THE UNIVERSITY OF CHICAGO

PLAYING HARD TO GET: THE EFFECTS OF ANODAL TDCS ON MEMORY PERFORMANCE AS A FUNCTION OF TASK DIFFICULTY AND SLEEP QUALITY

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE SOCIAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF PSYCHOLOGY

BY
GABRIELLA VICTORIA HIRSCH

CHICAGO, ILLINOIS

AUGUST 2021

Table of Contents

List of Tables v

List of Figures....................vi

Acknowledgments....................vii

Abstract....................viii

Chapter 1: Pre-registered Analyses on the Effect of tDCS On Memory....................1

Introduction....................1

1.1. Prefrontal Cortex, Memory and Aging....................1

1.2 tDCS Effects on Memory....................4

tDCS to left dorsolateral prefrontal cortex (dlPFC).................... 5

tDCS to left posterior parietal cortex (PPC)....................7

Inconsistencies in the Effects of tDCS on Memory Performance in Prior Work....................9

The Current Study....................12

2.1 Current Project Objectives....................12

2.2 Pre-registered Hypotheses & Predictions....................14

3. Methods....................16

3.1 Transcranial Direct Current Stimulation (tDCS)....................16

3.2 Materials & Procedure....................17

3.3 Participants....................20

Sampling & Inclusion Criteria....................20

Enrollment, Randomization and Blinding Procedures....................21

Compensation....................22

Participant characteristics (enrolled as of March 2020) 23

3.4 Assessments..25

4. Memory Tasks...29

4.1 Episodic Memory Task...29

4.2 Working Memory Task..31

4.3 Power and sampling..31

4.4 Statistical significance..32

Results...33

5.1 Baseline Day Analyses..33

5.2 Pre-registered Effects of tDCS on Memory Performance 36

Model 1.a. Effect of tDCS in Younger Adults: Episodic Memory...........................38

Model 1.a. Effect of tDCS in Younger Adults: Working Memory...........................39

Model 1.b: Effect of tDCS and in Younger & Older Adults: Episodic Memory.........39

Model 1.b: Effect of tDCS and in Younger & Older Adults: Working Memory.........40

Model 2.a Effect of tDCS and in Younger Adults: dlPFC vs Parietal vs Sham effects in Episodic Memory...42

Model 2.a Effect of tDCS and in Younger Adults: dlPFC vs Parietal vs Sham effects in Working Memory..43

Model 2.b. Effect of tDCS: Models from 1.a, 1.b & 2.a with baseline performance as a covariate...45

5.3 Effect of tDCS on Subjective Reports of Arousal..50

Discussion...51

Baseline Day Analyses...51

The Effect of tDCS on Memory Performance..53

Chapter 2: The Effect of Circadian Preference & Sleep Quality on tDCS Effects in

Memory Performance...56

2.1 tDCS, Time-of-Day and Circadian Preference..56

2.2 Measuring Circadian Preference: MEQ & Wrist-Worn Actigraphy...........................60

2.3 Circadian Preference on Memory Performance & tDCS Effects.................................63

2.4 Measuring Sleep Quality...66

2.5 Impact of Sleep Quality on Memory Performance & tDCS Effects.............................70

The Modulatory Effects of Sleep Quality on Task-based Factors in Episodic Memory....70

The Effect of Sleep Quality on the Impact of tDCS Effects of Episodic Memory Performance...75

2.6 Impact of Sleep Quality on Working Memory Performance.......................................78

2.7 Discussion...79

Chapter 3. Blinding Integrity & Sensation Effects in tDCS : An Argument for Important Design Considerations...83

3.1 Introduction: Blinding & Shamming in tDCS..83

3.2 Sensation Effects: Prior Work 86

3.3 Sensation Effects: Current Study...89

3.4 The Impact of Sensation Effects on Performance..92

3.5 Discussion...95

General Discussion...99

References...107

Appendix A: Comparison of the β estimates for the linear mixed effects models pt.1 125

Appendix B: Comparison of the β estimates for the linear mixed effects models pt.2 127

List Of Tables

Table 1: Participant characteristics……24

Table 2: Baseline performance accuracy……36

Table 3: tDCS session performance accuracy……49

Table 4: Participant reported tDCS sensations: Exp. 3 from Wong, et al., (2018)……88

Table 5: Participant reported tDCS sensations: Exp. 4 from Wong, et al., (2018)……89

Table 6: Distribution of reported extent of tDCS sensations during tDCS ("select best match") ……91

Table 7: Distribution of reported type of tDCS sensations during tDCS ("select all that apply") ……91

List Of Figures

Figure 1: Experimental design arms..........13

Figure 2: Task protocol..........19

Figure 3: Working memory accuracy performance for younger and older adults..........41

Figure 4: dlPFC vs PPC vs sham in working memory. 44

Figure 5: Sample of midpoints of sleep for 53,689 US-based individuals (Fischer et al., 2017)..........57

Figure 6: Time-of-day effects on recollection accuracy (Wong et al., 2018)..........60

Figure 7: Participant MEQ score distribution..........62

Figure 8: Episodic performance as a function of format and sleep quality..........74

Figure 9: The effect of stimulation on episodic memory as a function of stimulation, adjusted for sleep quality. 75

Figure 10: The effect of stimulation on episodic memory as a function of format and sleep quality..........77

Figure 11: The effect of tDCS expectations on memory performance..........94

Acknowledgements

First and foremost, I would like to thank my advisor, Dr. David Gallo, who has been a pillar of support and reassurance throughout my graduate school experience. In our discipline, your academic experience is often shaped by your mentors, and I feel grateful to have had one who has been so understanding, patient, thoughtful and caring. Not everyone is so lucky, I'm not certain I would have gotten through graduate school without such support. I would also like to thank my committee members, Dr. Wilma Bainbridge, Dr. Edward Awh and Dr. Brian Prendergast, who have all been so supportive and understanding despite the challenges and limitations associated with completing a dissertation during a global pandemic.

My sincerest thanks go out to the team of people who helped manage and collect the data described in this dissertation. First and foremost, many thanks to our former lab manager Taylor Chamberlain, who played a crucial role in managing the day-to-day of the project along with my two research assistants, Miranda Malone and Cheyenne Wakeland-Hart, for all the years of hard work in data collection and data cleaning. I would also like to extend my thanks to Philip Schumm, our consultant biostatistician, who provided critical input and feedback around the development of the statistical models described in this dissertation. I would also like to thank Dr. Manoj Doss, who took time away from his own dissertation writing during my early years in graduate school to help develop my coding and technical expertise and build my confidence in that domain.

Finally, I would like to thank my incredible husband, Isaac, who acted as emotional and physical support system, proof-reader and sanity-checker while I talked through ideas and statistical interpretations throughout the ups and downs of dissertation writing. I couldn't have done it without any of you!

Abstract

Over the past decade, cognitive research using Transcranial Direct Current Stimulation (tDCS) sparked enormous interest in its potential to safely, easily, and affordably boost cognitive function in healthy and clinical populations. However, cognitive effects from single session tDCS have been mixed, especially as it pertains to its potential to enhance higher-order cognitive functions such as episodic and working memory. Recent work in our own lab (Wong et al. 2018) suggested that time-of-day may be a critical factor in tDCS effects in younger adults. To examine whether this effect replicates and extends to older adults who have known changes in circadian preferences, we conducted the first NIH-funded clinical trial of tDCS in younger and older adults at different times of day, with considerably larger sample sizes than are typical of this literature. Specifically, we used a double-blind, sham-controlled, between-subjects stimulation design, administering anodal tDCS to left dorsolateral prefrontal cortex (dlPFC) prior to episodic memory retrieval and working memory tasks at different times of day (i.e., in both AM and PM testing sessions). We also investigated the effects of left posterior parietal cortex (PPC) stimulation in younger adults.

In Chapter 1, we report the effects of tDCS on our two memory measures. Results demonstrated the potential role of task difficulty in eliciting stimulation-related boosts in performance as it relates to the effects of anodal left dlPFC stimulation on working memory performance, but not episodic memory retrieval. Additionally, these tDCS - elicited boosts were only observed in our younger adults, not our older adults, without any modulating effects of time of day.

In Chapter 2, we report the effects of circadian preference and sleep quality data and its impact on tDCS effects in memory performance. While the optimal methods for

obtaining reliable tDCS results continue to be elusive, these results point to the possibility that tDCS may be conditional on sleep quality -- a variable never investigated in this literature. Specifically, adjusting our models to account for actigraphy-derived sleep quality underscores the potential of tDCS to boost episodic memory performance impairments associated with poor sleep quality. Overall, these results provide some support for the hypothesis that tDCS benefits performance "when needed", but given the historically tenuous nature of tDCS effects, we emphasize the need for further replication of this potentially important discovery.

Finally, in Chapter 3, we report the effects of tDCS expectations on performance. These findings raise serious questions about the validity of single-blind and within-subjects tDCS designs that are frequent in the literature and emphasize the potential importance of between-subjects designs using robust double-blind protocols, as used in the current study. We conclude by discussing important methodological considerations centered around the importance of rigorous blinding and shamming protocols necessary to achieve more reliable (and replicable) tDCS effects of healthy cognitive function and beyond.

Chapter 1: Pre-registered Analyses on the Effect of tDCS On Memory

Introduction

1.1. Prefrontal Cortex, Memory and Aging

Ever since the first neuropsychological cases of frontal lobe damage, it has been acknowledged that frontal lobes are critical for executive control processes (Miller & Wallis, 2009) including inhibition, planning, evaluating consequences as well as the general ability to coordinate thoughts and actions to internal goals (Koechlin et al., 2003). Indeed, there is mounting evidence that general executive processes are heavily reliant on dorsolateral prefrontal cortex (dlPFC) function (Brodmann's areas, BA 9 and BA 46, also described as middle frontal gyrus; e.g., Alvarez & Emory, 2006; Curtis & D'Esposito, 2003; Fuster, 2000) where dlPFC has been shown to subserve those mechanisms subserving working memory (Barbey et al., 2013; Hill et al., 2016; Levy & Goldman-Rakic, 2000; Tremblay et al., 2014), as well as both the encoding and retrieval processes specific to episodic memory (Ranganath & Knight, 2003; Wong et al., 2014). Converging neuroimaging evidence has highlighted subdivisions of the prefrontal cortex (PFC) as crucial for long-term or episodic memory (Dobbins et al., 2002; Fletcher, 1998b), characterized by the encoding, storage and retrieval of information connected to specific, personal events (Tulving, 2002). Additionally, this same region has been demonstrated as critical for short-term or working memory (Nyberg et al., 2003), a cognitive system that is able to store, process and manipulate information for transient use (Baddeley, 2003), with an emphasis on left dorsolateral prefrontal cortex (dlPFC) as important for both domains (Blumenfeld, 2006).

Understanding the role of frontal function in cognitive aging (Suzuki et al., 2018) is critical as older adults become an ever-growing segment of the population. With the number of Americans aged 65 and older projected to more than double (to 98 million) by 2060 (Mather et al., 2015), coupled with the finding that older adults are expected to participate in the labor force for longer than ever, it is crucial to invest in understanding age-related effects of frontal function and potential ways to mitigate the effects of age on declining memory performance. Specifically, the degree of demand placed on dlPFC increases with advancing age, which is often accompanied by gradual declines in episodic memory (Fraundorf et al., 2019) and working memory performance (Reuter-Lorenz & Sylvester, 2004).

From an episodic memory perspective, these age-related deficits manifest in several ways, including a reduced ability to recall or recognize previously studied information (e.g., fewer hits to target items) and increased false recall, or recognition of non-studied information (e.g., more false alarms to lure items). Indeed, older adults also show impairments in neuropsychological tasks designed to tap into PFC function (including executive function). These declines have been correlated with observed impairments in episodic memory performance (Daselaar & Cabeza, 2013; Shing et al., 2010) in the form of both true (Wilckens et al., 2012) and false (Devitt & Schacter, 2016) memories. Along these same lines, Lyle et al., (2006) also demonstrated age-related deficits in binding source and content information in encoding. Furthermore, in addition to encoding deficits, impaired strategic retrieval also plays a role in age-related associative deficits (Cohn et al., 2008). Therefore, even when source information is successfully encoded, older adults may not use this information efficiently during retrieval to make monitoring decisions. Reduced efficiency of retrieval monitoring processes may thus lead to a reliance on less effortful monitoring strategies (Thomas & McDaniel, 2013). These behavioral findings are consistent with neuroimaging work pointing to structural and functional deterioration in prefrontal regions. For example, the PFC also contributes to the strategic encoding of relational information (Addis & McAndrews, 2006), which has been specifically linked to reduced dorsolateral (as well as ventrolateral) PFC volume (Becker et al., 2015; see also Blumenfeld et al., 2011).

Mounting evidence has shown aging also detrimentally affects various aspects of working memory for both verbal and non-verbal information (Grady & Craik, 2000; Reuter-Lorenz & Sylvester, 2004), including in tasks probing verbal span, visual object manipulation, as well as updating and switching. Cognitive accounts have attributed the observed age-related working memory declines to a general slowing of cognitive processing (Salthouse, 1996), as well as declines in attentional resources (Craik & Byrd, 1982) and reduced efficiency of inhibitory processes (Pliatsikas et al., 2019). The executive processes of selective attention and inhibitory control have figured prominently in several accounts of aging and working memory decline (Hasher & Zacks, 1988; McDowd & Shaw, 2000) with age-related changes in executive attentional control and inhibition increasing vulnerability to interference, resulting in declines in working memory. From a structural perspective, working memory changes have been linked to age-related changes in PFC, including age-related reductions in activation in the left PFC, although these can be accompanied by increased activity in the right PFC, which may play a compensatory role (Pliatsikas et al., 2019)

1.2 tDCS Effects on Memory

Transcranial Direct Current Stimulation (or tDCS) is a non-invasive brain stimulation technique that has been leveraged by the scientific community to meet a variety of research and treatment goals. This stimulation technique may provide a novel alternative to pharmacological solutions (Brunoni et al., 2012) for the treatment, prevention, or deceleration of both clinical psychopathologies, such as Major Depression (Salehinejad et al., 2017) and Attention Deficit Hyperactivity Disorder (ADHD) (Nejati et al., 2017), as well as age-related cognitive dysfunction or declines in functional connectivity (Meinzer et al., 2013). Overall, tDCS may be a safe and well-tolerated alternative to Transcranial Magnetic Stimulation (TMS) to temporarily modulate brain activity and behavior in healthy adults. The accessibility associated with tDCS has increasingly led to its adoption as a tool to enhance executive and cognitive performance in healthy adults, including tasks requiring episodic retrieval and working memory (e.g., Cespón et al., 2017; see also Reinhart et al., 2017).

Within a typical tDCS procedure, a constant low-intensity current (1-2 milliamperes) is delivered directly to the cortex through the cranium via surface electrode pads typically for a 20-30-minute duration (for recent reviews, see Bartl et al., 2020; Galli et al., 2019; Reinhart et al., 2017; Yavari et al., 2018). The anodal electrode is often placed over the target brain region one aims to stimulate, and the cathodal electrode is placed, where it is assumed to have minimal effect on underlying cortex (e.g., over the contralateral eyebrow or supraorbital position, see Wagner et al., 2007). The electrical current thus passes through the skull to induce changes in membrane potential of cortical neurons (Nitsche & Paulus, 2000; Nitsche et al., 2003), thus modulating cortical excitability (Hummel & Cohen, 2005) and increasing the activity of the underlying cortical neurons (Michael A. Nitsche et al., 2008). With the anodal-cathodal montage, it is assumed that tDCS elicits either neuronal membrane depolarization or hyperpolarization on the base of its polarity, respectively anodal and cathodal (Tatti et al., 2016).

tDCS can be considered a pure neuromodulatory technique altering the spontaneous firing rate of neurons and synaptic responses to afferent inputs (Miniussi & Ruzzoli, 2013) in contrast to TMS, which elicits action potentials Its effects on excitability are thought to be related to transient changes in the synaptic efficacy of different neurotransmitter systems (Nitsche et al., 2008), including glutamatergic, serotonergic, GABAergic and dopaminergic system modifications (see Medeiros et al., 2012 for a review on neurobiological mechanisms of tDCS).

While some research suggests applying the cathode electrode over regions of interest (e.g., dlPFC) can increase performance (e.g., memory accuracy), placing the anode electrode over the region of interest has been found to be the more reliable way of modulating cognitive control (Weller et al., 2020), as consistent within the episodic (Galli et al., 2019) and working memory (Mancuso et al., 2016) literatures specifically.

tDCS to left dorsolateral prefrontal cortex (dlPFC)

Emerging evidence suggests that tDCS of specific regions of PFC can benefit both episodic and working memory. With respect to episodic memory, large meta-analyses of neuroimaging work (Kim, 2011), coupled with results from noninvasive brain stimulation studies (Manenti et al., 2012) provides compelling evidence to suggest left dlPFC may be causally involved in the encoding and retrieval of information. If the left dlPFC is indeed involved in both encoding and retrieval, then anodal stimulation of left dlPFC should improve recollection. Previous work from the lab (Gray et al., 2015; Wong et al., 2018) supports this supposition, particularly for tasks that require effortful cognitive control, such as cognitively demanding tasks. Other studies too have found that applying anodal tDCS to dlPFC during encoding or retrieval in younger adults can enhance episodic memory across stimulus format, including words (Fiori et al., 2013; Habich et al., 2017; Javadi & Cheng, 2013; Javadi & Walsh, 2011; Leshikar et al., 2017) and pictures (Balzarotti & Colombo, 2016; Chua et al., 2017; Penolazzi et al., 2010; Pergolizzi & Chua, 2017; Ruf et al., 2017; Zwissler et al., 2014). In addition to these tDCS effects in younger adults, several studies have demonstrated that tDCS to dlPFC can enhance and working memory and episodic memory in healthy older adults as well (Berryhill & Jones, 2012; Cespón et al., 2017; Park et al., 2014).

With respect to working memory, anodal tDCS to dlPFC has been found to have beneficial effects in a wide variety of working memory tasks, including n-back tasks (Andrews et al., 2011; Fregni et al., 2005; Mulquiney et al., 2011; Zaehle et al., 2011), the Pacet Auditory Serial Addition Task (PASAT), and the Pacet Auditory Serial Subtraction Task (PASST) (Pope et al., 2015) as well as the Operation Span (OSpan) task (Jones et al., 2015) and others (Au et al., 2016; Baumert et al., 2020; Maheux-Caron et al., 2021; Trumbo et al., 2016, see Katsoulaki et al., 2017 for a review).

Given the likely role of dlPFC in both episodic and working memory processes, it is perhaps not surprising that many previous studies have claimed reliable tDCS effects to dlPFC in both domains, along with many other forms and/or components of memory (e.g., procedural or motor learning, sleep consolidation, etc., see Blumenfeld, 2006 and Galea et al., 2009). Considering this converging evidence, we may speculate that explicitly modulating the dlPFC might affect performance on cognitive tasks that rely heavily on

PFC function in general, and dlPFC in particular, especially for those highly demanding retrieval and working memory tasks that become all the more challenging as we age.

tDCS to left posterior parietal cortex (PPC)

As an alternative to left dlPFC, anodal stimulation to left posterior parietal cortex (PPC) has been used in a wide range of studies as the target stimulation site for enhanced performance in a variety of episodic tasks (see Galli et al., 2019 for review) including source memory tasks (Chen et al., 2016), associative memory tasks (Bjekić et al., 2019), as well as episodic memory reconsolidation (Crossman et al., 2019). Additionally, left PPC has been used to enhance select working memory tasks (Zivanovic et al., 2021). However, the PPC has not been targeted as frequently as PFC in stimulation studies of memory, most likely because PPC is not typically thought to play a causal role to the same extent in memory retrieval compared to stimulation of PFC.

Imaging studies have shown PPC to be highly correlated with memory retrieval (e.g., Cabeza et al., 2008; Dobbins et al., 2003; Schoo et al., 2011), yet investigations into the causal involvement of PPC have been mixed (Pergolizzi & Chua, 2015). For example, unlike damage to PFC, which causes profound memory impairments, damage to PPC is not typically associated with such impairments (Simons et al., 2008). In one neuroimaging study of patients with parietal brain lesions, lesioned areas that overlapped closely with the parietal activations of healthy volunteers during recollection nevertheless exhibited normal source recollection performance (Simons et al., 2008). On the other hand, parietal activations are also seen frequently in functional neuroimaging studies of episodic memory (Cabeza et al., 2008), leading to the possibility that while PPC is likely involved in episodic recollection, it may play a more supporting role (Schoo et al., 2011).

Regarding the use of active brain stimulation such as tDCS on PPC to boost episodic memory, previous work from the lab observed no benefit to recollection accuracy in a young adult population (Gray et al., 2015). Other studies also found similar null effects (Crossman et al., 2019; Meier & Sauter, 2018). However, some studies have shown that active tDCS to left PPC does benefit memory, but only under certain conditions. For example, Jones et al., (2014) found anodal tDCS to left PPC benefitted episodic memory only when applied during the encoding phase; whereas Bjekić and colleagues (2019) observed that anodal stimulation to both left and right PPC enhanced performance in a face-word and object-location associative memory task. Others still found tDCS to left PPC particularly beneficial for modulating attention in a recognition task (Minamoto et al., 2014).

Overall, these findings are consistent with the idea that parietal cortex, while likely not causally involved in the monitoring or evaluative processes that characterizes episodic recollection, may aid in directing attention towards recollected information *after* it has been retrieved (Cabeza et al., 2011; Jacobson et al., 2012; Yazar et al., 2012). While there are comparatively few studies investigating the effect of anodal tDCS to parietal cortex in working memory (M. E. Berryhill et al., 2010; Sandrini et al., 2012), reports have shown benefits for difficult tasks (Jones & Berryhill, 2012) as well as visuospatial tasks (Zivanovic et al., 2021). However the role of left parietal cortex in working memory remains poorly understood. Given these mixed findings, additional research directly comparing active tDCS of left PPC to active tDCS to left dlPFC will help shed light on the role of left dlPFC versus left parietal cortex in episodic memory retrieval as well as working memory.

Inconsistencies in the Effects of tDCS on Memory Performance in Prior Work

Despite the evidence that tDCS can improve episodic and working memory, this evidence is not robust, and there are widespread inconsistency in the reliability and magnitude of the effects of tDCS (e.g., Fraundorf et al., 2019; Huo et al., 2018; Manenti et al., 2013; Nilsson et al., 2015; Sandrini et al., 2014 see Galli et al., 2019 for a recent meta-analysis). More recent meta-analyses (e.g., Galli et al., 2019; Reinhart et al., 2017) suggest that these inconsistencies have led to failures in interpretability and replicability, making definitive conclusions hard to draw. Furthermore, while reviews from the literature are important and beneficial, they also suffer from the problem of modeling a variety of differing stimulation parameters (e.g., electrode configuration, blinding and sham procedures, subject populations, etc.) within the constraints of traditional meta-analyses (Bartl et al., 2020; Hurley & Machado, 2018).

The inconsistency of evidence within the tDCS literature is exacerbated by the suspicion that tDCS studies historically have had too few participants to make appropriate statistical inferences or to find the kinds of tDCS effects that we have observed (see Minarik et al., 2016). Underpowered studies, or studies with smaller sample sizes, often have inflated effect sizes (Kühberger et al., 2014). Based on the power estimates for the current study (described later), previous tDCS studies showing unreliable effects on memory are often severely underpowered (often with 20 or fewer participants per stimulation group). This dearth of direct or appropriate statistical comparison of stimulation treatments, as well as statistical power, has resulted in a lack of consensus or guidance for researchers who are otherwise motivated to leverage tDCS to investigate their questions of interest.

Additionally, with respect to episodic memory, there is evidence that the effect of tDCS is specific to *effortful* recollection, consistent with the proposed role of dlPFC in the cognitively controlled aspects of high task demands (Fletcher, 1998b, 1998a). Indeed, in our previous tDCS work, we found that stimulation of left dlPFC just prior to retrieval reliably boosted accuracy on a word recollection task but not on a (less effortful) picture recollection task (Gray et al., 2015). This distinction might explain why some studies have failed to find consistent effects of anodal tDCS to left dlPFC during retrieval, because these studies have used traditional old/new recognition memory tasks that can rely on familiarity as opposed to item recollections (Hammer et al., 2011; Manenti et al., 2013; Smirni et al., 2015). That is, these studies used a task that may not have sufficiently challenged prefrontal regions. However, based on the extant literature, it is not currently clear whether this finding is due to task difficulty (whereby tDCS privileges highly taxing tasks, e.g., a more effortful word retrieval task vs. a less effortful picture retrieval task) or due to laterality*,* particularly given left dlPFC may simply privilege verbal or semantic processing (Poldrack et al., 1999; Wagner et al., 2001). Relatedly, an aging study using stimulation prior to retrieval on an associative memory task (in which participants learned face-name and place-name pairs) found tDCS benefitted memory performance only when successful retrieval was not easily achieved (evidenced by long reaction times) (Ross et al., 2011). This suggests that the modulatory effects of tDCS effects may be particularly pronounced when memory access is difficult; intuitively, given the induction of changes in neuronal firing during anodal stimulation, it follows that when the tasks are easy the addition of tDCS does not impact performance. By contrast, on very difficult trials, tDCS effects emerge (Berryhill et al., 2014).

Another source of inclusive evidence regarding the effects of tDCS may be the presence of overlooked mediating variables, such as the time of day at which stimulation is administered. In Wong, et al., (2018) post-hoc analyses of three experiments revealed intriguing effects whereby the positive effect of tDCS on episodic memory performance were conditional on time of day. Specifically, in a sample of 120 younger adults, participants benefited from active anodal left dlPFC stimulation in the morning, but not the afternoon. To test this prospectively, Wong et al., (2018) also described a fourth experiment with the goal of replicating the pooled time of day analysis. Here, using an identical episodic recollection task, results demonstrated an effect such that participants randomized to the morning testing time had recollection accuracy that was significantly greater for stimulation than sham. By contrast, for those tested in the afternoon, there was no significant difference between stimulation and sham, and if anything, there was a trend for afternoon stimulation to reduce recollection accuracy (Wong et al., 2018).

Converging evidence between the pooled retrospective analysis and prospective time of day finding reported in Wong, et al., (2018) provides the primary motivating factor for the current study, pointing to a variable potentially overlooked in previous work in tDCS. In addition to time of day, certain task demands also may moderate tDCS effects. Our prior work demonstrated a greater effect of left dlPFC stimulation for verbal compared to picture materials (Gray et al., 2015). This difference might reflect a greater role for left PFC in processing verbal compared to pictorial materials, or the fact that the verbal test was more difficult than the picture test in that study. In order to tease these factors apart, we factorially crossed materials and task difficulty manipulations in the current experiment.

The Current Study

2.1 Current Project Objectives

Motivated by the initial findings in (Gray et al., 2015 and Wong et al., 2018), we sought to use a rigorous and well-powered experiment to determine the importance of time of day for detecting tDCS effects on memory in both younger and older adults, sample populations that have been targeted in many prior tDCS studies but may have different optimal times of day. We are unaware of any tDCS studies aimed at investigating age effects of stimulation on episodic or working memory tasks with high degrees of statistical power with time of day taken into consideration, despite converging evidence that aging alters the optimal time of day for cognitive processing (described in greater detail in Chapter 2) (May et al., 2005; Schmidt et al., 2007).

Given the discovery that time-of-day may be a crucial factor for obtaining reliable tDCS effects when stimulating dlPFC, one main goal of the current project was to attempt to replicate our previous time of day findings from Wong et al., (2018) in younger adults. Another primary goal was to extend our understanding of the tDCS time of day effects in older adults, and potential interactions with time of day, given older adults' circadian shifts. Circadian preference measures were acquired for each participant via standard circadian preference questionnaires (i.e., the Morningness-Eveningness Questionnaire, or MEQ) as well as via wrist-worn actigraphy data obtained for each participant for the duration of their enrollment in the study.

In addition to dlPFC, we assessed the spatial resolution of the standard tDCS technique by comparing an additional stimulation site -- left posterior parietal cortex, or P5 according to the EEG 10-20 system-- to sham in younger adults. This parietal stimulation site acts primarily as an additional control region to lend additional support to previous findings revealing no robust effects of anodal stimulation to left parietal cortex. This is intuitive, given it is not hypothesized to be causally involved in recollection in the same way as dlPFC as discussed previously (see Cabeza et al., 2008; Dobbins et al., 2012).

To achieve these ends, the current study had five arms, with younger and older adults randomized into stimulation and sham conditions (within-subjects) and into one of two stimulation areas subject to anodal stimulation (left dlPFC for younger and older adults, in PPC for younger adults only) (see Figure 1). Note that for the sham arm, given there are no hypothesized differences between the sham condition for left dlPFC and the sham condition for the left parietal, they were collapsed and modeled as one.

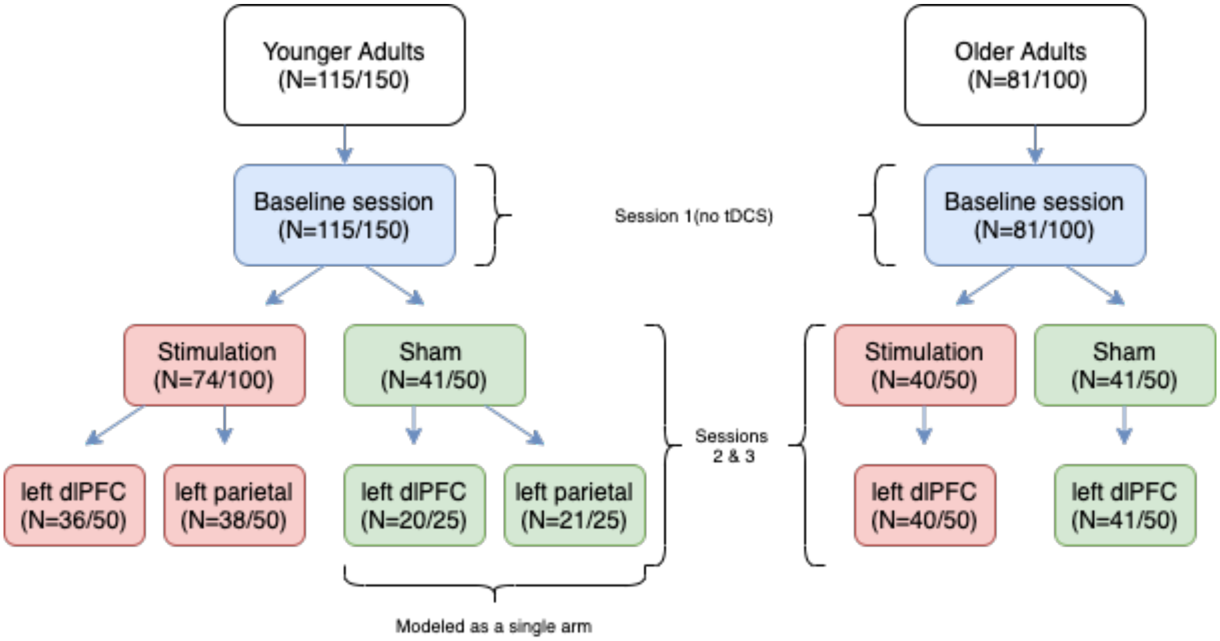

Figure 1. Experimental design arms.

At the time of writing, N=115 (out of 150) younger adults and N=81 (out of 100) older adults have completed the study. During the baseline session, during which there was no administration of stimulation, participants were randomized to either stimulation or sham, and in the case for younger adults, to either dlPFC or parietal. Note the target N (in parentheses) was not achieved due to the COVID-19 pandemic (described in our sampling section), but data collection to reach this target is expected to resume in mid 2021.

To test memory performance, we employed both an episodic and a working memory recollection measure, specifically episodic memory accuracy (hits - false alarms) and working memory accuracy (hits - misses). These measures were assessed separately in their own statistical models. Each measure was also characterized by a difficulty manipulation (easy vs hard blocks) and a format manipulation (words or verbal stimuli in the episodic task and pictures or visuospatial versions of the working memory task. (These manipulations are described later in more detail). The methods for collecting data on circadian preferences and sleep quality, as well as questionnaires related participant sensations and expectations, will be described in Chapters 2 and 3, respectively.

2.2 Pre-registered Hypotheses & Predictions

All a-priori predictions and analysis plans for the current study were pre-registered and published on the Open Science Framework (see https://osf.io/t5xhj). Considering our previous findings and the current state of the tDCS literature, the current study aims to address four primary hypotheses:

1. Younger Adults Primary Hypothesis: dlPFC tDCS/Sham X AM/PM. Given the hypothesis that tDCS benefits may be larger during suboptimal times of cognitive function, i.e., "when needed", we predict that tDCS benefits may be larger during suboptimal times of cognitive function. For younger adults, we predict that tDCS of the dlPFC will improve episodic memory accuracy and working memory, relative to sham tDCS or active parietal tDCS. We also predict larger tDCS benefits during the AM than PM session (i.e., the suboptimal time of cognitive function for many younger adults). This hypothesis also serves as a replication of Wong et al., 2018.

2. Older Adults Primary Hypothesis: dlPFC tDCS /Sham X AM/PM. We predict that tDCS of the dlPFC will improve episodic memory accuracy and working memory in older adults, relative to sham tDCS, with larger benefits during the PM session than the AM session (i.e., the suboptimal time of cognitive function for many older adults).

3. Owl-Lark Hypotheses: Although there are average differences between younger and older adults in terms of optimal time-of-day, there also are individual differences within each of these age groups. Because tDCS effects may be moderated by these time-of-day preferences, in a secondary analysis of tDCS effects we will assess tDCS effects as a function of an individual's optimal time of processing (measured by self-report and wrist accelerometry). We predict larger tDCS benefits during an individual's suboptimal times of processing.

4. Task-based Hypotheses: To the extent that tDCS boosts memory by improving cognitively controlled processes, high difficulty items should benefit more from tDCS than low difficulty items on each memory task. To the extent that tDCS to left dlPFC

boosts verbal/conceptual processing more than pictorial/visuospatial processing, the former should benefit more from tDCS than the latter.

3. Methods

3.1 Transcranial Direct Current Stimulation (tDCS)

Researchers have used a wide variety of tDCS techniques to stimulate dlPFC to enhance cognitive control (and healthy cognition broadly). TDCS techniques in prior research have varied across a number of key parameters including stimulation montage (e.g., unilateral or bilateral), sponge size, and current intensity (and resulting current density transmitted). Given outcomes of stimulation have been found to be highly dependent on the stimulation parameters chosen (Weller et al., 2020), the parameters selected for the current project reflect those that have received the most consistency in the modulatory effects within the memory literature (e.g., Galli et al., 2019).

For the current project, we used a standard 1x1 tDCS device (Soterix Medica, New York), delivering 2 mA of current using 2 electrodes in 5 x 7 cm saline-dampened sponges, resulting in a current density of 0.057 mA/cm^2. The anodal electrode is placed over areas F3 (left dlPFC) or P5 (left parietal) according to the 10-20 EEG-system, with the cathodal electrode on the contralateral supraorbital region. In the sham stimulation condition, participants experience a brief 20 second ramping up of stimulation (up to the full 2 mA) before ramping completely back down. This spam technique is a uniquely advantageous sham condition relative to other neurostimulation techniques (e.g., TMS), not only due to its lack of physiological effects, but also because it is typically perceived by participants to be a convincing placebo (more on this in Chapter 3).

3.2 Materials & Procedure

During the 7 (min) -12 (max) day enrollment period, participants came to the lab for three separate testing sessions. The first session was a baseline orientation day (no tDCS), and subjects returned to the lab for the two tDCS testing sessions (a morning and afternoon session, 1-day minimum apart). Subjects were given the wrist-worn actigraphy watch following completion of the baseline session and returned the watch and sleep logs during the final tDCS session. See section 3.4 for a description of the different assessments and questionnaires across the three testing sessions.

The experimental protocol followed a mixed design whereby subjects were assigned to either stimulation or sham for both tDCS sessions but were tested at both AM and PM time slots (thus, between-subjects for stimulation and within-subjects for time of day). The decision behind a between-subjects paradigm for stimulation was motivated by previous findings showing that 20 minutes of active tDCS elicits sensations that can be differentiated from sham. For example, in one experiment from the lab (described in Wong et al., 2018), participants in the stimulation condition were more likely to report as having been in the stimulation condition when asked (79%) compared to participants in the sham condition (50%), 2(n = 48) = 4.46, $p = 0.03$. A similar pattern was found in a second experiment from the paper (rates = 83% and 42%), 2 (n = 48) = 8.89, $p = 0.002$. Although many of the sham participants in these two experiments also believed they were in the active stimulation condition, it is a noteworthy consideration in tDCS experiment design.

During the first visit to the lab (called the “baseline” day) participants took a baseline version of the tasks (i.e., without tDCS), serving as a no-tDCS baseline. These baseline sessions were scheduled at the convenience of the participant and experimenter, thereby minimizing time constraints on the completion of the project. The primary purpose of this measure was to assess the value of a pre-tDCS baseline in detecting tDCS effects, and not necessarily in assessing time-of-day effects. The baseline session also provided task-initiation practice during this initial stage of the protocol, thereby minimizing the likelihood that significant practice effects would impact the subsequent AM/PM tDCS testing sessions.

The two subsequent testing sessions were scheduled for either 8 A.M or 9 A.M (for the morning session), and for either 3 P.M or 4 P.M (for the afternoon session). These times were selected from previous findings in the circadian preference literature, which found age-related differences in performance based on time of day. More specifically, it typically found that on average older adults' peak hours are earlier in the day, whereas younger adults peak in the afternoon (more on this in Chapter 2) (May & Hasher, 2017; Ngo et al., 2018; Rowe et al., 2009).

On each of the two tDCS testing days, participants first studied the materials, then received 20 minutes of tDCS or sham tDCS. After removing the tDCS equipment, they then completed the cognitive task that involves both episodic recognition tests for the studied stimuli, as well as working memory tests. In line with prior work and for the purposes of simplicity, the episodic tasks always preceded the working memory task across all sessions.

During the two tDCS sessions, only tDCS/sham took place between study and test, and no other tasks or activities that could introduce confounds (see Figure 2). To balance the design for blinding, each of the two different electrode placements in the active stimulation conditions (namely, active parietal and active dlPFC) were evenly represented in the sham condition (younger adults only). To rule out general arousal effects, participants are prompted to make an arousal rating immediately prior to tDCS and immediately following tDCS (though, our prior work found that tDCS did not affect reported arousal, compared to sham, see Wong et al., 2018).

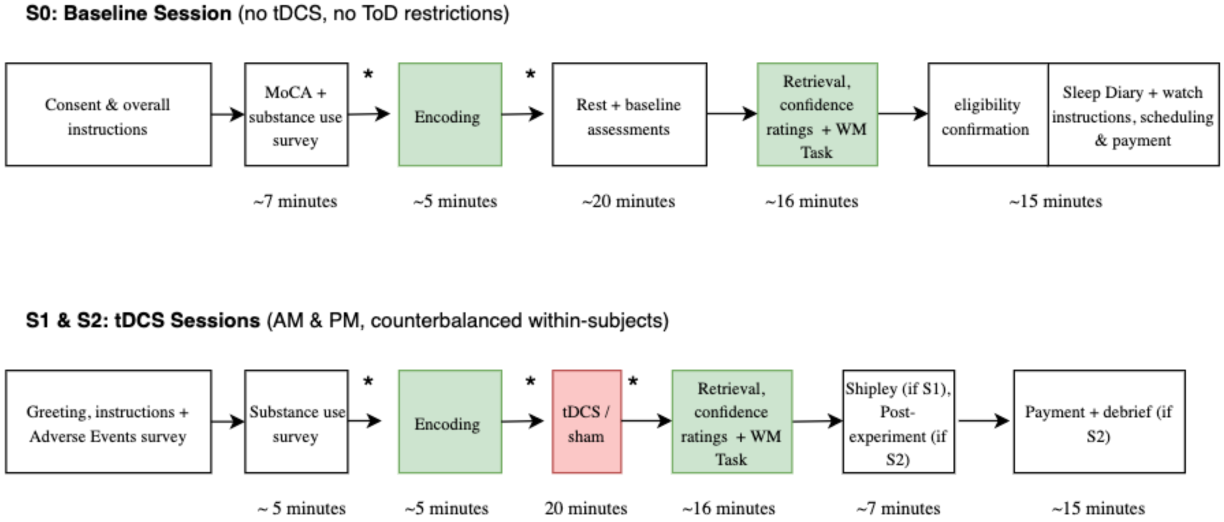

Figure 2. Task Protocol.

During the first visit to the lab ("baseline" session), participants went through a tDCS -free version of the protocol, which is also void of the time of day (AM/PM) restriction. To maintain similar intervals between encoding and retrieval across all three sessions, participants were tasked with completing ~20 minutes worth of surveys during baseline, i.e., the time allocated for tDCS stimulation (or sham) during sessions 1 and 2. If on the baseline day subjects are deemed eligible to continue in the study (see section 3.3a), participants are randomly assigned to complete either the AM session or PM session first for their two subsequent tDCS sessions. Finally, in line with prior studies, episodic memory testing always precedes working memory testing, and both are completed within 15 minutes of receiving tDCS (or sham), when post-stimulation effects are most likely to be active. Asterisks (*) indicate recording of arousal ratings.

3.3 Participants

Sampling & Inclusion Criteria

Participants were pre-screened (via an online or phone-administered survey) for standard inclusion/exclusion criteria for tDCS. These screening criteria include being right-handed as assessed by the Edinburgh Handedness Inventory, having normal or corrected vision and fluent in English (learned by age 6). Participants must not have been on any psychoactive medications, be at risk of pregnancy, have a history of neuropsychiatric disorder or seizures or have a low tolerance of skin irritation. Both younger and older adults were pre-screened for depression, with individuals yielding a score of 10 or above on the PHQ-9 (Manea et al., 2012) being excluded from enrolment. Additionally, all participants with non-removable metal earrings, cochlear implants and metal dental braces were excluded out of an abundance of caution due to unknown interactions with the flow of current between tDCS electrodes. Notably, all participants with prior experience with tDCS in the past 5 years were excluded from enrollment to reduce the possibility for confounding expectation effects from stimulation. Additionally, all participants completed the Montreal Cognitive Assessment (MoCA) to characterize overall cognitive functioning, which was administered during baseline day. To minimize the inclusion of suspected Mild Cognitive Impairment (MCI), we used a MoCA cutoff of 23 (out of 30, education-corrected), thereby targeting individuals who score in the normal range according to the recent meta-analysis of MoCA's ability to differentiate normal aging from MCI (Carson et al., 2018).

Finally, participants were required to perform above threshold on the episodic memory task during the baseline session. This threshold was defined as having a hit rate that is at least 5% greater than the false alarm rate (where hit rate was defined as the number of studied items identified as studied divided by the total number of studied items), and false alarm rate (defined as the number of new items identified as studied divided by the total number of new items). For subjects enrolled as of March 2020, this threshold did not exclude any subjects, though we believe this method will exclude any future participants who are unable (or unwilling) to adequately perform the task.

Enrollment, Randomization and Blinding Procedures

In accordance with our pre-registered power analyses, original enrollment plans included recruiting 150 younger adults (age 18-30) from the University of Chicago and surrounding community, and 100 older adults (age 60-75) from a database maintained by the Gallo lab, as well as newly recruited from the Chicago area using word-of-mouth and online advertisements (e.g., Facebook, the Chicago Tribune). As part of COVID-19-related testing restrictions, however, we were unable to complete enrollment as planned. At the time of writing (July 2021), 115 younger adults and 81 older adults have completed the Baseline session and at least one tDCS session.

Once participants were deemed eligible and confirmed their decision to enroll in the study, we used the REDCap Randomization Module to randomize each subject to specific counterbalance conditions, with randomization being stratified by age group (i.e., young and older adults). Following the Baseline assessment (without tDCS, not subject to any session time restrictions), each participant was randomized to either AM (session 1) -> PM (session 2) or PM (session 1) -> AM (session 2) for their first and second tDCS testing sessions (after baseline). Upon arriving for the Baseline testing session, each participant was randomly assigned to one of 12 counterbalancing conditions designed to ensure that memory task conditions are balanced across participants and are not confounded with session order. At this point, stratified randomization (i.e., within strata based on age, AM -> PM versus PM -> AM) was used to assign treatment (i.e., active anodal tDCS versus sham tDCS). Treatment selection at the time of administration was performed by entering a unique numeric code assigned at the time of randomization, thereby blinding both the participant and the experimenter(s) to the treatment condition (ensuring double-blinding procedures). Once testing resumes, additional participants will be recruited to ensure 50 participants complete the study in each group.

Finally, just before the first tDCS session, each participant was assigned to a Soterix stimulation code, and to an electrode placement (if a younger adult, either PFC or parietal), using the Participation REDCap database. The participants were then scheduled for all 3 sessions. Just prior to completing the Baseline session, the participants were also assigned to a cognitive task counterbalance condition using the Task Condition Randomization REDCap database.

Compensation

Compensation was disbursed in incentive-compatible installments; younger adults were paid $10.00 USD for the first session, $20.00 for the second session and $40.00 for the final session, for a total of $70 USD for full participation. Younger adults enrolled as undergraduates at the University of Chicago could also exchange $10.00 USD for one course credit, for up to three credits. Older adults were paid $20.00 USD for the first session, $30.00 USD for the second session and $50.00 USD for the final session, for a total of $100 USD for full participation. Additionally, older adults were given the option of a fully compensated rideshare service (via Lyft) for transport to and from the study sessions. We decided that the challenge of recruiting eligible older adults warranted this increased compensation relative to the young adult sample.

Participant characteristics (enrolled as of March 2020)

At the time of writing (July 2021), 81 older adults (mean age = 67.12) and 115 younger adults (mean age = 20.9) have been enrolled in the study, having gone through the first baseline session and at least one tDCS session (enrollment was halted March 10, 2020 due to COVID-19). Data from one or both tDCS sessions from 16 participants were removed due to experimenter error and 16 participants withdrew after baseline day or after the first tDCS session. A further 2 subjects were excluded due to contraindications in eligibility criteria, and a final 4 participants did not complete the study due to COVID-19 testing restrictions. It follows that we have usable cognitive task data for all three sessions for 77 (episodic memory) and 81 (working memory) older adults and 106 (episodic memory) and 111 (working memory) younger adults. See Table 1 for participant demographics and key characteristics.

Table 1. Participant characteristics

Demographics		Younger adults (N= 115)	Older adults (N= 81)
Gender %	Female	58.2	66.6
	Male	41.7	33.3
Ethnicity %	Not hispanic/latino	72.2	82.7
	Hispanic/Latino	25.2	6.1
	Unknown/not reported	2.6	11.1
Race %	White	51.3	44.4
	Asian	26.1	0
	Black	11.3	49.3
	More than one race	6.9	6.1
	Unknown/not reported	4.3	0
Education (years)	Mean	14.43	15.48
	Range	12-21	10-22
Age	Mean (SD)	21.41 (3.41)	67.12 (4.65)
	Range	18-30	60-75
MoCA	Mean	28.10	25.75
Shipley (Verbal only; max score = 20)	Mean	17.63	17.70
MEQ	Mean (SD)	47.20 (8.84)	57.16 (9.43)
	Range	24-72	29-72
SFI	Mean % (SD)	8.9% (7.9)	10.7% (8.9)
SE	Mean % (SD)	85.1% (7.2)	84.8% (7.5)

3.4 Assessments

Baseline Assessments

During their first visit to the lab, participants were briefed and instructed to complete the following baseline assessments throughout their enrollment in the study:

-Morningness-Eveningness Questionnaire (MEQ)- The MEQ is a self-assessment questionnaire consisting of 19 mixed-format questions regarding the time individuals get up and go to bed, preferred times for physical and mental activity, and subjective alertness (Horne & Östberg, 1976).

-Sleep Log - During the initial orientation session participants were equipped with an actigraphy watch and were provided instructions for using the watch and keeping the sleep log. These data were collected over a minimum 7-day period (max 12 days). During this period, participants returned to the lab for 2 testing sessions (AM/PM, nonconsecutive testing days), returning the actigraphy watch and sleep logs on the final testing session.

-Montreal Cognitive Assessment (MoCA) - The MoCA is a cognitive screening tool that aims to differentiate healthy cognitive aging from Mild Cognitive Impairment (MCI), and examines visuospatial/executive function, object naming, episodic memory, attention, language, abstraction, and orientation (Carson et al., 2018). For the purposes of completeness, this assessment was given to both older and younger adults once during the Baseline Day after the end of the cognitive tasks.

-Subject Information Form - This demographic questionnaire includes questions related to education attainment and retirement status, birth control and menopausal status (if applicable) along with important information around medical history and prescribed medications.

-Baseline post-rest survey - During this questionnaire, participants were asked about what was on their mind during a rest period during the Baseline Day (e.g., rehearsing studied information, mind wandering, etc).

Assessments given during tDCS Sessions 1 and/or 2.

-Arousal Ratings - Participants were asked about level of alertness several times throughout the course of the experimental protocol, by asking participants to rate their current level of alertness from 0-10 (10 being extremely alert). This question was asked once before the encoding portion of the cognitive task and once after the rest period (Baseline session) as well as before and after each tDCS session (for the tDCS days).

-Shipley-2 Assessment (verbal only) - The Shipley provides a brief yet robust measure of crystallized and fluid cognitive ability, generating a quick estimate of overall cognitive functioning and impairment. For the purpose of brevity, only the verbal portion of assessment (vocabulary scale) was given. Participants were given the verbal portion of the Shipley to test cognitive ability after the end of the first tDCS session.

-Substance Use Survey - Subjects were asked not to consume more than twice the amount of caffeine and nicotine they normally consume 4 hours prior to each session, and not to consume more than twice the amount of alcohol they normally consume 24 hours prior to each session. To monitor this substance intake, we had participants record their substance use in this survey prior to each session.

-Post-tDCS Application Survey - This questionnaire was administered twice, once after the end of each tDCS session, to i) rate the "tolerability" of the stimulation session from 0-10 (0 being "no discomfort" to 10 being "very uncomfortable); ii) report any and all applicable sensations (e.g., tingling, itching, burning, etc.,). iii) determine if participants intentionally rehearsed studied items prior to the memory test or if they engaged in some other mental activity (e.g., mind wandering).

-Post-experiment Questionnaire - Given as a final step at the end of the third experimental session, this questionnaire was designed to determine how participants' expectations about the stimulation procedure may have affected their performance. Here, participants were asked if they believed they "received electricity to their brain", their confidence in this rating, the degree of their sensations (e.g., they felt sensations for the whole 20 minutes) as well as whether they thought they performed better during the AM or PM tDCS session.

-Adverse events survey - In compliance with FDA-specific regulations for clinical trials, adverse events were reported by asking participants at the beginning of each session whether they suffered any unusual health events (e.g., hospitalizations, diagnoses) or accidents during their enrollment, as well as the severity/seriousness of the event. If the participant indicates any adverse events, these were recorded and then assessed as “expected” or “not expected” based on an a-priori classifications determined by the research team.

4. Memory Tasks

4.1 Episodic Memory Task

Within the episodic memory task, we manipulated the format of to-be-remembered studied materials (i.e., words or pictures), crossed with the difficulty of the items (via study repetition at encoding: once or twice). Thus, we crossed stimulus type with a recollection difficulty manipulation all within-subjects, presented in an alternating-block format. To ensure that performance is in intermediate ranges for both age groups (thereby allowing sensitivity for tDCS effects), we used a slower presentation rate for older adults than younger adults across all sessions and difficulty levels. For younger adults, encoding trails for words were paced at 750 ms (with a 50 ms ITI -- a label is presented along with the picture at each trial), and 750 ms (with a 750 ms ITI) for pictures. For older adults, encoding trails were paced at 1500 ms (with a 1000 ms ITI) for words and 1500 ms (with a 1500 ms ITI) for pictures. At test, retrieval trials were self-paced across all sessions, difficulty levels and age groups.

At encoding, for the picture study list participants studied words (in black font on a white screen, centered) followed by a corresponding picture of the object (half colored pictures, half line drawings). Participants then decided if each picture was high or low detail (“Is this a relatively detailed image?”) at encoding, thereby drawing attention to perceptual features. For the word study list, participants were presented with the names of common objects and prompted to make one of two semantic judgments in a blocked encoding format (“Is this made in a factory? “Is this found in a house?”), thereby drawing attention to conceptual or semantic features.

At retrieval, we gave two recollection tests alternating across mini-blocks to avoid order effects. On the picture test blocks, labels for the studied pictures were intermixed with non-studied items, and participants made one of three response options (“color”, “line”, or “new”) plus a confidence judgment (1-4, from “guessing” to “certain”). The structure of the word test blocks was similar, and participants made one of three response options (studied with a “factory” judgment, the “house” judgment, or “new”) plus the same confidence judgment. Within each test, the items studied in the two different picture formats (or semantic judgments) were matched on familiarity, so that participants needed to rely on recollection to make source judgments. Previously, we found that discriminating between these two different picture formats (picture test) and these two different semantic judgments (word test) was equally difficult (Sarfan et al., 2014), allowing us to disentangle material-specific effects from recollection difficulty.

Our primary dependent variable for the episodic memory task was recollection accuracy, computed as false alarms subtracted from hits to targets. A “hit” is the probability of saying “studied” when the correct item and correct subtype is selected (i.e., house vs factory judgment for word stimuli or line vs color picture for picture stimuli). A false alarm is the probability of saying “studied” to studied items but of the incorrect subtype. Non-studied items indicated as “studied" were not included in false alarms. From a signal detection theory perspective, this represents a memory discrimination score analogous to *d*’, but assuming a threshold-like memory process for recollection as opposed to a continuous process (for justification of this assumption, see Snodgrass & Corwin, 1988, and Yonelinas, 2002).

4.2 Working Memory Task

Similar to the episodic memory task, the working memory task involved a stimulus format manipulation (verbal vs. visuospatial) as well as a difficulty manipulation (easy vs. difficult), all manipulated within-subjects and across mini-blocks to control for order effects. We used the n-back task, with a verbal version (i.e., presenting the numbers 1-9 in a varied sequence) and a matched visuospatial version (i.e., presenting a colored square in one of 9 locations on a 3x3 grid in a varied sequence). Based on prior neuroimaging work, both tasks rely on bilateral PFC regions, but the former relies more heavily on left PFC, and the latter more heavily on the right PFC (for meta-analysis, see Owen et al., 2005). Within the working memory task, the format of the studied to-be-remembered materials (i.e. verbal or, visuospatial) was crossed with the difficulty of the items (2-back and 3-back for younger adults, 1-back and 2-back for older adults). This matching in task difficulty for n-back tasks was assessed via initial piloting, though this is also consistent with age-based difficulty matching used in the literature (e.g. Cespon, et al., 2017). Presentation speed remained constant across age groups and difficulty levels, paced at 500 ms per trial with a 500 ms ITI. Our primary dependent variable was working memory accuracy, defined as the proportion of targets correctly identified minus the proportion of lures incorrectly endorsed.

Statistical Considerations & Analysis Plan

4.3 Power and sampling

Our power analysis was based on our most recent and largest tDCS experiment (Wong, 2018), which, at 30 participants per stimulation group, yielded a 12% difference in word test accuracy between sham (0.23, SD = 0.21) and active tDCS (0.35, SD = 0.21) in the morning condition (between-subjects), predicting that we would need 50 participants in each stimulation group in order to obtain a similar effect size with 80% power at $p<.05$ (2-tailed). Thus, while the goal is ideally to recruit 50 participants per group, at the time of writing approximately 40 subjects per stimulation group have undergone all three testing sessions. In a within-subjects paradigm, a similar effect size as above yields an estimated power of at least ~70% at $p<.05$ (2-tailed) for primary analyses. However, we expect to still reach the planned N per group starting Summer 2021.

4.4 Statistical significance

A two-sided p-value cutoff of 0.05 was used for all null-hypothesis significance testing. In addition, point estimates for all first order and interaction effects were reported, together with 95% confidence intervals. Between-individual contrasts (e.g., overall treatment effects) were standardized (i.e., equivalent to Cohen's d). Results of all analyses performed were reported (not just those that meet the 0.05 cutoff). Since Hypotheses 1-4 are distinct, we do not need to make any adjustment for multiple testing across the corresponding analyses. For each analysis, we use a nested approach, beginning with an overall test of the null hypothesis, conducted separately for episodic and working memory, using the coarsest model available. If the coarse model is statistically significant, we then precede to less coarse models and conducted further analysis of subgroups. If the coarse model fails to reach statistical significance, we do not conduct further analysis to reduce the possibility of "fishing" for statistical significance.

Results

5.1 Baseline Day Analyses

As previously described, all participants underwent a tDCS-free version of the experimental protocol during their first visit to the lab in order to get a baseline for cognitive performance (see Figure 2). These baseline data allow us to test for expected age-related and task difficulty-based differences in recollection accuracy absent any stimulation, time of day or sleep quality effects. Furthermore, these baseline measures are added as covariates in a subset of our analyses (see section 7.2) to account for the potential of individual variability to confound the effects of stimulation.

Task-based analyses for each task are reported below. To anticipate key results, the baseline cognitive data confirmed that we had successfully achieved two different levels of difficulty for each task (episodic memory, working memory) within each age group. Moreover, performance on each task within each age group avoided both ceiling and floor effects, thereby providing the ideal test bed for assessing the effects of tDCS on performance.

Baseline Day Analyses: Episodic Memory

For episodic recollection accuracy, a 2 (age: younger vs older) x 2 (format: picture vs word) x 2 difficulty (easy vs hard) ANOVA yielded a main effect of age (F(1, 194) = 72.18, p = 0.000, MSE = 0.124, n^2p= 0.27), along with a main effect of task difficulty (F(1, 194) = 222.44, p = 0.000, MSE = 0.017, n^2p= 0.53), as would be expected. Additionally, there were a number of interaction effects, including an age x format interaction (F(1, 194) = 36.88, p = 0.000, MSE = 0.052, n^2p= 0.16), an age x difficulty interaction (F(1, 194) =

4.45, $p = 0.036$, MSE = 0.017, $n^2p = 0.02$) as well as a format x difficulty interaction (F(1, 194) = 30.72, $p = 0.000$, MSE = 0.019, $n^2p = 0.12$). There was no main effect of format or 3-way interaction of age, format and difficulty (all *p*'s > 0.2).

With respect to stimulus difficulty, for the "hard" items (presented once at encoding), older adults performed better on pictures (0.29) than on words (0.23), (t(80) = 2.03, $p = 0.045$, $d = 0.29$). This finding is consistent with prior work showing that older adults find pictures easier to recollect than words (see Gallo et al., 2007). Interestingly, younger adults did better on hard words (0.54) compared to hard pictures (0.37), (t(114) = 7.04, $p = 0.000$, $d = 0.73$), suggesting that under these conditions they were able to engage in elaborative semantic processing that further enhanced memory for the words. With respect to easy items (presented twice at encoding), while there was a boost in memory overall compared to items presented once, there is no difference in memory between the two item formats for younger adults (0.64 words, 0.61 pictures, $t < 1$). By contrast, in older adults the boost for pictures was even more prominent for easy items (0.45 pictures, 0.31 words; t(80) = 4.67, $p = 0.000$, $d = 0.58$).

Baseline Day Analyses: Working Memory

In terms of the working memory task, a 2 (age: younger vs older) x 2 (format: visuospatial vs verbal) x 2 difficulty (easy vs hard) ANOVA on accuracy yielded a main effect of format (F(1, 193) = 65.96, $p = 0.000$, MSE = 0.007, $n^2p = 0.25$), and difficulty (F(1, 193) = 833.54, $p = 0.000$, MSE = 0.019, $n^2p = 0.81$), without a main effect of age ($p > 0.1$). While this might have been surprising if both age groups were given an identical task, in this case the task was designed with built-in age-specific difficulty matching whereby older adults were tasked with easier version of the n-back task across both difficulty levels, to make "easy" and "hard" versions of the task more comparable across age groups (see Table 2). Despite this, the ANOVA still yielded an age x difficulty interaction (F(1, 193) = 21.08, p = 0.000, MSE = 0.020, n^2p= 0.09) as well as a trending age x format interaction (F(1, 193) = 3.05, p = 0.08, MSE = 0.007). No format x difficulty or age x format x difficulty 3-way interaction was found (all p's > 0.3).

On the easy versions of the task, older adults outperformed younger adults (0.80 and 0.73 respectively, collapsed across format), (t(281.69) = 4.01, p = 0.000, d = 0.43), likely due to the 1-back being much easier than the 2-back given to younger adults. By contrast, on the hard version of the task, younger adults (0.49, collapsed across format) performed similarly to older adults (0.47, collapsed across format), (p > 0.3), meaning the 3-back task in younger adults and 2-back task in older adults yields comparable working memory accuracy. Looking specifically at stimulus format, both younger (t(227) = 5.72, p = 0.000, d = 0.19), and older adults (t(161) = 7.57, p = 0.000, d =0.24), performed worse on the visuospatial task (0.61 for older and 0.59 for younger) compared to the verbal (0.67 for older adults, 0.63 for younger), collapsing across difficulty.

Episodic memory accuracy

	Pictures		Words	
	Older adults	Younger adults	Older adults	Younger adults
Easy	0.453 (0.02)	0.605 (0.02)	0.312 (0.02)	0.636 (0.02)
Hard	0.292 (0.02)	0.374 (0.02)	0.229 (0.02)	0.542 (0.02)

Working memory accuracy

	Visuospatial		Verbal	
	Older adults	Younger adults	Older adults	Younger adults
Easy	0.776 (0.02)	0.717 (0.01)	0.837 (0.01)	0.746 (0.01)
Hard	0.440 (0.02)	0.463 (0.01)	0.503 (0.02)	0.514 (0.01)

Table 2: Baseline performance accuracy.

Baseline episodic recollection accuracy (hits - false alarms) and working memory accuracy (hits-misses), for older and younger adults, split by stimulus format and difficulty. “Easy” refers to stimuli presented 2x during encoding for the episodic task and 1-back (for OA) and 2-back (for YA) during the working memory task. “Hard” refers to stimuli presented 1x during encoding for the episodic task and a 2-back (for OA) and 3-back (for YA) during the n-back task. Values are means with SEM in parentheses.

5.2 Pre-registered Effects of tDCS on Memory Performance

In line with our hypotheses (described in section 2.2), these primary analyses estimate the effect of anodal tDCS to left dlPFC (active stimulation vs sham) on cognitive performance and the extent to which tDCS affects different aspects of the cognitive task (i.e., stimulus format and difficulty). These analyses were conducted separately for episodic and working memory in a linear mixed (i.e., random participant-level intercepts) model as implemented by lme4 (Bates et al., 2014) in R 4.0.5 (R Core Team, 2020), with a stimulation condition (stimulation or sham) as a between-subjects predictor along with task manipulations (stimulus format and difficulty) as within-subjects predictors. Session order was also added as a covariate (session 1 and session 2) in all models. We model participants as a random effect and utilize interaction terms between stimulation condition and both task manipulations and time of day to examine whether these variables mediate the effect of stimulation on accuracy. We assessed significance of fixed-effects with a type III ANOVA using Kenward–Roger approximations of degrees of freedom, a method which has been shown to produce acceptably conservative Type I error rates, even with relatively smaller sample sizes (Luke, 2017).

Model 1.a. Effect of tDCS in Younger Adults: Episodic Memory

This first analysis, conducted exclusively in younger adults, was an effort to replicate previous findings of a stimulation x time of day effect in younger adults (Wong et al., 2018). To investigate this in episodic memory, recollection accuracy (hits - false alarms) was used as the dependent variable, and time of day (AM or PM testing sessions) as a within-subjects factor in the model, with interactions between it, difficulty, format and stimulation. In line with the baseline analyses, we find a main effect of difficulty (F(1, 504.04) = 154.23, p = 0.00, 95% CI = [0.068, 0.094]) as well as a main effect of stimulus format (F(1, 504.04) = 6.23, p = 0.012, 95% CI = [-0.029, -0.003]). Additionally, we also observe a difficulty x format interaction (F(1, 504.04) = 7.21, p = 0.007, 95% CI = [0.004, 0.030]). Indeed, among young adults, the difficulty manipulation works as expected, with subjects performing better on easy items relative to hard items (0.562 and 0.399, collapsing across all other factors), (t(594) = 8.65, *p* = 0.00, *d* = 0.71). With respect to format, the trend replicates what we observed in the baseline session with subjects recollecting words (0.498) marginally better than pictures (0.464), collapsing across other factors (t(594) = 1.69, *p* = 0.09, *d* = 0.14). As we found in the baseline analyses, the interaction effect between format and difficulty highlights young adults performing similarly for easy pictures (0.563) and easy words (0.562), but performing better on hard words (0.434) relative to hard pictures (0.365), (t(296) = 2.75, *p* = 0.006, *d* = 0.32). Finally, there was also a trending stimulation x format (F(1, 504.04) = 2.26, *p* = 0.132, 95% CI = [-0.09, 0.106]). Here, there appears to be a slight benefit of sham for pictures (0.47) compared to stimulation for pictures (0.45), marginal boost for word stimuli for sham (0.52) compared to stimulation for words (0.46) as well.

There was no main effect of stimulation condition, time of day, and no other interaction effects (all *p*'s > 0.3). Thus, the predicted effects of stimulation and time-of-day, and their prediction interaction, were not observed in younger adults in the current study.

Model 1.a. Effect of tDCS in Younger Adults: Working Memory

In terms of investigating working memory, we applied the same linear mixed effect model described above with working memory accuracy (hits-misses) as the dependent measure. This model yields a main effect of difficulty (F(1, 508.02) = 550.83, *p* = 0.00, 95% CI = [1.119, 0.132]) and format (F(1, 508.02) = 21.75, *p* = 0.00, 95% CI = [-3.430, -0.014]), as well as a trending difficulty x format interaction (F(1, 508.02) = 3.77, *p* = 0.052, 95% CI = [3.851, 0.020]). These format trends are similar to what we observed in episodic memory, whereby performance is comparable for the easy verbal task (0.776) and easy visuospatial task (0.747), however performance is higher for the hard verbal task (0.551) relative to the hard visuospatial task (0.482), (t(298) = 2.66, *p* = 0.008, *d* = 0.31). Finally, while there was no main effect of stimulation condition (active anodal stimulation vs sham) there was a significant stimulation x difficulty interaction F(1, 508.02) = 9.02, *p* = 0.002, 95% CI = [-2.567, -0.005]). For the easy stimuli young adults did not benefit from tDCS (0.764) compared to the sham (0.759), but for the hard stimuli there was a benefit from stimulation compared to sham (0.551 and 0.484, respectively), (t(298) = 2.57, *p* =0.010, *d* = 0.29) (see Figure 3). No other main effects or interaction effects were found (all *p*'s > 0.1).

Model 1.b: Effect of tDCS and in Younger & Older Adults: Episodic Memory

This analysis used the same model as in 1.a (above) but includes data from both younger and older adults and adds a corresponding age-group factor in the model. Interaction terms between age group and stimulation condition were used to determine whether the overall stimulation effect is the same for older as for younger adults. In line with baseline analyses, this model yielded a main effect of age (F(1, 153.92) = 34.40, *p* = 0.00, 95% CI = [-0.108, -0.054]), and a main effect of difficulty (F(1, 1041.09) = 238.46, *p* = 0.00, 95% CI = [0.063, 0.082]) and format (F(1, 1041.09) = 20.60, *p* = 0.00, 95% CI = [0.012, 0.030]). Furthermore, an age x format interaction effect (F(1, 1041.09) = 64.48, *p* = 0.00, 95% CI = [0.028, 0.046]) as well as a format x difficulty interaction (F(1, 1041.09) = 19.09, *p* = 0.00, 95% CI = [0.011, 0.029]) highlight how older adults perform better on picture stimuli (0.37) relative to word stimuli (0.25). In younger adults, this trend reverses (0.49 words, 0.46 pictures). However, overall subjects perform better overall on easy pictures (0.51) relative to easy words (0.42) when collapsed across age groups. This finding is corroborated by a marginal age group x difficulty interaction (F(1, 1057.10) = 3.69 *p* = 0.054, 95% CI = [-0.018, 0.0001]), indicating that young adults maintain a moderately higher performance for the hard stimuli (0.39) relative to the easy stimuli (0.562), compared to the comparatively smaller performance gap observed between hard (0.254) and easy stimuli (0.381) for older adults. Finally, a significant four-way interaction between age, difficulty, format and time of day (F(1, 1041.09) = 4.86 *p* = 0.027, 95% CI = -0.019, -0.001]), indicates that older adults demonstrate better memory for pictures in the morning (0.314), relative to the afternoon (0.266), whereas this effect was not seen for memory performance for words. No other main effects or interaction effects were found in episodic memory (all *p*'s > 0.2).

Model 1.b: Effect of tDCS and in Younger & Older Adults: Working Memory

This analysis uses the same model described above (data from both younger and older adults with corresponding age-group factor) and uses working memory accuracy as the dependent variable. This model yielded a main effect of difficulty (F(1, 1061.02) = 1370.32, *p* = 0.00, 95% CI = [0.132, 0.147]) and format (F(1, 1061.02) = 45.93, *p* = 0.00, 95% CI = [-0.032, -0.018]), session order (F(1, 1066.27) = 4.63, *p* = 0.031, 95% CI = [0.001, 0.031]), as well as a significant age x difficulty interaction (F(1, 1061.02) = 22.02, *p* = 0.00, 95% CI = [0.010, 0.025]). Here we see similar effects to the previously described model of episodic recollection accuracy, whereby a bigger performance gap exists between hard (0.499) and easy stimuli (0.814) for older adults compared to younger adults (0.516 and 0.761, easy and hard respectively). This effect is likely explained by the relative ease of the "easy" 1-back given to the older adults compared to the "easy" 2-back given to the younger adults. Although we anticipated an age effect, given the built-in age-specific difficulty matching of the task, we found no main effect of age (*p* > 0.4) in this model.

Finally, this model also yielded a three-way interaction between stimulation condition x age x difficulty (F(1, 1061.02) = 13.75, *p* = 0.0002, 95% CI = [0.006, 0.021]). This finding reiterates the stimulation x difficulty effect observed in younger adults in model 1.a, this time including an interaction with age. This suggests that, when comparing the two age groups, the young adults benefit from tDCS for the hard stimuli, while older adults' performance for hard stimuli is similar across the two stimulation conditions. No other main effects or interaction effects were found (all *p*'s > 0.1) (see Figure 3).

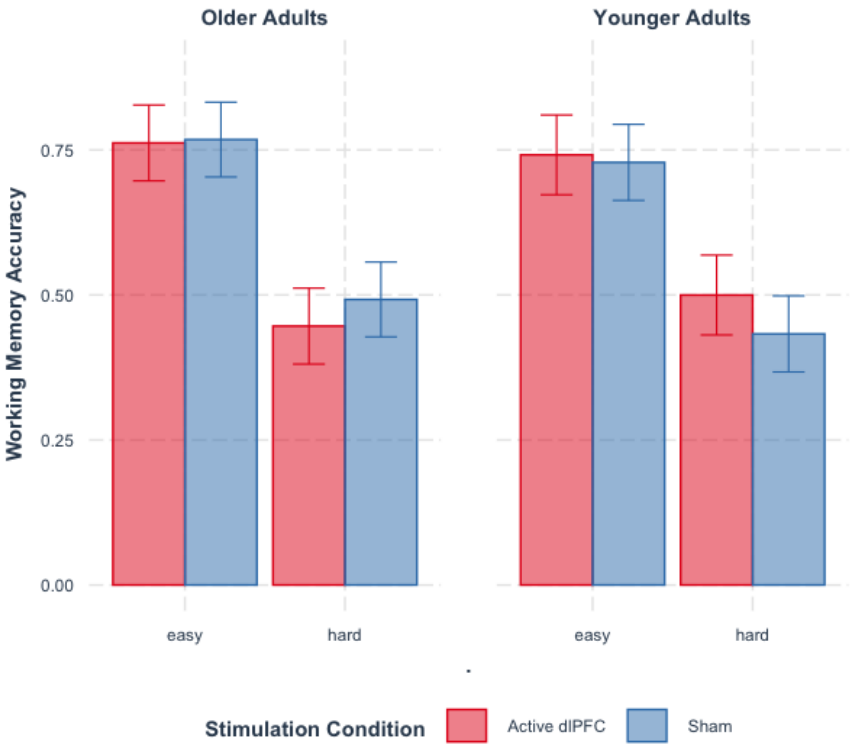

Figure 3. Working memory accuracy performance for younger and older adults. Error bars are confidence intervals.

Model 2.a Effect of tDCS and in Younger Adults: dlPFC vs Parietal vs Sham effects in Episodic Memory

This second set of primary analyses focused on differentiating between stimulation applied to dlPFC vs parietal vs sham effects in younger adults only. For these analyses, similar a model to that described in model 1a above was used except we included 3 levels for tDCS (active dlPFC, active PPC, sham).

With respect to episodic memory, similar trends are observed to previous outcomes, including main effects for difficulty (F(1, 739.09) = 207.08, *p* = 0.000, 95% CI = [0.067, 0.088]) and format (F(1, 739.09) = 18.49, *p* = 0.000, 95% CI = [-0.033, -0.012]). Collapsing across all other factors, this finding highlights participants performing better on easy (0.56) relative to hard stimuli (0.40), (t(437) = 16.49, *p* =0.000, *d* = 0.67) and also performing better on the verbal (0.51) relative to the picture stimuli (0.46), (t(437) = 4.08, *p* =0.000, *d* = 0.19). Relatedly, there is a format x difficulty interaction (F(1, 739.09) = 7.52, *p* = 0.006, 95% CI = [0.004, 0.025]), highlighting once again that for the easy stimuli, there is not much difference in performance between pictures and words, while for the hard stimuli, younger adults perform better on words relative to pictures.

In terms of differences between the three stimulation conditions (left dlPFC, left parietal and sham), there is no difference in episodic memory performance across the three stimulation locations when collapsed across other factors (*p*'s > 0.8). However, when breaking down the three conditions by stimulus format, there does seem to be a small advantage of both active left PPC (0.528) and sham (0.524) compared to active left dlPFC (0.468) for words, as indicated by a marginal stimulation condition x format interaction (F(1, 739.09) = 2.63, *p* = 0.072, 95% CI = [-0.028, 0.001]. However, Tukey post-hoc analyses indicated no significant differences between the three conditions, indicating this interaction effect is likely not meaningful. There were also no differences between the three stimulation conditions among picture stimuli (all *p*'s > 0.5), and when breaking down the three conditions by difficulty, there were no statistical differences between the three conditions for easy and hard stimuli (all p's > 0.2 in a Tukey post-hoc analysis). No other main effects or interaction effects were detected (all *p*'s > 0.3).

<u>Model 2.a Effect of tDCS and in Younger Adults: dlPFC vs Parietal vs Sham effects in Working Memory</u>

Turning our attention to working memory accuracy, trends are found once again in the form of main effects for session order (F(1, 763.03) = 5.81, *p* =0.016, 95% CI = [-0.018, -0.002], stimulus difficulty (F(1, 755.03) = 878.33, *p* = 0.000, 95% CI = [0.115, 0.131] and format (F(1, 755.03) = 25.15, *p* = 0.000, 95% CI = [-0.028, -0.012], as well as the format x difficulty interaction (F(1, 755.03) = 6.58, *p* = 0.010, 95% CI = [0.002, 0.018], indicating a slight boost for hard verbal stimuli compared to hard picture stimuli.

Finally, similar to what was observed in analysis 1a, there was a stimulation condition x difficulty interaction (F(1, 755.03) = 4.81, *p* =0.008, 95% CI = [-0.028, -0.005], showing a significant boost in working memory performance as a result of active left dlPFC stimulation for hard stimuli (but no boost from parietal stimulation) and negligible differences between the three stimulation conditions across easy stimuli. To confirm, post-hoc t-tests revealed a significant performance boost for active left dlPFC (0.55) compared to sham (0.48) (t(298) = 2.57, *p* =0.010, *d* = 0.29). By contrast, performance differences between active left PPC (0.52) and sham were marginal (t(300) = 1.77, *p* =0.08), and performance differences between active left PPC and active left dlPFC were statistically equivalent (t(288) = 0.99, *p* =0.31) (see Figure 4). Taken together, these results indicate that active dlPFC was the most robust in successfully modulating working memory performance among the three tDCS conditions.

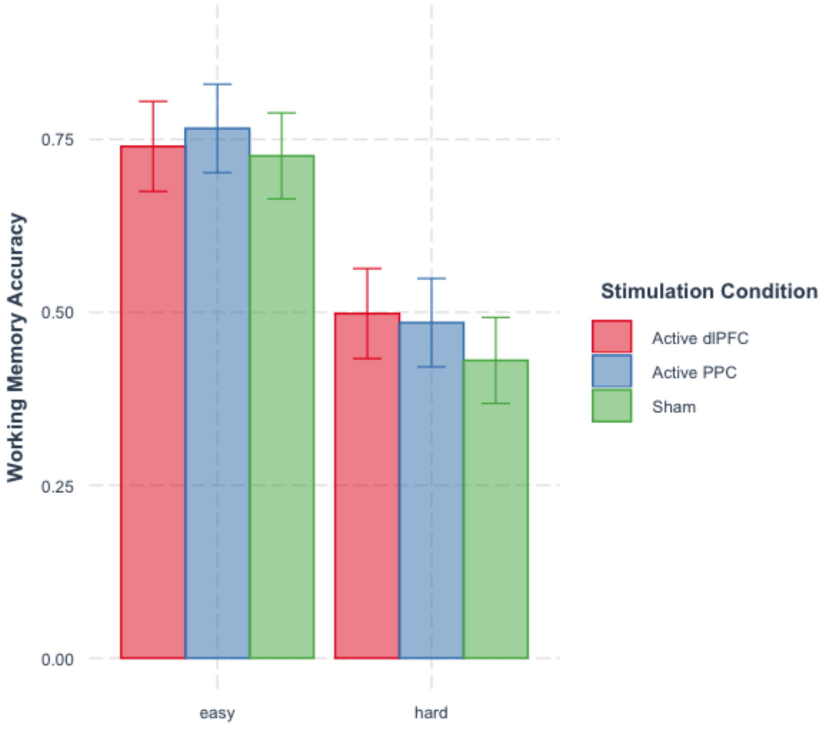

Figure 4: dlPFC vs PPC vs sham in working memory. Working memory accuracy in younger adults as a function of active left dlPFC, active left PPC and sham, as a function of task difficulty. Error bars are confidence intervals.

Model 2.b. Effect of tDCS: Models from 1.a, 1.b & 2.a with baseline performance as a covariate

A final set of primary analyses adjusted for individual variability in cognitive performance by re-running each of the analyses described above while including baseline performance as a covariate. To the extent that the cognitive measures are highly correlated across timepoints, the latter analyses might provide additional power to detect effects of stimulation.

To anticipate the key results, variability in performance driven by tDCS was considerably smaller than individual variability in performance as assessed on baseline. While we had assumed that controlling for individual variability as proxied by including baseline as a covariate might increase our ability to detect stimulation effects, this did not occur. The reason for this is likely the same reason as to why all the other effects were no longer obtained when controlling for baseline; the effect of tDCS was not sufficiently strong enough to survive this correction, or, put another way, the effect of tDCS was smaller than the effect of baseline.

2b (1.a) Effect of tDCS and in Younger Adults: Episodic Recollection Accuracy & Working Memory Accuracy with baseline performance as a covariate

Re-running model 1.a (younger adults only) with baseline performance as a covariate and episodic memory recollection as the dependent variable, we observe a main effect of baseline performance. This indicates that baseline performance was correlated with subsequent performance across subjects. This finding is to be expected, as performance for any given subject is likely to be correlated across sessions. Here, the original main effect of stimulus difficulty remains, (F(1, 330.14) = 23.99, *p* =0.000, 95%

CI = [0.038, 0.066]. However, the main effect of format found in model 1.a disappears (p > 0.5) when adding baseline episodic memory performance as a covariate. Similarly, the stimulus difficulty x format interaction observed in the original model also disappears (p > 0.4). No other main effects or interactions were found, again providing no evidence for an impact of tDCS on performance in episodic memory.

When re-running model 1.a with working memory accuracy as the dependent variable and including baseline performance as a covariate, both the main effect and interaction effect found in the original model are no longer significant. The significant effect of baseline performance F(1, 115.97) = 2360.75, p =0.000, 95% CI = [0.996, 1.078], results in the original main effects of stimulus difficulty (p > 0.7) and format (p > 0.8) as well as the interaction effect of stimulation condition x difficulty (p > 0.6) previously observed being no longer significant. However, there is a small trending effect of session order that survives the correction for baseline F(1, 518.13) = 3.07, p =0.080, 95% CI = [-0.013, 0.0001]. No other main effects or interactions were found, including the effects of stimulation.

2b (1.b) Effect of tDCS and in Younger & Older Adults: Episodic Recollection Accuracy & Working Memory Accuracy with baseline performance as a covariate

In re-running model 1.b (both age groups) with episodic memory as the dependent variable and including baseline performance as a covariate, a significant main effect of the baseline score (F(1, 1062.27) = 237.01, p = 0.000, 95% CI = [0.362, 0.478] indicates a significant adjustment of several factors in this new model. While we found a main effect of age (F(1, 172.73) = 14.21, p = 0.0002, 95% CI = [-0.057, -0.018] and stimulus difficulty

(F(1, 1126.63) = 78.54, *p* = 0.000, 95% CI = [0.033, 0.053] as in the original model, we also observed a main effect of stimulus format (F(1, 1056.47) = 19.85, *p* = 0.000, 95% CI = [0.011, 0.029] not previously observed, along with a format x age interaction (F(1, 1096.13) = 13.28, *p* = 0.0002, 95% CI = [0.007, 0.026]. This finding highlights that, while picture stimuli (0.419) are remembered better overall compared to words (0.375) when collapsing across all factors, the trend remains that in younger adults, words (0.498) benefit marginally from better episodic memory performance compared to pictures (0.464), (t(594) = 1.69, *p* = 0.09, *d* = 0.14). This trend reverses in older adults, who perform better on pictures (0.377) compared to words (0.258), (t(315) = 7.88, *p* = 0.000, *d* = 0.48). Finally, a trending difficulty x format interaction (F(1, 1070.53) = 3.64, *p* = 0.056, 95% CI = [-0.0002, 0.017] suggests that, in this new model, the overall difference between hard words (0.323) and hard pictures (0.326) is close to zero, while the difference between easy pictures (0.511) and easy words (0.426) is significant (t(612) = 4.05, *p* = 0.000, *d* = 0.33). No other main effects or interactions were found.

In re-running model 1.b with working memory as the dependent variable and adding baseline performance as a covariate, a similar trend is observed whereby the baseline performance covariate comes out as a significant main effect in the model, (F(1, 1222) = 4874.07, *p* = 0.000, 95% CI = [0.990, 1.047], suggesting baseline performance to have an adjusting effect on our dependent measure. Indeed, where stimulus difficulty came out previously as a significant factor, in this new model the effect is only marginal (F(1, 1222) = 3.66, *p* = 0.055, 95% CI = [-0.013, 0.0001]. However, the previously observed age x difficulty interaction remains (F(1, 1222) = 6.85, *p* = 0.008, 95% CI = [-0.012, -0.001]. Furthermore, while the effect of age was previously not observed, it comes out as significant in this model (F(1, 1222) = 4.43, *p* = 0.035, 95% CI = [-0.010, -0.0004].

These trends are a result of younger adults performing slightly better on their hard version of the task (3-back, 0.513) compared to older adults' hard version of the task (2-back, 0.499). However, older adults perform quite a bit better on their easy version of the n-back (1-back, 0.814) compared to younger adults' version of the easy 2-back (0.759), resulting in older adults having an overall superior working memory performance when collapsed across all measures. Yet when comparing age groups on an equivalent task (2-back), younger adults (0.759) outperform older adults (0.499), as would be expected. Finally, the age x stimulation x difficulty 3-way interaction effect previously observed in the original model is no longer significant (*p* >0.3), meaning that the tDCS effect found in working memory for younger adults in the original model was not obtained when controlling for baseline differences in performance.

2b (2.a) Effect of tDCS and in Younger Adults: dlPFC vs Parietal vs Sham effects with baseline performance as a covariate

We re-ran model 2.a (only younger adults) to investigate the effects of active left dlPFC and active left PPC to sham with baseline performance as a covariate. For episodic memory accuracy, the model yielded a main effect of the baseline performance (F(1, 817.80) = 106.32, *p* = 0.000, 95% CI = [2.698, 0.405]) resulting in some different outcomes in this updated model. The original main effect of difficulty remains (F(1, 792.49) = 71.13, *p* = 0.000, 95% CI = [3.824, 0.061] however the original effect of format does not (*p* > 0.2). Similarly, the trending stimulation x format effect is also no longer significant (*p* > 0.1).

Turning our attention to working memory accuracy, the same model described in 2.a adding baseline performance as a covariate yields a main effect of baseline performance (F(1, 178.81) = 3352.15, *p* = 0.000, 95% CI = [1.018, 1.088]. Here, the previously observed main effects of difficulty (*p* > 0.2), format (*p* > 0.8) as well as the stimulation x difficulty interaction (*p* > 0.7) and difficulty x format interaction (*p* > 0.2) are no longer significant.

Episodic memory accuracy

	Pictures - dlPFC Stim		Pictures - PPC Stim		Pictures - Sham	
	Older	Younger	Older	Younger	Older	Younger
Easy	0.470 (0.02)	0.558 (0.02)	-	0.534 (0.02)	0.456 (0.02)	0.567 (0.02)
Hard	0.291 (0.02)	0.351 (0.02)	-	0.374 (0.02)	0.290 (0.02)	0.378 (0.02)

	Words - dlPFC Stim		Words - PPC Stim		Words - Sham	
	Older	Younger	Older	Younger	Older	Younger
Easy	0.299 (0.02)	0.526 (0.02)	-	0.590 (0.02)	0.299 (0.02)	0.594 (0.02)
Hard	0.253 (0.02)	0.410 (0.02)	-	0.467 (0.02)	0.184 (0.02)	0.455 (0.02)

Working memory accuracy

	Visuospatial - dlPFC Stim		Visuospatial - PPC Stim		Visuospatial - Sham	
	Older	Younger	Older	Younger	Older	Younger
Easy	0.791 (0.02)	0.753 (0.02)	-	0.775 (0.02)	0.782 (0.02)	0.741 (0.02)
Hard	0.441 (0.02)	0.520 (0.02)	-	0.499 (0.02)	0.504 (0.02)	0.446 (0.02)

	Verbal - dlPFC Stim		Verbal - PPC Stim		Verbal - Sham	
	Older	Younger	Older	Younger	Older	Younger
Easy	0.845 (0.02)	0.774 (0.01)	-	0.780 (0.02)	0.837 (0.02)	0.777 (0.01)
Hard	0.515 (0.02)	0.581 (0.02)	-	0.551 (0.02)	0.535 (0.02)	0.522 (0.02)

Table 3. tDCS session performance accuracy.

Performance means for tDCS sessions (days 2 & 3, collapsed) for episodic recollection accuracy (hits - false alarms) and working memory accuracy (hits-misses), for older and younger adults, parsed by stimulus format and difficulty. “Easy” refers to stimuli presented 2x during encoding for the episodic task and 1-back (for OA) and 2-back (for YA) during the working memory task. “Hard” refers to stimuli presented 1x during encoding for the episodic task and a 2-back (for OA) and 3-back (for YA) during the n-back task. Values are means with SEM in parentheses.

5.3 Effect of tDCS on Subjective Reports of Arousal

To explore the influence of subjective arousal in tDCS effects, participants were asked to rate their “level of alertness” from 0-10, both immediately prior to receiving tDCS and immediately after completing 20 minutes of stimulation. We computed pre/post arousal rating by subtracting the pre-stimulation arousal rating from the post-stimulation arousal rating, so that positive values would reflect an increase in arousal post-stimulation, generating a pre-post score for sessions 1 and 2, as well as averaged score for both sessions. When running a two-sample t-test between the average score for both sessions, there was in fact a significantly higher arousal ratings for sham (0.01) compared to active stimulation (collapsing dlPFC and PPC active stimulation) (-0.27) (t(1558) = 5.60, p =0.000, d = 0.28). The significance of the test does not change from running the t-test for either session 1 or 2 on its own, or when only including subjects who received dlPFC active stimulation. Historically, it has been considered important to determine whether there is either increased subjective attentiveness or decreased fatigue as a result of stimulation, hinting at the possibility that the effects may not be due to regionally specific stimulation, but instead to an overall change in arousal levels. However, prior work in our lab (Wong et al., 2018) as well as others (e.g., Roy et al., 2015) have not found that subjective reports of arousal are typically improved following stimulation, a pattern replicated in the current study. While this may be surprising, it is also important to note that even though the average alertness for participants who received sham is positive (reflecting an increase in arousal), this number is only just above zero making this result difficult to draw strong conclusions.

Discussion

Baseline Day Analyses

Assessing performance for the task during the Baseline Day (conducted on the first visit to the lab without any stimulation or time of day restrictions), we found that, overall, younger adults performed better on hard words relative to hard pictures during the episodic memory task. While this pattern may be initially surprising, it is important to note that the word blocks required semantic elaboration at encoding ("Is this made in a factory? "Is this found in a house?"), thereby driving deep, elaborate processing of conceptual or semantic features known to facilitate learning (e.g., Kapur et al., 1994). The notion that this deeper level of processing benefitted younger adults is likely due to their ability to leverage this at retrieval on tasks that are more effortful and difficult, particularly when compared to their older counterparts. This cognitive demand thus resulted in superior recollection on words relative to pictures in our younger sample. Conversely, older adults were found to perform better on picture stimuli. By contrast to the word blocks, picture blocks directed focus solely on the perceptual features of the stimulus ("Is this a relatively detailed image?"). As a result, older adults' performance was facilitated by the relative ease of encoding perceptual features of images compared to the semantic processing of words (Paivio & Csapo, 1973), a self-initiated process that, intuitively, has been shown to exacerbate age-related differences in performance when comparing age groups (Craik & Simon, 1980).

Turning our attention to the working memory n-back task, this analysis yielded main effects of difficulty and format without a main effect of age. Given the age-matching constraints imposed on the task, older adults yielded superior n-back performance for the easy version of the task (1-back), which is intuitive given the relative ease of this compared to relatively harder 2-back given to younger adults. On the harder versions of the task (2-back for older, 3-back for younger), however both age groups perform similarly. When it comes to age-specific difficulty matching, these patterns replicate previous findings as reported in a recent meta-analysis, with consistent age-related costs attributed going from the 1-back to the 2-back in older adults, and from the 2-back to the 3-back in younger adults (Bopp & Verhaeghen, 2018).

Additionally, we also found a main effect of format, with both age groups performing worse on the visuospatial version of the task compared to the verbal version. The precise reason for this effect is unclear, though one potential explanation is that individuals are continuously exposed to verbal information (e.g., letters) and therefore have rehearsal and maintenance abilities that are more developed for this modality (Cansino et al., 2013). Retaining spatially-dependent positions as required in the visuospatial task may have been a novel mental activity for which any strategies used by participants were less useful. Other studies comparing verbal and visuospatial modalities have also observed this format difference (Thürling et al., 2012), including a higher likelihood of decline with age for the visuospatial version of the n-back (Cansino et al., 2013). While testing continuous decline of the visuospatial n-back was outside of the scope of this task, these converging data highlight a consistent disadvantage for maintaining and/or manipulating visuospatial information when compared with verbal information. Along similar lines, prior evidence also suggests that verbal working memory might be less severely affected by aging across the adult lifespan relative to visuospatial working memory (Hale et al., 2011; Pliatsikas et al., 2019).

This format difference might also be explained by a gender difference in visuospatial memory performance. A considerable amount of previous research has pointed to favoring male participants on tasks that require transformations in visuospatial working memory (Loring-meier & Halpern, 1999; Voyer et al., 2017). Given that 58% of younger adults and 66% of older adults in our sample are female, a gender difference in visuospatial memory performance may be driving the overall format effect within our model. We find some statistical evidence for this explanation. An identical ANOVA with participant gender included as a between-subject factor produces a format x gender interaction effect (F(1, 190) = 6.78, p = 0.009, MSE = 0.007, $n^2p=$ 0.03), featuring a small performance advantage for male participants (0.62) compared to female participants (0.58) for the visuospatial version of the task collapsing across all other factors. By contrast, males (0.64) and females (0.64) perform comparably on the verbal version of the task.

The Effect of tDCS on Memory Performance

Assessing the outcome for model 1.b with episodic memory accuracy as the dependent measure, we find many repeated outcomes from baseline but no effects of stimulation. This suggests that, across baseline and the two stimulation sessions, there was reasonable task reliability, and that our predictors in model 1.b were largely not affected by stimulation, with the exception that model 1.b gives way to a main effect of format that was not observed in the baseline analyses. However, given the order confound between the baseline and following sessions it is difficult to draw conclusions as to whether the effect of format is due to the added factor of stimulation.

By contrast, the two-way stimulation x difficulty interaction 1.a (young adults only) and the stimulation x age x difficulty interaction in model 1.b (both age groups) with working memory indicates that task difficulty may very well be an important mediator in yielding tDCS effects. Furthermore, the fact that this boost was most robust in left dlPFC (compared to active left PPC) is corroborated by previous work (Mancuso et al., 2016) and appears to corroborate the notion that tDCS benefit is due to task difficulty rather than an effect of brain laterality between verbal and visuospatial processing, given a lack of a performance disparity between these two n-back modalities.

Additionally, we noted an age effect whereby the benefit leveraged by tDCS in our difficult working memory task was only evident in younger adults, not older adults. While we cannot draw strong conclusions about the disparity between age groups, one explanation may be that older adults do not rely as heavily on prefrontal regions for difficult tasks (particularly during working memory tasks) compared to younger adults (Hurley & Machado, 2018), with frontal recruitment being contingent on external factors such as education. One corroborating study evaluating the effect of anodal tDCS on working memory in older adults found stimulation only benefited those with higher degrees of education, highlighting the potential role for differential frontal recruitment as a function of strategy when older adults perform working memory tasks (Berryhill & Jones, 2012). Others still have suggested that higher stimulation strength may be needed in aged cohorts due to age-related physical changes in the brain and skull, including bone density/thickness and cerebrospinal fluid volume (Hurley & Machado, 2018; Laakso et al., 2015).

While the mechanisms that drive tDCS-elicited boosts of high-difficulty tasks continue to be elusive, this is not a novel finding. Others too have found similar effects by modulating task difficulty to enhance the behavioral effects of anodal tDCS effects when applied to left dlPFC. This has been observed within the domain of working memory (e.g., Fregni et al., 2005; Gill et al., 2015; Pope et al., 2015; Trumbo et al., 2016), as well as other outcomes associated with left dlPFC, including tasks dependent on cognitive control (Metuki et al., 2012) and on sustained attention, conflict monitoring and response inhibition (Dubreuil-Vall et al., 2019). Complicating matters further, some researchers have posited that tDCS may exhibit a “Goldilocks” conundrum, whereby a task that is indeed too difficult (resulting in floor effects and and/or related participant frustration) or too easy (ceiling effects and/or lacking effortful cognition) can be equally detrimental to detecting tDCS effects (Fregni et al., 2005; Kwon et al., 2015). We see this as an unlikely explanation of our results, as our experiment avoided ceiling and floor effects, by design, and had a large range of task difficulty upon which to assess tDCS effects, but we cannot rule out this possibility either. Additionally, determining the “correct” level of difficulty to achieve tDCS effects is likely be sample and task-dependent, and undoubtedly requires further investigation.

Chapter 2: The Effect of Circadian Preference & Sleep Quality on tDCS Effects in Memory Performance

2.1 tDCS , Time-of-Day and Circadian Preference

Post-hoc analyses conducted as part of prior research from the lab revealed that tDCS boosted episodic recollection accuracy for words when participants were tested in the morning, but not for participants tested in the afternoon (Gray et al., 2015). This analysis suggested that the time at which an individual is stimulated (referred to from here on simply as "time of day") may be critical for finding tDCS effects on memory in younger adults. Time of day as a factor has been overlooked in prior studies and may potentially mediate the effect of tDCS, providing a potential explanation for the difficulty in reliably detecting tDCS effects.

Outside of the tDCS literature, there are many well established physiological findings that posit that attentional control is tied to daily arousal patterns, highlighting the relevance of circadian fluctuations in cognitive alertness, which in turn may contribute to individual performance on cognitive tasks. These fluctuations in circadian arousal have been found to cause a synchrony effect whereby performance on tasks requiring effortful top-down cognitive and attentional control (such as many memory tasks) increases if performed during one's optimal time of day (Anderson et al., 2014; Hidalgo et al., 2004). Additionally, this synchrony effect may be increasingly important as we age (May & Hasher, 2017; Rowe et al., 2009).

Circadian preferences appear to follow a gaussian distribution across the U.S. population, with the majority of individuals falling into a largely "intermediate" chronotype (Fischer et al., 2017), i.e., not having a strong preference towards either "eveningness" or "morningness". However, circadian preference also interacts with biological age, such that people on average inch towards a preference for "morningness" as they get older. This shift is consistent with results from the American Time Use Survey; based on twelve years (2003–2014) of pooled diary data, chronotype is not static but instead shifts over the course of the lifespan, with younger people typically falling into intermediate and evening-type ranges (reaching a peak of "eveningness" at ~19 years), and shifting increasingly towards morningness thereafter (Fischer et al., 2017, see Figure 5). Thus, younger adults are expected, on average, to express at least a mild preference for the afternoon and/or evening hours and older adults at least a mild preference for the morning hours (Yoon et al., 1999). These data also converge nicely with many samples described in the literature investigating the intersection of age and circadian preference cited above, as well as our own sample described here (see Figure 7).

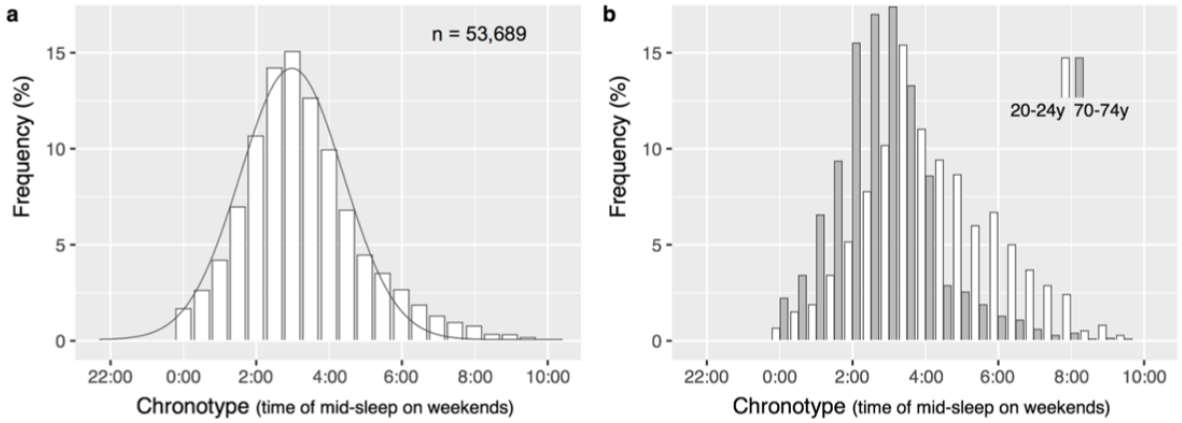

Figure 5. Sample of midpoints of sleep for 53,689 US-based individuals (Fischer et al., 2017).

Indeed, this shift of circadian preferences with age may explain an early study by May and colleagues (1993), which found age-related differences in a recognition memory task were exacerbated in the late afternoon, when younger adults were at their optimal times and older adults were at their suboptimal times. Intriguingly, a follow-up study by the same authors conducted in the morning found no age differences in memory performance among the same sample. This pair of findings highlights testing time as a potentially critical variable for determining age differences in cognitive performance -- one that is likely undervalued in tasks requiring attention regulation. Other work by May and Hasher (1998) found that inhibitory control was optimal at peak times of day (for both younger and older adults), but was particularly important for older adults, suggesting that age-related declines in inhibition may be mediated by circadian variations in frontal functioning. Subsequent work yielded converging evidence, supporting the idea that synchronizing testing with individual circadian preference is predictive of a range of cognitive performance measures, including problem solving under distraction (May & Hasher, 1998) as well as memory for stories (Winocur & Hasher, 2002) and false memory errors (Intons-Peterson et al., 1998). Similar findings have been shown in the working memory domain as well. In a visuospatial working memory span task, Rowe et al., (2009) showed that both younger and older adults performed better when tested during their relative peak time, which seemed to be of particular benefit to older adults for reducing the effect of interference.

Given this, it is plausible that tDCS subjects on the more extreme ends of the circadian preference distribution have their performance undermined by synchrony effects if chronotype is not taken into account experimentally, contributing to the mixed findings in the tDCS literature. While the mechanisms by which tDCS interacts with synchrony effects (if any) are still to be defined, these findings coupled with our post-hoc discoveries in Gray et al., (2005) yielded speculation that tDCS may boost cognitive performance "when needed", such as during one's nonoptimal time of day.

To more definitively test this initial time-of-day hypothesis, (Wong et al., 2018) conducted a large-scale tDCS study of episodic memory on healthy young adults, where participants committed to both a morning (9 AM) and afternoon (1 PM) testing time, and subsequently randomly assigned to either one or the other in a between-subject, single-session design (n = 30 per stimulation group at each testing time, for a total of N = 120). The results showed a robust effect of tDCS on the word test in the morning (Figure 6), which most younger adult participants reported as their least-preferred time of day. While there was only a trending effect of tDCS on the picture test, there were no reliable effects of tDCS in the afternoon session, to the extent that recollection was somewhat greater in the sham condition (.43 and .36, collapsing across tests). When comparing the two sham conditions, performance was significantly greater in the afternoon than in the morning (.43 and .31, collapsing across tests), demonstrating the expected effect of time-of-day on recollection accuracy in younger adults. This suggested that tDCS to dlPFC has the potential to reliably improve recollection accuracy for words, but only with relatively large samples of healthy young adults tested at their suboptimal time (i.e., the morning).

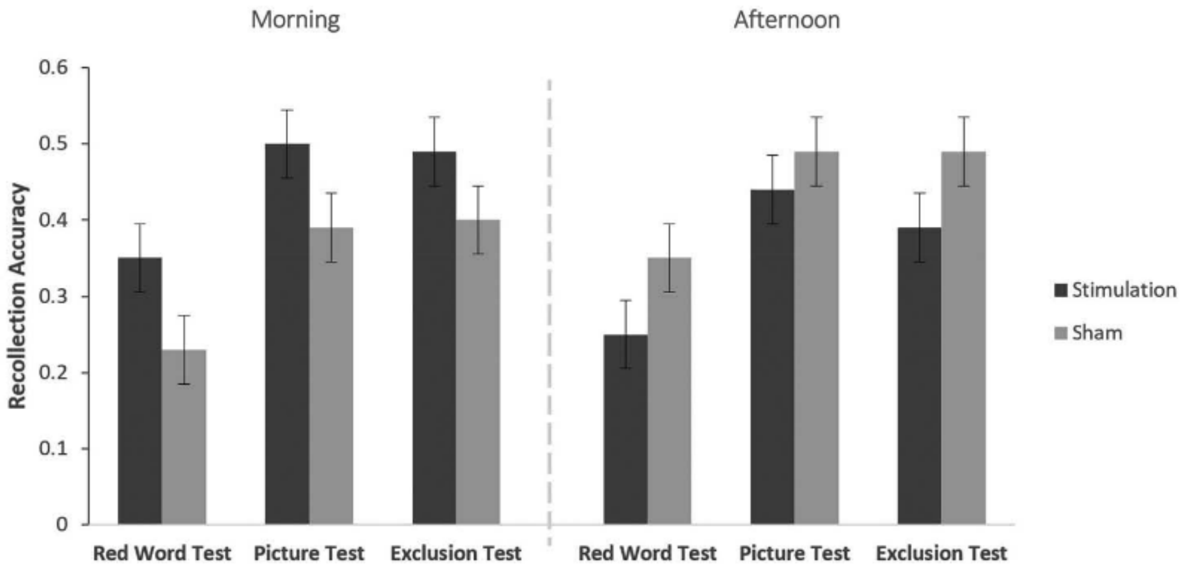

Figure 6. Time-of-day effects on recollection accuracy (Wong et al., 2018). In the morning, stimulation of dlPFC reliably boosted accuracy (hits-false alarms) on the red word test, but not on the picture test. N=30 per group.

2.2 Measuring Circadian Preference: MEQ & Wrist-Worn Actigraphy

To assess the impact of circadian preference on tDCS effects in the current study, we utilized both the self-report data collected from the Morningness-Eveningness Questionnaire (MEQ) (as in Wong et al., 2018), regular sleep logs, as well as objective wrist-worn actigraphy data. Note that, in line with previous work (e.g., Miguel et al., 2014), there was a significant (expected) negative correlation between MEQ scores and actigraphy-derived midsleep times in our sample (r(172) = -0.25, *p* = 0.0009), such that earlier midsleep times correlated with higher scores of the MEQ (corresponding to increased morningness), and vice versa.

The Morningness-Eveningness Questionnaire (MEQ)

The MEQ was one of the first and (still is) the most widely used self-report measures of circadian arousal (first developed by (Horne & Östberg, 1976), comprised of a 19-item questionnaire that asks a series of questions around the preferred daily timing for a range of habits and activities (e.g., physical exercise, eating, preferred wake up and sleep times, etc.), resulting in an aggregate “score” that can be used to categorize participants into one of five chronotypes: definitely morning, moderately morning, neutral, moderately evening, and definitely evening. Individuals who score within the “morningness” range experience their optimal arousal level early in the day and often prefer to engage in challenging cognitive and physical activities in the morning. By contrast, those with an “eveningness” chronotype experience their optimal arousal level later in the day and prefer to reserve their more intellectually or physically demanding tasks for the afternoon or evening (May & Hasher, 2017). Finally, those who show neither strong morningness nor strong eveningness preferences are classified as “neutral” chronotypes, with a peak in arousal level between that of morning-types and evening-types (May & Hasher, 2017; Roenneberg et al., 2007).

Looking at the distribution of MEQ chronotype in our current sample, it appears the scores are roughly normally distributed, as reflected in the general population, with expected age-related skews (see Figure 7). Older adults are much more likely to be considered “morning types” (N=45.6%), rather than evening types (N=6.1%), and the contrary holds true for younger adults, where more are “evening types” (N=25.2%) rather than “morning types” (N=11.3%). However, despite the majority of participants (younger and older) being considered intermediate (YA = 63.5%; OA = 48.1%), there was still a large significant difference in average MEQ score distributions between younger (M=47.2) and older (M=57.1) adults (t(194) = 7.54, *p* =0.000, *d* = 1.09).

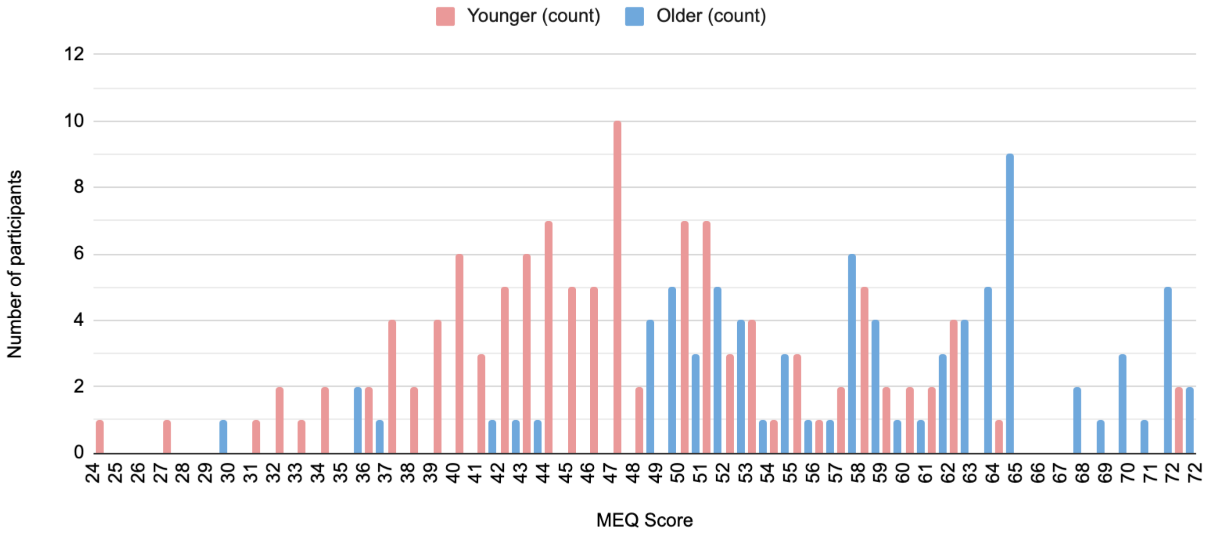

Figure 7. Participant MEQ score distribution

Scores on the MEQ can range from 16 at the extreme end of "evening types" to 86 at the extreme end of "morning types". Enrolled participant scores ranged from 24 to 72, with scores between 42 and 58 classified as "intermediate" (Horne and Ostberg, 1976). Older participants on average had higher MEQ scores (M= 57.16) indicating a higher tendency towards "morningness". Younger adults showed an opposite trend (M=47.20), indicating a tendency towards "intermediate" and "eveningness".

Wrist-worn Actigraphy

In addition to completing the MEQ, participants were equipped with a wrist-worn accelerometry watch at the end of the baseline day (along with detailed instructions for use). These data were be collected across a minimum of 7 consecutive days (max of 12), providing an affordable and noninvasive technique for ambulatory monitoring of rest-activity cycles, as well as a range of other sleep-related behaviors. For the purposes of determining an objective index of circadian preference, we used sleep midpoint or midsleep, which can be defined as the midpoint between actigraphy-derived sleep onset and wake onset (sleep onset + wake onset / 2). This was calculated as an aggregate over the days of enrollment as well as separately for each workday and free day and averaged within each day type (Wong et al., 2015). Based on the relevant literature, we chose midsleep given its assessment as the optimal phase reference point for sleep (Benoit et al., 1981; Fischer et al., 2017; Roenneberg et al., 2007) and the best phase anchor point for melatonin onset (Terman et al., 2001).

2.3 Circadian Preference on Memory Performance & tDCS Effects

Impact of Circadian Preference on Performance

Given the literature spearheaded by Hasher and May described earlier, it is prudent to first investigate the standalone effects of time of day on performance (collapsing across any effects of stimulation), and whether this interacts with age. Based on the literature supporting age-related differences in circadian preferences described previously, we might expect older adults to perform better in the morning and younger adults to perform better in the afternoon. In contrast to this expectation, there was no observed main effect of time of day in our data when running a linear mixed effects model with episodic memory ($p > 0.6$) or working memory ($p > 0.5$) as dependent variables, and interaction terms between time of day and age group as predictors. This analysis however does not utilize individual circadian preferences directly, which are likely to vary, and instead uses age-group averages.

To account for individual-variability in circadian preferences, we also sought to match participants' testing time (AM or PM) with their preferred time of day as indexed by the MEQ, restricting "morning types" to those who scored as "definitely morning" or "moderately morning" and restricting "evening types" to those who scored as "definitely evening" or "moderately evening". When assessing episodic performance within "morning" people at both AM and PM testing times however, there was no difference in their performance based on testing time ($p > 0.6$). The same holds true for "evening" people between AM and PM testing times ($p > 0.7$). A similar outcome is true for working memory accuracy as well (both p's > 0.3). Thus, our task did not yield significant evidence for a synchrony effect -- individual's performance did not vary based upon whether the testing time corresponded to their circadian preferences or not.

However, while there were no differences in overall performance between AM and PM testing times between younger and older adults, it is still possible that tDCS could differentially boost performance based on individually measured circadian preference. To assess whether there is an impact of circadian preference on tDCS, we re-analyzed model 1.b., this time adjusting for circadian preference using two methods; once using wrist-worn accelerometry to measure preferred time of day indexed by midsleep, and once using the self-reported MEQ score. For both sets of analyses, the index of circadian preference was added as a covariate in two separate models 1.b., with interaction terms between time of day, age group, format and difficulty and stimulation effects.

Adjusting Performance for MEQ and Actigraphy

Episodic Memory adjusted for MEQ

With episodic recollection as the dependent measure, running this model adjusting for MEQ score did not yield main effects or interactions that differed dramatically from those described for the original model 1.b detailed in Chapter 1. The same main effects of age group, difficulty, format as well as the two-way interaction effects between age and format, and two-way interaction between format and difficulty and trending three-way interaction between age x stimulation x format remain. Additionally, the same four-way interaction effect between time of day, age group, difficulty and format also remains from the original model 1.b.

Episodic Memory adjusted for Midsleep

Adjusting model 1.b for midsleep with episodic memory as the dependent measure yields outcomes consistent with the original model 1.b., as well as the model adjusted with MEQ (described above). This includes main effects of age, difficulty and format, along with two-way age x difficulty and two-way format x difficulty interactions. However, here the trending three-way interaction between stimulation x age x format is no longer trending, and the four-way interaction between time of day, age group, difficulty and format is also only trending in this model $F(1, 926.07) = 3.28$, $p = 0.070$, 95% CI = [-0.006, 0.012] compared to the significant four-way effect in the model adjusted for MEQ (described above).

Note that given the periodic nature of midsleep scores (over 24h), midsleep was added as a predictor to the given linear model by adding both the sine and the cosine of the angle to the regression, so that we predict the outcome as $\hat{y} = \beta 1 \cos(\pi * \text{hour}/12) + \beta 2 \sin(\pi * \text{hour}/12)$, as recommended in Pewsey et al., (2013).

Working Memory adjusted for MEQ

When using working memory accuracy as the dependent measure, the main effects and interactions described in the original model 1.b remain unaffected, including the main effect of session order, difficulty and format, as well as the two-way age x difficulty interaction and the three-way stimulation x age group x difficulty interaction, without changing the magnitude of these effects. As a result, it appears adding circadian preference as indexed by MEQ score does little to influence the patterns yielded by the original model in working memory.

Working Memory adjusted for Midsleep

When adjusting working memory accuracy for midsleep, the main effects and interactions once again remain largely unaffected. The same main effects of difficulty and format, as well as the two-way age x difficulty interactions and three-way stimulation x age x difficulty interaction remain.

2.4 Measuring Sleep Quality

There has been considerable interest and investigation into the association between sleep quality and cognitive performance (broadly defined), using a range of physiological (e.g., polysomnography or PSG, and actigraphy) and self-report methods (Hokett et al., 2021; Rasch & Born, 2013; Scullin & Bliwise, 2015). While polysomnography (PSG) has historically been considered the gold standard for objective sleep measurement, newer technologies such as wrist-worn actigraphy have allowed to quantify objective sleep physiology and measurement over extended periods of time (e.g., days or weeks) in a noninvasive and unobtrusive manner (Hokett et al,. 2021), while still yielding accurate characterizations of sleep. Collectively, these sleep measurement tools have yielded robust indices sleep quality which can be used to infer the potential impacts of sleep on behavior and cognitive function.

In the current study, in addition to using the wrist-worn actigraphy to estimate an objective index of circadian preference (i.e., midsleep), we leveraged the power of this technology to investigate how sleep quality may be impacting performance on episodic and working memory performance, as well as whether sleep quality is important for better understanding the effects of stimulation. Of the available indices of actigraphy-derived sleep quality, two that are frequently used in the literature are the Sleep Fragmentation Index (SFI) and Sleep Efficiency (SE). The SFI represents an index of restlessness during sleep time, described as a percentage, with a higher value indicating poorer sleep quality (Youn & Lee, 2020). In particular, high levels of sleep fragmentation, defined as the total number of awakenings (after sleep onset), and sleep stage shifts divided by total sleep time, has been associated with reduced Slow Wave Sleep (SWS), a sleep parameter known to favor episodic memory consolidation (Cherdieu et al., 2014; Hokett et al., 2021). This measure is used widely in the sleep literature for assessments of sleep quality, particularly in relation to a wide range of psychological, neurological and sleep disorders (Haba-Rubio et al., 2004; Morrell et al., 2000; Stepanski, 2002).

Sleep efficiency, by contrast, is frequently defined as the "ease in falling asleep as well as the ease staying asleep" (Reed & Sacco, 2016), computed by dividing the time between the start and end of the first and last nocturnal inactivity period by total sleep duration (Webb & Agnew, 1975). Like SFI, sleep efficiency is similarly ubiquitous in the sleep literature, frequently selected as an indicator of sleep quality applicable across all age groups in line with the National Sleep Foundation, and is consistent with past epidemiologic and meta-analytic findings (Ohayon et al., 2017).

Furthermore, research into age-related differences in sleep quality measures has yielded a consistent pattern that, on average, sleep quality decreases over the course of the lifespan. For example, sleep efficiency has been found to decline from approximately 86% between 37–54 years to 79% at age 70+ years in previous longitudinal work (Bliwise et al., 2005; Cherdieu et al., 2014). Similar age-related patterns are observed in sleep fragmentation, which in turn is associated with a decline in the quality and quantity of the "deep" stages of sleep, including SWS and rapid eye movement sleep (Ohayon et al., 2004; Scullin & Bliwise, 2015).

Intriguingly, however, in our sample we did not find a significant difference in SFI ($p > 0.2$) or SE ($p > 0.7$) between the two age groups, although the age group difference for SFI was trending ($t(141) = 1.27$, $p = 0.20$). Overall, the vast majority of both younger (85%) and older adults (84%) exhibited relatively high sleep efficiency on average, and relatively low sleep fragmentation on average (10.7% in older and 8.9% in younger adults).

Effects of Sleep Quality on Episodic Memory Performance

In terms of the impacts of sleep quality on episodic memory specifically, there have been many studies to date (see Hokett et al., 2021, for review) showing strong evidence that people experience a sleep-dependent episodic memory benefit, with poor sleep quality tied to poorer episodic memory outcomes. Furthermore, while the physiological mechanisms underlying sleep-related memory impairments remain somewhat elusive, on average both younger and older adults have been found to benefit equally from high quality sleep (Aly & Moscovitch, 2010; Hokett et al., 2021). Intriguingly, while our current sample only yielded marginal age differences in actigraphy-derived sleep quality measures, the fact that age-related declines in sleep quality are common in longitudinal investigations of sleep quality (Cherdieu et al., 2014) makes the collection and analysis of sleep quality data in conjunction with age-related changes all the more important. However, this is relatively uncommon in the cognitive literature. Given the heightened degree of variability often observed within the cognitive aging literature, sleep quality may be playing a role in driving this variability (Hokett et al., 2021).

While there is some work investigating the impact of sleep on emotional memory valence (Tempesta et al., 2015), and on the subjective experience of autobiographical memories (Lukowski et al., 2017), there appears to be relatively few investigations to date on how long-term sleep quality assessments (as measured over the course of days or weeks) may differentially affect or interact with other experimental parameters in episodic memory tasks (e.g., stimulus format and difficulty).

Effects of Sleep Quality on Working Memory Performance

Similar to the episodic memory literature, a robust literature highlights that naturally occurring and experimentally-induced sleep loss can significantly impair working memory (Chee & Chuah, 2007; Smith et al., 2002). However comparatively few studies have investigated whether reduced working memory is also related to everyday sleep quality. To date, from the studies using self-reported measures of sleep quality, (e.g., Pittsburgh Sleep Quality Index or PSQI, Buysse et al., 1989) or actigraphy-derived sleep quality (Steenari et al., 2003) it does appear that sleep quality as indexed by sleep efficiency has been associated with working memory capacity (Xie et al., 2019) and working memory accuracy (Miyata et al., 2013). Unfortunately, these findings are mixed and not always observed in the literature. While these few studies seem promising, further research is needed to better understand how, and under what circumstances, working memory is affected by sleep quality (including possible effects selective to the working memory paradigm, as well as task characteristics).

2.5 Impact of Sleep Quality on Memory Performance & tDCS Effects

To assess the impact of sleep quality on memory performance and the effect of tDCS on memory performance, we used two estimates of sleep quality obtained from the wrist-worn accelerometer (namely, sleep efficiency and sleep fragmentation, described previously). For these analyses, we conducted a linear mixed model identical to model 1.b., using the two indices of sleep quality (i.e., sleep fragmentation and sleep efficiency) as a covariate in two separate models (repeated once for episodic and once for working memory accuracy as dependent measures), with interaction terms between that and age group, stimulation, time of day as well as stimulus difficulty and format.

The Modulatory Effects of Sleep Quality on Task-based Factors in Episodic Memory

Sleep Fragmentation Index (SFI)

When assessing the relationship between SFI and episodic memory collapsing across all factors via a correlation analysis, there appears to be a strong negative relationship between SFI and episodic recollection accuracy, such that lower sleep fragmentation (i.e., better sleep) was associated with higher recollection scores when collapsing across all factors (Rs = -0.19, p =0.000). This relationship holds true for both older and younger adults, though the association was weaker in younger adults (Rs = -0.09, p =0.006) compared to older adults (Rs = -0.25, p =0.000).

When adjusting model 1.b (dlPFC participants only) for sleep fragmentation (SFI) with episodic recollection as the dependent measure, the outcomes are consistent with the original model described in Chapter 1. These included the same main effects of age group and difficulty, as well as the significant two-way age x format interaction and two-way difficulty x format interaction. However, a main effect of SFI (F(1, 137.36) = 5.10, p = 0.025, 95% CI = [-0.753, -0.057]) indicates sleep quality as indexed by SFI significantly modulates episodic memory. Additionally, there is a two-way interaction between sleep fragmentation and stimulus format (F(1, 912.07) = 7.55, p = 0.006, 95% CI = [0.055, 0.303]), with performance for picture stimuli being less impacted overall by poor sleep fragmentation compared to words stimuli, collapsing across all other factors. However, this effect is modulated significantly by age as indicated by a three-way interaction between sleep fragmentation, age and format (F(1, 912.07) = 5.47, p = 0.019, 95% CI = [-0.276, -0.028]). Indeed, when parsing by age group and format, we observe stark differences in the way pictures and words are affected by sleep quality within the two age groups. In older adults the effect of poor sleep extended similarly to both stimulus formats, with both pictures (Rs = -0.26, p =0.000) and words (Rs = -0.26, p =0.000) being negatively impacted among poor sleepers to similar extents. In younger adults, however, this effect is characterized by performance for pictures being only mildly affected by high rates of SFI (i.e., poor sleep) (Spearman Rank Correlation, Rs = 0.07, p

=0.19). By contrast, episodic performance for words is significantly impacted in poor young adult sleepers (Rs = -0.13, p =0.008) (see Figure 7).

Sleep Efficiency (SE)

When assessing the relationship between SE and episodic memory collapsing across all factors via a correlation analysis, there appears to be a strong positive relationship between SE and episodic recollection accuracy. Higher sleep efficiency (i.e., better sleep) was associated with higher recollection scores when collapsing across all factors (Rs = 0.15, p =0.000). The sleep-memory relationship was significant for older and marginally for younger adults, with the association being considerably weaker in younger adults (Rs = 0.07, p =0.051) compared to older adults (Rs = 0.25, p =0.000).

When adjusting model 1.b. for sleep efficiency (with dlPFC participants only), there is only a trending main effect of sleep efficiency itself, (F(1, 137.08) = 3.67, p =0.057, 95% CI = [-0.0002, 0.787]) indicating that sleep efficiency is positively associated with episodic memory. The strength of this association is weaker than the negative association between episodic recollection and sleep fragmentation (described above). Interestingly, while the SE-episodic memory association (collapsing across all factors) does yield a significant Spearman Rank correlation when including both age groups (Rs= 0.14, p =0.000), this relationship is primarily driven by the older adults (Rs= 0.25, p = 0.000), given the association is virtually absent in younger adults (Rs= -0.02, p = 0.495). The weakness of the sleep-memory association (as indexed by SE) in younger adults indicates that sleep efficiency is less predictive of episodic memory performance in younger adults compared to older adults.

Compared to the original model 1.b, main effects of age and format survive the model adjustment for SE, however the effect of difficulty (p = 0.2) and the difficulty x format interaction (p = 0.9) observed in the original model 1.b do not. Similarly, the age x format interaction is now only marginal (p = 0.070) along with a now marginal stimulation x age x format interaction (p = 0.056). In addition to these differences, we observe two sleep quality effects also observed in the model adjusted or sleep fragmentation (described above), including a two-way sleep efficiency x format interaction (F(1, 926.08) = 5.50, p = 0.019, 95% CI = [-0.295, -0.030]) as well as a three-way sleep efficiency x age x format interaction (F(1, 926.08) = 5.96, p = 0.014, 95% CI = [0.037, 0.302]).

Again, we observe an age-related difference in the way younger and older adults are affected by sleep efficiency. In older adults, episodic memory performance is positively correlated with greater sleep efficiency for both words (Rs = 0.22, p =0.000) and pictures (Rs = 0.28, p =0.000) while in younger adults, episodic memory performance for picture stimuli (Rs = -011, p =0.051) does not benefit from higher sleep efficiency and may have a marginal negative relationship. For words, the trend was positive, but not significant (Rs = 0.05, p = 0.3) (see Figure 7).

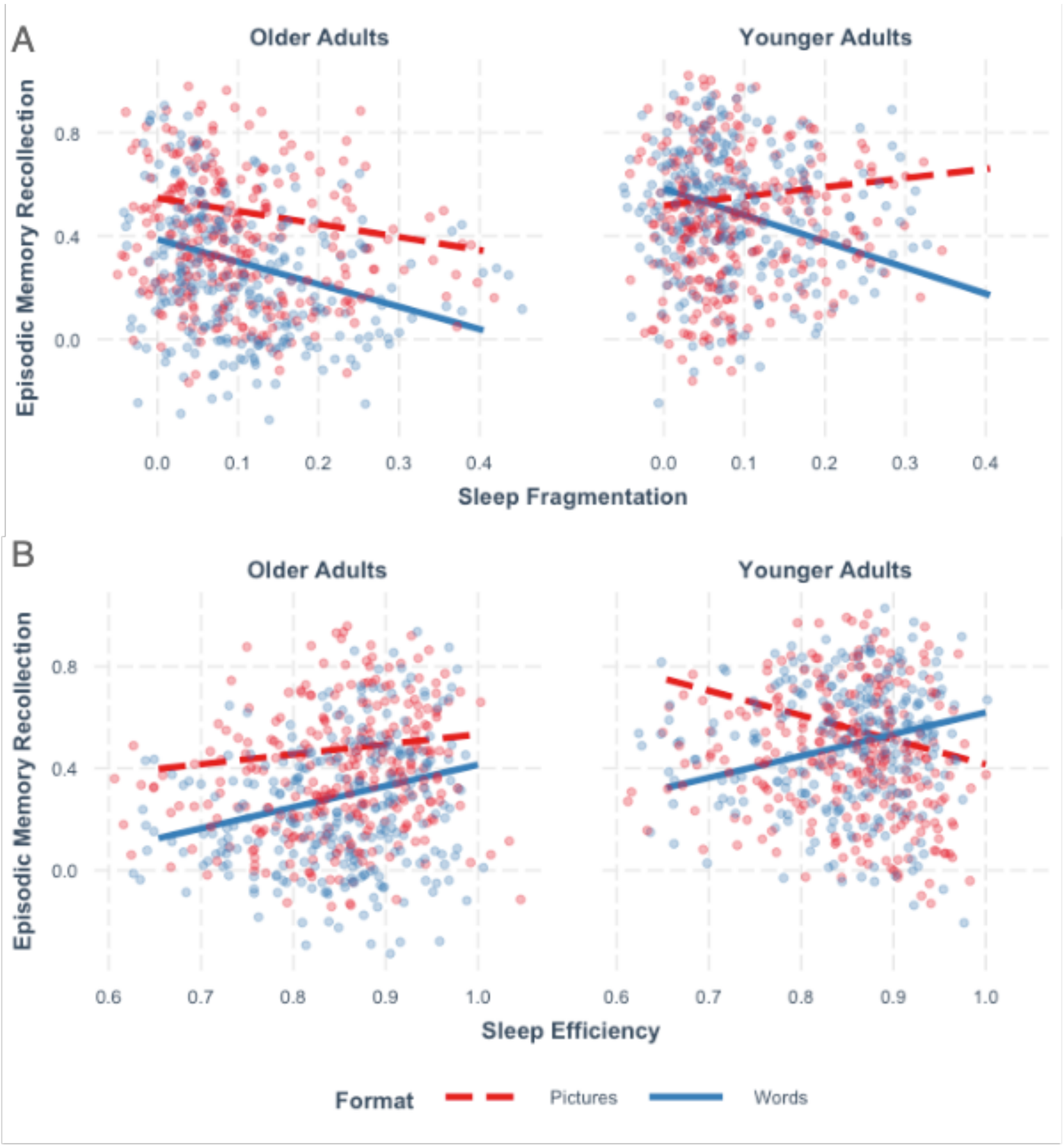

Figure 8. Episodic performance as a function of format and sleep quality. Episodic memory performance for older and younger adults as a function of word and picture stimuli, when adjusted for SFI (A) and SE (B). Note, lower SFI = better sleep, higher SE = better sleep

The Effect of Sleep Quality on the Impact of tDCS Effects of Episodic Memory Performance

In addition to those effects described previously, adjusting model 1.b for SE also yields a two-way stimulation x format interaction not previously observed in the original model (F(1, 926.08) = 10.17, *p* = 0.001, 95% CI = [0.076, 0.303]). Indeed, when adjusted for sleep efficiency, the significant two-way interaction underscores that pictures benefit from more from active stimulation compared to sham, whereas this pattern is less pronounced for words stimuli, collapsing across other factors (see Figure 9). This effect was trending in the same direction in the model adjusted for SFI, though not statistically significant (*p* = 0.15)

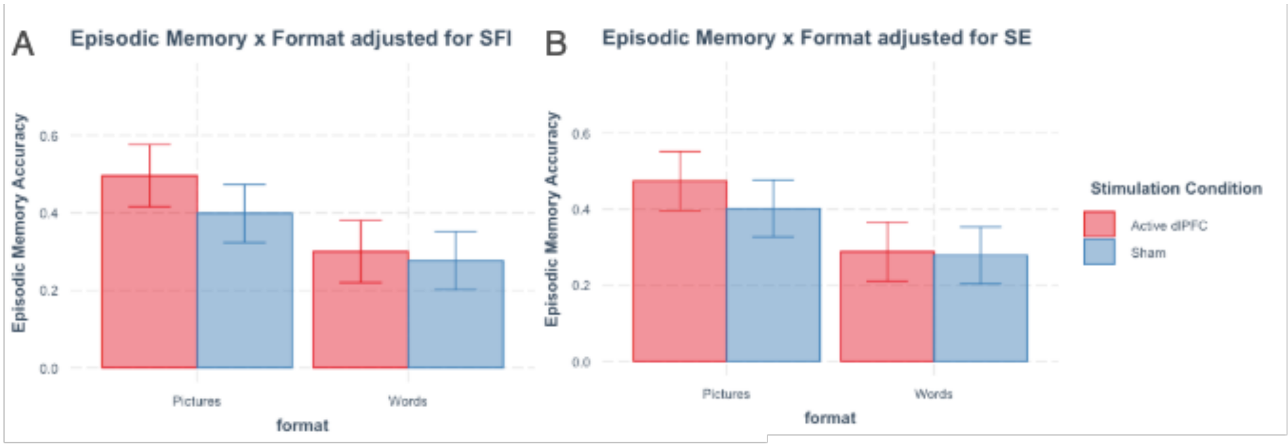

Figure 9. The effect of stimulation on episodic memory as a function of stimulation, adjusted for sleep quality. Episodic memory accuracy adjusted for SFI (A) and SE (B) as a function of stimulation, parsed by stimulus format (pictures vs words).

Additionally, for both model 1.b adjusted for SFI and model 1.b adjusted for SE, there is a three-way interaction between sleep quality, stimulation and format. This was the case for both SFI (F(1, 912.08) = 8.11, *p* = 0.004, 95% CI = [0.061, 0.310]), as well as SE (F(1, 926.08) = 9.74, *p* = 0.001, 95% CI = [-0.349, -0.084]). These three-way interactions were consistent with the two-way interaction described above, pointing to a stimulation benefit for pictures, less so for words when collapsing across other factors. When juxtaposed with sleep quality (Figure 10), we can see that active stimulation reduces the impairment of poor sleep quality on episodic performance for pictures. The story for words is less clear cut, with active stimulation not providing the same benefit to poor sleepers compared to that observed for picture stimuli. The reason for this is unclear, and likely requires further data collection.

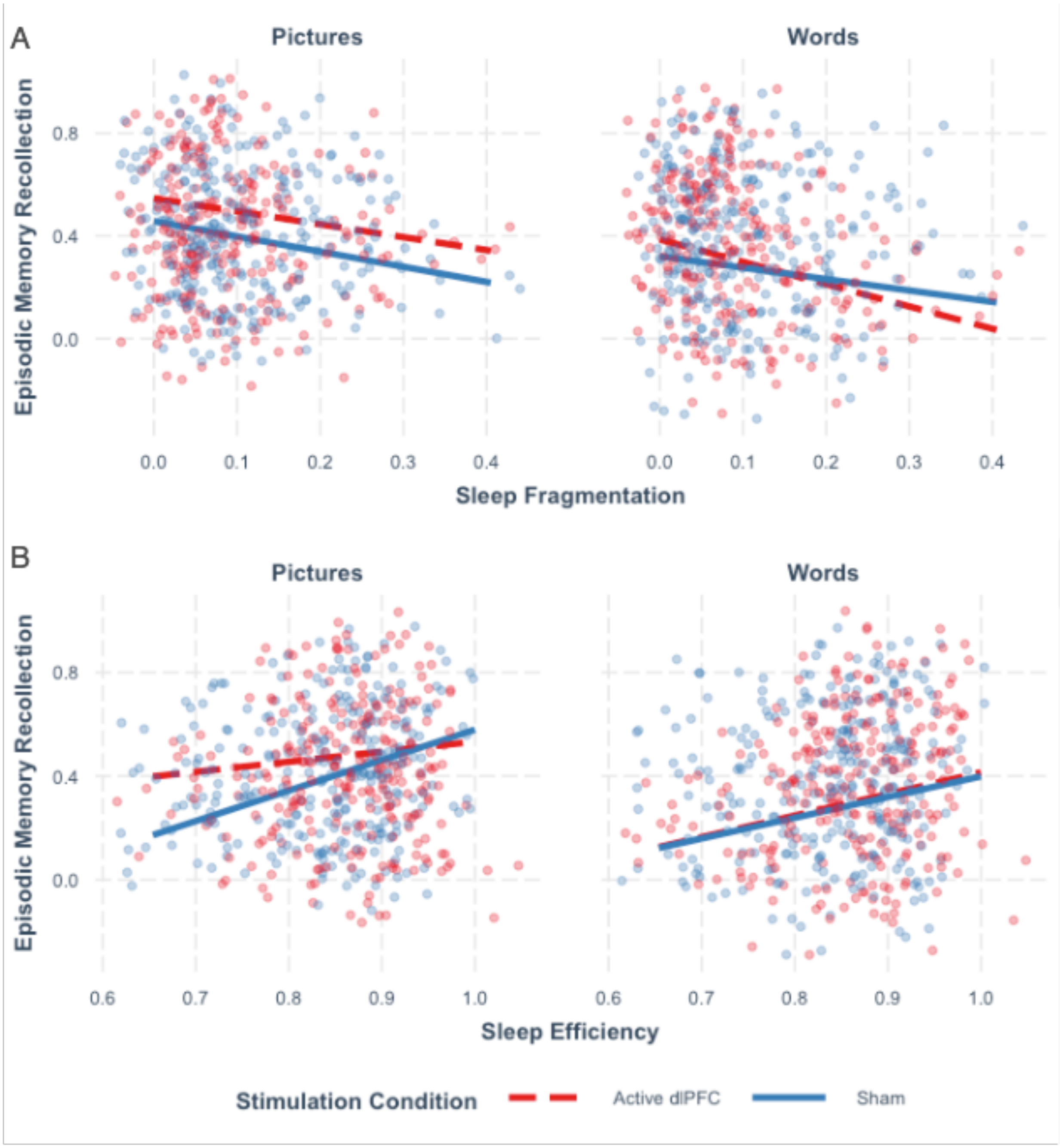

Figure 10. The effect of stimulation on episodic memory as a function of format and sleep quality. The effect stimulation (active dlPFC stimulation) on episodic memory accuracy as a function of sleep fragmentation (A) and sleep efficiency (B). Note that high SFI = worse sleep, high SE = better sleep.

2.6 Impact of Sleep Quality on Working Memory Performance

Sleep Fragmentation Index (SFI)

When assessing the relationship between SFI and working memory collapsing across all factors via a correlation analysis, the relationship is a lot less clear, in that there is little association between sleep quality and working memory performance (Rs = 0.043, p =0.11), and if anything, the relationship is opposite to what we might expect.

Re-running the same model with working memory accuracy as the dependent measure, model 1.b adjusted for SFI yields the same main effects for session order, difficulty and format, as well as the same stimulation condition x age x difficulty interaction as that observed in the original model 1.b. However, there was no main effect of sleep fragmentation (p > 0.7) or interactions between sleep fragmentation and other factors in the model (all p's > 0.1), suggesting adjusting our model for sleep fragmentation yielded no significant impact on to the variables in model 1.b.

Sleep Efficiency (SE)

When assessing the relationship between SE and working memory collapsing across all factors via a correlation analysis, the outcome is similar to what was observed for SFI, in that the association between sleep quality and working memory performance is weak (Rs = 0.02, p =0.3). Again, the observed relationship is opposite to what we might expect.

Adjusting model 1.b. for sleep efficiency in working memory yields a similar pattern, with significant main effects for session order and difficulty, yet the main effect of format as well as the stimulation condition x age x difficulty observed in the original model do not survive. No other main effects or interaction effects were observed (all *p*'s > 0.1), suggesting sleep efficiency yielded no significant impact on this model in working memory. These results do not change when including just younger or just older adults.

2.7 Discussion

Among our analyses investigating the effect of age-related circadian preference in performance, we only find a significant effect in a four-way interaction between age, difficulty, format and time of day (reported in Chapter 1) from the original model 1b, where pictures benefit from a morning testing time in older adults. Given older adults showed a performance benefit overall for pictures compared to words, it is perhaps not surprising that picture stimuli benefit most during a given group's preferred time of day. This finding corresponds with the existing synchrony effect literature that posits a performance advantage during one's optimal time of day (which would be the morning in older adults). However, we find little evidence that individual circadian preference - whether measured via self-reported MEQ or actigraphy-derived midsleep - impacted performance in episodic or working memory. Nor did we find evidence that circadian preference influences the effects of the effects of tDCS.

In contrast to the relatively weak evidence of effects related to circadian preference, we did strong evidence for the effect of sleep quality on performance. We did observe some modulatory effects in how accounting for sleep quality can differentially impact episodic memory performance for words and pictures, which was also selective for age.

In older adults, poor sleepers, as indexed by both measures of sleep quality, demonstrated impaired episodic memory performance relative to good sleepers, regardless of stimulus format, with both words and pictures being similarly impacted by poor sleep. However, the story is more complicated in younger adults, where poor sleepers were not impaired equally on both pictures and word trials. Specifically, whereas episodic performance for pictures is not predicted by poor sleep quality, memory for words was impaired among poor young adult sleepers. It is not immediately clear why this might be the case, as previous findings in this area (e.g., Hokett et al., 2021) did not observe sleep-memory associations were selective based on stimulus format, or why this might vary as a function of age.

One reason or this may be due to the differentiated judgment at encoding for pictures and words at encoding; given participants were tasked with a semantic elaboration task for words (compared to a perceptual judgment for pictures), that memory for words that relied on a more taxing semantic judgment may be more taxed by poor sleep compared to pictures, even if younger adults performed better on words overall when sleep quality is not taken into account. However, given the relative novelty of this area, it is difficult to draw strong conclusions as to what is driving this. Along these same lines, it is unclear as to why sleep quality was not predictive of working memory performance in the same way it was for episodic memory, given there are previously reported associations between poor sleep quality and working memory performance overall (Rana et al., 2018; Xie et al., 2019).

When it comes to the effect of stimulation, given the lack of prior work in both episodic and working memory utilizing sleep quality to characterize performance, we were agnostic as to the extent or direction of the outcomes when adjusting our original model for sleep quality. However, when looking at model 1.b adjusted for sleep efficiency (SE), the most notable effects were a significant two-way stimulation x format interaction whereby pictures benefit from active stimulation compared to sham, whereas the same trend is not seen for words. While a similar trend was observed for the model adjusted for SFI, this effect was not statistically significant ($p = 0.13$).

Additionally, in the three-way significant interaction between stimulation, format and sleep quality it appears words and pictures behave differently when plotted against sleep quality. Specifically, for models adjusted for either SE or SFI, the impairment associated with memory for pictures in poor sleepers was reduced under active stimulation, but not sham (Figure 10). Interestingly, this was not as clear-cut for words. This hints at the possibility that episodic memory for words might be more strongly impaired by poor sleep quality than pictures, in a way that is not aided by active stimulation or easily ascertained by the sleep quality indices used in these analyses. In this case, it is important to collect additional data to better understand the robustness of this format-specific effect, particularly given there are no existing studies to date that have investigated the effect of tDCS on cognitive or behavioral outcomes as modulated by sleep quality. However, there is some recent evidence showing tDCS has the capacity to benefit sleep quality among patient populations. For example, repeated sessions of anodal tDCS to left dlPFC has shown to improve sleep quality in depressed populations with insomnia as indexed by the total score on the PSQI (Buysse et al., 1989) (Zhou et al., 2020), and has also shown to improved sleep efficiency (also indexed by the PSQI) in migraine patients following 10 sessions of tDCS to Cz (Kosari et al., 2019). While this work did not administer cognitive tasks, it is encouraging to note that tDCS and sleep quality might interact in meaningful ways.

In terms of thinking of the specific sleep quality indices used in this analysis, it is not completely clear why there may be slightly different outcomes between the effects found in the models adjusted for SFI and SE, seeing as both measures are generally considered robust measures of sleep quality (Shrivastava et al., 2014). However, one key difference is that while sleep efficiency gives an overall sense of how well the patient slept (by computing the amount of time in bed actually spent asleep), but it does not distinguish the frequent, brief episodes of wakefulness that is captured by sleep fragmentation (Shrivastava et al., 2014). If it is the case that sleep fragmentation may be a superior method for detecting poor sleep specifically, then it is intuitive that SFI plays a stronger modulatory role in episodic memory compared to SE, the main effect of which is only trending in the SE-adjusted model (see table in appendix). Additionally, in thinking of how SFI may be important for tDCS effects, the unique capacity of SFI to detect poor sleep may highlight the capacity of tDCS to benefit "when needed".

Chapter 3. Blinding Integrity & Sensation Effects in tDCS : An Argument for Important Design Considerations

3.1 Introduction: Blinding & Shamming in tDCS

The tDCS literature, regardless of the subfield, target site and overarching treatment or experimental goal, is fraught with inconsistencies in its effects. A likely source of inconsistent findings is unaccounted-for variation in outcome expectations on behalf of tDCS participants. Previous reports (e.g., Bikson et al., 2018) of participants experiencing physical sensations during stimulation have led to the speculation that expectations about the intervention's effects may be driving unexpected variation in tDCS outcomes. These expectations may be exacerbated by poor blinding procedures and experimental design choices by experimenters. Blinding is a cornerstone of randomized controlled trials but especially challenging to obtain for non-pharmacological interventions (Fonteneau et al., 2019). In tDCS, to achieve successful subject-level blinding, the sham method most used is based on mimicking typical initial sensations of active tDCS underneath the electrode sites (e.g., tingling, itching). The most common procedures use a ramp-up of current, brief real stimulation, followed by ramp-down or alternatively a ramp-up/down, followed by a similar ramp up/down at the end of the session. For robust experimenter-level (double) blinding, treatment assignment is concealed by entering numeric codes assigned to sham or active. Yet, the vast majority of tDCS studies in the psychological sciences have made use of a single-blind A/B toggle, which is flipped by the experimenter immediately prior to turning on the stimulator. In these cases, experimenters may be unconsciously anticipating the treatment assignment (active stimulation vs sham) during tDCS montage setup, potentially undermining the blinding of the experiment for the participant.

This is problematic, given participant beliefs about the expected outcome of the treatment can influence whether they respond to that treatment, and to what degree they respond (Evers et al., 2018). This effect is well-documented in both clinical practice and placebo-controlled experimental settings with pharmacological interventions. In fact, placebo responses have been observed in other non-invasive brain stimulation trials (e.g., TMS) (Razza et al., 2018) and non-blinded experiments have been known to overestimate the effects of subjective and objective outcomes (Wood et al., 2008).

tDCS research is no exception. Even when using standard shamming procedures, expectation effects alone may possess the ability to produce outcomes that may be mistaken for "true" effects of the stimulation but may in fact be unrelated to the effects of the actual intervention. These expectation effects may occur even when participant is aware they are in the placebo condition (Fontaine et al., 2016; Ray et al., 2019). In fact, several studies suggest standard, frequently used shamming procedures are not always effective at masking active from sham tDCS (Fonteneau et al., 2019; Horvath et al., 2014; Turi et al., 2019). For example, in a 2014 randomized, double-blind repeated-measures clinical trial for major depression including 120 participants, 87% of subjects randomized to receive either active or sham tDCS were able to correctly guess whether they received active tDCS and 37% correctly guessed when they received sham tDCS. The inadequacy of standard shamming procedures appears to be especially true for the most commonly used level of stimulation (2 mA), particularly in light of active stimulation inducing known physical sensations including itching, burning and tingling for the duration of the session (compared to sham) (Bikson et al., 2016; Ray et al., 2019). Increasing the number of repeated sessions appears to exasperate issues with common shamming procedures, with participants becoming more likely to correctly guess their stimulation condition in later experimental sessions compared to early experimental sessions (Brunoni et al., 2014). Similar work was carried out by O'Connell et al., (2012) who found participants were able to correctly judge the stimulation condition at rates greater than chance after completing both the first session and as well as after the second (with higher accuracy after the second session), in a within-subjects, double-blinded procedure. These findings were exacerbated by higher rates of skin redness on the scalp at the reference electrode site (visual to the naked eye), which was worse following active stimulation relative to sham, and has been shown to increase the chances of correct guessing particularly in experimenters (Ezquerro et al., 2017; Palm et al., 2013).

As a result, while the double-blind method likely is beneficial in bolstering blinding integrity, this was not always adequate to sufficiently mask correct guessing – particularly in protocols with repeated sessions (Brunoni et al., 2014). Together, it appears that even double-blinding may be inadequate to achieve "true" double-blind (and avoid expectation effects) in a within-subject design (O'Connell et al., 2012), highlighting that protocol design parameters are interdependent and must be considered holistically to achieve the best possible blinding and shamming strategy for any given protocol. Others with similar findings have also issued provisos advocating for double-blinding procedures coupled with between-subjects (parallel) designs in tDCS protocols, even when utilizing lower current densities (Neri et al., 2020; Turi et al., 2019).

Furthermore, given the heterogeneity of tDCS effects across stimulation parameters and tasks (Galli et al, 2019), these kinds of patterns behoove researchers in the tDCS community to think carefully about the specific parameters of experimental design in tDCS protocols, including the blinding and shamming procedures that are often underreported, underestimated and overlooked, yet necessary to observe reliable and replicable effects of the stimulation.

To examine the extent of these effects within the context of the current (double blind, parallel) study, sensations and expectation effects were examined and discussed within the context of previous tDCS work from the lab that utilized single-blind methods (Wong, et al., 2018).

3.2 Sensation Effects: Prior Work

As discussed, an important consideration in interpreting tDCS effects is the potential for sensation and/or expectation effects on behalf of the participants when undertaking the cognitive task following stimulation. In our previously published work using single-blind between-subject designs (i.e., Wong et al., 2018, Experiments 1-2), we investigated this by asking participants directly if they believed they had been assigned to the active or sham stimulation conditions upon completing the study. Here, subjects in the stimulation condition were more likely to self-identify as having been in the stimulation condition (79%) than were participants in the sham condition (50%), $\chi2(1, N = 48) = 4.46, p = .03$. A similar pattern was found in Experiment 2 (rates = 83% and 42%, $\chi2(1, N = 48) = 8.89, p = .002$).

In Experiments 3-4, participants were not asked directly whether they self-identified in either the active or sham conditions, but instead where asked if they thought "electricity was being delivered to [their] brain," prior to selecting one of four options that best described their sensations; these included whether they i) felt stimulation for the full duration of the tDCS experience, ii) felt stimulation initially but the sensation attenuated over time, iii) felt stimulation initially but then the sensation ceased, or iv) did not feel any stimulation at all. The goal of these questions was to determine if there were any differences between the stimulation and sham experiences that might lead to differences in expectations and, ultimately, task performance. In response to the questionnaire in Experiment 3, there were no differences between stimulation to left dlPFC, stimulation to right dlPFC, and sham participants in their response to "do you think electricity was being delivered to your brain?" question, ($\chi2 = 0.55$, $p > .76$), with most participants believing electricity was being delivered to their brains ("yes", 86%). When asked to describe their sensations during stimulation, however, participants responded differently depending on the tDCS condition they were assigned, $\chi2 = 24.9$, $p < .001$. More specifically, 32% of the left stimulation group and 43% of the right stimulation group reported feeling stimulation throughout the whole 20 minutes of the procedure; however, only 5% of the sham stimulation group reported this. In contrast, 43% of the sham stimulation group reported feeling strong stimulation at the start, but then wondered if stimulation had been turned off for the remaining 20 minutes of the experiment, whereas only 15% of the left stimulation group and 8% of the right stimulation group reported this. This finding is consistent with those responses from Experiment 2 and 3, which suggested that, when asked, participants are better than chance at indicating whether they received real or sham stimulation – at least, in a single-blind, between-subjects protocol as used in Wong et al., (2018).

The questionnaire in Experiment 4 showed that the majority of participants in both the stimulation conditions (92%) and sham conditions (77%) indicated that they believed electricity had been delivered to their brain, but significantly more stimulation participants held this belief, $\chi2$ ($n = 120$) $= 5.07$, $p = .02$. Moreover, when asked about their sensations, participants between the stimulation and sham conditions responded differently, $\chi 2$ $(n = 120) = 39.14$, $p < .001$ (see Table 4). Participants in the stimulation condition were most likely to report constant stimulation for the full 20 minutes (58%), whereas those in the sham condition were most likely to report feeling stimulation only at the start but then ceased (45%). These findings align with the patterns observed in Experiments 1, 2 and 3, as participants were able to tell a difference between the two conditions on average, though the sham condition was still quite effective.

	I felt stimulation through the whole 20 minutes	I felt strong timulation at th start, but then I felt weaker stimulation luring the rest o the time	I felt strong stimulation at the start, but then I wondered if the stimulation had been turned off	I didn't feel any stimulation, and I wondered if I received any stimulation at all
Active - Left	33%	43%	15%	10%
Active - Right	43%	40%	8%	10%
Sham	5%	48%	43%	5%

Table 4. Participant reported tDCS sensations: Exp. 3 from Wong, et al., (2018).

Percentage of participants reporting different sensations in the two active stimulation conditions (left and right dlPFC) and sham from Wong, et al., (2018) Experiment 3. N=120

	I felt stimulation through the whole 20 minutes	I felt strong stimulation at the start, but then I felt weaker stimulation during the rest of the time	I felt strong stimulation at the start, but then I wondered if the stimulation had been turned off	I didn't feel feel any stimulation, and I wondered if I received any stimulation at all
Active	58%	28%	3%	10%
Sham	13%	27%	45%	15%

Table 5. Participant reported tDCS sensations: Exp. 4 from Wong, et al., (2018).

Percentage of young adult participants reporting different sensations in the different stimulation conditions, from Wong, et al., (2018) Experiment 4. N=120

3.3 Sensation Effects: Current Study

As part of the current study, the same tDCS post-experiment questionnaire used in the previous experiments described above was used and was administered upon completion of the final tDCS session. Looking at the outcome of the initial question "Do you think electricity was being delivered to your brain?", the result replicates previous studies, with no differences between active stimulation and sham participants in their yes/no response to this question ($\chi2 = 0.23$, $p > .64$), with most participants reporting they had received stimulation to their brain across stimulation conditions (71.6%). However, upon examining the results to the 4-option sensation questionnaire inquiring the extent to which they felt sensations associated with tDCS (Table 6), there was a departure from what was observed in Wong et al., (2018). Whereas previously there was a significant difference in responses between sham and active participants in the (see

Table 4), the current study revealed no significant differences in responses between the two stimulation groups, (χ2 = 0.68, *p* > .87). This outcome does not change when parsing by age group, or by parietal vs dlPFC stimulation location, indicating that the sensation reports do not differ as a function of age or by active electrode location.

In addition to reporting the extent of sensations experienced during tDCS, the post-stimulation questionnaire in the current study also included an additional expectation-related question to probe the *type* of reported sensations (e.g., itching, tingling, etc.) after each of the two stimulation sessions (Table 7). Here, participants could select multiple options to report experienced sensations during the tDCS session. Results indicated the type of sensations did not differ as a product of receiving stimulation or sham when collapsed across age groups for session 1 (χ2 = 1.58, *p* > .89) or session 2 (χ2 = 1.27, *p* > .94) , or when parsed by age group (all *p*'s > 0.4).

These results have important implications for the current study, highlighting that the double-blinding procedure used was likely more effective in masking participants from their tDCS treatment assignment relative to the single-blind procedure used in previous studies described in Wong, et al., (2018).

	I felt stimulation through the whole 20 minutes	I felt strong stimulation at the start, but then I felt weaker stimulation during the rest of the time	I felt strong stimulation at the start, but then I wondered if the stimulation had been turned off	I didn't feel any stimulation, and I wondered if I received any stimulation at all
YA Active (72)	6.9%	68%	19.4%	5.5%
OA Active (39)	53.8%	38.5%	0%	7.6%
YA Sham (38)	2.6%	84.2%	10.5%	2.6%
OA Sham (41)	46.3%	36.6%	7.3%	9.7%

Table 6. Distribution of reported extent of tDCS sensations during tDCS ("select best match")

	burning	discomfort	itching	tingling/ tickling	no noticeable sensations	other
Session 1						
YA Active	51.4%	37.8%	62.2%	58.1%	6.8%	2.7%
OA Active	37.5%	12.5%	47.5%	62.5%	7.5%	1.0%
YA Sham	70.7%	34.1%	73.2%	65.9%	4.9%	4.9%
OA Sham	48.8%	22.0%	58.5%	78.0%	4.9%	4.9%
Session 2						
YA Active	45.9%	45.9%	64.9%	73.0%	6.8%	1.4%
OA Active	55.0%	12.5%	52.5%	72.5%	2.5%	7.5%
YA Sham	56.4%	20.5%	66.7%	64.1%	5.1%	2.6%
OA Sham	52.1%	31.7%	51.2%	87.8%	4.9%	4.9%

Table 7. Distribution of reported type of tDCS sensations during tDCS ("select all that apply")

3.4 The Impact of Sensation Effects on Performance

As discussed earlier, one potentially striking outcome of sensation effects is the possibility that the expected outcome as perceived by participants may result in experimental outcomes that fall in line with expected "true" behavioral effects of tDCS. To better understand the potential power of expectation effects in tDCS, one group in particular sought to investigate the impact of expectation effects prospectively by incorporating them into the experimental intervention itself. Ray et al., (2019) included 74 adults in a single-session design investigating the effects of tDCS on the amount of food craving and eating. Active tDCS involved 2 mA of current for 20 minutes, and sham included a standard ramp-up/down procedure of 2 mA of current during the first and the last minute of the 20-minute session. After being informed of the "known effects" of tDCS to suppress food cravings, half the participants were told they would be receiving active tDCS, and the other being told they would receive "fake tDCS", with approximately half the subjects in each group being randomized to receive actual active or sham stimulation. The authors observed that participants who were told they would be receiving real tDCS craved and ate less food compared to participants told they were receiving sham (both $p < 0.01$), regardless of the tDCS condition administered. However, there was no main effect of stimulation itself.

Along similar lines, a related study argued for the potential for expectation effects and "true" tDCS to interact. Rabipour et al., (2018) assessed expectations outcomes of anodal tDCS in 88 healthy young adults on three occasions: i) at baseline; ii) after reading information implying either high or low effectiveness of stimulation (expectation priming); and iii) after a single-session of sham-controlled tDCS during an n-back working memory task. While this did not result in a main effect of expectation priming (or stimulation condition), there was a stimulation x expectation interaction effect whereby participants who received low expectation priming and active tDCS had significantly fewer correct trials compared to their counterparts who received high expectation priming and active tDCS.

Considering this possibility, we decided to investigate this in our own data, by examining memory performance differences between those who responded “yes” and “no” to the “electricity to your brain?” question from the post-experiment tDCS questionnaire. To remove confounding variability around low-confidence answers to the “yes”/”no” questionnaire, subjects who indicated a low confidence rating in response to this question (i.e., responding with a “guessing” or “low” level of confidence) were excluded from the analysis. To investigate the impact of expectations on performance, we ran a linear mixed model with episodic memory as the dependent variable and, stimulation condition and expectation as predictor variables, while correcting for session order. As with our other models, significance of fixed-effects was assessed with a type III ANOVA using Kenward–Roger approximations of degrees of freedom.

While there was no main effect for the factor of “expectation” (as defined by the yes/no responses to the “electricity to the brain” question), or stimulation condition, there was a significant interaction between expectation and stimulation condition ($F(1, 140.64) = 5.47$, $p = 0.020$, 95% CI = [-0.075, -0.006]), suggesting that people in the active condition who believed they got electricity to the brain performing better than those active participants who did not, while participants in the sham condition who did not think they got electricity to the brain performed better than those who did. When looking specifically at only those participants in the active stimulation condition (collapsed across age groups), those who responded “yes” (0.44) to question significantly outperformed those who answered “no” (0.34), (t(622) = 4.12, *p* = 0.00, *d* = 0.37).

These effects were not as strong in the working memory data, which yielded a nonsignificant difference in the linear mixed effects model described previously (all *p*’s > 0.2). However, a difference remains for young adult participants in the active stimulation condition (t(566) = 2.38, *p* = 0.017, *d* = 0.23), with those responding “yes” (0.67) performing better than those who said “no” (0.61). Running the same analysis for the data from Experiment 4 in Wong et al., (2018) did not yield significant results, but was trending in the same direction for measures of episodic memory.

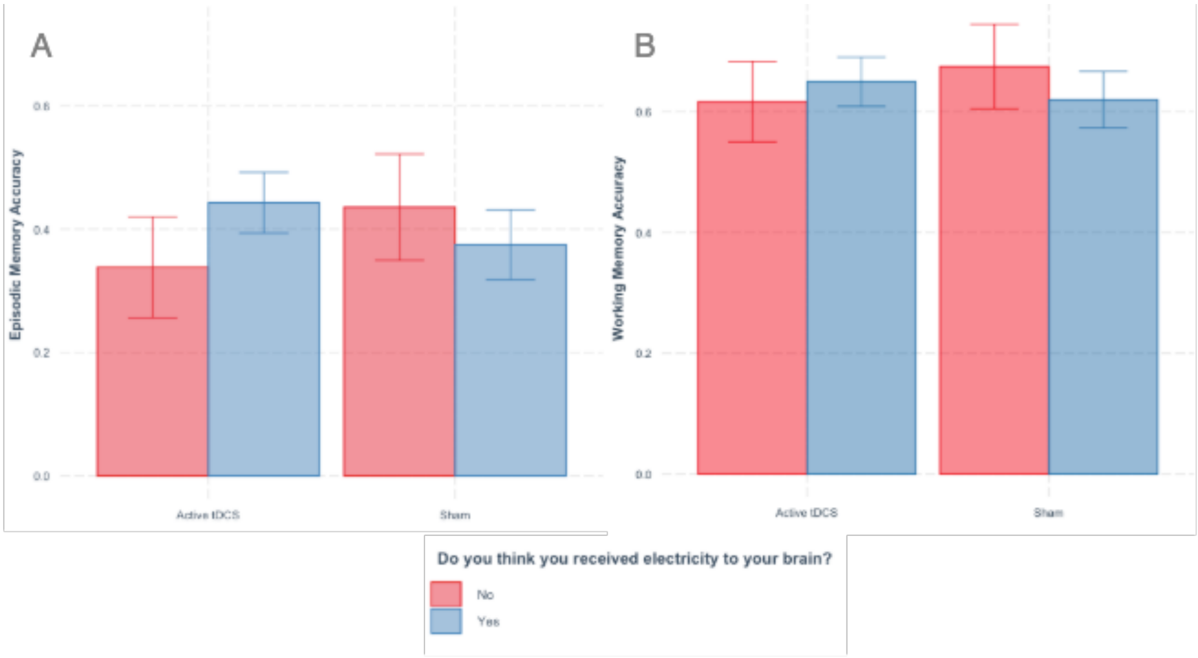

Figure 11. The effect of tDCS expectations on memory performance. Episodic memory (A) and working memory (B) accuracy performance as parsed by tDCS condition in response to the question “During tDCS , do you think you received electricity to your brain?”

Finally, we also compared performance for active stimulation vs sham groups, restricted to those participants who responded “yes” to the “electricity to your brain” question, excluding those who responded with low confidence in their answer (i.e., “low” or “guessing”). The motivation behind this analysis was to restrict performance only for those who most likely *believed* they were receiving real stimulation, removing some of the variability in expectation that may confound or obscure potentially true effects of stimulation. Collapsing across all task-factors and age groups, a two-sample t-test revealed a significant difference in episodic performance between those participants in sham (0.37) and active stimulation (0.44), (t(810) = 3.58, p = 0.0003, d = 0.25) among participants who responded “yes” to the “electricity to your brain” question with moderate-to-high degrees of confidence. While this same analysis was not significant for working memory, it was trending in the same direction (p = 0.14).

Together, these findings, while not necessarily conclusive, add weight to the importance of examining expectations and sensations in tDCS research even in tightly controlled double-blinded studies, particularly given the potential for the variance associated with expectation to be equivalent (or supersede) the effect of stimulation itself.

3.5 Discussion

The purpose behind this chapter was to shed light on some important variables often overlooked in the tDCS literature, namely crucial shamming and blinding procedures required to mask possible sensation effects and required to minimize expectation effects, and best experimental design choices to minimize expectations and maintain blinding integrity.

Using our own datasets, we were able to corroborate arguments put forth in the literature advocating for parallel, double-blinded protocols by demonstrating the superiority of these experimental design choices. Wherein the experiments detailed in Wong, et al (2018) were all single-blind sham-controlled protocols, significant differences emerged in participants' reporting in sensations between those who received active stimulation and sham. By contrast, using a double-blind procedure the current study failed to yield differences between stimulation groups. While this may be only one comparison, it does exemplify the potentially insidious nature of how experienced sensations of stimulation may impact (and possibly compromise) the integrity of the experiment, yielding questionable tDCS effects. This concern is highlighted when comparing memory performance between groups selective on whether they believed they received stimulation, showing that those who were convinced of receiving active stimulation outperformed those who were not. This is not a novel observation in the broad cognitive literature. For example, there is evidence of participants showing more resistance to the effects of misleading information in a misinformation task when given a fake "cognitive enhancing drug" as a placebo, (Clifasefi et al., 2007). In this case, it led researchers to speculate that placebo effects might drive more stringent monitoring processes (Parker et al., 2008).

Furthermore, we were able to corroborate some of these patterns in tDCS in the current study; the finding of an interaction between tDCS and expectation coupled with a performance boost from active tDCS (but not sham) among participants who believed they received real tDCS, brings new questions about the impact of perceived sensations on tDCS outcomes. Of course, there is still a long road ahead in determining the extent and reliability of these effects; for example, while the tDCS x expectation interaction effect we reported was also observed in Rabipour et al., (2018), a follow-up study by the same authors was unable to replicate it (Rabipour et al., 2019). Coupled with the null result for this same analysis for data presented in Wong, et al., (2018), it is clear these kinds of analyses are not always reliable and warrant further research.

However, despite these mixed findings, thinking carefully about these questions could lead to real implications for the future of cognitive tDCS research, particularly when it comes to blinding integrity protocols. Unfortunately, however, these practices are far from ubiquitous within the tDCS community (Horvath et al., 2014). In a 2018 NIMH workshop report investigating the rigor and reproducibility in transcranial electrical stimulation (both tDCS and tACS) research, a review found that of the 206 articles included in the analysis, only 39% reported experimenter-level (double) blinding (Bikson et al., 2018). Additionally, despite strong recommendations throughout the tDCS community to record sensations and any adverse events that may occur, only 33% of the studies reviewed reported collection of these variables (Bikson et al., 2018). As of 2019, this was found to still hold true, whereby one of the more comprehensive meta-analyses investigating tDCS in episodic memory listed only 11 double-blinded studies out of 54 included in the analysis (Galli et al., 2019).

Collectively, it is likely the widespread inconsistencies in blinding and shamming procedures, underreporting of participant sensations, and dearth of double-blinded protocols has clearly contributed to compromises in the integrity of tDCS experiments and as a result, the observed outcomes. Importantly, the underreporting of participant sensations coupled with relatively small number double-blinded studies may have contributed to the high number of false positive outcomes, and low rates of successful replication. Together, this “muddying of the water” for potentially true effects of stimulation creates novel challenges for motivated investigators in a field that is already plagued by small sample sizes and a plethora of experimental design choices.

General Discussion

The present research investigated the impact of anodal tDCS to left dlPFC and left posterior parietal cortex on episodic memory recollection and working memory accuracy. Based on previous findings from the lab (Wong et al., 2018), we sought to better understand how time of day, or circadian preference, impacts the effect of anodal tDCS, and whether this differs as a function of age. To do this, we conducted a double-blind sham-controlled clinical trial with both younger and older adults participating in three testing sessions, including a baseline session (no tDCS or time of day constraints) and two tDCS sessions (one in the AM and one in the PM). To minimize any effects that can result from experiencing both active stimulation and sham, the factor of stimulation was kept between-subjects, such that participants were allocated to either active stimulation or sham for both tDCS sessions.

The first session involved a "baseline day", with participants undergoing each cognitive task without any tDCS or with any time-of-day testing restrictions. The purpose of this was to expose participants to the task protocol, carry out necessary questionnaires and confirm eligibility (e.g., collect MOCA scores, ensure they are able and willing to complete the cognitive tasks, etc.), as well as provide them with the wrist-worn actigraphy device which they were instructed to wear continuously for the duration of their enrollment. The second and third testing sessions involved very similar procedures with the added inclusion of anodal tDCS stimulation (or sham) after encoding but prior to retrieval (i.e., the episodic retrieval task followed by the working memory task), counterbalancing the order of AM and PM sessions.

In Chapter 1, we report the pre-registered analyses investigating the baseline task effects as well as the effect of tDCS on episodic and working memory accuracy. Here, when looking at both model 1.a (younger adults only, in replication of Experiment 4 in Wong et al., 2018) or model 1.b (including both younger and older adults with an age-factor in the model) we did not observe any main effects or interaction effects due to active stimulation compared to sham in episodic memory accuracy, with task-based effects similar to those observed in the baseline day. However, we did observe age-specific effects of active stimulation for working memory accuracy, with younger adults benefitting from anodal left dlPFC stimulation compared to sham for the difficult version of the task (3-back), but not for the easy version (2-back). By contrast, older adults did not benefit from stimulation for either difficulty version.

The driver behind the age-related disparity in tDCS-elicited boosts is not immediately apparent, though one may speculate on two potentially important considerations. First, the degree of frontal recruitment during the working memory task likely played a role. In other words, if anodal tDCS primarily benefits the region being stimulated, it is then contingent on robust functional recruitment of this region for the benefit to be observed in behavior (in this case, a boost in working memory performance). This is consistent with the notion that our tDCS-elicited boosts were observed only in the difficult version of the task, where frontal recruitment of dlPFC was most salient. Thus, perhaps our older adult sample did not exhibit sufficient functional left dlPFC recruitment to yield a benefit in task performance, resulting in a lack of observed tDCS effects for this group. This possibility is corroborated by previous work showing that, while functional recruitment of frontal regions in working memory is not strictly unilateral in standard adult samples, in younger adults this recruitment is often asymmetrical in nature, favoring left dlPFC. However, it seems that this asymmetry lessens with aging, as evidenced by more bilateral activation in older adults as correlated with working memory performance (e.g., Eyler et al., 2011; Reuter-Lorenz et al., 2000; Schulze et al., 2011). This lack of asymmetry might make specific targeting of left dlPFC less consistent in aged cohorts, leading to mixed results.

A second consideration concerns frontal structural changes that come with age that are not accounted for in many age comparisons in tDCS. A recent meta-analysis investigating the use of tDCS in N=532 healthy older adults to mitigate cognitive decline supports this view, in that diverse effect sizes seen across similar studies may largely be influenced by heterogeneity in age-related structural and functional changes across participants (Indahlastari et al., 2021). For example, given the PFC is the first to structurally decline with age (Nissim et al., 2017), when brain volume shrinks due to atrophy, the amount of cerebrospinal fluid (CSF) inside the brain cavity is increased, causing a higher ratio of CSF compared to brain (Mahdavi & Towhidkhah, 2018). If this is the case, then it could result in less current entering the brain in an older participant relative to a younger counterpart.

To account for these age-related compensatory shifts among older adults, tDCS applications in older adults may need to be tailored to each participant to offset increased inter-individual variability across aging samples (Indahlastari et al., 2021). This can then be combined with novel tDCS techniques, such as high-definition tDCS (HD-tDCS) that allows for more focused delivery of the current to the target site, and with better cortical penetration (Parlikar et al., 2021). Alternatively, exciting new co-registered techniques are emerging such as joint stimulation with EEG to add electrophysiological markers using EEG to stimulation protocols (e.g., Reinhart & Nguyen, 2019). While these novel techniques are still in their infancy, it shows promise for the capacity of tDCS (and other noninvasive brain stimulation techniques) to modulate cognitive performance in exciting new ways.

In Chapter 2, we discuss the impact of circadian preference and sleep quality, and whether these variables influence the effects of stimulation on our memory measures. One of the original objectives of this project was to better understand whether the time-of-day effect observed in Wong, et al., (2018) was due to tDCS boosting performance during one's nonoptimal time of day (which is considered the morning for younger adults, on average), and if so, whether this effect would extend to older adults (whose nonoptimal time of day is in the afternoon, on average).

We were unable to replicate the time of day finding reported in Wong et al., (2018) or show any benefit of using circadian preference (either using the MEQ or wrist-worn actigraphy) to modulate the effect of active stimulation. However, there does appear to be an effect of adjusting our model for sleep quality, both in episodic memory performance broadly as well as on the effects of stimulation on episodic memory. Namely, when model 1.b is adjusted for sleep quality (particularly sleep efficiency), active stimulation benefitted picture stimuli in a way that is not evident in word stimuli (Figure 9). Furthermore, when plotting this same effect as a function of sleep quality (Figure 10), it appears stimulation differentially boosts memory for pictures and words depending on the degree to which the participant exhibited poor sleep. Specifically, the impairment experienced by poor sleepers for picture memory is reduced under active tDCS, but not sham. When it comes to word stimuli within the context of sleep quality, the effects of stimulation are less clear cut, and likely require additional power to uncover more consistent patterns.

It is difficult to draw definitive conclusions on the underlying reasons for this format effect, in part due to the novelty of this result and lack of prior findings investigating format-selective differences among tDCS benefits. However, two possible interpretations for this observation come to mind; first, it is plausible that word stimuli are simply more heavily impacted by poor sleep quality relative to picture stimuli in a way that is not ameliorated by tDCS. The observation that younger adults show sleep-memory impairment for words but not pictures provides support for this argument, in that it is possible words are simply impacted by sleep in nonobvious ways (and ways not observable in the current paradigm), but are nonetheless impaired in a way not ameliorated by tDCS. This may in part be driven by the cognitive effort required by the semantic elaboration task at encoding, compared to the relative ease of the picture blocks which merely drew attention to perceptual details. Overall, while there is reasonable corroborating evidence to yield speculation on the underlying mechanisms for these observations, they remain elusive and warrant further investigation to determine their extent and influence of these factors in the cognitive tDCS literature.

In Chapter 3, we discuss important methodological considerations underscoring the importance of rigorous blinding and shamming protocols necessary to achieve reliable and replicable tDCS effects. More specifically, we outline the potential for sensations and/or expectation effects experienced by tDCS participants to play a role in shaping performance (including the degree of tDCS effects), potentially obscuring real experimental outcomes. We demonstrate this possibility by first examining "expectations" (as indexed by the prompt "Do you think you received electricity to your brain?") as well as the type of sensations (e.g., itching, tingling, burning, etc.) from the single-blind tDCS studies described in Wong et al., (2018), as well as those reported in the current study.

In contrast to the single-blind studies described in Wong et al., (2018), we observed that in the current study we were not able to detect significant differences in sensations experienced by subjects in the active stimulation and sham conditions. The finding that our participants were largely unable to ascertain their treatment assignment indicates that our double-blinded study likely yielding superior shamming conditions relative to the single-blind studies described in Wong, et al., (2018). This finding points to important implications for outcomes of single-blind studies, which still make up the majority of tDCS studies in this literature.

However, to complicate matters, even though participant-reported sensations were, on average, indistinguishable between stimulation and sham, it appears that when parsing participants based on whether they *believed* they received stimulation or not impacted how they performed on the task. Furthermore, when restricting the sample to include only those participants who responded “yes” to the “electricity to your brain” question with high confidence, there was a boost in episodic performance for those in the active stimulation group but not in sham. While the underlying reasons for this difference in performance is not immediately obvious (or why sham participants who responded “no” outperformed those who said “yes”), it still does warrant consideration in future tDCS protocols, particularly given the often too-small effect sizes and underpowered samples that populate tDCS research.

Conclusions

Despite the inherent challenges associated with using tDCS to improve complex cognitive functions underpinned by heterogeneous brain regions, several studies have established that tDCS has the capacity to elicit episodic and working memory enhancements in healthy young adults, as well as ameliorate decline related to healthy aging. Unfortunately, results within this literature are mixed, exacerbated by a lack of consensus on optimal design procedures or parameters to enhance between-study reliability and replicability. Of note, we suspect that the inconsistent outcomes reflect the considerable variation in design parameters related to tDCS montage, current density and stimulation duration, as well as the participant characteristics and cognitive tasks used. Variability in these design parameters add noise, making similar studies with different parameter choices more difficult to compare. Critically, many studies fail to use proper blinding procedures to mask expectations of tDCS outcomes in behavior; coupled with small sample sizes, these further clouds interpretations and likely obscures genuine tDCS effects.

To contribute meaningfully to the literature in healthy memory modulation, this study was designed to comprise the largest double-blinded sham-controlled tDCS trial to date investigating the effects of anodal tDCS in episodic memory retrieval and working memory in both younger and older adults, using parameters that yield the most consistent outcomes in the memory literature. Our analyses underscored the need for double-blinding and between-subject designs to foster robust sham conditions, and it is encouraging to note that any effects described here are likely not compromised by poor blinding protocols (which cannot be said for many tDCS studies in this literature).

While we were unable to replicate previous work pointing to tDCS-elicited boosts at one's nonoptimal time of day, it might still be the case that tDCS provides the most benefit "when needed". Importantly, one of the underlying themes borne from this research is centered around tDCS benefitting performance under cognitively effortful conditions, whether that is due to a taxing cognitive task (e.g., a 3-back working memory task) or as a function of sleep quality. Of course, while these are potentially important discoveries, it is difficult to draw strong conclusions without further work, particularly given that many effects described are task and/or age group-specific, without strong existing corroborating evidence pointing to definitive underlying mechanisms. Moving forward, researchers should be mindful to employ thoughtful experimental design, prioritizing more focal electric fields that are sample and task-specific based on brain organization and responsiveness to tDCS, as well as desired outcome.

References

Alvarez, J. A., & Emory, E. (2006). Executive Function and the Frontal Lobes: A Meta-Analytic Review. *Neuropsychology Review*, *16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x

Aly, M., & Moscovitch, M. (2010). The effects of sleep on episodic memory in older and younger adults. *Memory*, *18*(3), 327–334. https://doi.org/10.1080/09658211003601548

Anderson, J. A. E., Campbell, K. L., Amer, T., Grady, C. L., & Hasher, L. (2014). Timing is Everything: Age Differences in the Cognitive Control Network are Modulated by Time of Day. *Psychology and Aging*, *29*(3), 648–657. https://doi.org/10.1037/a0037243

Au, J., Katz, B., Buschkuehl, M., Bunarjo, K., Senger, T., Zabel, C., Jaeggi, S. M., & Jonides, J. (2016). Enhancing Working Memory Training with Transcranial Direct Current Stimulation. *Journal of Cognitive Neuroscience*, *28*(9), 1419–1432. https://doi.org/10.1162/jocn_a_00979

Baddeley, A. (2003). Working memory and language: An overview. *Journal of Communication Disorders*, *36*(3), 189–208. https://doi.org/10.1016/S0021-9924(03)00019-4

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*(7), e0159555. https://doi.org/10.1371/journal.pone.0159555

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral Prefrontal Contributions to Human Working Memory. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *49*(5), 1195–1205. https://doi.org/10.1016/j.cortex.2012.05.022

Bartl, G., Blackshaw, E., Crossman, M., Allen, P., & Sandrini, M. (2020). Systematic review and network meta-analysis of anodal tDCS effects on verbal episodic memory: Modelling heterogeneity of stimulation locations. *Zeitschrift Für Psychologie*, *228*(1). https://doi.org/10.1027/2151-2604/a000396

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting Linear Mixed-Effects Models using lme4. *ArXiv:1406.5823 [Stat]*. http://arxiv.org/abs/1406.5823

Baumert, A., Buchholz, N., Zinkernagel, A., Clarke, P., MacLeod, C., Osinsky, R., & Schmitt, M. (2020). Causal underpinnings of working memory and Stroop interference control: Testing the effects of anodal and cathodal tDCS over the left DLPFC. *Cognitive, Affective, & Behavioral Neuroscience*, *20*(1), 34–48. https://doi.org/10.3758/s13415-019-00726-y

Benoit, O., Foret, J., Merle, B., & Bouard, G. (1981). Diurnal Rhythm of Axillary Temperature in Long and Short Sleepers: Effects of Sleep Deprivation and Sleep Displacement. *Sleep*, *4*(4), 359–365. https://doi.org/10.1093/sleep/4.4.359

Berryhill, M. E., & Jones, K. T. (2012). TDCS selectively improves working memory in older adults with more education. *Neuroscience Letters*, *521*(2), 148–151. https://doi.org/10.1016/j.neulet.2012.05.074

Berryhill, M. E. P., Peterson, D. J. P., Jones, K. T. P., & Stephens, J. A. M. (2014). Hits and Misses: Leveraging tDCS to Advance Cognitive Research. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.00800

Berryhill, M. E., Phuong, L., Picasso, L., Cabeza, R., & Olson, I. R. (2007). Parietal Lobe and Episodic Memory: Bilateral Damage Causes Impaired Free Recall of Autobiographical Memory. *Journal of Neuroscience*, *27*(52), 14415–14423. https://doi.org/10.1523/JNEUROSCI.4163-07.2007

Berryhill, M. E., Wencil, E. B., Branch Coslett, H., & Olson, I. R. (2010). A selective working memory impairment after transcranial direct current stimulation to the right parietal lobe. *Neuroscience Letters*, *479*(3), 312–316. https://doi.org/10.1016/j.neulet.2010.05.087

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

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., Mourdoukoutas, A. P., Kronberg, G., Truong, D., Boggio, P., Brunoni, A. R., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R. H., Hampstead, B. M., Jankord, R., Kirton, A., … Woods, A. J. (2016). Safety of transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimulation*, *9*(5), 641–661. https://doi.org/10.1016/j.brs.2016.06.004

Bjekić, J., Čolić, M. V., Živanović, M., Milanović, S. D., & Filipović, S. R. (2019). Transcranial direct current stimulation (tDCS) over parietal cortex improves associative memory. *Neurobiology of Learning and Memory*, *157*, 114–120. https://doi.org/10.1016/j.nlm.2018.12.007

Bliwise, D. L., Ansari, F. P., Straight, L.-B., & Parker, K. P. (2005). Age Changes in Timing and 24-Hour Distribution of Self-Reported Sleep. *The American Journal of Geriatric Psychiatry*, *13*(12), 1077–1082. https://doi.org/10.1097/00019442-200512000-00007

Blumenfeld, R. S. (2006). Dorsolateral Prefrontal Cortex Promotes Long-Term Memory

Formation through Its Role in Working Memory Organization. *Journal of Neuroscience*, *26*(3), 916–925. https://doi.org/10.1523/JNEUROSCI.2353-05.2006

Bopp, K. L., & Verhaeghen, P. (2018). Aging and n-Back Performance: A Meta-Analysis. *The Journals of Gerontology: Series B*. https://doi.org/10.1093/geronb/gby024

Brunoni, Andre Russowsky, Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D. J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P., & Fregni, F. (2012). Clinical Research with Transcranial Direct Current Stimulation (tDCS): Challenges and Future Directions. *Brain Stimulation*, *5*(3), 175–195. https://doi.org/10.1016/j.brs.2011.03.002

Brunoni, André Russowsky, Schestatsky, P., Lotufo, P. A., Benseñor, I. M., & Fregni, F. (2014). Comparison of blinding effectiveness between sham tDCS and placebo sertraline in a 6-week major depression randomized clinical trial. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *125*(2), 298–305. https://doi.org/10.1016/j.clinph.2013.07.020

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Cabeza, R., Mazuz, Y. S., Stokes, J., Kragel, J. E., Woldorff, M. G., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2011). Overlapping Parietal Activity in Memory and Perception: Evidence for the Attention to Memory Model. *Journal of Cognitive Neuroscience*, *23*(11), 3209–3217. https://doi.org/10.1162/jocn_a_00065

Cansino, S., Hernández-Ramos, E., Estrada-Manilla, C., Torres-Trejo, F., Martínez-Galindo, J. G., Ayala-Hernández, M., Gómez-Fernández, T., Osorio, D., Cedillo-Tinoco, M., Garcés-Flores, L., Beltrán-Palacios, K., García-Lázaro, H. G., García-Gutiérrez, F., Cadena-Arenas, Y., Fernández-Apan, L., Bärtschi, A., & Rodríguez-Ortiz, M. D. (2013). The decline of verbal and visuospatial working memory across the adult life span. *Age*, *35*(6), 2283–2302. https://doi.org/10.1007/s11357-013-9531-1

Carson, N., Leach, L., & Murphy, K. J. (2018). A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. *International Journal of Geriatric Psychiatry*, *33*(2), 379–388. https://doi.org/10.1002/gps.4756

Cespón, J., Rodella, C., Rossini, P. M., Miniussi, C., & Pellicciari, M. C. (2017). Anodal Transcranial Direct Current Stimulation Promotes Frontal Compensatory Mechanisms in Healthy Elderly Subjects. *Frontiers in Aging Neuroscience*, *9*. https://doi.org/10.3389/fnagi.2017.00420

Chee, M. W. L., & Chuah, Y. M. L. (2007). Functional neuroimaging and behavioral correlates of capacity decline in visual short-term memory after sleep deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(22), 9487–9492. https://doi.org/10.1073/pnas.0610712104

Chen, N.-F., Lo, C.-M., Liu, T.-L., & Cheng, S. (2016). Source memory performance is modulated by transcranial direct current stimulation over the left posterior parietal cortex. *NeuroImage*, *139*, 462–469. https://doi.org/10.1016/j.neuroimage.2016.06.032

Cherdieu, M., Reynaud, E., Uhlrich, J., Versace, R., & Mazza, S. (2014). Does age worsen sleep-dependent memory consolidation? *Journal of Sleep Research*, *23*(1), 53–60. https://doi.org/10.1111/jsr.12100

Chua, E. F., Ahmed, R., & Garcia, S. (2017). Effects of HD-tDCS on memory and metamemory for general knowledge questions that vary by difficulty. *Brain Stimulation*, *10*(2), 231–241. https://doi.org/10.1016/j.brs.2016.10.013

Clifasefi, S. L., Garry, M., Harper, D. N., Sharman, S. J., & Sutherland, R. (2007). Psychotropic placebos create resistance to the misinformation effect. *Psychonomic Bulletin & Review*, *14*(1), 112–117. https://doi.org/10.3758/BF03194037

Craik, F., & Simon, E. (1980). Age differences in memory: The roles of attention and depth of processing, in new directions in memory and aging. *Talland Memorial Conference*, 95–112.

Crossman, M., Bartl, G., Soerum, R., & Sandrini, M. (2019). Effects of transcranial direct current stimulation over the posterior parietal cortex on episodic memory reconsolidation. *Cortex*, *121*, 78–88. https://doi.org/10.1016/j.cortex.2019.08.009

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423. https://doi.org/10.1016/S1364-6613(03)00197-9

Daselaar, S., & Cabeza, R. (2013, December 1). *Age-Related Decline in Working Memory and Episodic Memory*. The Oxford Handbook of Cognitive Neuroscience, Volume 1. https://doi.org/10.1093/oxfordhb/9780199988693.013.0022

Davidson, P. S. R., Anaki, D., Ciaramelli, E., Cohn, M., Kim, A. S. N., Murphy, K. J., Troyer, A. K., Moscovitch, M., & Levine, B. (2008). Does lateral parietal cortex support episodic memory?: Evidence from focal lesion patients. *Neuropsychologia*, *46*(7), 1743–1755. https://doi.org/10.1016/j.neuropsychologia.2008.01.011

Dobbins, I. G., Rice, H. J., Wagner, A. D., & Schacter, D. L. (2003). Memory orientation and success: Separable neurocognitive components underlying episodic recognition. *Neuropsychologia*, *41*(3), 318–333. https://doi.org/10.1016/S0028-3932(02)00164-1

Dubreuil-Vall, L., Chau, P., Ruffini, G., Widge, A. S., & Camprodon, J. A. (2019). TDCS to the left DLPFC modulates cognitive and physiological correlates of executive function in a state-dependent manner. *Brain Stimulation*, *12*(6), 1456–1463. https://doi.org/10.1016/j.brs.2019.06.006

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

Ezquerro, F., Moffa, A. H., Bikson, M., Khadka, N., Aparicio, L. V. M., Sampaio-Junior, B. de, Fregni, F., Bensenor, I. M., Lotufo, P. A., Pereira, A. C., & Brunoni, A. R. (2017). The Influence of Skin Redness on Blinding in Transcranial Direct Current Stimulation Studies: A Crossover Trial. *Neuromodulation: Technology at the Neural Interface*, *20*(3), 248–255. https://doi.org/10.1111/ner.12527

Fiori, V., Cipollari, S., Di Paola, M., Razzano, C., Caltagirone, C., & Marangolo, P. (2013). tDCS stimulation segregates words in the brain: Evidence from aphasia. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00269

Fischer, D., Lombardi, D. A., Marucci-Wellman, H., & Roenneberg, T. (2017). Chronotypes in the US – Influence of age and sex. *PLoS ONE*, *12*(6). https://doi.org/10.1371/journal.pone.0178782

Fletcher, P. (1998a). The functional roles of prefrontal cortex in episodic memory. I. Encoding. *Brain*, *121*(7), 1239–1248. https://doi.org/10.1093/brain/121.7.1239

Fletcher, P. (1998b). The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain*, *121*(7), 1249–1256. https://doi.org/10.1093/brain/121.7.1249

Fontaine, K. R., Williams, M. S., Hoenemeyer, T. W., Kaptchuk, T. J., & Dutton, G. R. (2016). Placebo Effects in Obesity Research. *Obesity (Silver Spring, Md.)*, *24*(4), 769–771. https://doi.org/10.1002/oby.21456

Fonteneau, C., Mondino, M., Arns, M., Baeken, C., Bikson, M., Brunoni, A. R., Burke, M. J., Neuvonen, T., Padberg, F., Pascual-Leone, A., Poulet, E., Ruffini, G., Santarnecchi, E., Sauvaget, A., Schellhorn, K., Suaud-Chagny, M.-F., Palm, U., & Brunelin, J. (2019). Sham tDCS : A hidden source of variability? Reflections for further blinded, controlled trials. *Brain Stimulation*, *12*(3), 668–673. https://doi.org/10.1016/j.brs.2018.12.977

Fraundorf, S. H., Hourihan, K. L., Peters, R. A., & Benjamin, A. S. (2019). Aging and recognition memory: A meta-analysis. *Psychological Bulletin*, *145*(4), 339–371. https://doi.org/10.1037/bul0000185

Fregni, F., Boggio, P. S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M. A., Rigonatti, S. P., Silva, M. T. A., Paulus, W., & Pascual-Leone, A. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental Brain Research*, *166*(1), 23–30. https://doi.org/10.1007/s00221-005-2334-6

Fuster, J. M. (2000). The prefrontal cortex of the primate: A synopsis. *Psychobiology*, *28*(2), 125–131. https://doi.org/10.3758/BF03331972

Galea, J. M., Albert, N. B., Ditye, T., & Miall, R. C. (2009). Disruption of the Dorsolateral Prefrontal Cortex Facilitates the Consolidation of Procedural Skills. *Journal of Cognitive Neuroscience*, *22*(6), 1158–1164. https://doi.org/10.1162/jocn.2009.21259

Galli, G., Vadillo, M. A., Sirota, M., Feurra, M., & Medvedeva, A. (2019). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) on episodic memory. *Brain Stimulation*, *12*(2), 231–241. https://doi.org/10.1016/j.brs.2018.11.008

Gill, J., Shah-Basak, P. P., & Hamilton, R. (2015). It's the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function. *Brain Stimulation*, *8*(2), 253–259. https://doi.org/10.1016/j.brs.2014.10.018

Gray, S. J., Brookshire, G., Casasanto, D., & Gallo, D. A. (2015). Electrically stimulating prefrontal cortex at retrieval improves recollection accuracy. *Cortex*, *73*, 188–194. https://doi.org/10.1016/j.cortex.2015.09.003

Haba-Rubio, J., Ibanez, V., & Sforza, E. (2004). An alternative measure of sleep fragmentation in clinical practice: The sleep fragmentation index. *Sleep Medicine*, *5*(6), 577–581. https://doi.org/10.1016/j.sleep.2004.06.007

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*. https://doi.org/10.3389/fnhum.2017.00542

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. https://doi.org/10.1186/1471-2202-12-72

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In *The psychology of learning and motivation: Advances in research and theory, Vol. 22* (pp. 193–225). Academic Press. https://doi.org/10.1016/S0079-7421(08)60041-9

Hidalgo, M. P. L., Zanette, C. B., Pedrotti, M., Souza, C. M., Nunes, P. V., & Chaves, M. L. F. (2004). Performance of Chronotypes on Memory Tests during the Morning and the Evening Shifts. *Psychological Reports*, *95*(1), 75–85. https://doi.org/10.2466/pr0.95.1.75-85

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

Hokett, E., Arunmozhi, A., Campbell, J., Verhaeghen, P., & Duarte, A. (2021). A systematic review and meta-analysis of individual differences in naturalistic sleep quality and episodic memory performance in young and older adults. *Neuroscience & Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2021.05.010

Horne, J. A., & Östberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, *4*, 97–110.

Horvath, J. C., Carter, O., & Forte, J. D. (2014). Transcranial direct current stimulation: Five important issues we aren't discussing (but probably should be). *Frontiers in Systems Neuroscience*, *8*. https://doi.org/10.3389/fnsys.2014.00002

Hu, S., Ide, J. S., Chao, H. H., Castagna, B., Fischer, K. A., Zhang, S., & Li, C. R. (2018). Structural and functional cerebral bases of diminished inhibitory control during healthy aging. *Human Brain Mapping*, *39*(12), 5085–5096. https://doi.org/10.1002/hbm.24347

Hummel, F., & Cohen, L. G. (2005). Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. *Neurorehabilitation and Neural Repair*, *19*(1), 14–19. https://doi.org/10.1177/1545968304272698

Huo, L., Zheng, Z., Li, J., Wan, W., Cui, X., Chen, S., Wang, W., & Li, J. (2018). Long-Term Transcranial Direct Current Stimulation Does Not Improve Executive Function in Healthy Older Adults. *Frontiers in Aging Neuroscience*, *10*. https://doi.org/10.3389/fnagi.2018.00298

Hurley, R., & Machado, L. (2018). Using transcranial direct current stimulation to improve verbal working memory: A detailed review of the methodology. *Journal of Clinical and Experimental Neuropsychology*, *40*(8), 790–804. https://doi.org/10.1080/13803395.2018.1434133

Intons-Peterson, M. J., Rocchi, P., West, T., McLellan, K., & Hackney, A. (1998). Aging, optimal testing times, and negative priming. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *24*(2), 362–376. https://doi.org/10.1037/0278-7393.24.2.362

Jacobson, L., Goren, N., Lavidor, M., & Levy, D. A. (2012). Oppositional transcranial direct current stimulation (tDCS) of parietal substrates of attention during encoding modulates episodic memory. *Brain Research*, *1439*, 66–72. https://doi.org/10.1016/j.brainres.2011.12.036

Javadi, A. H., & Cheng, P. (2013). Transcranial Direct Current Stimulation (tDCS) Enhances Reconsolidation of Long-Term Memory. *Brain Stimulation*, *6*(4), 668–674. https://doi.org/10.1016/j.brs.2012.10.007

Javadi, A.-H., & Walsh, V. (2011). Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. *Brain Stimulation*, *5*, 231–241. https://doi.org/10.1016/j.brs.2011.06.007

Jones, K. T., & Berryhill, M. (2012). Parietal Contributions to Visual Working Memory Depend on Task Difficulty. *Frontiers in Psychiatry*, *3*. https://doi.org/10.3389/fpsyt.2012.00081

Jones, K. T., Gözenman, F., & Berryhill, M. E. (2014). Enhanced long-term memory encoding after parietal neurostimulation. *Experimental Brain Research*, *232*(12), 4043–4054. https://doi.org/10.1007/s00221-014-4090-y

Kapur, S., Craik, F. I., Tulving, E., Wilson, A. A., Houle, S., & Brown, G. M. (1994). Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proceedings of the National Academy of Sciences*, *91*(6), 2008–2011.

Katsoulaki, M., Kastrinis, A., & Tsekoura, M. (2017). The Effects of Anodal Transcranial Direct Current Stimulation on Working Memory. In P. Vlamos (Ed.), *GeNeDis 2016* (pp. 283–289). Springer International Publishing. https://doi.org/10.1007/978-3-319-57379-3_25

Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *NeuroImage*, *54*(3), 2446–2461. https://doi.org/10.1016/j.neuroimage.2010.09.045

Kosari, Z., Dadashi, M., Maghbouli, M., & Mostafavi, H. (2019). Comparing the Effectiveness of Neurofeedback and Transcranial Direct Current Stimulation on Sleep Quality of Patients With Migraine. *Basic and Clinical Neuroscience*, *10*(6), 579–588. https://doi.org/10.32598/BCN.10.6.651.3

Kwon, Y., Kang, K., Son, S., & Lee, N. (2015). Is effect of transcranial direct current stimulation on visuomotor coordination dependent on task difficulty? *Neural Regeneration Research*, *10*(3), 463. https://doi.org/10.4103/1673-5374.153697

Laakso, I., Tanaka, S., Koyama, S., De Santis, V., & Hirata, A. (2015). Inter-subject Variability in Electric Fields of Motor Cortical tDCS . *Brain Stimulation*, *8*(5), 906–913. https://doi.org/10.1016/j.brs.2015.05.002

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. https://doi.org/10.1016/j.neuropsychologia.2017.10.022

Levy, R., & Goldman-Rakic, P. S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research*, *133*(1), 23–32. https://doi.org/10.1007/s002210000397

Luke, S. G. (2017). Evaluating significance in linear mixed-effects models in R. *Behavior Research Methods*, *49*(4), 1494–1502. https://doi.org/10.3758/s13428-016-0809-y

Lukowski, A. F., Valentovich, V., Bohanek, J. G., & Slonecker, E. M. (2017). Sleep Quality and the Subjective Experience of Autobiographical Memory: Differential Associations by Memory Valence and Temporality: Sleep and autobiographical memory. *Applied Cognitive Psychology*, *31*(6), 604–614. https://doi.org/10.1002/acp.3356

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*(5472), 1835–1838. https://doi.org/10.1126/science.288.5472.1835

Maheux-Caron, V., Trémolière, B., Lepage, J., & Blanchette, I. (2020). Transcranial direct current stimulation of the left dorsolateral prefrontal cortex can reduce the detrimental effect of stress on working memory. *Psychology & Neuroscience*. https://doi.org/10.1037/pne0000206

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

Manea, L., Gilbody, S., & McMillan, D. (2012). Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): A meta-analysis. In *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*. Centre for Reviews and Dissemination (UK). https://www.ncbi.nlm.nih.gov/books/NBK99968/

Manenti, R., Brambilla, M., Petesi, M., Ferrari, C., & Cotelli, M. (2013). Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. *Frontiers in Aging Neuroscience*, *5*. https://doi.org/10.3389/fnagi.2013.00049

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*(7), 2592–2598. https://doi.org/10.1016/j.clinph.2016.04.015

May, C. P., & Hasher, L. (1998). Synchrony effects in inhibitory control over thought and action. *Journal of Experimental Psychology. Human Perception and Performance*, *24*(2), 363–379. https://doi.org/10.1037//0096-1523.24.2.363

May, Cynthia P., & Hasher, L. (2017a). Synchrony Affects Performance for Older but not Younger Neutral-Type Adults. *Timing & Time Perception*, *5*(2), 129–148. https://doi.org/10.1163/22134468-00002087

May, Cynthia P., & Hasher, L. (2017b). Synchrony Affects Performance for Older but not Younger Neutral-Type Adults. *Timing & Time Perception*, *5*(2), 129–148. https://doi.org/10.1163/22134468-00002087

May, Cynthia P., Hasher, L., & Foong, N. (2005). Implicit Memory, Age, and Time of

Day. *Psychological Science*, *16*(2), 96–100. https://doi.org/10.1111/j.0956-7976.2005.00788.x

May, Cynthia P., Hasher, L., & Stoltzfus, E. R. (1993). Optimal time of day and the magnitude of age differences in memory. *Psychological Science*, 326–330.

Medeiros, L. F., de Souza, I. C. C., Vidor, L. P., de Souza, A., Deitos, A., Volz, M. S., Fregni, F., Caumo, W., & Torres, I. L. S. (2012). Neurobiological Effects of Transcranial Direct Current Stimulation: A Review. *Frontiers in Psychiatry*, *3*. https://doi.org/10.3389/fpsyt.2012.00110

Meier, B., & Sauter, P. (2018). Boosting memory by tDCS to frontal or parietal brain regions? A study of the enactment effect shows no effects for immediate and delayed recognition. *Frontiers in Psychology*, *9*(JUN). https://doi.org/10.3389/fpsyg.2018.00867

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Floel, A. (2013). Anodal Transcranial Direct Current Stimulation Temporarily Reverses Age-Associated Cognitive Decline and Functional Brain Activity Changes. *Journal of Neuroscience*, *33*(30), 12470–12478. https://doi.org/10.1523/JNEUROSCI.5743-12.2013

Meiron, O., & Lavidor, M. (2013). Unilateral Prefrontal Direct Current Stimulation Effects are Modulated by Working Memory Load and Gender. *Brain Stimulation*, *6*(3), 440–447. https://doi.org/10.1016/j.brs.2012.05.014

Metuki, N., Sela, T., & Lavidor, M. (2012). Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. *Brain Stimulation*, *5*(2), 110–115. https://doi.org/10.1016/j.brs.2012.03.002

Miguel, M., Oliveira, V. C. de, Pereira, D., & Pedrazzoli, M. (2014). Detecting chronotype differences associated to latitude: A comparison between Horne--Östberg and Munich Chronotype questionnaires. *Annals of Human Biology*, *41*(2), 105–108. https://doi.org/10.3109/03014460.2013.832795

Minamoto, T., Azuma, M., Yaoi, K., Ashizuka, A., Mima, T., Osaka, M., Fukuyama, H., & Osaka, N. (2014). The anodal tDCS over the left posterior parietal cortex enhances attention toward a focus word in a sentence. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00992

Miniussi, C., & Ruzzoli, M. (2013). Transcranial stimulation and cognition. *Handbook of Clinical Neurology*, *116*, 739–750. https://doi.org/10.1016/B978-0-444-53497-2.00056-5

Miyata, S., Noda, A., Iwamoto, K., Kawano, N., Okuda, M., & Ozaki, N. (2013). Poor sleep quality impairs cognitive performance in older adults. *Journal of Sleep Research*, *22*(5), 535–541. https://doi.org/10.1111/jsr.12054

Morrell, M. J., Finn, L., Kim, H., Peppard, P. E., Safwan Badr, M., & Young, T. (2000). Sleep Fragmentation, Awake Blood Pressure, and Sleep-Disordered Breathing in a Population-based Study. *American Journal of Respiratory and Critical Care Medicine*, *162*(6), 2091–2096. https://doi.org/10.1164/ajrccm.162.6.9904008

Mulquiney, P. G., Hoy, K. E., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Improving working memory: Exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *122*(12), 2384–2389. https://doi.org/10.1016/j.clinph.2011.05.009

Nejati, V., Salehinejad, M. A., Nitsche, M. A., Najian, A., & Javadi, A.-H. (2017). Transcranial Direct Current Stimulation Improves Executive Dysfunctions in ADHD: Implications for Inhibitory Control, Interference Control, Working Memory, and Cognitive Flexibility. *Journal of Attention Disorders*, 1087054717730611. https://doi.org/10.1177/1087054717730611

Neri, F., Mencarelli, L., Menardi, A., Giovannelli, F., Rossi, S., Sprugnoli, G., Rossi, A., Pascual-Leone, A., Salvador, R., Ruffini, G., & Santarnecchi, E. (2020). A novel tDCS sham approach based on model-driven controlled shunting. *Brain Stimulation*, *13*(2), 507–516. https://doi.org/10.1016/j.brs.2019.11.004

Nilsson, J., Lebedev, A. V., & Lövdén, M. (2015). No Significant Effect of Prefrontal tDCS on Working Memory Performance in Older Adults. *Frontiers in Aging Neuroscience*, *7*, 230–230. https://doi.org/10.3389/fnagi.2015.00230

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*(Pt 3), 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, Michael A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*(3), 206–223. https://doi.org/10.1016/j.brs.2008.06.004

Nitsche, Michael 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*(4), 619–626. https://doi.org/10.1162/089892903321662994

O'Connell, N. E., Cossar, J., Marston, L., Wand, B. M., Bunce, D., Moseley, G. L., & De Souza, L. H. (2012). Rethinking Clinical Trials of Transcranial Direct Current Stimulation: Participant and Assessor Blinding Is Inadequate at Intensities of 2mA. *PLoS ONE*, *7*(10). https://doi.org/10.1371/journal.pone.0047514

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, *27*(7), 1255–1273. https://doi.org/10.1093/sleep/27.7.1255

Ohayon, M., Wickwire, E. M., Hirshkowitz, M., Albert, S. M., Avidan, A., Daly, F. J., Dauvilliers, Y., Ferri, R., Fung, C., Gozal, D., Hazen, N., Krystal, A., Lichstein, K., Mallampalli, M., Plazzi, G., Rawding, R., Scheer, F. A., Somers, V., & Vitiello, M. V. (2017). National Sleep Foundation's sleep quality recommendations: First report. *Sleep Health*, *3*(1), 6–19. https://doi.org/10.1016/j.sleh.2016.11.006

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 46–59. https://doi.org/10.1002/hbm.20131

Paivio, A., & Csapo, K. (1973). Picture superiority in free recall: Imagery or dual coding? *Cognitive Psychology*, *5*(2), 176–206. https://doi.org/10.1016/0010-0285(73)90032-7

Palm, U., Reisinger, E., Keeser, D., Kuo, M.-F., Pogarell, O., Leicht, G., Mulert, C., Nitsche, M. A., & Padberg, F. (2013). Evaluation of Sham Transcranial Direct Current Stimulation for Randomized, Placebo-Controlled Clinical Trials. *Brain Stimulation*, *6*(4), 690–695. https://doi.org/10.1016/j.brs.2013.01.005

Park, S.-H., Seo, J.-H., Kim, Y.-H., & Ko, M.-H. (2014). Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. *NeuroReport*, *25*(2), 122–126. https://doi.org/10.1097/WNR.0000000000000080

Parker, S., Garry, M., Engle, R. W., Harper, D. N., & Clifasefi, S. L. (2008). Psychotropic placebos reduce the misinformation effect by increasing monitoring at test. *Memory*, *16*(4), 410–419. https://doi.org/10.1080/09658210801956922

Penolazzi, B., Domenico, A. D., Marzoli, D., Mammarella, N., Fairfield, B., Franciotti, R., Brancucci, A., & Tommasi, L. (2010). Effects of Transcranial Direct Current Stimulation on Episodic Memory Related to Emotional Visual Stimuli. *PLOS ONE*, *5*(5), e10623. https://doi.org/10.1371/journal.pone.0010623

Pergolizzi, D., & Chua, E. F. (2015). Transcranial direct current stimulation (tDCS) of the parietal cortex leads to increased false recognition. *Neuropsychologia*, *66*, 88–98. https://doi.org/10.1016/j.neuropsychologia.2014.11.012

Pergolizzi, D., & Chua, E. F. (2017). Increased contextual cue utilization with tDCS over the prefrontal cortex during a recognition task. *Brain Research*, *1655*, 1–9. https://doi.org/10.1016/j.brainres.2016.11.008

Peter, J., Neumann-Dunayevska, E., Geugelin, F., Ninosu, N., Plewnia, C., & Klöppel, S. (2019). Reducing negative affect with anodal transcranial direct current stimulation increases memory performance in young—But not in elderly—Individuals. *Brain Structure and Function*, *224*(8), 2973–2982. https://doi.org/10.1007/s00429-019-01946-1

Pewsey, Arthur., Neuhäuser, Markus., & Ruxton, G. D. (2013). *Circular Statistics in R* (1st ed.). Oxford University Press. http://pi.lib.uchicago.edu/1001/cat/bib/12014378

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1999). Functional Specialization for Semantic and Phonological Processing in the Left Inferior Prefrontal Cortex. *NeuroImage*, *10*(1), 15–35. https://doi.org/10.1006/nimg.1999.0441

Pope, P. A., Brenton, J. W., & Miall, R. C. (2015). Task-Specific Facilitation of Cognition by Anodal Transcranial Direct Current Stimulation of the Prefrontal Cortex. *Cerebral Cortex*, *25*(11), 4551–4558. https://doi.org/10.1093/cercor/bhv094

Rabipour, S., Vidjen, P. S., Remaud, A., Davidson, P. S. R., & Tremblay, F. (2019). Examining the Interactions Between Expectations and tDCS Effects on Motor and Cognitive Performance. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00999

Rabipour, S., Wu, A. D., Davidson, P. S. R., & Iacoboni, M. (2018). Expectations may influence the effects of transcranial direct current stimulation. *Neuropsychologia*, *119*, 524–534. https://doi.org/10.1016/j.neuropsychologia.2018.09.005

Rana, B. K., Panizzon, M. S., Franz, C. E., Spoon, K. M., Jacobson, K. C., Xian, H., Ancoli-Israel, S., Lyons, M., & Kremen, W. S. (2018). Association of Sleep Quality on Memory-Related Executive Functions in Middle Age. *Journal of the International Neuropsychological Society : JINS*, *24*(1), 67–76. https://doi.org/10.1017/S1355617717000637

Ranganath, C., & Knight, R. (2003). Prefrontal cortex and episodic memory: Integrating findings from neuropsychology and functional brain imaging. *Memory Encoding and Retrieval: A Cognitive Neuroscience Perspective*.

Rasch, B., & Born, J. (2013). About Sleep's Role in Memory. *Physiological Reviews*, *93*(2), 681–766. https://doi.org/10.1152/physrev.00032.2012

Ray, M. K., Sylvester, M. D., Helton, A., Pittman, B. R., Wagstaff, L. E., McRae, T. R., Turan, B., Fontaine, K. R., Amthor, F. R., & Boggiano, M. M. (2019). The Effect of Expectation on Transcranial Direct Current Stimulation (tDCS) to Suppress Food Craving and Eating in Individuals with Overweight and Obesity. *Appetite*, *136*, 1–7. https://doi.org/10.1016/j.appet.2018.12.044

Razza, L. B., Moffa, A. H., Moreno, M. L., Carvalho, A. F., Padberg, F., Fregni, F., & Brunoni, A. R. (2018). A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *81*, 105–113. https://doi.org/10.1016/j.pnpbp.2017.10.016

Reed, D. L., & Sacco, W. P. (2016). Measuring Sleep Efficiency: What Should the Denominator Be? *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine*, *12*(2), 263–266. https://doi.org/10.5664/jcsm.5498

Reinhart, R. M. G., Cosman, J. D., Fukuda, K., & Woodman, G. F. (2017). Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. *Attention, Perception, and Psychophysics*, *79*(1), 3–23. https://doi.org/10.3758/s13414-016-1224-2

Roenneberg, T., Kuehnle, T., Juda, M., Kantermann, T., Allebrandt, K., Gordijn, M., & Merrow, M. (2007). Epidemiology of the human circadian clock. *Sleep Medicine Reviews*, *11*(6), 429–438. https://doi.org/10.1016/j.smrv.2007.07.005

Ross, L. A., McCoy, D., Coslett, H. B., Olson, I. R., & Wolk, D. A. (2011). Improved Proper Name Recall in Aging after Electrical Stimulation of the Anterior Temporal Lobes. *Frontiers in Aging Neuroscience*, *3*. https://doi.org/10.3389/fnagi.2011.00016

Rowe, G., Hasher, L., & Turcotte, J. (2009). Short article: Age and synchrony effects in visuospatial working memory. *Quarterly Journal of Experimental Psychology*, *62*(10), 1873–1880. https://doi.org/10.1080/17470210902834852

Roy, L. B., Sparing, R., Fink, G. R., & Hesse, M. D. (2015). Modulation of attention functions by anodal tDCS on right PPC. *Neuropsychologia*, *74*, 96–107. https://doi.org/10.1016/j.neuropsychologia.2015.02.028

Ruf, S. P., Fallgatter, A. J., & Plewnia, C. (2017). Augmentation of working memory training by transcranial direct current stimulation (tDCS). *Scientific Reports*, *7*(1), 1–11. https://doi.org/10.1038/s41598-017-01055-1

Salehinejad, M. A., Ghanavai, E., Rostami, R., & Nejati, V. (2017). Cognitive control dysfunction in emotion dysregulation and psychopathology of major depression (MD): Evidence from transcranial brain stimulation of the dorsolateral prefrontal cortex (DLPFC). *Journal of Affective Disorders*, *210*, 241–248. https://doi.org/10.1016/j.jad.2016.12.036

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*. https://doi.org/10.3389/fnagi.2014.00289

Sandrini, M., Fertonani, A., Cohen, L. G., & Miniussi, C. (2012). Double dissociation of working memory load effects induced by bilateral parietal modulation. *Neuropsychologia*, *50*(3), 396–402. https://doi.org/10.1016/j.neuropsychologia.2011.12.011

Schmidt, C., Collette, F., Cajochen, C., & Peigneux, P. (2007). A time to think: Circadian rhythms in human cognition. *Cogn Neuropsychol*, *24*(7), 755–789. https://doi.org/10.1080/02643290701754158

Scullin, M. K., & Bliwise, D. L. (2015). Sleep, Cognition, and Normal Aging: Integrating a Half Century of Multidisciplinary Research. *Perspectives on Psychological Science*, *10*(1), 97–137. https://doi.org/10.1177/1745691614556680

Sexton, C. E., Storsve, A. B., Walhovd, K. B., Johansen-Berg, H., & Fjell, A. M. (2014). Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology*, *83*(11), 967–973. https://doi.org/10.1212/WNL.0000000000000774

Shing, Y. L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S. C., & Lindenberger, U. (2010). Episodic memory across the lifespan: The contributions of associative and strategic components. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1080–1091. https://doi.org/10.1016/j.neubiorev.2009.11.002

Shrivastava, D., Jung, S., Saadat, M., Sirohi, R., & Crewson, K. (2014). How to interpret the results of a sleep study. *Journal of Community Hospital Internal Medicine Perspectives*, *4*(5). https://doi.org/10.3402/jchimp.v4.24983

Siebner, H. R. (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*(13), 3379–3385. https://doi.org/10.1523/JNEUROSCI.5316-03.2004

Simons, J. S., Peers, P. V., Hwang, D. Y., Ally, B. A., Fletcher, P. C., & Budson, A. E. (2008). Is the parietal lobe necessary for recollection in humans? *Neuropsychologia*, *46*(4), 1185–1191. https://doi.org/10.1016/j.neuropsychologia.2007.07.024

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*(12), e0144838. https://doi.org/10.1371/journal.pone.0144838

Smith, M. E., McEvoy, L. K., & Gevins, A. (2002). The impact of moderate sleep loss on neurophysiologic signals during working-memory task performance. *Sleep*, *25*(7), 784–794.

Steenari, M.-R., Vuontela, V., Paavonen, E. J., Carlson, S., Fjällberg, M., & Aronen, E. T. (2003). Working Memory and Sleep in 6- to 13-Year-Old Schoolchildren. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*(1), 85–92. https://doi.org/10.1097/00004583-200301000-00014

Stepanski, E. J. (2002). The Effect of Sleep Fragmentation on Daytime Function. *Sleep*, *25*(3), 268–276. https://doi.org/10.1093/sleep/25.3.268

Tempesta, D., De Gennaro, L., Natale, V., & Ferrara, M. (2015). Emotional memory processing is influenced by sleep quality. *Sleep Medicine*, *16*(7), 862–870. https://doi.org/10.1016/j.sleep.2015.01.024

Terman, J. S., Terman, M., Lo, E. S., & Cooper, T. B. (2001). Circadian time of morning light administration and therapeutic response in winter depression. *Archives of General Psychiatry*, *58*(1), 69–75. https://doi.org/10.1001/archpsyc.58.1.69

Thürling, M., Hautzel, H., Küper, M., Stefanescu, M. R., Maderwald, S., Ladd, M. E., & Timmann, D. (2012). Involvement of the cerebellar cortex and nuclei in verbal and visuospatial working memory: A 7T fMRI study. *NeuroImage*, *62*(3), 1537–1550. https://doi.org/10.1016/j.neuroimage.2012.05.037

Tremblay, S., Lepage, J.-F., Latulipe-Loiselle, A., Fregni, F., Pascual-Leone, A., & Théoret, H. (2014). The uncertain outcome of prefrontal tDCS . *Brain Stimulation*, *7*(6), 773–783. https://doi.org/10.1016/j.brs.2014.10.003

Trumbo, M. C., Matzen, L. E., Coffman, B. A., Hunter, M. A., Jones, A. P., Robinson, C. S. H., & Clark, V. P. (2016). Enhanced working memory performance via transcranial direct current stimulation: The possibility of near and far transfer. *Neuropsychologia*, *93*, 85–96. https://doi.org/10.1016/j.neuropsychologia.2016.10.011

Trumbo, M. C. S. (2016). *Using Brain Stimulation to Enhance Working Memory: A Charged Topic*. 141.

Tulving, E. (2002). Episodic Memory: From Mind to Brain. *Annual Review of Psychology*, *53*(1), 1–25. https://doi.org/10.1146/annurev.psych.53.100901.135114

Turi, Z., Csifcsák, G., Boayue, N. M., Aslaksen, P., Antal, A., Paulus, W., Groot, J., Hawkins, G. E., Forstmann, B., Opitz, A., Thielscher, A., & Mittner, M. (2019). Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 min in young healthy adults. *The European Journal of Neuroscience*, *50*(8), 3261–3268. https://doi.org/10.1111/ejn.14403

Velanova, K., Jacoby, L. L., Wheeler, M. E., McAvoy, M. P., Petersen, S. E., & Buckner, R. L. (2003). Functional–Anatomic Correlates of Sustained and Transient Processing Components Engaged during Controlled Retrieval. *Journal of Neuroscience*, *23*(24), 8460–8470. https://doi.org/10.1523/JNEUROSCI.23-24-08460.2003

Wagner, A. D., Maril, A., Bjork, R. A., & Schacter, D. L. (2001). Prefrontal Contributions to Executive Control: FMRI Evidence for Functional Distinctions within . . . *Neuroimage*, *14*, 1337–1347.

Wagner, T., Fregni, F., Fecteau, S., Grodzinsky, A., Zahn, M., & Pascual-Leone, A. (2007). Transcranial direct current stimulation: A computer-based human model study. *NeuroImage*, *35*(3), 1113–1124. https://doi.org/10.1016/j.neuroimage.2007.01.027

Webb, W. B., & Agnew, H. W. (1975). Sleep Efficiency for Sleep-Wake Cycles of Varied

Length. *Psychophysiology*, *12*(6), 637–641. https://doi.org/10.1111/j.1469-8986.1975.tb00063.x

Wilckens, K. A., Erickson, K. I., & Wheeler, M. E. (2012, August 28). *Age-Related Decline in Controlled Retrieval: The Role of the PFC and Sleep* [Review Article]. Neural Plasticity; Hindawi. https://doi.org/10.1155/2012/624795

Winocur, G., & Hasher, L. (2002). Circadian rhythms and memory in aged humans and animals. In *Neuropsychology of memory, 3rd ed* (pp. 273–285). The Guilford Press.

Wong, L. Y. X., Gray, S. J., & Gallo, D. A. (2018). *Does tDCS Stimulation of Prefrontal Cortex at Retrieval Improve Recollection? Importance of Time of Day*. 1–57.

Wong, P. M., Hasler, B. P., Kamarck, T. W., Muldoon, M. F., & Manuck, S. B. (2015). Social Jetlag, Chronotype, and Cardiometabolic Risk. *The Journal of Clinical Endocrinology & Metabolism*, *100*(12), 4612–4620. https://doi.org/10.1210/jc.2015-2923

Wong, S., Flanagan, E., Savage, G., Hodges, J. R., & Hornberger, M. (2014). Contrasting Prefrontal Cortex Contributions to Episodic Memory Dysfunction in Behavioural Variant Frontotemporal Dementia and Alzheimer's Disease. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0087778

Wood, L., Egger, M., Gluud, L. L., Schulz, K. F., Jüni, P., Altman, D. G., Gluud, C., Martin, R. M., Wood, A. J. G., & Sterne, J. A. C. (2008). Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: Meta-epidemiological study. *BMJ*, *336*(7644), 601–605. https://doi.org/10.1136/bmj.39465.451748.AD

Xie, W., Berry, A., Lustig, C., Deldin, P., & Zhang, W. (2019). Poor Sleep Quality and Compromised Visual Working Memory Capacity. *Journal of the International Neuropsychological Society*, *25*(6), 583–594. https://doi.org/10.1017/S1355617719000183

Yavari, F., Jamil, A., Mosayebi Samani, M., Vidor, L. P., & Nitsche, M. A. (2018). Basic and functional effects of transcranial Electrical Stimulation (tES)-An introduction. *Neuroscience and Biobehavioral Reviews*, *85*, 81–92. https://doi.org/10.1016/j.neubiorev.2017.06.015

Yazar, Y., Bergström, Z. M., & Simons, J. S. (2012). What is the parietal lobe contribution to long-term memory? *Cortex*, *48*(10), 1381–1382. https://doi.org/10.1016/j.cortex.2012.05.011

Yoon, C., May, C. P., & Hasher, L. (1999). Aging, Circadian Arousal Patterns, and Cognition. In N. Schwarz, D. C. Park, B. Knäuper, & S. Sudman, *COGNITION, AGING, AND SELF-REPORTS* (pp. 117–117). Taylor & Francis. https://doi.org/10.4324/9780203345115_chapter_6

Youn, I.-H., & Lee, J.-M. (2020). Seafarers' Physical Activity and Sleep Patterns: Results from Asia-Pacific Sea Routes. *International Journal of Environmental Research and Public Health*, *17*(19), 7266. https://doi.org/10.3390/ijerph17197266

Zaehle, T., Beretta, M., Jäncke, L., Herrmann, C. S., & Sandmann, P. (2011). Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: Direct electrophysiological evidence. *Experimental Brain Research*, *215*(2), 135. https://doi.org/10.1007/s00221-011-2879-5

Zhou, Q., Yu, C., Yu, H., Zhang, Y., Liu, Z., Hu, Z., Yuan, T.-F., & Zhou, D. (2020). The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. *Sleep Medicine, 70*, 17–26. https://doi.org/10.1016/j.sleep.2020.02.003

Zivanovic, M., Paunovic, D., Konstantinović, U., Vulić, K., Bjekic, J., & Filipović, S. (2021). The Effects of Offline and Online Prefrontal vs Parietal Transcranial Direct Current Stimulation (tDCS) on Verbal and Spatial Working Memory. *Neurobiology of Learning and Memory*, *179*, 107398. https://doi.org/10.1016/j.nlm.2021.107398

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*

Appendix A: Comparison of the β estimates for the linear mixed effects models pt.1.

	Episodic Memory – Model 1b					Episodic Memory – Model 1b (adj. SFI)					Episodic Memory – Model 1b (adj. SE)				
Predictors	*Estimates*	*std. Error*	*CI*	*Statistic*	*p*	*Estimates*	*std. Error*	*CI*	*Statistic*	*p*	*Estimates*	*std. Error*	*CI*	*Statistic*	*p*
session	0	0.01	-0.01 – 0.02	0.45	0.651	0	0.01	-0.02 – 0.02	-0.1	0.919	0	0.01	-0.02 – 0.02	-0.04	0.969
Stimulation	0	0.01	-0.03 – 0.02	-0.18	0.861	0.01	0.02	-0.04 – 0.05	0.27	0.788	0.1	0.18	-0.24 – 0.45	0.59	0.553
Age Group	-0.08	0.01	-0.11 – -0.05	-5.87	<0.001	-0.05	0.02	-0.10 – -0.01	-2.34	0.02	-0.35	0.18	-0.69 – -0.00	-1.99	0.047
Difficulty	0.07	0	0.06 – 0.08	15.44	<0.001	0.07	0.01	0.05 – 0.09	8.89	<0.001	0.08	0.06	-0.04 – 0.19	1.27	0.206
Format	0.02	0	0.01 – 0.03	4.54	<0.001	0.01	0.01	-0.01 – 0.03	1.23	0.218	0.16	0.06	0.05 – 0.28	2.76	0.006
Time of Day	0	0	-0.01 – 0.01	-0.58	0.561	0	0.01	-0.01 – 0.02	0.59	0.555	-0.04	0.06	-0.16 – 0.07	-0.74	0.46
Stim * Age	0.01	0.01	-0.01 – 0.04	1.05	0.296	0.01	0.02	-0.04 – 0.05	0.4	0.691	0.13	0.18	-0.22 – 0.47	0.73	0.465
Stim * Difficulty	0	0	-0.01 – 0.01	-0.87	0.385	-0.01	0.01	-0.02 – 0.01	-1.16	0.245	0.1	0.06	-0.02 – 0.21	1.64	0.101
Age * Difficulty	-0.01	0	-0.02 – 0.00	-1.91	0.056	-0.01	0.01	-0.02 – 0.01	-0.73	0.466	-0.03	0.06	-0.15 – 0.09	-0.49	0.624
Stim * Format	0	0	-0.01 – 0.01	0.31	0.754	-0.01	0.01	-0.03 – 0.00	-1.43	0.154	0.19	0.06	0.07 – 0.31	3.19	0.001
Age * Format	0.04	0	0.03 – 0.05	8.03	<0.001	0.05	0.01	0.04 – 0.07	6.63	<0.001	-0.11	0.06	-0.22 – 0.01	-1.81	0.071
Difficulty * Format	0.02	0	0.01 – 0.03	4.37	<0.001	0.02	0.01	0.01 – 0.04	2.72	0.007	0.01	0.06	-0.11 – 0.12	0.12	0.902
Stim * Time of Day	0	0	-0.01 – 0.01	0	0.999	0	0.01	-0.01 – 0.02	0.54	0.59	-0.05	0.06	-0.17 – 0.07	-0.82	0.413
Age * Time of Day	0	0	-0.01 – 0.01	-0.39	0.697	-0.01	0.01	-0.02 – 0.01	-0.72	0.469	-0.02	0.06	-0.14 – 0.10	-0.29	0.773
Difficulty * Time of Day	-0.01	0	-0.02 – 0.00	-1.41	0.159	-0.01	0.01	-0.02 – 0.01	-1.16	0.248	-0.05	0.06	-0.17 – 0.06	-0.87	0.384
Format * Time of Day	0	0	-0.01 – 0.01	0.56	0.575	0	0.01	-0.01 – 0.02	0.05	0.962	0.05	0.06	-0.07 – 0.16	0.81	0.421
Stim * Age * Difficulty	0	0	-0.01 – 0.01	-0.72	0.471	0	0.01	-0.02 – 0.01	-0.25	0.806	-0.05	0.06	-0.16 – 0.07	-0.77	0.443
Stim * Age * Format	-0.01	0	-0.02 – 0.00	-1.79	0.073	0	0.01	-0.02 – 0.01	-0.41	0.679	-0.11	0.06	-0.23 – 0.00	-1.91	0.056
Stim * Difficulty * Format	0.01	0	-0.00 – 0.02	1.61	0.108	0.01	0.01	-0.00 – 0.03	1.85	0.065	0.02	0.06	-0.10 – 0.13	0.28	0.782
Age * Difficulty * Format	0	0	-0.01 – 0.01	0.62	0.538	0.01	0.01	-0.01 – 0.02	0.96	0.336	-0.04	0.06	-0.15 – 0.08	-0.63	0.527
Stim * Age * Time of Day	0	0	-0.01 – 0.01	0.72	0.47	0.01	0.01	-0.00 – 0.03	1.5	0.134	-0.03	0.06	-0.15 – 0.09	-0.46	0.644
Stim * Difficulty * Time of Day	0.01	0	-0.00 – 0.02	1.38	0.168	0.01	0.01	-0.01 – 0.02	0.9	0.37	0.03	0.06	-0.09 – 0.14	0.47	0.64
Age * Difficulty * Time of Day	0	0	-0.01 – 0.01	-0.53	0.596	-0.01	0.01	-0.02 – 0.01	-0.81	0.416	0.04	0.06	-0.08 – 0.16	0.67	0.506
Stim * Format * Time of Day	0	0	-0.01 – 0.01	0.1	0.92	0	0.01	-0.02 – 0.01	-0.15	0.882	0.06	0.06	-0.06 – 0.18	0.99	0.323
Age * Format * Time of Day	0	0	-0.01 – 0.01	-0.02	0.985	0	0.01	-0.01 – 0.02	0.63	0.527	-0.01	0.06	-0.13 – 0.10	-0.21	0.834
Difficulty * Format * Time of Day	0	0	-0.01 – 0.00	-1.02	0.31	-0.01	0.01	-0.03 – 0.00	-1.71	0.087	0.05	0.06	-0.07 – 0.16	0.76	0.45
Stim * Age * Difficulty * Format	0	0	-0.01 – 0.01	0.5	0.614	0	0.01	-0.01 – 0.02	0.31	0.76	-0.01	0.06	-0.13 – 0.10	-0.21	0.835
Stim * Age * Difficulty * Time of Day	0	0	-0.01 – 0.01	0.59	0.557	0.01	0.01	-0.00 – 0.03	1.41	0.159	-0.05	0.06	-0.17 – 0.06	-0.9	0.37
Stim * Age * Format * Time of Day	0	0	-0.01 – 0.01	0.83	0.406	-0.01	0.01	-0.02 – 0.01	-0.9	0.368	0.08	0.06	-0.04 – 0.19	1.28	0.201
Stim * Difficulty * Format * Time of Day	0	0	-0.01 – 0.01	0.79	0.43	0	0.01	-0.01 – 0.02	0.49	0.623	0.01	0.06	-0.10 – 0.13	0.23	0.815
Age * Difficulty * Format * Time of Day	-0.01	0	-0.02 – -0.00	-2.21	0.027	-0.01	0.01	-0.02 – 0.01	-1.05	0.292	-0.02	0.06	-0.13 – 0.10	-0.26	0.792
Stim * Age * Difficulty * Format * Time of Day	0	0	-0.01 – 0.01	0.86	0.388	0.01	0.01	-0.01 – 0.02	0.99	0.323	-0.04	0.06	-0.16 – 0.08	-0.66	0.508

Appendix A: Comparison of the β estimates for the linear mixed effects models pt.1.

Comparison between the original model 1.b, model 1.b adjusted for SFI and model 1.b adjusted for SE (no SQ-related variables, original variables from model 1.b only)

Appendix B: Comparison of the β estimates for the linear mixed effects models pt. 2. Comparison between model 1.b adjusted for SFI and model 1.b adjusted for SE (only SQ-related effects)

Episodic Memory – Model 1b adjusted for SFI

Predictors	*Estimates*	*std. Error*	*CI*	*Statistic*	*p*
Session	-0.00	0.01	-0.02 – 0.02	-0.10	0.919
SFI	-0.40	0.19	-0.77 – -0.02	-2.08	**0.037**
SFI * Stim	-0.07	0.19	-0.45 – 0.30	-0.37	0.709
SFI * Age	-0.19	0.19	-0.57 – 0.18	-1.02	0.309
SFI * Difficulty	0.02	0.07	-0.11 – 0.15	0.33	0.738
SFI * Format	0.18	0.07	0.05 – 0.31	2.75	**0.006**
SFI * Time of Day	-0.07	0.07	-0.20 – 0.06	-1.03	0.301
SFI * Stim * Age	0.14	0.19	-0.23 – 0.52	0.75	0.456
SFI * Stim * Difficulty	0.07	0.07	-0.06 – 0.20	1.07	0.284
SFI * Age * Difficulty	-0.04	0.07	-0.17 – 0.09	-0.62	0.535
SFI * Stim * Format	0.19	0.07	0.06 – 0.31	2.85	**0.004**
SFI * Age * Format	-0.15	0.07	-0.28 – -0.02	-2.34	**0.019**
SFI * Difficulty * Format	-0.00	0.07	-0.13 – 0.13	-0.02	0.986
SFI * Stim * Time of Day	-0.07	0.07	-0.20 – 0.07	-0.98	0.330
SFI * Age * Time of Day	0.05	0.07	-0.08 – 0.18	0.79	0.427
SFI * Difficulty * Time of Day	0.01	0.07	-0.12 – 0.14	0.19	0.849
SFI * Format * Time of Day	0.02	0.07	-0.11 – 0.15	0.31	0.755
SFI * Stim * Age * Difficulty	-0.02	0.07	-0.15 – 0.11	-0.34	0.734
SFI * Stim * Age * Format	-0.07	0.07	-0.20 – 0.05	-1.14	0.255
SFI * Stim * Difficulty * Format	-0.07	0.07	-0.20 – 0.06	-1.06	0.287
SFI * Age * Difficulty * Format	-0.04	0.07	-0.17 – 0.09	-0.59	0.556
SFI * Stim * Age *	-0.05	0.07	-0.18 – 0.08	-0.78	0.435

Time of Day					
SFI * Stim * Difficulty * Time of Day	-0.01	0.07	-0.14 – 0.12	-0.14	0.890
SFI * Age * Difficulty * Time of Day	0.01	0.07	-0.11 – 0.14	0.21	0.830
SFI * Stim * Format * Time of Day	0.02	0.07	-0.11 – 0.15	0.34	0.734
SFI * Age * Format * Time of Day	-0.02	0.07	-0.15 – 0.11	-0.33	0.743
SFI * Difficulty * Format * Time of Day	0.10	0.07	-0.03 – 0.22	1.46	0.144
SFI * Stim * Age * Difficulty * Format	0.00	0.07	-0.12 – 0.13	0.06	0.954
SFI * Stim * Age * Difficulty * Time of Day	-0.08	0.07	-0.21 – 0.05	-1.19	0.236
SFI * Stim * Age * Format * Time of Day	0.11	0.07	-0.02 – 0.23	1.62	0.104
SFI * Stim * Difficulty * Format * Time of Day	0.00	0.07	-0.13 – 0.13	0.02	0.987
SFI * Age * Difficulty * Format * Time of Day	-0.03	0.07	-0.15 – 0.10	-0.41	0.681
SFI * Stim * Age * Difficulty * Format * Time of Day	-0.05	0.07	-0.17 – 0.08	-0.72	0.472

	Episodic Memory – Model 1b adjusted for SE				
Predictors	*Estimates*	*std. Error*	*CI*	*Statistic*	*p*
Session	-0.00	0.01	-0.02 – 0.02	-0.04	0.969
SE	0.39	0.21	-0.01 – 0.80	1.92	*0.055*
SE * Stim	-0.13	0.21	-0.53 – 0.28	-0.61	0.540
SE * Age	0.32	0.21	-0.08 – 0.72	1.55	0.121
SE * Difficulty	-0.00	0.07	-0.14 – 0.13	-0.05	0.964
SE * Format	-0.16	0.07	-0.30 – -0.03	-2.35	**0.019**
SE * Time of Day	0.05	0.07	-0.09 – 0.19	0.70	0.483
SE * Stim * Age	-0.13	0.21	-0.53 – 0.27	-0.64	0.525
SE * Stim * Difficulty	-0.12	0.07	-0.25 – 0.02	-1.69	0.091
SE * Age * Difficulty	0.02	0.07	-0.11 – 0.16	0.33	0.741
SE * Stim * Format	-0.22	0.07	-0.35 – -0.08	-3.12	**0.002**
SE * Age * Format	0.17	0.07	0.03 – 0.31	2.44	**0.015**
SE * Difficulty * Format	0.02	0.07	-0.12 – 0.15	0.24	0.814
SE * Stim * Time of Day	0.06	0.07	-0.09 – 0.20	0.78	0.434
SE * Age * Time of Day	0.02	0.07	-0.12 – 0.16	0.25	0.799

SE * Difficulty * Time of Day	0.05	0.07	-0.08 – 0.19	0.75	0.454
SE * Format * Time of Day	-0.05	0.07	-0.19 – 0.08	-0.77	0.439
SE * Stim * Age * Difficulty	0.05	0.07	-0.09 – 0.19	0.72	0.473
SE * Stim * Age * Format	0.12	0.07	-0.01 – 0.26	1.75	0.081
SE * Stim * Difficulty * Format	-0.01	0.07	-0.15 – 0.13	-0.16	0.875
SE * Age * Difficulty * Format	0.05	0.07	-0.09 – 0.18	0.68	0.496
SE * Stim * Age * Time of Day	0.04	0.07	-0.10 – 0.18	0.54	0.587
SE * Stim * Difficulty * Time of Day	-0.03	0.07	-0.16 – 0.11	-0.39	0.700
SE * Age * Difficulty * Time of Day	-0.05	0.07	-0.19 – 0.08	-0.75	0.452
SE * Stim * Format * Time of Day	-0.07	0.07	-0.20 – 0.07	-0.98	0.329
SE * Age * Format *	0.02	0.07	-0.12 – 0.15	0.24	0.808

Time of Day					
SE * Difficulty * Format * Time of Day	-0.06	0.07	-0.19 – 0.08	-0.82	0.412
SE * Stim * Age * Difficulty * Format	0.02	0.07	-0.12 – 0.15	0.23	0.814
SE * Stim * Age * Difficulty * Time of Day	0.07	0.07	-0.07 – 0.20	0.98	0.328
SE * Stim * Age * Format * Time of Day	-0.09	0.07	-0.22 – 0.05	-1.25	0.211
SE * Stim * Difficulty * Format * Time of Day	-0.01	0.07	-0.15 – 0.12	-0.16	0.869
SE * Age * Difficulty * Format * Time of Day	0.01	0.07	-0.13 – 0.14	0.11	0.916
SE * Stim * Age * Difficulty * Format * Time of Day	0.05	0.07	-0.08 – 0.19	0.74	0.456