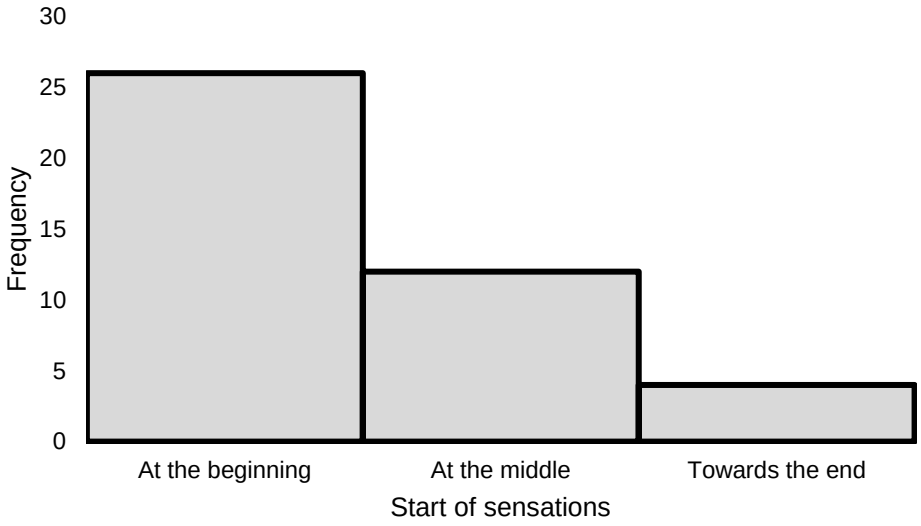


Figure N4. Frequency of start of sensations for any reported sensations.

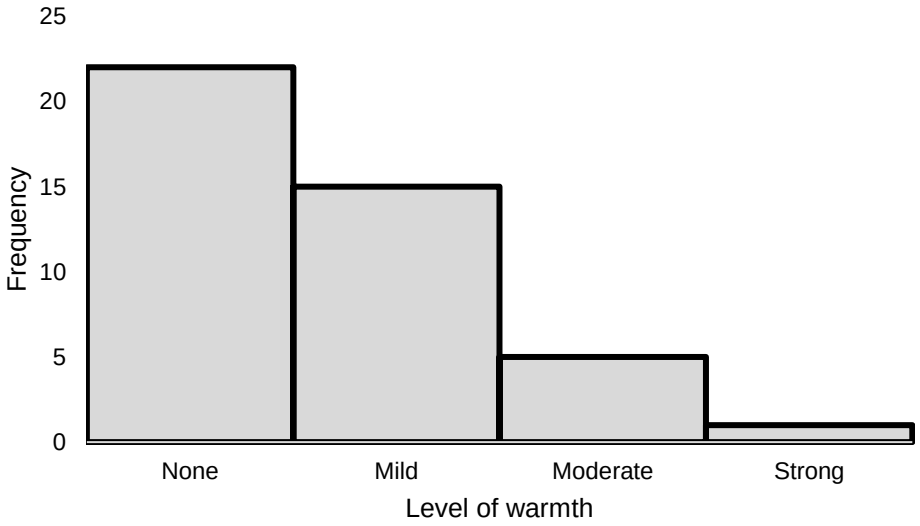


Figure N5. Frequency of sensations of warmth reported across levels (none, mild, moderate, strong).

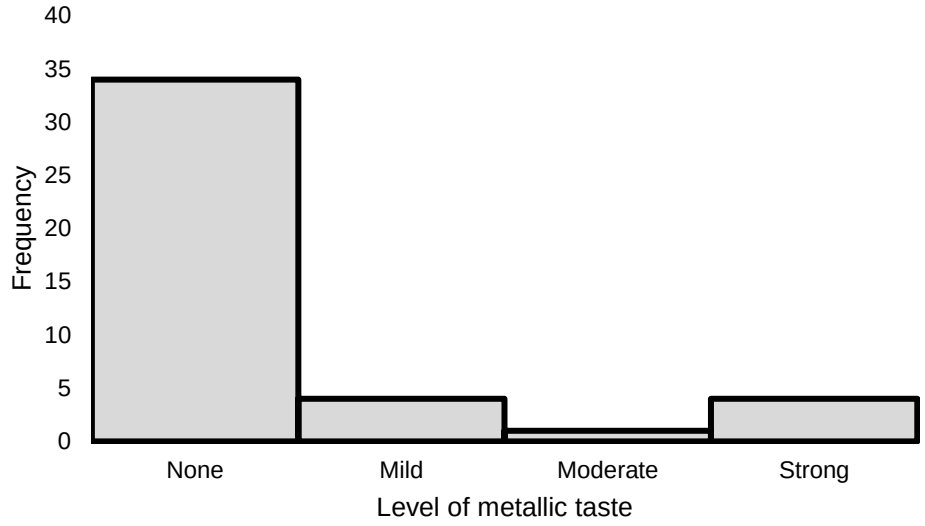


Figure N6. Frequency of metallic taste reported across levels (none, mild, moderate, strong).

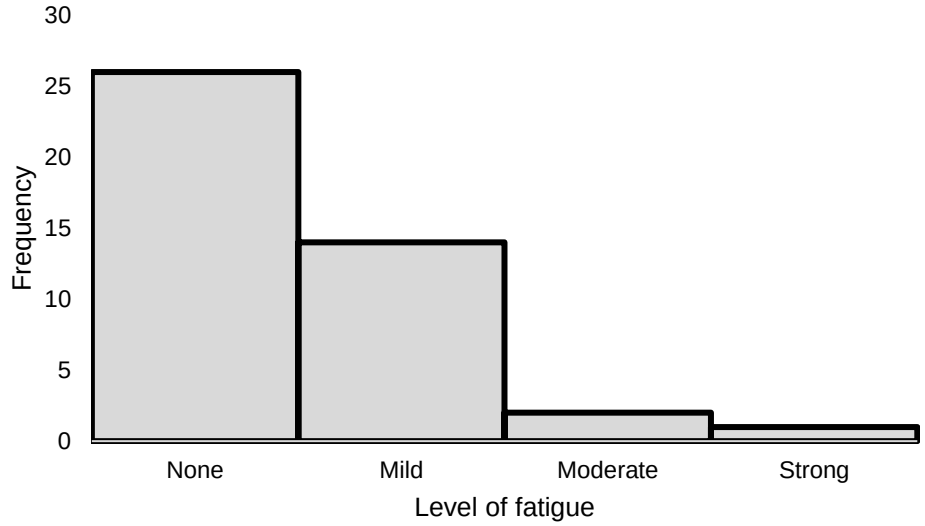


Figure N7. Frequency of fatigue reported across levels (none, mild, moderate, strong).

Figure N8. Frequency of durations for any reported sensations.

APPENDIX P

Experiment 5 participant sensations

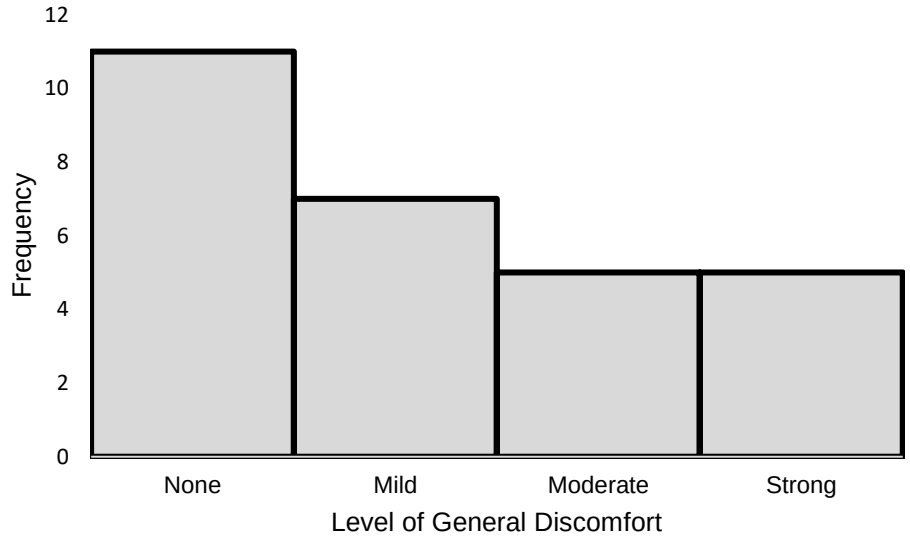


Figure O1. Frequency of general discomfort reported across levels (none, mild, moderate, strong).

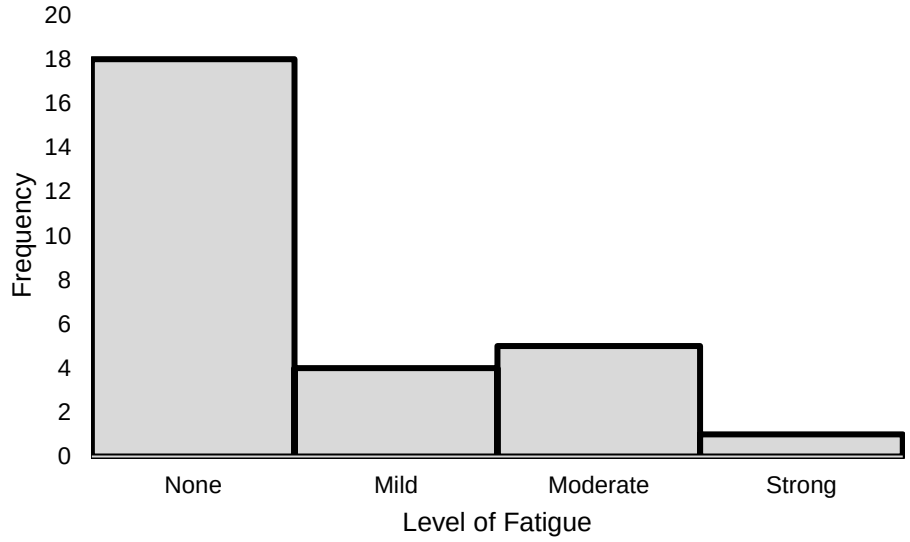


Figure O2. Frequency of fatigue reported across levels (none, mild, moderate, strong).

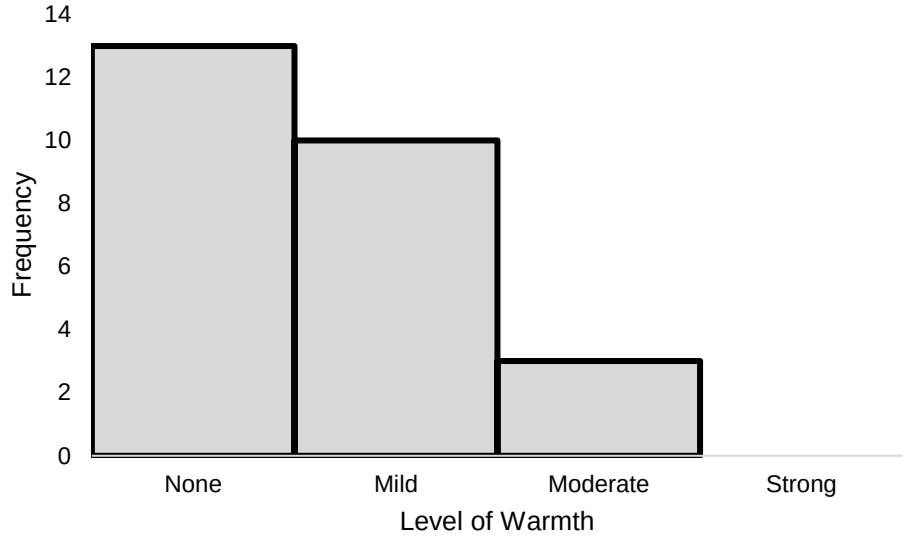


Figure O3. Frequency of sensations of warmth reported across levels (none, mild, moderate, strong

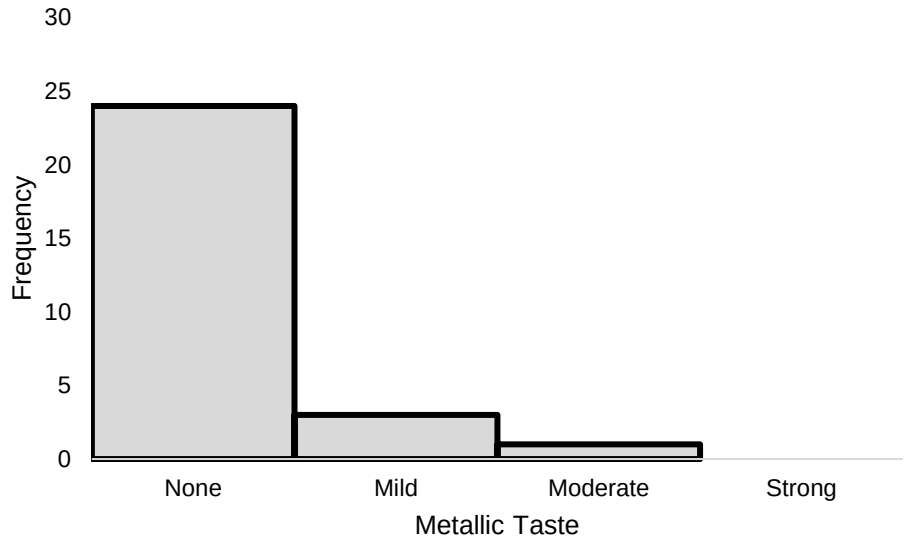


Figure O4. Frequency of metallic taste reported across levels (none, mild, moderate, strong).

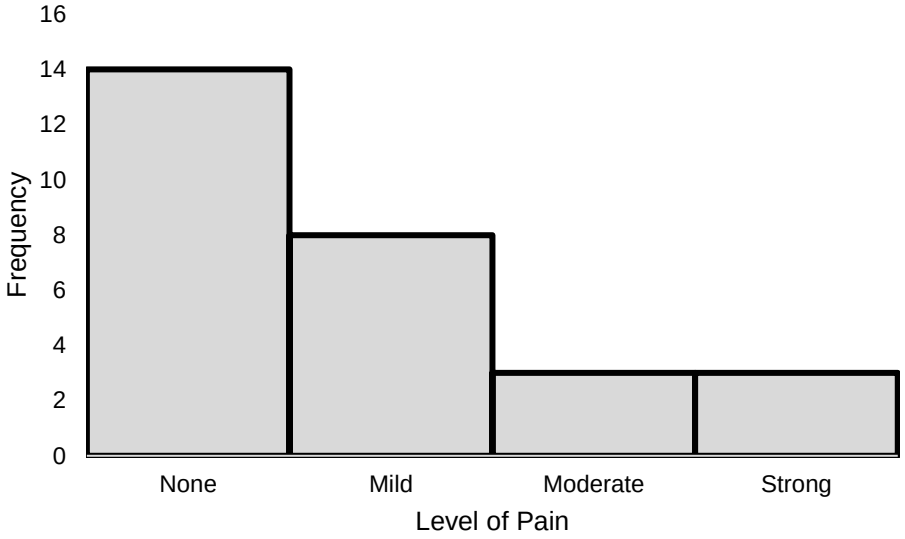


Figure O5. Frequency of pain reported across levels (none, mild, moderate, strong).

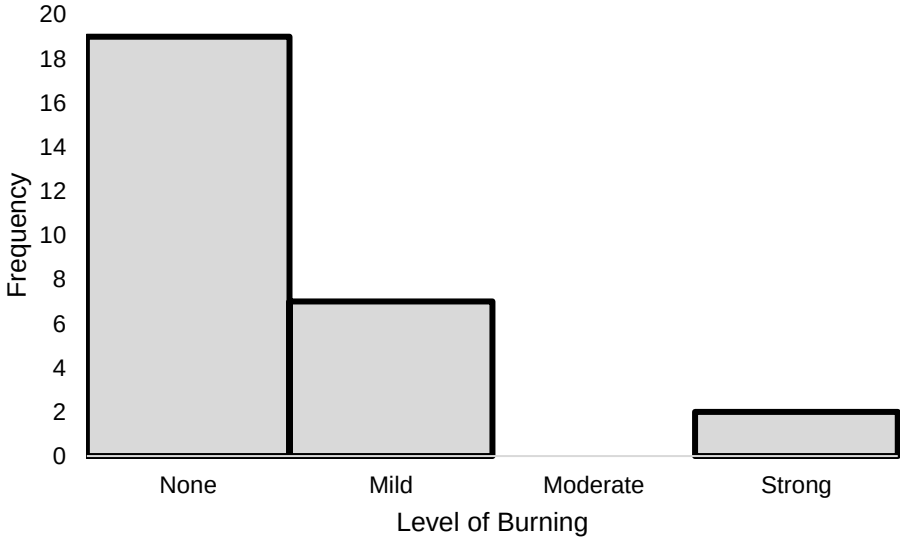


Figure O6. Frequency of burning sensations reported across levels (none, mild, moderate, strong).

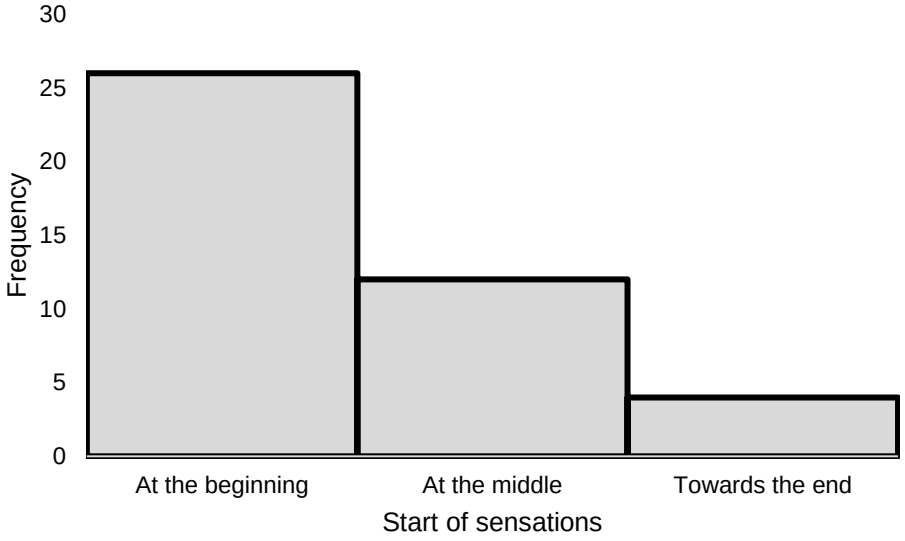


Figure O7. Frequency of start of any reported sensations.

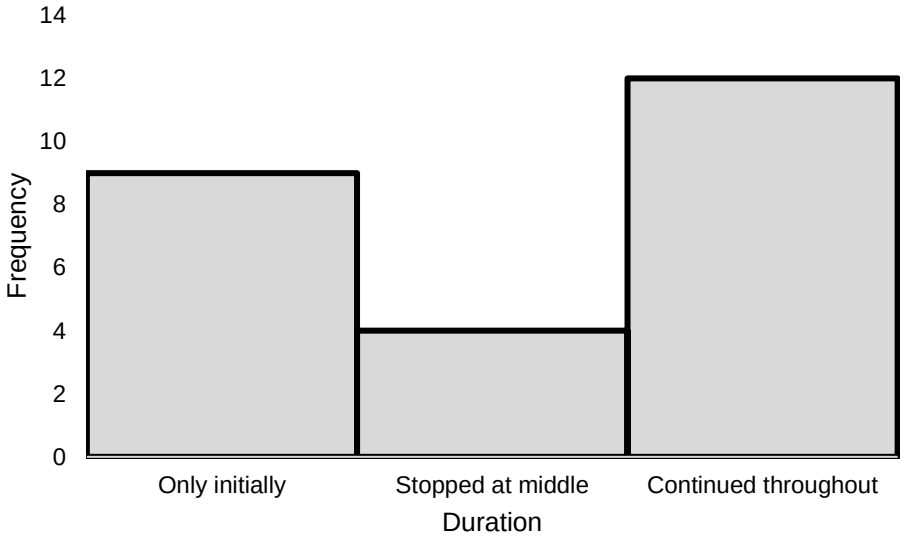
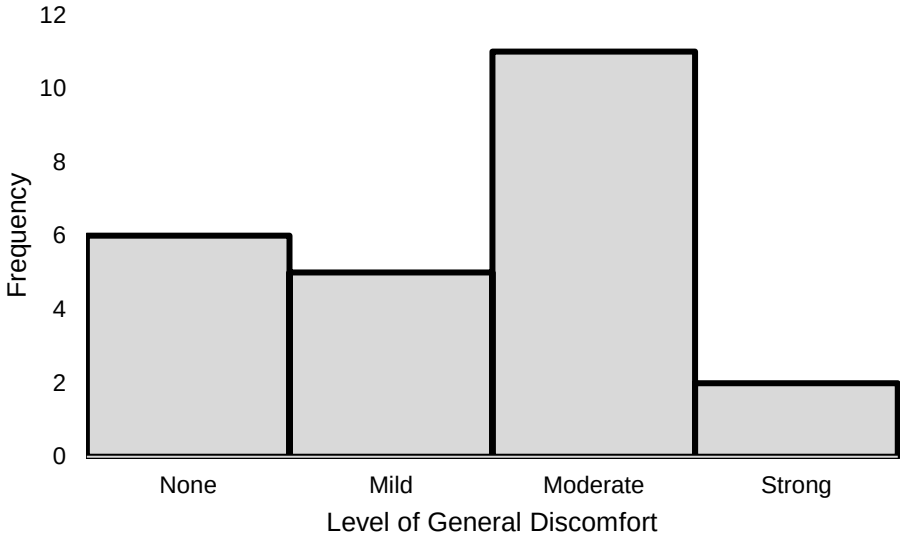
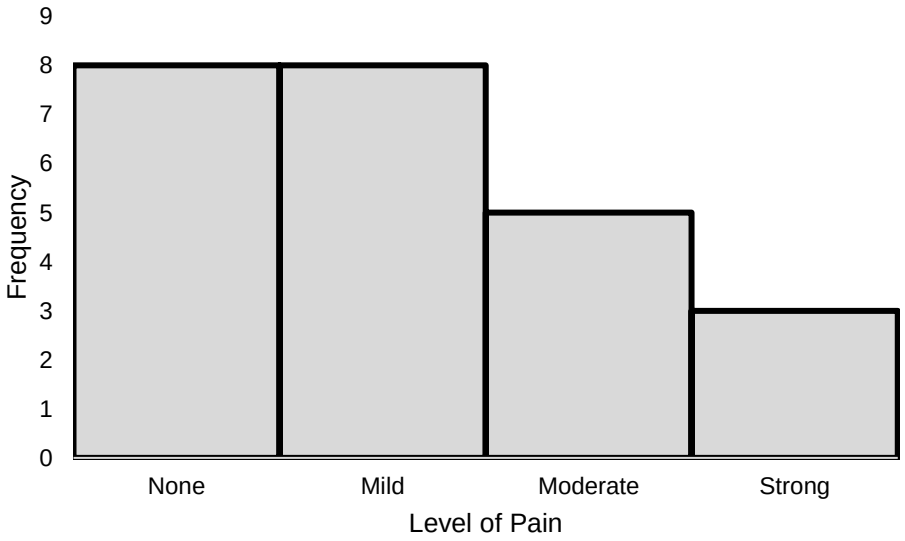


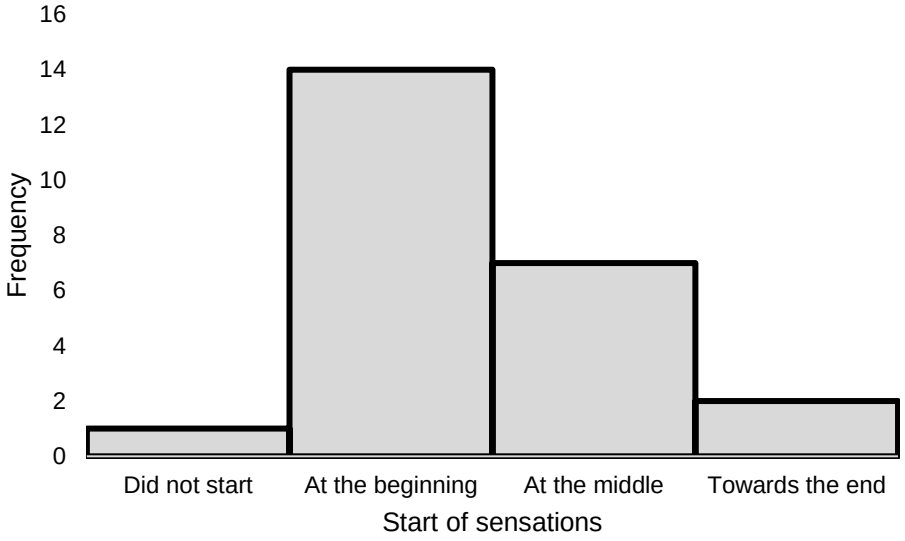
Figure O8. Frequency of durations for any reported sensations.

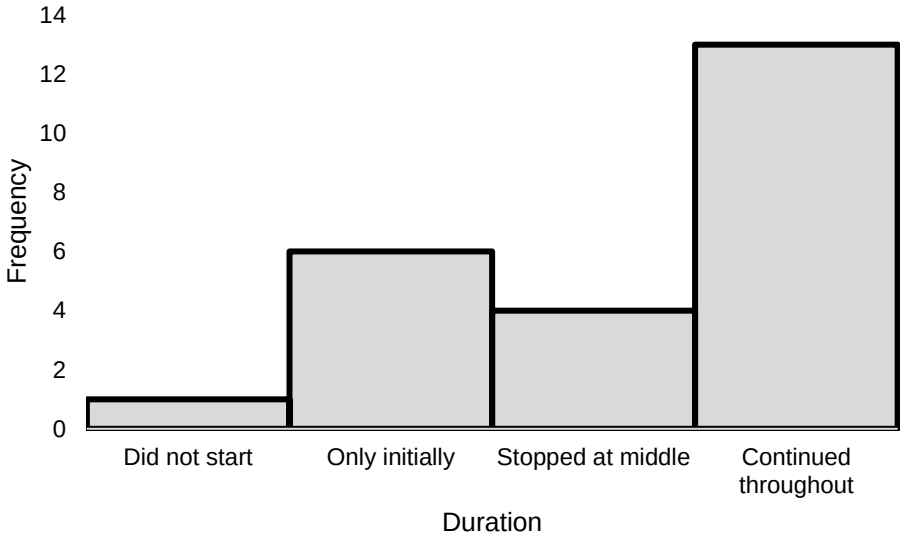
APPENDIX Q

Chapter 7 participant sensations






16
14
12
10
8
6
4
2
0
Frequency
Did not start
At the beginning
At the middle
Towards the end
Start of sensations


14
12
10
8
6
4
2
0
Frequency
Did not start
Only initially
Stopped at middle
Continued throughout
Duration

APPENDIX R

Results of exploratory analysis on block in Experiment 1

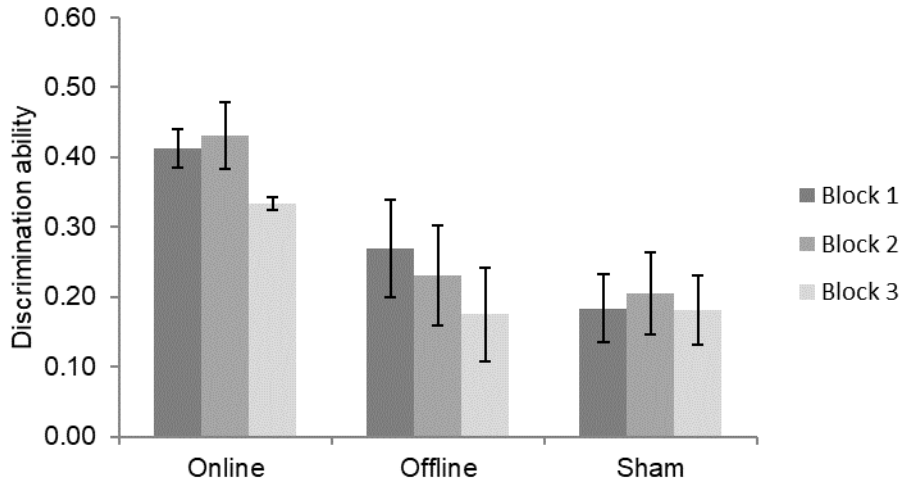


Figure 5.1.6. Recognition accuracy across blocks (B1 = Block 1, B2 = Block 2, B3 = Block 3) for each group.

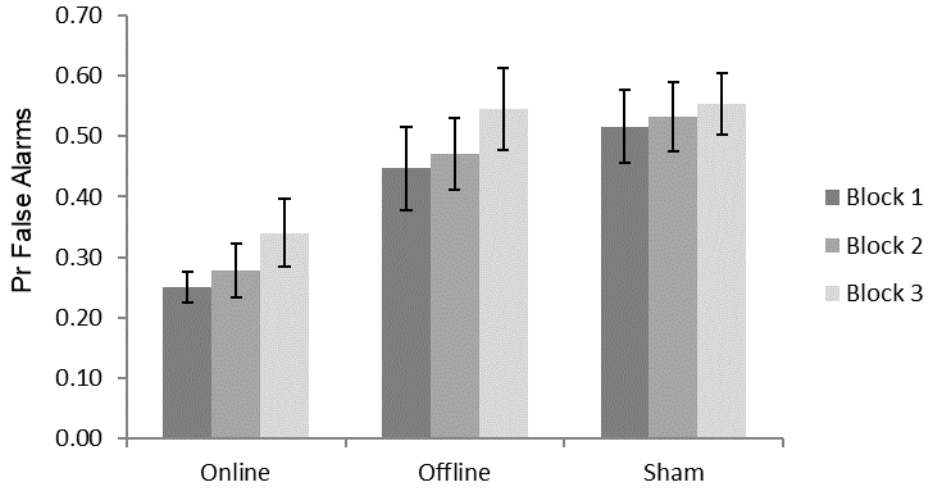


Figure 5.1.7. False alarm rate across blocks for each group.

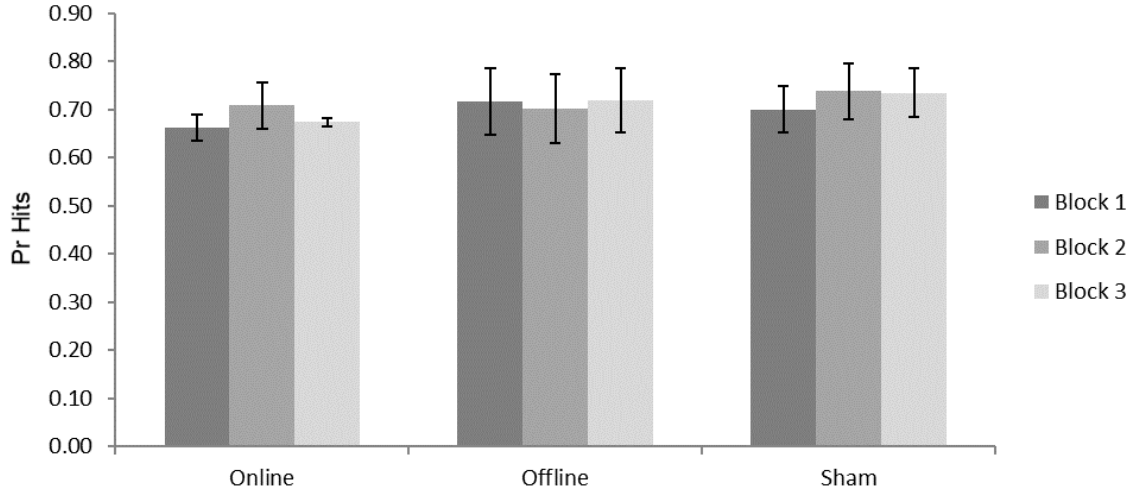


Figure 5.1.8. Hit rate across blocks for each group.

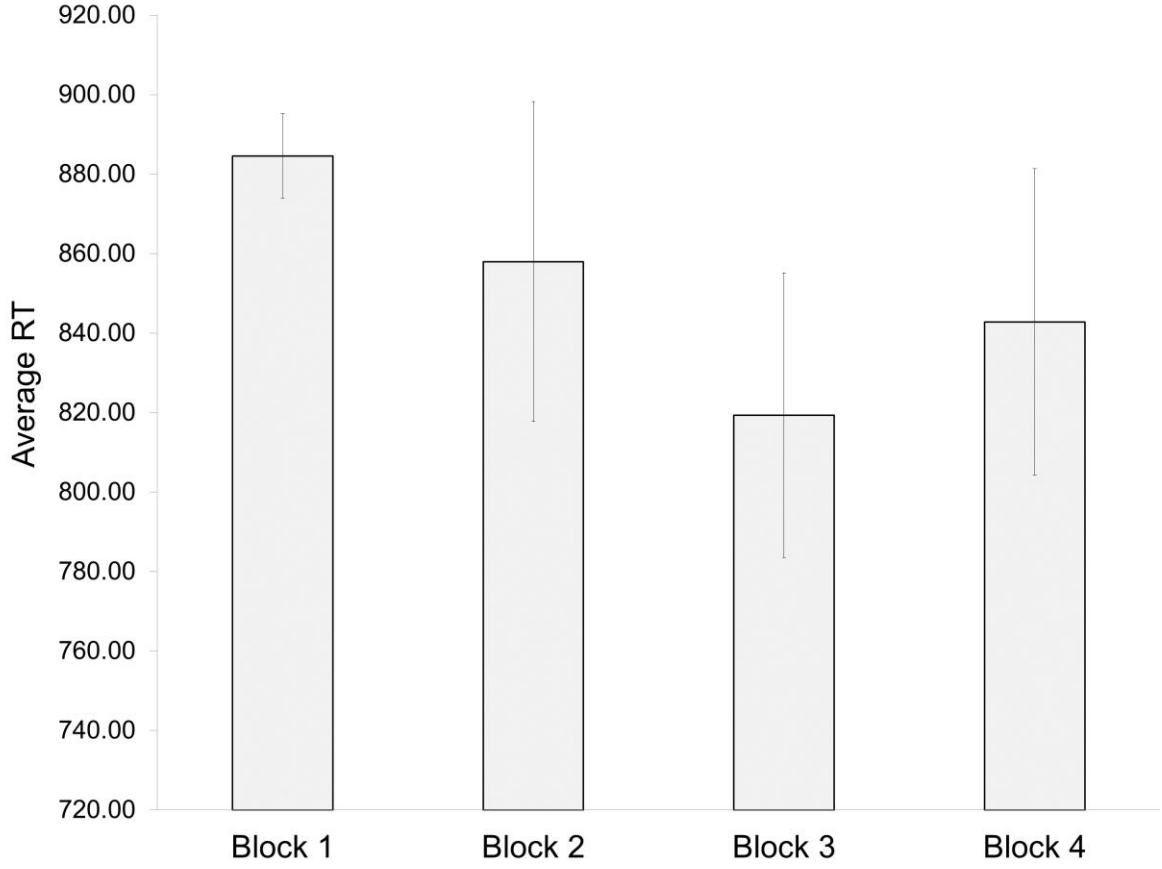


Figure 5.1.9. Reaction time for Online Encoding across blocks. Note: error bars represent standard error.

APPENDIX S

Individual differences in TMS effect

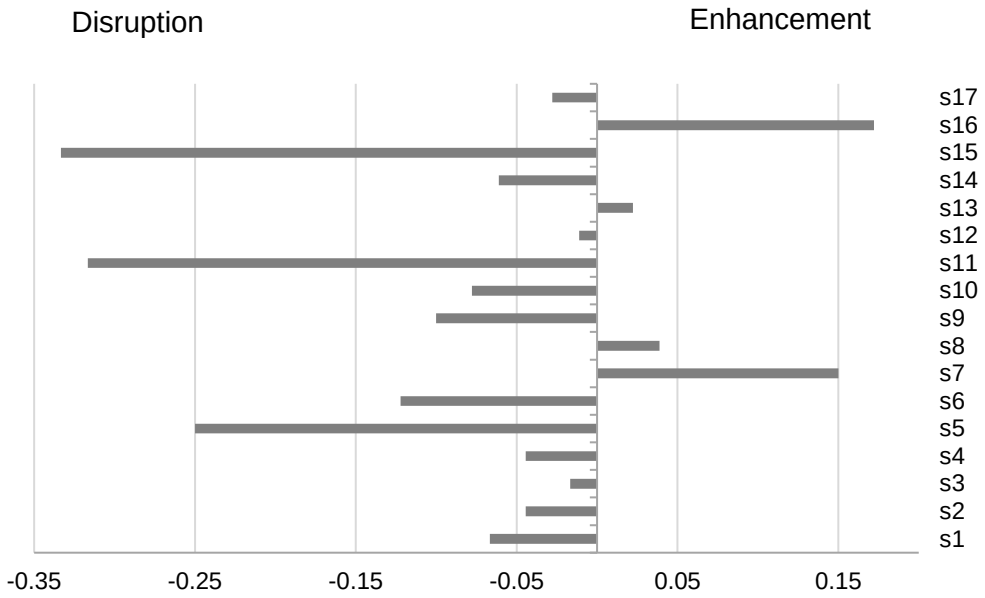


Figure R1. Individual differences in rTMS-induced accuracy impairment when delivered at 1000 ms post-stimulus onset for a 1200-ms word.

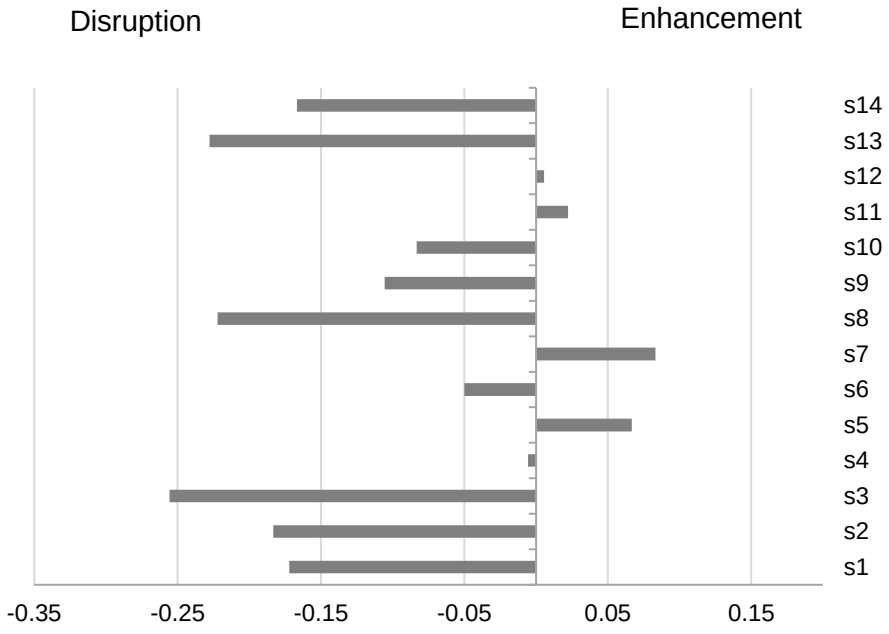


Figure R2. Individual differences in rTMS-induced accuracy impairment when delivered at 1000 ms or 1100 ms at the offset of the word.

APPENDIX T

Supplementary results for Experiment 3

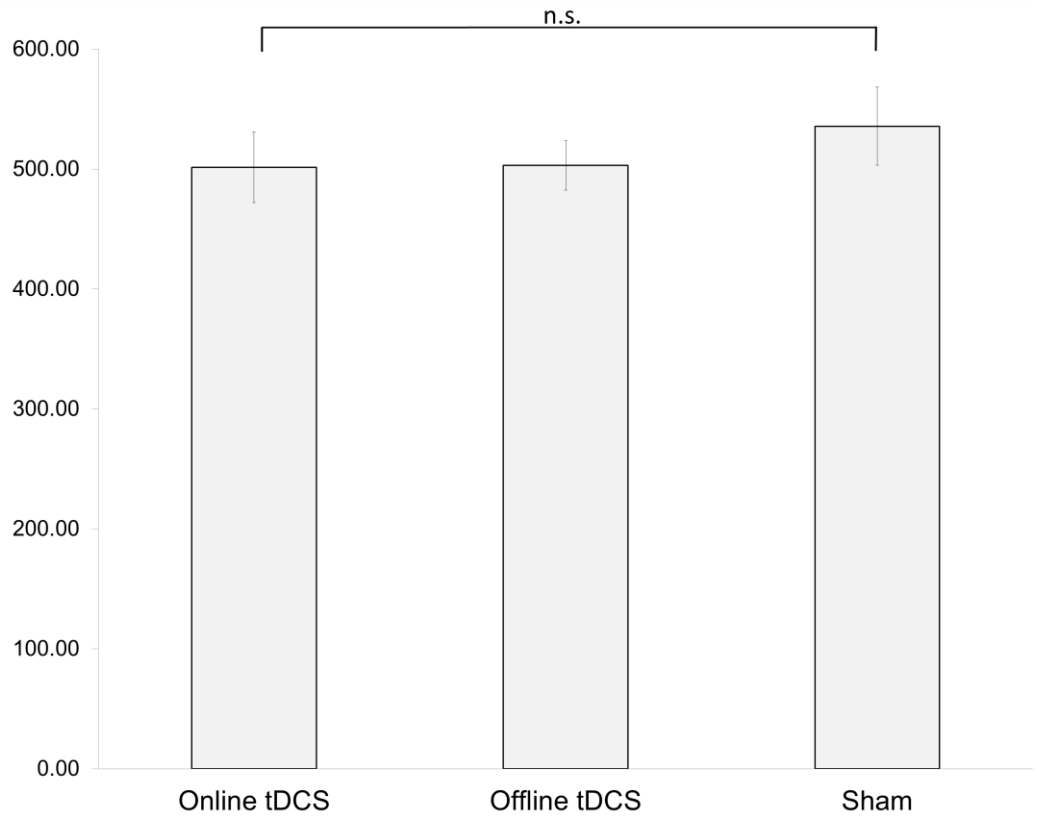


Figure T1. Average reaction times for DLPFC groups.

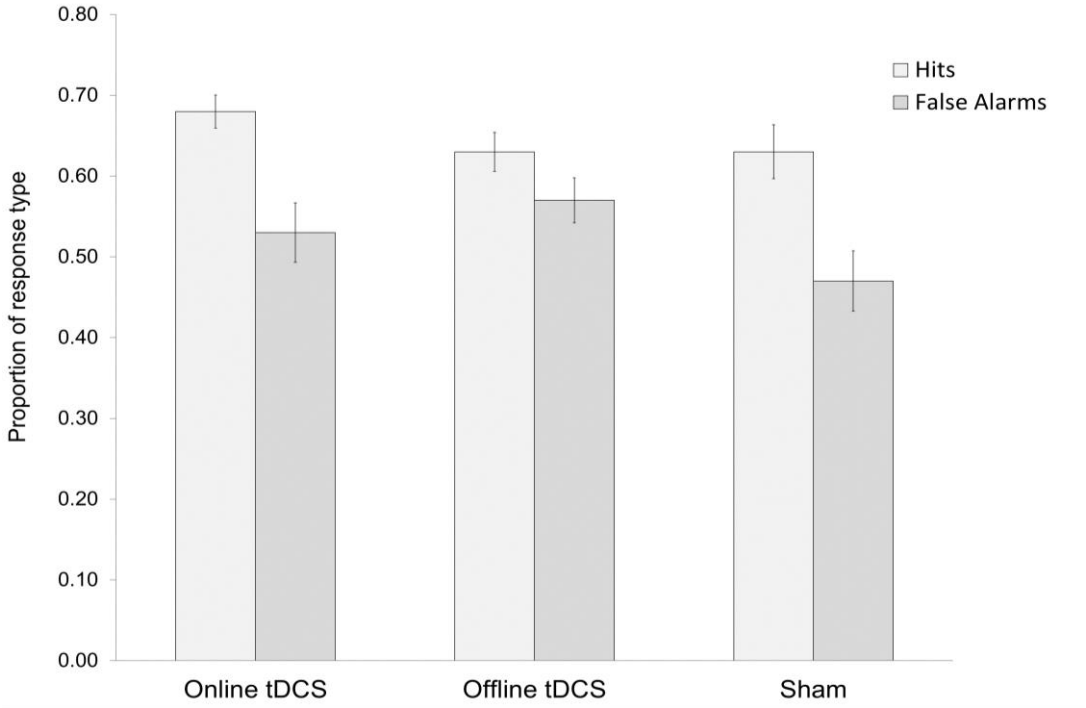


Figure T2. Proportion of hits and false alarms for each DLPFC group.

APPENDIX U

Pre-registration for Experiment 5 and Chapter 6

ASPREDICTED

You are logged in as: **a.medvedeva@kingston.ac.uk** (Log out (logout.php))

HOME (index.php) See List (see_list.php)
Make Suggestion (mailto:larry@AsPredicted.org?Subject=I have a suggestion for AsPredicted)
Change my email (update_email1.php)

As Predicted: *"Mechanisms of atDCS effects on episodic memory"* (#11960)

Created: 06/18/2018 08:41 AM (PT)

Author(s)
Angela Medvedeva (Kingston University) - a.medvedeva@kingston.ac.uk
Giulia Galli (Kingston University) - g.galli@kingston.ac.uk

1) Have any data been collected for this study already?
No, no data have been collected for this study yet.

2) What's the main question being asked or hypothesis being tested in this study?
The hypothesis is that atDCS delivered over the left ventrolateral prefrontal cortex (VLPFC), compared to a sham condition, increases recognition memory by decreasing false alarms. More specifically, we expect that the reduction in false alarms will be more evident when the stimuli are encoded with item-specific processing compared to relational processing.

3) Describe the key dependent variable(s) specifying how they will be measured.
The dependent variables will be:
1) Recognition accuracy. Proportion of hits and false alarms at the old/new memory task; discrimination index (PrHits – Pr False Alarms); reaction times. This is a measure of memory performance.
2) Source memory accuracy. Proportion of hits and false alarms at the source memory task; discrimination index (PrHits – Pr False Alarms); reaction times. Hits will be defined as correct responses to the source task for old words, and false alarms will be defined as incorrect responses to new words. This is a measure of item-specific encoding and relational encoding (depending on the source memory task).

4) How many and which conditions will participants be assigned to?
There will be 2 conditions in a mixed design experiment:
1) Group (between-subjects). Participants will be randomly assigned to a sham or active atDCS. In the active atDCS group, participants will receive 20 minutes of atDCS (2mA, current density 0.05 mA/cm2) over the left VLPFC during the whole duration of the encoding task. In the sham group, participants will only receive the stimulation for 30 seconds.

2) Encoding type (within subjects). The way in which participants encoded words at study will be measured with 2 different source tasks. One source task will measure the degree of item-specific encoding, by asking participants to indicate the colour background on which words were originally presented. The other source task

will measure the degree of relational encoding by asking participants to indicate the subsequent word in an order task.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
A two-way ANOVA will be conducted using group (sham, atDCS) as the between-subject factor and encoding type (item-specific, relational) as the within-subject factor on recognition and source memory accuracy measures. Significant Group x Encoding Type interactions will be followed-up by planned comparisons between the sham and active atDCS groups for each encoding condition.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Outliers will be defined as scores or reaction times of 2 standard deviations below or above the mean. These outliers will be excluded. Participants with 2 standard deviations above or below the mean on all dependent measures will be excluded.

7) How many observations will be collected or what will determine sample size?
No need to justify decision, but be precise about exactly how the number will be determined.
Data collection will stop after data for 20 eligible participants per group have been collected. This will enable us to detect an effect of tDCS of d = 1.29 (as in Medvedeva et al. 2018, Cerebral Cortex), using a between-subjects t-test, assuming α = 0.05 and 1- β = 0.95. The sample size is adjusted upwards to account for possible attrition rate and subject exclusions.

8) Anything else you would like to pre-register?
(e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)

If you click the red button you will make this pre-registration public, creating a permanent .pdf document that will be viewable by anyone who knows its URL. The .pdf is also copied to the web-archive (https://web.archive.org/), a permanent archive outside our control. Making a pre-registration public is a permanent non-reversible decision. We recommend you discuss with co-authors first, and that you make the pre-registration public after the paper containing the relevant study has been accepted for publication. Before publication you probably want to create an anonymous .pdf to share with reviewers.

Make anonymous .PDF for reviewers (share.php?a_id=11960) Make Public .PDF for everyone

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(make_public.php?a_id=11960)
(make_public.php?a_id=11960)
(make_public.php?a_id=11960)

(make_public.php?a_id=11960) Wharton University of Pennsylvania CREDIBILITY LAB (http://credlab.wharton.upenn.edu)

APPENDIX V

R code for Meta-Analysis I

Note: a modified version of the script by Dr Miguel A. Vadillo (https://osf.io/9cxeu/)

```
# ------------------------------------------------------------------
# clear workspace, load libraries and data
# ------------------------------------------------------------------

rm(list = ls())
require(metafor)
data.hits.anodal   <- read.csv2("ma_data_hit_anodal1.csv", dec=".")
data.hits.cathodal <- read.csv2("ma_data_hit_cathod1.csv", dec=".")
data.rt.anodal     <- read.csv2("ma_data_rts_anodal1.csv", dec=".")
data.rt.cathodal   <- read.csv2("ma_data_rts_cathod1.csv", dec=".")


# ------------------------------------------------------------------
# general functions
# ------------------------------------------------------------------

compute.J <- function(df) (1 - (3/(4*df-1)))
compute.g.within <- function(m1,m2,sd1,j) (j*((m1-m2)/sd1))
compute.vg.within <- function(g,n,r,j) ((j^2) * ((2*(1-r))/n) * ((n-1)/(n-3)) *
(1+((n*(g^2))/(2*(1-r)))) - g^2)
compute.g.between <- function(m1,m2,sd1,sd2,n1,n2,j) (j * (m1-m2) / sqrt((((n1-
1)*(sd1^2)) + ((n2-1)*(sd2^2))) / (n1+n2-1)))
compute.vg.between <- function(g,n1,n2,j) ((j^2) * (((n1+n2)/(n1*n2)) +
((g^2)/(2*(n1+n2)))))

build.dataframe <- function(data, r.within, m.exp, sd.exp, n.exp, m.con, sd.con,
n.con){
# This function takes as input the unprocessed dataframe, assumed correlation
between DVs
# in within-participants studies, and the M, SDs and N columns of each condition
# (experimental and control). It outputs the same dataframe with additional
columns for
# df, J, g and Vg, removing outliers, abs(g)>5, and rows with NAs
  data$df[data$DesignWB==1] <- n.exp[data$DesignWB==1] - 1
  data$df[data$DesignWB==2] <- n.exp[data$DesignWB==2] +
n.con[data$DesignWB==2] - 2
  data$J <- compute.J(data$df)
  data$g[data$DesignWB==1] <- compute.g.within(
                              m1=m.exp[data$DesignWB==1],
                              m2=m.con[data$DesignWB==1],
                              sd1=sd.con[data$DesignWB==1],
                              j=data$J[data$DesignWB==1])
  data$g[data$DesignWB==2] <- compute.g.between(
                              m1=m.exp[data$DesignWB==2],
                              m2=m.con[data$DesignWB==2],
                              sd1=sd.exp[data$DesignWB==2],
                              sd2=sd.con[data$DesignWB==2],
                              n1=n.exp[data$DesignWB==2],
```

```
                        n2=n.con[data$DesignWB==2],
                        j=data$J[data$DesignWB==2])
  data$Vg[data$DesignWB==1] <- compute.vg.within(
                        g=data$g[data$DesignWB==1],
                        n=n.exp[data$DesignWB==1],
                        r=r.within,
                        j=data$J[data$DesignWB==1])
  data$Vg[data$DesignWB==2] <- compute.vg.between(
                        g=data$g[data$DesignWB==2],
                        n1=n.exp[data$DesignWB==2],
                        n2=n.con[data$DesignWB==2],
                        j=data$J[data$DesignWB==2])
  data <- subset(data, abs(g)<5)
  return(data)
}


# ------------------------------------------------------------------
# build dataframes for each meta-analysis
# ------------------------------------------------------------------

# assumed correlation between DVs in within-participants designs...
within.correlation <- 0.50

data.hits.anodal   <- build.dataframe(data=data.hits.anodal,
                              r.within=within.correlation,
                              m.exp=data.hits.anodal$AnodalM,
                              m.con=data.hits.anodal$ShamM,
                              sd.exp=data.hits.anodal$AnodalSD,
                              sd.con=data.hits.anodal$ShamSD,
                              n.exp=data.hits.anodal$AnodalN,
                              n.con=data.hits.anodal$ShamN)

data.hits.cathodal <- build.dataframe(data=data.hits.cathodal,
                              r.within=within.correlation,
                              m.exp=data.hits.cathodal$CathodalM,
                              m.con=data.hits.cathodal$ShamM,
                              sd.exp=data.hits.cathodal$CathodalSD,
                              sd.con=data.hits.cathodal$ShamSD,
                              n.exp=data.hits.cathodal$CathodalN,
                              n.con=data.hits.cathodal$ShamN)

data.rt.anodal     <- build.dataframe(data=data.rt.anodal,
                              r.within=within.correlation,
                              m.exp=data.rt.anodal$RT_anodal_hits,
                              m.con=data.rt.anodal$RT_sham_hits,
                              sd.exp=data.rt.anodal$RT_anodal_hits_SD,
                              sd.con=data.rt.anodal$RT_sham_hits_SD,
                              n.exp=data.rt.anodal$AnodalN,
                              n.con=data.rt.anodal$ShamN)

data.rt.cathodal  <- build.dataframe(data=data.rt.cathodal,
```

```
                    r.within=within.correlation,
                    m.exp=data.rt.cathodal$RT_cathodal_hits,
                    m.con=data.rt.cathodal$RT_sham_hits,
                    sd.exp=data.rt.cathodal$RT_cathodal_hits_SD,
                    sd.con=data.rt.cathodal$RT_sham_hits_SD,
                    n.exp=data.rt.cathodal$CathodalN,
                    n.con=data.rt.cathodal$ShamN)

# recode name of first column in data frame
names(data.hits.anodal)[1] <- "IdS"
names(data.hits.cathodal)[1] <- "IdS"
names(data.rt.anodal)[1] <- "IdS"
names(data.rt.cathodal)[1] <- "IdS"

# ------------------------------------------------------------------
# main meta-analyses
# ------------------------------------------------------------------

Random1 = rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal)

forest(Random1)
# ------------------------------------------------------------------
# tests for funnel plot asymmetry
# ------------------------------------------------------------------

Random = rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal,
mods=sqrt(Vg))
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal,   mods=sqrt(Vg))
CathodalHits = rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal,
mods=sqrt(Vg))
AnodalRT = rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal,
mods=sqrt(Vg))
CathodalRT = rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal,
mods=sqrt(Vg))

funnel(Random, main = "% Hits - Anodal", xlab = "Effect size (Hedges' g)")
funnel(CathodalHits, main = "% Hits - Cathodal", xlab = "Effect size (Hedges' g)")
funnel(AnodalRT, main = "RT - Anodal", xlab = "Effect size (Hedges' g)")
funnel(CathodalRT, main = "RT - Cathodal", xlab = "Effect size (Hedges' g)")


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - ActiveE.N
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(ActiveE.N),
            data=subset(data.hits.anodal, ActiveE.N!="N/A"))
```

```
data.hits.anodal.LF <- subset(data.hits.anodal, data.hits.anodal$ActiveE.N=="Left
Frontal")
data.hits.anodal.LP <- subset(data.hits.anodal, data.hits.anodal$ActiveE.N=="Left
Parietal")
data.hits.anodal.LT <- subset(data.hits.anodal, data.hits.anodal$ActiveE.N=="Left
Temporal")
data.hits.anodal.MO <- subset(data.hits.anodal,
data.hits.anodal$ActiveE.N=="Midline occipital")
data.hits.anodal.RF <- subset(data.hits.anodal,
data.hits.anodal$ActiveE.N=="Right Frontal")
data.hits.anodal.RP <- subset(data.hits.anodal,
data.hits.anodal$ActiveE.N=="Right Parietal")
data.hits.anodal.RT <- subset(data.hits.anodal,
data.hits.anodal$ActiveE.N=="Right Temporal")

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.LF)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.LP)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.LT)
data.hits.anodal.MO
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.RF)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.RP)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.RT)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - Montage
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Montage),
               data=subset(data.hits.anodal, Montage!="N/A"))

data.hits.anodal.Uni <- subset(data.hits.anodal, data.hits.anodal$Montage==0)
data.hits.anodal.Bil <- subset(data.hits.anodal, data.hits.anodal$Montage==1)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Uni)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Bil)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - PHASE.N
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Phase.N),
              data=subset(data.hits.anodal, Phase.N!="N/A"))

data.hits.anodal.PhaseN.0 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==0)
data.hits.anodal.PhaseN.1 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==1)
data.hits.anodal.PhaseN.2 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==2)
```

```
data.hits.anodal.PhaseN.3 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==3)
data.hits.anodal.PhaseN.4 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==4)
data.hits.anodal.PhaseN.5 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==5)
data.hits.anodal.PhaseN.6 <- subset(data.hits.anodal,
data.hits.anodal$Phase.N==6)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.0)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.3)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.4)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.5)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.PhaseN.6)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - MEMORY
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Memory.testN),
                data=subset(data.hits.anodal, Memory.testN!="N/A"))

data.hits.anodal.Recogn <- subset(data.hits.anodal,
data.hits.anodal$Memory.testN==1)
data.hits.anodal.Recall <- subset(data.hits.anodal,
data.hits.anodal$Memory.testN==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Recogn)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Recall)

#moderator and sub-group analyses for % hits-anodal - ENCODING TASK
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Encoding.task),
      data=subset(data.hits.anodal))

data.hits.anodal.Int <- subset(data.hits.anodal,
data.hits.anodal$Encoding.task==1)
data.hits.anodal.Inc <- subset(data.hits.anodal,
data.hits.anodal$Encoding.task==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Int)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Inc)


#moderator and sub-group analyses for % hits-anodal - LEVELS OF
PROCESSING
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Depth.encoding),
      data=subset(data.hits.anodal, Depth.encoding!="N/A"))
```

```
data.hits.anodal.Deep <- subset(data.hits.anodal,
data.hits.anodal$Depth.encoding==1)
data.hits.anodal.Shallow <- subset(data.hits.anodal,
data.hits.anodal$Depth.encoding==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Deep)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Shallow)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - Stimulation duration
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Duration.min.N),
            data=subset(data.hits.anodal, Duration.min.N!="N/A"))

data.hits.anodal.Less <- subset(data.hits.anodal,
data.hits.anodal$Duration.min.N==1)
data.hits.anodal.More <- subset(data.hits.anodal,
data.hits.anodal$Duration.min.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Less)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.More)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - Current
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(CurrentDensity.mA.cm2.N),
            data=subset(data.hits.anodal, CurrentDensity.mA.cm2.N!="N/A"))

data.hits.anodal.Curr1 <- subset(data.hits.anodal,
data.hits.anodal$CurrentDensity.mA.cm2.N==1)
data.hits.anodal.Curr2 <- subset(data.hits.anodal,
data.hits.anodal$CurrentDensity.mA.cm2.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Curr1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.Curr2)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - Delay
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(delay.N),
            data=subset(data.hits.anodal, delay.N!="N/A"))

data.hits.anodal.del.1 <- subset(data.hits.anodal, data.hits.anodal$delay.N==1)
data.hits.anodal.del.2 <- subset(data.hits.anodal, data.hits.anodal$delay.N==2)
data.hits.anodal.del.3 <- subset(data.hits.anodal, data.hits.anodal$delay.N==3)
data.hits.anodal.del.4 <- subset(data.hits.anodal, data.hits.anodal$delay.N==4)
```

```
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.del.1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.del.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.del.3)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.del.4)


# ------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - Age
# ------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Age),
      data=subset(data.hits.anodal, Age!="N/A"))

data.hits.anodal.age.y <- subset(data.hits.anodal, data.hits.anodal$Age=="Y")
data.hits.anodal.age.e <- subset(data.hits.anodal, data.hits.anodal$Age=="E")

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.age.y)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.anodal.age.e)


# ------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - ActiveE.N
# ------------------------------------------------------------
# there are only: left frontal, left parietal, left temporal, right frontal, right parietal
# for left parietal, left temporal, right parietal k=1

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(ActiveE.N),
                data=subset(data.hits.cathodal, ActiveE.N!="N/A"))

data.hits.cathodal.LF <- subset(data.hits.cathodal,
data.hits.cathodal$ActiveE.N=="Left Frontal")
data.hits.cathodal.LP <- subset(data.hits.cathodal,
data.hits.cathodal$ActiveE.N=="Left Parietal")
data.hits.cathodal.LT <- subset(data.hits.cathodal,
data.hits.cathodal$ActiveE.N=="Left Temporal")
data.hits.cathodal.RF <- subset(data.hits.cathodal,
data.hits.cathodal$ActiveE.N=="Right Frontal")
data.hits.cathodal.RP <- subset(data.hits.cathodal,
data.hits.cathodal$ActiveE.N=="Right Parietal")

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.LF)
data.hits.cathodal.LP
data.hits.cathodal.LT
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.RF)
data.hits.cathodal.RP

#moderator and sub-group analyses for % hits-cathodal - ENCODING TASK
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Encoding.task),
      data=subset(data.hits.cathodal))
```

```
data.hits.cathodal.Int <- subset(data.hits.cathodal,
data.hits.cathodal$Encoding.task==1)
data.hits.cathodal.Inc <- subset(data.hits.cathodal,
data.hits.cathodal$Encoding.task==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Int)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Inc)


#moderator and sub-group analyses for % hits-cathodal - LEVELS OF
PROCESSING
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Depth.encoding),
      data=subset(data.hits.cathodal, Depth.encoding!="N/A"))

data.hits.cathodal.Deep <- subset(data.hits.cathodal,
data.hits.cathodal$Depth.encoding==1)
data.hits.cathodal.Shallow <- subset(data.hits.cathodal,
data.hits.cathodal$Depth.encoding==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Deep)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Shallow)
# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - NOT ENOUGH DATA
FOR MONTAGE OR AGE
# ------------------------------------------------------------------


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - PHASE.N
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Phase.N),
                data=subset(data.hits.cathodal, Phase.N!="N/A"))

# no data for 0
# k=1 for 4 and 5
# both effect sizes for Phase.N==6 are from the same study
data.hits.cathodal.PhaseN.1 <- subset(data.hits.cathodal,
data.hits.cathodal$Phase.N==1)
data.hits.cathodal.PhaseN.2 <- subset(data.hits.cathodal,
data.hits.cathodal$Phase.N==2)
data.hits.cathodal.PhaseN.3 <- subset(data.hits.cathodal,
data.hits.cathodal$Phase.N==3)
data.hits.cathodal.PhaseN.6 <- subset(data.hits.cathodal,
data.hits.cathodal$Phase.N==6)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.PhaseN.1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.PhaseN.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.PhaseN.3)
data.hits.cathodal[data.hits.cathodal$Phase.N==4,]
data.hits.cathodal[data.hits.cathodal$Phase.N==5,]
```

```
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.PhaseN.6) # from
same study


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - MEMORY
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Memory.testN),
                data=subset(data.hits.cathodal, Memory.testN!="N/A"))

data.hits.cathodal.Recogn <- subset(data.hits.cathodal,
data.hits.cathodal$Memory.testN==1)
data.hits.cathodal.Recall <- subset(data.hits.cathodal,
data.hits.cathodal$Memory.testN==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Recogn)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Recall)



# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - DURATION
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Duration.min.N),
                data=subset(data.hits.cathodal, Duration.min.N!="N/A"))

data.hits.cathodal.Less <- subset(data.hits.cathodal,
data.hits.cathodal$Duration.min.N==1)
data.hits.cathodal.More <- subset(data.hits.cathodal,
data.hits.cathodal$Duration.min.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Less)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.More)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - CURRENT
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(CurrentDensity.mA.cm2.N),
                data=subset(data.hits.cathodal, CurrentDensity.mA.cm2.N!="N/A"))

data.hits.cathodal.Curr1 <- subset(data.hits.cathodal,
data.hits.cathodal$CurrentDensity.mA.cm2.N==1)
data.hits.cathodal.Curr2 <- subset(data.hits.cathodal,
data.hits.cathodal$CurrentDensity.mA.cm2.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Curr1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.Curr2)
```

```
# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-cathodal - Delay
# no instances of 4
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(delay.N),
                data=subset(data.hits.cathodal, delay.N!="N/A"))

data.hits.cathodal.del.1 <- subset(data.hits.cathodal,
data.hits.cathodal$delay.N==1)
data.hits.cathodal.del.2 <- subset(data.hits.cathodal,
data.hits.cathodal$delay.N==2)
data.hits.cathodal.del.3 <- subset(data.hits.cathodal,
data.hits.cathodal$delay.N==3)
data.hits.cathodal.del.4 <- subset(data.hits.cathodal,
data.hits.cathodal$delay.N==4)

# there is only one instance of 1 and none of 4
data.hits.cathodal.del.1
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.del.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.hits.cathodal.del.3) # same study


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - ActiveE.N
# stimulation location (there is no midline occipital or right temporal)
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(ActiveE.N),
                data=subset(data.rt.anodal, ActiveE.N!="N/A"))

data.rt.anodal.LF <- subset(data.rt.anodal, data.rt.anodal$ActiveE.N=="Left
Frontal")
data.rt.anodal.LP <- subset(data.rt.anodal, data.rt.anodal$ActiveE.N=="Left
Parietal")
data.rt.anodal.LT <- subset(data.rt.anodal, data.rt.anodal$ActiveE.N=="Left
Temporal")
data.rt.anodal.RF <- subset(data.rt.anodal, data.rt.anodal$ActiveE.N=="Right
Frontal")
data.rt.anodal.RP  <- subset(data.rt.anodal, data.rt.anodal$ActiveE.N=="Right
Parietal")

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.LF)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.LP)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.LT)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.RF)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.RP)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Montage
```

```
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Montage),
                data=subset(data.rt.anodal, Montage!="N/A"))

data.rt.anodal.Uni <- subset(data.rt.anodal, data.rt.anodal$Montage==0)
data.rt.anodal.Bil  <- subset(data.rt.anodal, data.rt.anodal$Montage==1)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Uni)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Bil)



# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Phase.N
# Phase.N (no data for 6; only 1 study for 0 and 4)
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Phase.N),
                data=subset(data.rt.anodal, Phase.N!="N/A"))

data.rt.anodal.PhaseN.0 <- subset(data.rt.anodal, data.rt.anodal$Phase.N==0)
data.rt.anodal.PhaseN.1 <- subset(data.rt.anodal, data.rt.anodal$Phase.N==1)
data.rt.anodal.PhaseN.2 <- subset(data.rt.anodal, data.rt.anodal$Phase.N==2)
data.rt.anodal.PhaseN.3 <- subset(data.rt.anodal, data.rt.anodal$Phase.N==3)
data.rt.anodal.PhaseN.4 <- subset(data.rt.anodal, data.rt.anodal$Phase.N==4)
data.rt.anodal.PhaseN.5 <- subset(data.rt.anodal, data.rt.anodal$Phase.N==5)

data.rt.anodal.PhaseN.0
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.PhaseN.1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.PhaseN.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.PhaseN.3)
data.rt.anodal.PhaseN.4
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.PhaseN.5)



# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Memory
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Memory.testN),
                data=subset(data.rt.anodal, Memory.testN!="N/A"))

data.rt.anodal.Recogn <- subset(data.rt.anodal, data.rt.anodal$Memory.testN==1)
data.rt.anodal.Recall <- subset(data.rt.anodal, data.rt.anodal$Memory.testN==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Recogn)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Recall)

# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Duration
```

```
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Duration.min.N),
                data=subset(data.rt.anodal, Duration.min.N!="N/A"))

data.rt.anodal.Less <- subset(data.rt.anodal, data.rt.anodal$Duration.min.N==1)
data.rt.anodal.More <- subset(data.rt.anodal, data.rt.anodal$Duration.min.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Less)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.More)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Current
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(CurrentDensity.mA.cm2.N),
                data=subset(data.rt.anodal, CurrentDensity.mA.cm2.N!="N/A"))

data.rt.anodal.Curr1 <- subset(data.rt.anodal,
data.rt.anodal$CurrentDensity.mA.cm2.N==1)
data.rt.anodal.Curr2 <- subset(data.rt.anodal,
data.rt.anodal$CurrentDensity.mA.cm2.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Curr1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Curr2)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Delay (only 1,2,3)
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(delay.N),
                data=subset(data.rt.anodal, delay.N!="N/A"))

data.rt.anodal.del.1 <- subset(data.rt.anodal, data.rt.anodal$delay.N==1)
data.rt.anodal.del.2 <- subset(data.rt.anodal, data.rt.anodal$delay.N==2)
data.rt.anodal.del.3 <- subset(data.rt.anodal, data.rt.anodal$delay.N==3)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.del.1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.del.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.del.3)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % hits-anodal - Age
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Age),
      data=subset(data.rt.anodal, Age!="N/A"))

data.rt.anodal.age.y <- subset(data.rt.anodal, data.rt.anodal$Age=="Y")
```

```
data.rt.anodal.age.e <- subset(data.rt.anodal, data.rt.anodal$Age=="E")

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.age.y)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.age.e)

#moderator and sub-group analyses for % rt-anodal - ENCODING TASK
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Encoding.task),
      data=subset(data.rt.anodal))

data.rt.anodal.Int <- subset(data.rt.anodal, data.rt.anodal$Encoding.task==1)
data.rt.anodal.Inc <- subset(data.rt.anodal, data.rt.anodal$Encoding.task==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Int)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Inc)


#moderator and sub-group analyses for % rt-anodal - LEVELS OF PROCESSING
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Depth.encoding),
      data=subset(data.rt.anodal, Depth.encoding!="N/A"))

data.rt.anodal.Deep <- subset(data.rt.anodal, data.rt.anodal$Depth.encoding==1)
data.rt.anodal.Shallow <- subset(data.rt.anodal,
data.rt.anodal$Depth.encoding==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Deep)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.anodal.Shallow)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-cathodal - ActiveE.N
# stimulation location (K=1 for "left temporal" and "right frontal")
# no studies for left parietal, , midline occipital, right parietal, right temporal
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(ActiveE.N),
                data=subset(data.rt.cathodal, ActiveE.N!="N/A"))

data.rt.cathodal.LF <- subset(data.rt.cathodal, data.rt.cathodal$ActiveE.N=="Left
Frontal")

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.LF)
data.rt.cathodal[data.rt.cathodal$ActiveE.N=="Left Temporal",]
data.rt.cathodal[data.rt.cathodal$ActiveE.N=="Right Frontal",]



#moderator and sub-group analyses for % rt-cathodal - ENCODING TASK
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Encoding.task),
      data=subset(data.rt.cathodal))

data.rt.cathodal.Int <- subset(data.rt.cathodal, data.rt.cathodal$Encoding.task==1)
data.rt.cathodal.Inc <- subset(data.rt.cathodal, data.rt.cathodal$Encoding.task==2)
```

```
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Int)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Inc)


#moderator and sub-group analyses for % rt-cathodal - LEVELS OF
PROCESSING
rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Depth.encoding),
      data=subset(data.rt.cathodal, Depth.encoding!="N/A"))

data.rt.cathodal.Deep <- subset(data.rt.cathodal,
data.rt.cathodal$Depth.encoding==1)
data.rt.cathodal.Shallow <- subset(data.rt.cathodal,
data.rt.cathodal$Depth.encoding==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Deep)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Shallow)
# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-cathodal - Phase
# FOR PHASES 2 AND 4, K=1
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Phase.N),
                data=subset(data.rt.cathodal, Phase.N!="N/A"))

data.rt.cathodal.Phase1 <- subset(data.rt.cathodal, data.rt.cathodal$Phase.N==1)
data.rt.cathodal.Phase2 <- subset(data.rt.cathodal, data.rt.cathodal$Phase.N==2)
data.rt.cathodal.Phase3 <- subset(data.rt.cathodal, data.rt.cathodal$Phase.N==3)
data.rt.cathodal.Phase4 <- subset(data.rt.cathodal, data.rt.cathodal$Phase.N==4)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Phase1)
data.rt.cathodal.Phase2
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Phase3)
data.rt.cathodal.Phase4

# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-cathodal - Memory
# memory (k=1 for recall)
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(Memory.testN),
                data=subset(data.rt.cathodal, Memory.testN!="N/A"))

data.rt.cathodal.Recogn <- subset(data.rt.cathodal,
data.rt.cathodal$Memory.testN==1)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Recogn)
data.rt.cathodal[data.rt.cathodal$Memory.testN==2,]


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-cathodal - Current
```

```
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(CurrentDensity.mA.cm2.N),
                data=subset(data.rt.cathodal, CurrentDensity.mA.cm2.N!="N/A"))

data.rt.cathodal.Curr1 <- subset(data.rt.cathodal,
data.rt.cathodal$CurrentDensity.mA.cm2.N==1)
data.rt.cathodal.Curr2 <- subset(data.rt.cathodal,
data.rt.cathodal$CurrentDensity.mA.cm2.N==2)

rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Curr1)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.Curr2)


# ------------------------------------------------------------------
# moderator and sub-group analyses for % rt-anodal - Delay (only 1,2,3)
# ------------------------------------------------------------------

rma.mv(yi=g, V=Vg, random=~1|IdS, mods=~factor(delay.N),
                data=subset(data.rt.cathodal, delay.N!="N/A"))

data.rt.cathodal.del.1 <- subset(data.rt.cathodal, data.rt.cathodal$delay.N==1)
data.rt.cathodal.del.2 <- subset(data.rt.cathodal, data.rt.cathodal$delay.N==2)
data.rt.cathodal.del.3 <- subset(data.rt.cathodal, data.rt.cathodal$delay.N==3)

data.rt.cathodal.del.1
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.del.2)
rma.mv(yi=g, V=Vg, random=~1|IdS, data=data.rt.cathodal.del.3) # K=2 from
same cluster


# ------------------------------------------------------------------
# make combined funnel plot for all four meta-analysis
# ------------------------------------------------------------------

make.funnelplot <- function(g, se, title){
  min.g <- min(g) - .15
  max.g <- max(g) + .15
  max.se <- max(se) + .05
  plot(x="", y="", type="n", main=title,
       xlab="Effect size (Hedges' g)", ylab="Standard error",
       cex.lab=1.2, xlim=c(min.g, max.g), ylim=c(max.se, 0))
  polygon(c(-1.96*max.se, 0, 1.96*max.se), y = c(max.se, 0, max.se),
          col=rgb(.6,.6,.6,.5), border=rgb(.3,.3,.3,.5), lwd=1.5)
  points(g, se, pch=19, col="black", cex=1, lwd=1.2)
}

tiff(filename="funnelplots3.tiff", compression = "lzw", width=5000, height=3500,
res=550)
layout(matrix(c(1,2,3,4), 2, 2, byrow = TRUE))
par(mar=c(5,5,3,2))
make.funnelplot(data.hits.anodal$g, sqrt(data.hits.anodal$Vg), "% Hits - Anodal")
```

```
make.funnelplot(data.hits.cathodal$g, sqrt(data.hits.cathodal$Vg), "% Hits -
Cathodal")
make.funnelplot(data.rt.anodal$g, sqrt(data.rt.anodal$Vg), "RT - Anodal")
make.funnelplot(data.rt.cathodal$g, sqrt(data.rt.cathodal$Vg), "RT - Cathodal")
dev.off()
```

APPENDIX W

R code for Meta-Analysis II

```
rm(list = ls())
require(metafor)

#switch files depending on which outcome measure/subset is used - default
average RT for entire subset:
#Chapter5_atDCS_FA
#Chapter5_atDCS_DI
#Chapter5_atDCS_averageRT
#all outcome measure variables will be called data.FA.anodal, but
#can substitute FA file for average RT or discrimination ability files

data.FA.anodal   <- read.csv2("Chapter5_atDCS_averageRT.csv", dec=".")

Study <- data.FA.anodal[,1]
number_control <- data.FA.anodal[,3]
number_stimulation <- data.FA.anodal[,4]
mean_control <- data.FA.anodal[,5]
mean_stimulation <- data.FA.anodal[,6]
sd_control <- data.FA.anodal[,7]
sd_stimulation <- data.FA.anodal[,8]


#compute degrees of freedom and J, correction factor from Cohen's d to g that is
needed to calculate variance
data_df <- number_stimulation - 1
compute.J <- function(df) (1 - (3/(4*df-1)))

#compute effect size and variance, Hedges' g and Vg
data_J <- compute.J(data_df)
data_g <- (data_J * (mean_stimulation-mean_control) /
sqrt((((number_stimulation-1)*(sd_stimulation^2)) + ((number_control-
1)*(sd_control^2))) / (number_stimulation+number_control-1)))
data_Vg <- ((data_J^2) *
(((number_stimulation+number_control)/(number_stimulation*number_control)) +
((data_g^2)/(2*(number_stimulation+number_control)))))

#random-effects meta-analysis using Hedges' g and variance Vg
Random <- rma(yi=data_g, vi=data_Vg, data=data.FA.anodal, method = "REML")


#if subset of k=3
#forest(Random,
#       xlab="Hedges' g",
#       slab=c("Chapter 5 Exp 1", "Chapter 5 Exp 3", "Medvedeva et al. 2018 Exp
4"))

#for entire sample k = 5
#average RT
forest(Random,
```

```
      xlab="Hedges' g",
      slab=c("Chapter 5 Exp 1", "Chapter 5 Exp 3", "Chapter 5 Exp 4", "Chapter 5
Exp 5", "Medvedeva et al. 2018 Exp 4"))


#funnel plot to estimate publication bias, select measure of interest for caption and
comment out others
funnel(Random, main = "% Average RT - Anodal", xlab = "Effect size (Hedges' g)")
#funnel(Random, main = "% FA - Anodal", xlab = "Effect size (Hedges' g)")
#funnel(Random, main = "% DI - Anodal", xlab = "Effect size (Hedges' g)")
```

APPENDIX X

Data for Meta-Analysis II

Table X1

Data file for atDCS effect on average reaction time

Study;Year;number_control;number_stimulation;mean_control;mean_stimulation;s
Chapter 5;Experiment 1;16;16;585.58;770.25;185.82;157.06;580.42;770.94;182.85;17
Chapter 5;Experiment 3;23;25;535.72;484;156.16;82.58;538.91;477.82;171.43;86.1
Chapter 5;Experiment 4;26;23;757.34;914.8;266.63;246.69;791.89;951.82;297.57;276
Chapter 5;Experiment 5;15;16;1188.78;1238.78;280.34;402.41;983.54;1115.5;184.73;
Medvedeva et al. 2018;Experiment 4;11;11;991.18;1072.35;109.01;154.79;994.01;108

Table X2

Data file for atDCS effect on DI

Study;Year;number_control;number_stimulation;mean_control;mean_stimulation;s
Chapter 5;Experiment 1;16;16;0.13;0.30;0.13;0.08;580.42;770.94;182.85;170.58
Chapter 5;Experiment 3;23;25;0.16;0.09;0.18;0.11;538.91;477.82;171.43;86.1
Chapter 5;Experiment 4;26;23;0.24;0.31;0.17;0.19;791.89;951.82;297.57;276.53
Chapter 5;Experiment 5;15;16;0.34;0.35;0.16;0.15;983.54;1115.5;184.73;376.01
Medvedeva et al. 2018;Experiment 4;11;11;0.15;0.27;0.12;0.12;994.01;1083.12;112.3

Table X3

Data file for atDCS effect on FA

Study;Year;number_control;number_stimulation;mean_control;mean_stimulation;s
Chapter 5;Experiment 1;16;16;0.57;0.34;0.19;0.11;580.42;770.94;182.85;170.58
Chapter 5;Experiment 3;23;25;0.47;0.59;0.18;0.12;538.91;477.82;171.43;86.1
Chapter 5;Experiment 4;26;23;0.54;0.43;0.18;0.14;791.89;951.82;297.57;276.53
Chapter 5;Experiment 5;15;16;0.43;0.44;0.16;0.16;983.54;1115.5;184.73;376.01
Medvedeva et al. 2018;Experiment 4;11;11;0.49;0.41;0.17;0.14;994.01;1083.12;112.3

APPENDIX Y

Table Y1

Data file for anodal tDCS effect on hits

IdS;IdC;StuComp;AnodalM;AnodalSD;AnodalN;ShamM;ShamSD;ShamN;DesignWB;A
1;1;Javadi and Walsh 2012 encoding group (Exp1);87.4;1.7;16;81;2;16;1;Left Frontal;(
1;2;Javadi and Walsh 2012 retrieval group (Exp2);82.8;2.6;16;80.6;1.8;16;1;Left Front
2;3;Elmer et al 2009 F3 group (same exp);76.4;15.7;10;79.6;14.4;10;1;Left Frontal;0;6
2;4;Elmer et al 2009 F4 group (same exp);75.2;14.7;10;78.8;15.9;10;1;Right Frontal;0;
3;5;Javadi and Cheng 2013 consolidation group (same exp);96.8;1.9;15;92.8;1.7;15;1;
3;6;Javadi and Cheng 2013 control group (same exp);85.3;1.7;15;85.5;1.9;15;1;Left Fr
4;7;Manenti et al 2013 Y frontal group (same exp) left hemisphere;88.5;6.2;16;88.8;5
4;8;Manenti et al 2013 Y frontal group (same exp) right hemisphere;88.1;6.9;16;88.8
4;9;Manenti et al 2013 Y parietal group (same exp) left hemisphere;84.9;7.9;16;89.2;
4;10;Manenti et al 2013 Y parietal group (same exp) right hemisphere;84.9;7;16;89.2
4;11;Manenti et al 2013 E frontal group (same exp) left hemisphere;82.9;7.9;16;81.4;
4;12;Manenti et al 2013 E frontal group (same exp) right hemisphere;83.2;6.6;16;81.
4;13;Manenti et al 2013 E parietal group (same exp) left hemisphere;80;8.2;16;81.8;9
4;14;Manenti et al 2013 E parietal group (same exp) right hemisphere;80;6.4;16;81.8
5;15;Boggio et al 2009 unilateral group (same exp) online+offline;85.5;12.9;15;92.2;8
5;16;Boggio et al 2009 unilateral group (same exp) offline;92.2;4.3;15;87.8;43;15;2;Le
5;17;Boggio et al 2009 bilateral group (same exp) online+offline;84.4;8.6;15;92.2;8.6;
5;18;Boggio et al 2009 bilateral group (same exp) offline;86.6;4.3;15;87.8;43;15;2;Lef
6;19;Jones et al 2014 encoding online left parietal anodal group (Exp1) delayed recall
6;20;Jones et al 2014 encoding online left parietal anodal group (Exp1) recognition;9
6;21;Jones et al 2014 offline left parietal group (Exp2) delayed recall;78.75;14.6;20;75
6;22;Jones et al 2014 encoding online right parietal anodal group (Exp3) delayed reca
7;24;Pergolizzi and Chua 2015 (Exp 1);87;10.2;26;87;10.2;26;2;Left Parietal;1;5;1;1;2;I
7;25;Pergolizzi and Chua 2015 Exp 2 left parietal group (same exp);88;4.9;24;86;9.8;2
7;26;Pergolizzi and Chua 2015 Exp 2 right parietal group (same exp);90;9.8;24;90;9.8;
8;27;Sandrini et al 2014 reminder group (same exp) delay 1;49.9;24.3;12;31.9;16.6;12
8;28;Sandrini et al 2014 reminder group (same exp) delay 2;56.3;25.6;12;27.7;17.6;12
8;29;Sandrini et al 2014 non reminder group (same exp) delay 1;49.9;17.3;12;31.9;16
8;30;Sandrini et al 2014 non reminder group (same exp) delay 2;47.2;25.9;12;27.7;17
9;31;Penolazzi et al 2010 right hemisphere;56.8;18.1;12;63.4;21.3;12;1;Right Frontal;
9;32;Penolazzi et al 2010 left hemisphere;54.2;24.4;12;63.4;21.3;12;1;Left Frontal;1;2
10;33;LaFontaine et al 2013 left hemisphere;62;0.1;11;60;0.1;11;1;Left Frontal;1;0;1;2
10;34;LaFontaine et al 2013 right hemisphere;59;0.1;11;60;0.1;11;1;Right Frontal;1;0;
11;35;Pisoni et al 2015b temporal anodal group (Exp1);68.7;12;12;78.6;12;12;1;Left T
11;37;Pisoni et al 2015b frontal anodal group (Exp3);78.6;12;12;74.5;12;12;1;Left Fro
12;38;Jacobson et al 2012 left hemisphere;65;12.7;12;65.4;10.7;12;2;Left Parietal;1;1
12;39;Jacobson et al 2012 right hemisphere;59.4;14.5;12;65.4;10.7;12;2;Right Parieta
13;40;Zwissler et al 2014 ;62.3;3.3;24;62;2.5;48;2;Left Frontal;0;2;1;2;1;2;Y;1;N/A
14;43;Smirni et al 2015 anodal group right PFC (Exp 2);70;11.8;8;69.2;10.6;8;1;Right F
14;44;Smirni et al 2015 anodal group left PFC (Exp 2);70.8;9.9;8;71.7;8.2;8;1;Left Fron
15;45;Gray et al 2015 left frontal group (same exp);77.3;14.7;24;73.3;19.6;24;2;Left F
15;46;Gray et al 2015 right frontal group (same exp);77;14.7;24;73.3;19.6;24;2;Right I

Table Y2

Data file for anodal tDCS effect on reaction times for hits

IdS;IdC;StuComp;RT_anodal_hits;RT_anodal_hits_SD;AnodalN;RT_sham_hits;RT_sha
1;1;Javadi and Walsh 2012 encoding group (Exp1);740;382;16;742;372;16;1;Left Fron
1;2;Javadi and Walsh 2012 retrieval group (Exp2);754;407;16;725;390;16;1;Left Front
3;5;Javadi and Cheng 2013 consolidation group (same exp);1382;291;15;1425;302;15
3;6;Javadi and Cheng 2013 control group (same exp);1320;349;15;1460;392;15;1;Left
4;7;Manenti et al 2013 Y frontal group (same exp) left hemisphere;770.9;129.4;16;80
4;8;Manenti et al 2013 Y frontal group (same exp) right hemisphere;778.6;112.1;16;
4;9;Manenti et al 2013 Y parietal group (same exp) left hemisphere;768.6;100.1;16;8
4;10;Manenti et al 2013 Y parietal group (same exp) right hemisphere;787.9;103.1;16
4;11;Manenti et al 2013 E frontal group (same exp) left hemisphere;941.4;174;16;105
4;12;Manenti et al 2013 E frontal group (same exp) right hemisphere;1046.5;226.6;1
4;13;Manenti et al 2013 E parietal group (same exp) left hemisphere;994.8;129.2;16;
4;14;Manenti et al 2013 E parietal group (same exp) right hemisphere;998;181.7;16;9
11;35;Pisoni et al 2015b temporal anodal group (Exp1);1516;355;12;1356;266;12;1;Le
11;37;Pisoni et al 2015b frontal anodal group (Exp3);1346;247;12;1218;247;12;1;Left
12;38;Jacobson et al 2012 left hemisphere;2502;1208;12;2133;585;12;2;Left Parietal;
12;39;Jacobson et al 2012 right hemisphere;2609;1013;12;2133;585;12;2;Right Pariet
13;40;Zwissler et al 2014 ;1183;37.8;24;1156.13;29.63;48;2;Left Frontal;0;2;1;2;1;2;Y;
14;43;Smirni et al 2015 anodal group right PFC (Exp 2);1727;234.4;8;1697.4;273.7;8;1
14;44;Smirni et al 2015 anodal group left PFC (Exp 2);1729.5;240.6;8;1755.2;191.8;8;1
16;48;Matzen et al 2015 recognition;3108;1573.5;12;3540.71;2024.62;12;2;Left Front
16;49;Matzen et al 2015 recall;4743.8;2439.7;12;4902.5;2885.38;12;2;Left Frontal;0;2
18;56;Pisoni et al 2015a parietal group (same exp);1440.6;173;15;1350.9;135;14;2;Le
18;57;Pisoni et al 2015a temporal group (same exp);1341.6;131.3;15;1350.9;135;14;2
25;68;Manuel & Schneider 2016 frontal group (same exp) left hemisphere;792;95.55
25;69;Manuel & Schneider 2016 frontal group (same exp) right hemisphere;776;99.1
25;70;Manuel & Schneider 2016 parietal group (same exp) left hemisphere;872.5;174
25;71;Manuel & Schneider 2016 parietal group (same exp) left hemisphere;893.3;232
29;79;Habich et al 2017 recognition;1667.1;453;22;1878.3;628.5;21;2;Left Frontal;0;2
34;99;Medvedeva et al Exp 1 online group;752.1;160;17;585.8;185;17;2;Left Frontal;0
34;100;Medvedeva et al Exp 1 offline group;578.8;197.9;15;585.8;185;17;2;Left Front
34;101;Medvedeva et al Exp 2 online group;684.4;246.1;16;669.3;153.1;18;2;Left Fro
34;102;Medvedeva et al Exp 2 offline group;641.4;234.5;15;669.3;153.1;18;2;Left Fro
34;103;Medvedeva et al Exp 2 parietal deep;1239.47;234.93;16;1325.54;291.80;16;1;
34;104;Medvedeva et al Exp 2 frontal deep;1287.00;281.49;15;1287.38;210.29;15;1;L
34;103;Medvedeva et al Exp 2 parietal shallow;1342.65;295.86;16;1376.18;269.22;16
34;104;Medvedeva et al Exp 2 frontal shallow;1354.66;272.17;15;1396.81;275.40;15;
34;105;Medvedeva et al Exp 4;1061.6;162.4;11;988.4;110.3;11;2;Left Frontal;0;2;1;2;

Table Y3

Data file for cathodal tDCS effect on hits

IdS;IdC;StuComp;CathodalM;CathodalSD;CathodalN;ShamM;ShamSD;ShamN;Design
1;1;Javadi and Walsh 2012 encoding group (Exp1);75.2;2.7;16;81;2;16;1;Left Frontal;(
1;2;Javadi and Walsh 2012 retrieval group (Exp2);76.1;3.1;16;80.6;1.8;16;1;Left Front
2;3;Elmer et al 2009 F3 group (same exp);70;22.4;10;79.6;14.4;10;1;Left Frontal;0;6;2
2;4;Elmer et al 2009 F4 group (same exp);83.2;13.32;10;78.8;15.9;10;1;Right Frontal;(
3;5;Javadi and Cheng 2013 consolidation group (same exp);92.5;2;15;92.8;1.7;15;1;Le
3;6;Javadi and Cheng 2013 control group (same exp);85;1.9;15;85.5;1.9;15;1;Left Fro
6;23;Jones et al 2014 encoding online right parietal cathodal group (Exp4) recall;71.3
11;36;Pisoni et al 2015a temporal cathodal group (Exp2);68.2;21.7;12;68.8;17.9;12;1;
13;40;Zwissler et al 2014 ;64.8;3.3;24;62;2.5;48;2;Left Frontal;0;2;1;2;1;2;Y;1;N/A
14;41;Smirni et al 2015 cathodal group right PFC (Exp1);74.7;7.7;10;67;4.8;10;1;Right
14;42;Smirni et al 2015 cathodal group left PFC (Exp1);64.3;3.8;10;69.8;7.8;10;1;Left F
22;64;Balzarotti & Colombo 2016;36.7;18.3;14;34.1;12.7;14;2;Left Frontal;0;2;2;2;2;2;
23;65;Chen et al 2016;85;6;18;89;5.5;18;1;Left Parietal;0;5;1;1;2;N/A;Y;1;2

Table Y4

Data file for cathodal tDCS effect on reaction times for hits

IdS;IdC;StuComp;RT_cathodal_hits;RT_cathodal_hits_SD;CathodalN;RT_sham_hits;R
1;1;Javadi and Walsh 2012 encoding group (Exp1);782.0;373.0;16;742;372;16;1;Left F
1;2;Javadi and Walsh 2012 retrieval group (Exp2);714.0;403.0;16;725;390;16;1;Left Fr
3;5;Javadi and Cheng 2013 consolidation group (same exp);1329.0;306.0;15;1425;302
3;6;Javadi and Cheng 2013 control group (same exp);1470.0;344.0;15;1460;392;15;1;
11;36;Pisoni et al 2015a temporal cathodal group (Exp2);1374.0;271.0;12;1394;237;1
13;40;Zwissler et al 2014;1201.3;39.4;24;1156.13;29.63;48;2;Left Frontal;0;2;1;2;1;2;Y
14;41;Smirni et al 2015 cathodal group right PFC (Exp1);1774.4;230.0;10;1730.03;255
14;42;Smirni et al 2015 cathodal group left PFC (Exp1);1693.3;186.1;10;1734.1;181.5;

Publications