# Non-Invasive Electrical Brain Stimulation: Effects on Cognitive Performance and Cerebral Hemodynamics in Younger Adults and Older Adults: A Scoping Review and Two Experimental Studies

by

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## Abstract

Clinicians including rehabilitation professionals use a variety of evidence-based behavioural techniques to help improve functioning for adults affected by cognitive and language disorders. In recent years, the use of non-invasive brain stimulation has been studied as a method to augment behavioural therapies; transcranial direct current stimulation (tDCS) is one such approach that is proposed to increase neural efficiency which can potentially improve cognitive processing. Although tDCS has been implemented with different groups of participants across several studies, questions remain about its effects on cognitive processing, particularly among older adults. Additionally, the effects of tDCS on the interaction between cognitive processing and cerebral hemodynamics remain poorly understood. Thus, the purpose of this thesis was to examine the effects of tDCS on cognition in older adults and to develop a fuller understanding of the interaction between cognitive processing and cerebral oxygenation hemodynamics, measured with functional near-infrared spectroscopy (fNIRS).

Three studies were conducted: a scoping review, and two small sample randomized controlled trials. In the first study, a scoping review and meta-analysis were conducted to investigate the effects of tDCS on the brain-cognition interaction in the context of aging. Findings revealed that tDCS has the greatest effect in healthy younger adults in both cognition and cerebral oxygenation hemodynamics. The second study, which was amended from an older adult sample to a healthy younger adult sample due to COVID-19, investigated the effects of tDCS on the interaction between cerebral oxygenation hemodynamics measured with fNIRS and working memory performance. Consistent with the previously mentioned scoping review and meta-analysis, anodal tDCS increased working memory performance and blood-oxygen concentrations, however, only during higher cognitive load demands. In the third study, the

effects of tDCS on a clinical geriatric inpatient sample with depression and/or anxiety were investigated. In this study, it was found that tDCS selectively modulated executive functioning subprocesses, notably inhibition processing, complex planning, and processing speeds.

Together, these results contribute to the ecological validity and feasibility of using tDCS in clinical care settings, while adding clinical and aging-specific considerations on the effect of tDCS between the brain and cognition interaction. Importantly, this series of studies adds to the literature on the use of tDCS, and the interaction with individualized resting-state cerebral oxygen hemodynamics, which helps to better control for variability across aging and disease status. Although COVID-19 impacted the sample recruited for both the second and the third studies presented, the results provided a foundation for future tDCS-fNIRS studies with healthy older adults and those with cognitive impairment from neurological diseases and disorders.

## Preface

I was the primary contributor and lead author on the three studies that form this thesis. However, interdisciplinary collaboration made the work possible, and I would like to describe contributions to the projects in the text that follows.

The scoping review presented in Chapter 4 was designed with the assistance of Dr. Esther Kim. I was responsible for database searches, data compilation, and data analysis. Data extraction, synthesis, and manuscript preparation was a collaborative effort between myself, Dr. Esther Kim, and Mr. Michael Zeeman (Faculty of Medicine and Dentistry). The authors would like to thank Liz Dennett for her assistance and consultation during the database search. Chapter 4 has been published as Figeys, M., Zeeman, M., & Kim, E.S. (2021). Effects of Transcranial Direct Current Stimulation (tDCS) on Cognitive Performance and Cerebral Oxygen Hemodynamics: A Systematic Review. *Frontiers in Human Neuroscience, 15.*

The randomized control trial in Chapter 5 was designed in collaboration with Dr. Esther Kim. In this study, I was responsible for programming the administered task, determining the neuroimaging parameters utilized, recruitment, data collection, intervention administration, data organization and integration, data pre-processing, data analysis, as well as teaching and supervising. Mr. Steven Buchan and Mr. Doyeon Hwang completed undergraduate research projects using data obtained from this project; Ms. Mira Wirzba and Ms. Thi Kim Truc (Tina) Huynh assisted in data collection. I led the manuscript writing, in collaboration with Dr. Kim. This research project received research ethics approval from the University of Alberta Research Ethics Board, titled *The Effects of tDCS on Cerebral Perfusion and Cognition in Young Adults* (Pro00106123) with an amendment added to the initial protocol approved on June 10$^{th}$, 2021. The manuscript will be submitted to *Brain and Behaviour* for peer review.

The clinical randomized controlled trial presented in Chapter 6 was a sub-study under a larger initiative at the Glenrose Rehabilitation Hospital (Alberta Health Services, Edmonton, Canada), led by Dr. Hubert Kammerer (Staff Physician) and Mr. Jim Raso (Senior Research Consultant). Alongside Dr. Esther Kim (Department of Communication Sciences and Disorders) and Dr. Ada Leung (Department of Occupational Therapy), we developed a cognitive battery for the study. I administered the cognitive assessments as well as the intervention 3-4 days per week (with Rehabilitation Engineers Ms. Terry Blois, Mr. Brendan Restall, and Mr. Hosein Bahari administering the intervention for the remaining days). I led the data analysis in collaboration with Ms. Sheryn Villarey, Dr. Esther Kim, and Dr. Ada Leung. I also led the manuscript writing, with assistance from Ms. Sheryn Villarey, Dr. Esther Kim, Dr. Ada Leung, Mr. Steven Buchan, Mr. Jim Raso, Dr. Hubert Kammerer, Dr. David Rawani, Ms. Megan Kohls-Wiebe, and Mr. Steven Buchan. We would like to acknowledge and thank all of the Occupational Therapists and Physicians on units 3D and 4C at the Glenrose Rehabilitation Hospital, as well as the Glenrose Geriatric Research Team. This project was approved by the University of Alberta Research Ethics Board (Pro00078317), conformed to the Declaration of Helsinki, and will be submitted for peer review.

## Dedication

The person with a cognitive impairment is not giving you a hard time. Rather, *the person living with a cognitive impairment is having a hard time.*

**Acknowledgements**

*"It is not how much you do, but how much love you put in the doing"*

Mother Teresa

I remember entering your office for the first time; I was struggling with my Master's project, using AAC in Primary Progressive Aphasia. "I don't even go here," I thought to myself, the Queen's student at the time; and yet, after walking through your office door that same day I have only been met with kindness and support. During our very first meeting, you drew four intersecting circles and took the time to explain the A-FROM model making sure I understood the concepts, while sharing your expertise. You asked to read my thesis when it was completed out of pure, genuine interest. When I decided to pursue a PhD, Dr. Esther Kim was the person I knew I wanted to learn from. You have always given me numerous opportunities to grow, even when my PhD topic changed a couple of times! After seeing the wholehearted joy you give people at Aphasia Camp, the student engagement in your lectures, and your passion for research and advocacy, it is clear that you "put a lot of love in the doing". From the world of academia, to attending my wedding festivities, to treating us for dinner out at the Fairmont Lake Louise, you have always gone beyond. That makes you a spectacular supervisor and mentor. Thank you for helping me throughout the program, and I hope this is the start of our journey working together!

To Drs. Tammy Hopper, Ada Leung, and Torrey Loucks, thank you for all your ongoing support, feedback, and understanding throughout this process. Over the past few years, you have all helped me further develop my projects, and promoted what it means to be an interdisciplinary clinical researcher. Dr. Hopper, thank you again for all your editing on the thesis (especially over the Easter holiday and while already being busy as the Dean); you have made this into a masterpiece! Dr. Kate Hoy, thank you for previously meeting with me and chatting about

neuromodulation research in Australia and answering some of my questions, I am pleased to have you as a committee member. Dr. Esther Fujiwara, I am still relatively new to neuromodulation as well as neuropsychology and your insights are greatly appreciated. Lastly, to all my previous Instructors and staff at the University of Alberta Faculty of Rehabilitation Medicine, thank you for helping me shape into the clinician and researcher I am today.

Carlee Wilson (Dr. Wilson now), Dr. Isabel Hubbard, and Dr. Mohammed ALHabri, thank you for being great lab mates, letting me bounce ideas off you, and going out for Korean Fried Chicken lunches. To the CSD students in the lab throughout the years, thank you for teaching me more about aphasia, and sharing your knowledge with me.

To my wife Leah, I couldn't have done this without you. Thank you for being a night-owl and staying up with me, keeping me company while I struggled to learn how to code, run statistics, and being supportive while I try to keep up with all the reading and writing. I would also like to thank my parents for passing down their "nerd" genetics to me. My younger sister Christine, who is finishing up her Master's in Nursing – you have to do a thesis defense soon too, so good luck (but you don't need it, you also inherited the "nerd" genetics). To my two cats – my goodness you two are annoyingly charming, walking all over my keyboard and fighting each other while I am on Zoom calls.

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## Abbreviations

AD: Alzheimer's Dementia
ANOVA: Analysis of Variance
AR: Autoregressive
APOE: Apolipoprotein E
APP: Amyloid Precursor Protein
$CMRO_2$: Cerebral Metabolic Rate of Oxygen
DLPFC: Dorsolateral Prefrontal Cortex
EEG: Electroencephalography
EF: Executive Functioning
fMRI: Functional Magnetic Resonance Imaging
fNIRS: Functional Near-Infrared Spectroscopy
GAI: Geriatric Anxiety Inventory
GDS: Geriatric Depression Scale
GLM: Generalized Linear Model
HbO: Oxyhemoglobin
HbR: Deoxyhemoglobin
HbT: Total Hemoglobin (HbO + HbR)
IRLS: Iteratively reweighted least squares
LTD: Long Term Depression
LTP: Long Term Potentiation
MANOVA: Multivariate Analysis of Variance
MCI: Mild Cognitive Impairment
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
RQ: Research Question
SDMT: Symbol Digit Modalities Test
tDCS: Transcranial direct current stimulation
TMS: Transcranial magnetic stimulation
TMT-A: Trail Making Test A
TMT-B: Trail Making Test B
WM: Working Memory

## Chapter 1: Introduction

Canadians are quickly aging; by 2030, it is predicted that nearly one-quarter of the population will be senior citizens (i.e., 65 years of age and older; Employment and Social Development Canada, 2014). As the population ages, the number of older-aged adults with pathological cognitive impairments will also increase. It is estimated that nearly one million Canadians will be living with cognitive impairment, including dementia, by 2031 (Alzheimer's Society of Canada, 2015). With these projections only a decade away, it is necessary to seek ways to improve and maintain cognitive function in older adults with neurological diseases and disorders.

One method of potential cognitive enhancement, which is being researched across various populations of interest, is the use of non-invasive brain stimulation including transcranial direct current stimulation (tDCS). The seminal work conducted by Nitsche and Paulus (2000) found that neuronal excitability can be altered by the application of weak electrical fields across the brain delivered by tDCS, which can alter membrane potentials. It is generally thought that excitability can be augmented over the anode and decreased over the cathode, in a process known as neuromodulation (Brunoni & Boggio, 2014). By doing so, the neuromodulatory effects of tDCS from a neurophysiological level may act on downstream networks, such as motor control, cognitive processing, and behaviour. Thus, there is significant potential for tDCS applications in both healthy and clinical populations; however, tDCS remains an experimental intervention (Fregni et al., 2015) and more research is needed to clarify its effects, particularly among older adults.

Measurement of cognitive enhancement is often based on neuropsychological test performance and focuses on broad cognitive domains including working memory and executive

functioning (Flöel, 2014; Dedoncker et al., 2016; de Boer et al., 2021). Changes in behaviour are often predicated on changes at the neuronal and neurophysiological levels; thus, neuroimaging has emerged as a valid measure of change as a result of myriad types of interventions. Functional Near-Infrared Spectroscopy (fNIRS) is a novel type of neuroimaging, which emits near-infrared light from LED or laser-based sources. Near-infrared light can be used to determine concentrations of hemoglobin chromophores (oxyhemoglobin and deoxyhemoglobin). This determination is achieved by applying an fNIRS emitter on the scalp and placing a photon detector a few centimetres away to quantify the number of photons (i.e., light) being returned; these optical values can then be converted into concentration data (Delpy et al., 1988; Pellicer & Bravo, 2011). fNIRS is a safe and very well tolerated approach to neuroimaging with some devices having a high degree of portability, making it advantageous in certain research paradigms (Pinti et al., 2020) while being easily paired with numerous interventions including non-invasive electrical brain stimulation (McKendrick et al., 2015). However, additional research is necessary to examine the feasibility and utility of fNIRS as a method to measure changes in cerebral oxygenation as a result of tDCS and paired with cognitive outcome measures.

### 1.1 Objectives and Research Questions

This doctoral thesis explores the use of tDCS to improve cognitive performance in younger and older adults. To date, studies utilizing tDCS for cognitive enhancement have been conducted with various participant populations across the lifespan; however, none has specifically examined cognitive effects in older-aged adults within a rehabilitative clinical-care environment. In addition, the mechanisms of potential tDCS enhancement remain largely unknown. Previous researchers have investigated the effect of tDCS on cerebral perfusion and

oxygenation using neuroimaging, including functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS), with mixed results. To the author's knowledge, within cognitive tDCS-fNIRS protocols, individualized cerebral oxygenation has not been incorporated within modeling; controlling for this factor may allow for a more accurate representation of regional neuronal activation when comparing across aging or disease status.

The objectives of this thesis were to examine the effects of tDCS on the cognition of older adults and to develop a fuller understanding of the interaction between cognitive processing and cerebral oxygenation hemodynamics, measured with fNIRS. The following research questions were of interest:

1. What are the effect sizes of tDCS on cognition and cerebral oxygenation hemodynamics measured with fNIRS in previously reported studies, taking aging into account? (Study 1: Scoping Review and Meta-Analysis)
2. What are the effects of tDCS on the interaction between working memory performance and cerebral oxygenation measured with fNIRS in healthy younger adults while accounting for individualized cerebral oxygenation? (Study 2: Randomized Controlled Trial)
3. What are the effects of tDCS on cognitive functioning in older-adult inpatients with symptoms of depression and/or anxiety? (Study 3: Pilot Randomized Controlled Trial)

### 1.2 COVID-19: Impacts on the Research

The emergence of COVID-19 posed several challenges which impacted the design and the feasibility of the randomized-controlled trials presented in this dissertation. In the third study presented (Chapter 6), data collection in geriatric inpatient units at the Glenrose Rehabilitation

Hospital was abruptly stopped in February 2020 due to the emergence of COVID. In addition, shortly after COVID-19 began, I returned to full-time clinical practice as a Registered Nurse in the Emergency Room, which limited the number of clinical sites I could be in because of healthcare restrictions. Additionally, hospital access was limited to essential services and clinical care. During this time, a study adding the use of functional neuroimaging with tDCS in older adult inpatients with Mild Cognitive Impairment was proposed; however, due to COVID-19, it was recommended by the committee to recruit a healthy younger adult sample. This resulted in shifting the focus from MCI and dementia in older adults to a healthy young adult population halfway through the doctoral program. With restrictions at the governmental and university levels, specific considerations were made to minimize in-person data collection time to make the second study presented in Chapter 5 feasible. Fortunately, data collection for the final study was completed prior to the emergence of the Omnicron variant.

### 1.3 Thesis Presentation

Following this Introduction (Chapter 1), Chapter 2 provides a literature review expanding on the fundamental knowledge relevant to the dissertation. Notably, this chapter provides details on cognition across aging, cerebral perfusion changes across the lifespan, and current clinical literature on MCI, depression, and anxiety. Furthermore, this chapter highlights neuroimaging studies related to the dorsolateral prefrontal cortex and cognition, as well as an overview of tDCS and fNIRS studies examining cognition. Chapter 3 provides further details regarding tDCS implementation and methodologies. Additionally, fNIRS methodologies are discussed, including background physics, implementation procedures, data collection, and statistical analysis. Chapters 4 through 6 include the three studies conducted to address the research questions (one

is published, one is submitted for review, and one is in preparation). Chapter 7 is a general discussion of the results from these studies, including future directions for research.

# Chapter 2: Literature Review

## 2.1 Cognition and Aging

Cognition is a multifaceted process, impacted by numerous neuroanatomical, psychological, and physiological factors. On a theoretical basis, Luria (1973) proposed a three-stage model of cognition consisting of (1) arousal; (2) processing of sensory information; (3) executive decision making and planning. To have effective cognitive processing, all three stages are required to be functional and dynamically interacting (Luria, 1973).

Using the metaphor of a company, Bayles and colleagues (2020) described the roles and functions of cognition. Within the company, numerous departments (structures in the brain) perform different tasks of analyzing sensory information. From here, departments report to a higher power, the executive team, to make decisions and actions best for the company (executive functioning within the frontal lobes). Expanding on the metaphor of a company, cognitive domains (i.e., company departments) include sensation, perception, motor skills, attention, memory, executive functioning, processing speed, and language; under each of these hierarchical categories exist further subdomains (Harvey, 2019).

Cognition changes with age; cognitive performance differs between younger and older adults, particularly in the areas of speed of processing, visuospatial skills, executive function and memory (Park et al., 2002; Park & Reuter-Lorenz, 2009). These changes are decremental and occur due to structural and functional brain changes associated with healthy aging (Cabeza, Nyberg & Park, 2016). The *frontal lobe hypothesis* (Dempster, 1992; further adapted by West, 1996) predicts that aging-related cognition declines as a result of aging-related changes within the frontal lobe. Decreases in prefrontal cortex volume and decreased connectivity in white-matter tracts are seen in structural imaging and examination of post-mortem brains of healthy

aged adults (Verwer et al., 2003; Yang et al., 2016). As per the frontal lobe hypothesis, these structural changes may explain the known cognitive decline seen with healthy aging, including memory, executive functioning, reasoning and judgement, attention, and processing speed (Levine et al., 2018).

Neuroimaging tools have provided insight into the relationships involving neuropsychological-physiological changes seen in aging. In particular, a correlation between cerebral volume and cognitive performance has been reported by researchers (Staffaroni et al., 2019; Alosco et al., 2013). The rate of global brain atrophy, as well as regional atrophy rates within the hippocampal body and entorhinal cortex, are highly correlated with aging-related cognitive performance (Zhang et al., 2011). Furthermore, decreased white matter tracts in the frontal lobe (as outlined in the *frontal lobe hypothesis,* may impair cognitive function, including working memory processing (Verwer et al., 2003; Burgmans et al., 2011; Yang et al., 2016). Ageing-related white matter degeneration may be an indicator of impaired myelin sheaths; this may be reflective of impaired myelination processes at the cellular level (Pakkenberg et al., 2003). The loss of myelinated tracts may be involved in the cognitive changes seen in aging, such as processing speed declines across aging (Harada et al., 2013; Levine et al., 2018). Grey matter volume in aging is associated with shrinkage and decreased synaptic activity, rather than neuronal apoptosis (Esiri, 2007). Ageing-associated volumetric changes appear to occur in an anterior to posterior fashion, starting in the frontal lobe (Raz et al., 2006). Supporting evidence in white-matter changes across aging, noted in a posterior-to-anterior manner in the frontal and parietal lobes (Gunning-Dixon et al., 2009; Davis et al., 2009), complement neurocognitive changes seen with aging which heavily draw on frontal and prefrontal pathways. Working memory is one area of cognition that is reliant upon these neural pathways and regions,

specifically the dorsolateral prefrontal cortex (DLPFC; Wager & Smith, 2003). Thus, working memory may become impaired due to anterior-to-posterior white matter pathway changes as proposed in the frontal lobe hypothesis.

**2.2 Working Memory**

WM is proposed to be a dynamic function that is highly integrated across cognitive domains, including executive functioning, language, visuospatial awareness, and attention. WM has previously been operationally defined as a process that can temporarily store, manipulate, and recall information, limited in terms of temporal and span capacities (Goldman-Rakic, 1995; Baddeley, 2010; Baddeley & Hitch, 2019). The conceptual model proposed by Baddeley and Hitch (1974), and further developed by Baddeley (2000) to include *the episodic buffer*, is a prominent WM framework. In this model, WM is broken down into the *central executive* and two shorter-temporal systems: *the phonological loop* and *the visuospatial sketchpad.*

*The Central Executive* controls and regulates the phonological loop, visuospatial sketchpad, the episodic buffer, and attention. Further, the central executive is responsible for the manipulation and flow of information, while being engaged during information storage processing (Baddeley & Hitch, 1974; Baddeley, 2003). The central executive can shift the focus of attention while inhibiting unwarranted stimuli (Baddeley, 2003).

*The Phonological Loop* is responsible for processing linguistic information. The model proposed by Baddeley & Hitch (1974) has two subcomponents under the phonological loop, consisting of a *short-lasting storage system* (information retention for several seconds) where stored information temporally decays, unless the second subcomponent, called *the subvocal rehearsal system*, is activated. This subvocal rehearsal system is used to prolong the duration that information is stored, and also integrates visual language stimuli into the phonological loop.

Encoding of the phonological stimuli can occur through rehearsal and can be paired with information stored within long-term memory (Baddeley, 1992; 2003).

*The visuospatial sketchpad* can be broken down into the visual and spatial components. The visual component is thought to be primarily responsible for the storage of static physical properties including physical imagery, mental imagery, the environmental context, object relation, and reading (Baddeley, 1992; 2003). In addition, the spatial component processes information on location and motion. Although the visuospatial sketchpad can operate independently, storage and rehearsal depend on the phonological loop transforming visual information into verbal or auditory information (Baddeley, 1992; 2003).

The more recently added *episodic buffer* (Baddeley, 2000), a new component to the previous WM model proposed, is also controlled by the central executive. This buffer is primarily thought to be a limited capacity storage system that obtains multiple information inputs. In contrast to the central executive, the episodic buffer does not alter attentional control. Instead, it turns multi-sourced information into "...chunks or episodes, hence the term 'episodic'; it is a buffer in the sense of providing a way of combining information from different modalities into a single multifaceted code" (Baddeley, 2003, pp. 203).

### *2.2.1 Measures of Working Memory*

One type of WM-specific task widely used in research studies is the *n*-back task. The *n*-back task requires the recall of individually presented stimuli*, n* cues previously. This involves the short-term storage of stimuli, while new stimuli are presented. For every new stimulus, the participant must determine if it matches the stimuli *n*-periods previously. In typical *n*-back paradigms, *n* ranges between 0-2. Owen and colleagues (2005) report several critical regions of activation when performing an *n*-back task, particularly the prefrontal cortex. As Owen and

colleagues (2005) discuss, the dorsolateral prefrontal cortex is believed to provide higher-order executive strategic control mechanisms for working memory.

The *n*-back task has been paired with fNIRS study protocols in younger and older healthy adults, as well as in older adults with disordered cognition as a result of Mild Cognitive Impairment (MCI). This makes the *n*-back task a valuable assessment for comparison of WM performance across age and health status. Niu and colleagues (2013) paired fNIRS with an *n*-back task in older adults with MCI and aged-matched healthy controls. A key finding is that individuals with MCI appear to have dampened hemodynamic signals during the working memory task when compared to healthy older adults. Decreased HbO signalling in MCI was especially noted in the dorsolateral prefrontal cortex (Niu et al., 2013), further supporting the evidence of the region in working memory and executive functioning. When examining behavioural outcomes, it was reported that there were no significant differences between healthy older adults, and those with MCI, when completing an *n*-back task (Yeung et al., 2016). Increased frontal lobe activation measured with fNIRS during the *n*-back task was seen in older controls; however, not in older adults with MCI (Yeung et al., 2016). Interestingly, this suggests that an increase in cerebral hemodynamics does not necessarily mean an increase in behavioural or cognitive performance.

Some have critiqued that the *n*-back task is not a working memory task; instead, it may be considered a continuous recall task as it does not involve the manipulation of information as discussed in the Baddeley and Hitch framework of WM (Baddeley and Hitch, 1974; Kane et al., 2007). Although there is face validity of the *n*-back task, construct validity remains in question (Kane et al., 2007). One potential solution is to integrate information manipulation tasks within an *n*-back task, which is achieved in the Toulouse *n*-back task. The Toulouse *n*-back task

incorporates simple mathematical addition or subtraction problems using numbers that are multiples of 5 five (e.g., 35-10, 15+20, 65-20, etc…) within the traditional *n*-back paradigm (Causse et al., 2017). Mandrick and colleagues (2016) paired the Toulouse *n*-back task with fNIRS and pupillometry in healthy young adults and demonstrated that an increase in cognitive load resulted in increased prefrontal oxygenation and pupil diameter. *n*-back tasks rely heavily on WM processes in the prefrontal cortex, including the DLPFC (Owen et al., 2005). In line with previous tDCS studies targeting working memory, anodal stimulation will be applied over the DLPFC (Hanley & Tales, 2019; Berryhill & Jones, 2012; Stephens & Berryhill, 2016; Di Rosa et al., 2019). Therefore, performance on the Toulouse *n*-back can be used to measure the WM changes due to tDCS, and fNIRS can be applied to quantify changes in cerebral oxygenation hemodynamics. Thus, the relationship between behavioural responses and cerebral perfusion can be investigated. A recent study reported a contra-hemispheric increase in cerebral oxygenation post-tDCS (Das et al., 2019); hence, it is advantageous to measure bilateral prefrontal cortices with fNIRS.

### *2.2.2 Working Memory Declines Across Ageing*

Although it is generally accepted that WM becomes slower or impaired with aging, it remains unknown which specific processes that make up WM become altered (Glisky, 2007). Within the literature, three main theories are proposed to address WM changes specifically observed in aging: (1) attentional resource deficits, (2) reduced information processing, and (3) loss of inhibitory control processes (Park, 2000; Park & Gutchess, 2000; Glisky, 2007, McNab et al., 2015). Attentional resource deficits are proposed to occur due to a lack of mental energy, which reduces with age (Craik & Byrd., 1982). It is well documented that attention becomes altered across aging (Harada et al., 2013). Slowing of information processing not only impacts

WM but can account for performance changes across other cognitive domains due to aging (Salthouse, 1996). Impaired inhibitory control results in the lack of ability to ignore irrelevant stimuli, which reduces the capacity of the phonological loop and visuospatial sketchpad within the Baddeley & Hitch Model (Hasher & Zacks, 1988; Glisky, 2007; McNab et al., 2015).

Given the neurocognitive changes observed in aging, it is generally expected that younger adults will perform better on working memory tasks compared to older adults. Rieck and colleagues (2017) investigated the effects of increasing cognitive load across the lifespan using fMRI; they report a reduced ability of neuronal modulation during states of increasing cognitive demand across increasing age; activation of prefrontal cortical regions were noted to be greater in younger adults (aged 20-34), compared to older adults (aged 55-69). One model, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008), supports the findings outlined by Rieck and colleagues (2017). CRUNCH suggests that aging-related cognitive decline across the lifespan occurs as a compensatory mechanism, with decreasing activation in higher-cognitive loads as age increases in older adults.

Additional subprocesses impacting working memory have also been noted to change across the lifespan, including emotional regulation and recognition memory (Berger et al., 2017). Further, inhibitory control deficits may also be present across aging (Yi & Friedman, 2014), as well as shifts in working memory-associated cognitive processes. It has been reported that WM is closely associated with executive functioning in young adults, whereas other cognitive processes including attention, short- and long-term memory may help prevent reductions in WM across aging (Gajewski et al., 2018). These potential changes in cognitive offsets may also represent a change in WM strategies from young adulthood to older age (Gajewski et al., 2018).

These changes in cognitive processes can impact working memory performance across the lifespan, however, the temporal factors of when these changes occur remain largely unknown. This being said, functional-structural imaging may provide insights. Evidence suggests that hemispheric asymmetry may occur in aging; the Hemispheric Asymmetry Reduction in OLDer adults (HAROLD), proposed that frontal activation in younger adults occurs in a lateralized pattern, whereas an increase in bihemispheric activation is seen in older adults (Cabeza, 2002). Whether these changes are compensatory or detrimental remains under investigation.

WM processes during higher-cognitive load states have been reported to begin to decline in the early thirties, and lower-cognitive loads begin to demonstrate declines between 40-70 years old (Cansino et al., 2013). During low-load WM tasks, the right DLPFC is highly engaged in older adults to achieve performance levels similar to younger adults; as WM load increases, a proposed DLPFC overactivation may negatively impact WM performance (Cappell et al., 2008). DLPFC overactivation in older adults compared to younger adults has further been replicated using recollection tests, with reported results more in line with dysfunction rather than compensatory mechanisms (McDunough, Wong, & Gallo, 2018).

Working memory training appears to be of benefit to ameliorating aging-related working memory decline; Vermeij and colleagues (2017) have demonstrated that there is a decrease in prefrontal cerebral oxygenation after working memory training in healthy older adults, concurrent with improved behavioural performance. Changes in cerebral oxygenation may represent compensatory or restorative processes, which may further overlap with increased neuronal efficiency; high hemodynamic activation patterns during lower WM tasks were associated with poorer treatment gains (Vermeij et al., 2017). It further appears that older adults

with “youth-like” prefrontal cortical activation may fare better with aging-related changes in cognitive performance and plasticity (Vermeij et al., 2017).

### *2.2.3 Cognitive Variability in Older Adults*

Cognitive performance becomes increasingly variable with age, being impacted by numerous biopsychosocial factors. Typical approaches to cognitive screening in older adults often *target the degree of cognitive impairment*, however, these approaches often overlook intraindividual (within-person) variability in cognition (Cerino et al., 2021). Lower intraindividual variability occurs when there is consistent performance across repeated cognitive measures, whereas high variability is a result of more inconsistent performance. Across ageing, a slow increase of variability occurs until the sixth decade of life, where a rapid progression of increasing cognitive variability is apparent for the remainder of one’s lifespan (LaPlume et al., 2022).

One major biopsychosocial factor impacting cognitive variability is disease status; previous research has demonstrated increased intraindividual variability in older adults with mild dementia compared to those without neuro-pathologies (Hultsch et al., 2000). Dispersion, or intraindividual performance variability across varying cognitive tasks and domains, has been shown to increase in older adults, as well as in those with maladaptive cognitive decline (Hilborn et al., 2009). Additionally, multiple intraindividual assessments have demonstrated greater variability in those with MCI compared to controls (Cerino et al., 2021). The line between normal and maladaptive-associated cognitive intraindividual variability remains unknown. Additionally, most older adults do not develop MCI or dementia, despite ageing-related changes in cognition (Harada et al., 2013).

It is well established that ageing-related changes in fluid abilities, including processing and information manipulation, occur across ageing. These includes processing speed, attention, as well as executive functioning processes (Murman, 2015; Harada et al., 2013). On the other hand, crystallized cognitive abilities (previously acquired through skills and past knowledge acquisition), typically increase across the lifespan (e.g., vocabulary; Murman, 2015, Harada et al., 2013). Therefore, in older adults, performance may decline or appear impaired on cognitive testing that targets fluid abilities when compared to healthy younger adults; thus, comparing cognition across the lifespan should be done so with due diligence regarding normal ageing-related changes.

### *2.2.4 Limitations in WM Literature in Ageing*

Several limitations and further questions arise from this previous literature when examining working memory across the lifespan. Largely, the temporal component of aging-related working memory decline is unknown. In other words, when in one's lifespan working memory declines occur, as well as protective mediating factors, remain abstruse. Early perfusional changes in adulthood may serve as potential markers of amyloid-beta deposition (Meier et al., 2020), which may lead to an increased risk of cognitive decline later in life. However, this hypothesis has not been proven due to a lack of longitudinal research studies. As age impacts cognitive processes including WM, comparing WM performance across age groups should be done so with caution.

Restoring "youth-like" prefrontal cortex perfusion may act as a cognitive protective factor in older adults and may be achieved by cognitive training (Mozolic et al., 2010; Vermeij et al., 2016). Other approaches, such as the effects of tDCS on WM performance and cerebral oxygenation in older adults also remain largely unestablished. The physiological implications of

tDCS may assist in altering perfusion to a youthful state in young adults at the cerebrovascular and neuronal levels. To begin exploring these effects across aging, it is necessary to determine what "youth-like" responses occur due to tDCS on the interaction between cognitive performance and perfusional biomarkers while controlling for individualized cerebral oxygenation across ages.

### 2.3 tDCS Neurophysiology, Applications, & Ageing

As previously highlighted in Chapter 1, tDCS involves the application of weak electrical currents across the brain. This delivered current is thought to modulate neurons at the cellular level, expanding across larger neuronal networks, which may act on downstream cognitive and behavioural domains. tDCS has been applied across the lifespan to numerous populations, including a wide range of psychiatric and cognitive disorders. tDCS has been applied in chronic pain, schizophrenia, depression, anxiety, and numerous other disorders (Moffa et al., 2018). Further, tDCS has previously been safely applied in individuals with MCI as well as dementia, with minimal side effects (Chang et al., 2018). It is believed that tDCS can achieve long-term potentiation (LTP) or long-term depression (LTD) like changes (Stagg & Nitsche, 2011). Thus, the main advantages of tDCS are to achieve these neuromodulatory effects without the use of pharmacological regimens, in addition to being relatively simple to apply, low cost, and often portable.

The exact neurobiological mechanisms underlying tDCS remains poorly understood (Medeiros et al., 2012). tDCS is proposed to modulate the resting membrane thresholds of neurons in an electrode-dependent manner (Nitsche & Paulus, 2000, 2001; Nitsche et al., 2003). Conventional current intensities appear to alter the resting electrical state by 0.2 to 0.5 mV, in

either a more negative direction (i.e., hyperpolarization) or a more positive direction (i.e., hypopolarization; Opitz et al. 2009, Radman et al., 2018). Although this is a small change relative to a 15mV difference to achieve an action potential, it is hypothesized that the summative effects of individual neuromodulation at the single-cell level impact the more extensive neural network (Hampstead et al., 2014). It is also hypothesized that the slight shifting of resting membrane potential alters temporal components of electrical current conduction (Opitz et al., 2009; Radman et al., 2018).

Part of the neurophysiologic mechanisms behind the neuromodulatory processes of tDCS during stimulation is believed to be related to two major cellular ions: sodium and calcium. Anodal tDCS is hypothesized to hypopolarize the neuron by creating a net influx of $Na^+$ ions (Nitsche et al., 2003), whereas the processes behind cathodal-induced hyperpolarization remain unclear (McLaren et al., 2018). Carbamazepine, a common sodium-channel blocking drug used for the management of seizures and neuropathic pain syndromes, has been shown to block the expected anodal tDCS hypopolarization (Nitsche et al., 2003). Similarly, the administration of flunarizine (a calcium-channel blocker) has also been shown to diminish the effects of anodal tDCS (Nitsche et al., 2003). Interestingly, no effects are seen with cathodal stimulation when looking at these ion-mediated processes (Nitsche et al., 2003). Although electromotive gradients may be part of the tDCS mechanism, cellular diffusion of ions from the extracellular space would cause the intracellular ion concentration to stabilize to baseline, reversing tDCS effects; therefore, electrical currents must somehow be involved in other neuronal processes and cellular signalling (Reinhart et al., 2017).

NMDA receptors have been established to be associated with neuroplastic processes, including long-term depression and potentiation (Bennett, as cited in Nitsche et al., 2000).

NMDA activation results in a postsynaptic cellular influx of calcium ions. The level of NMDA activation primarily determines the rise in intracellular calcium concentration. Intracellularly, varying concentrations of calcium yield different effects (Stagg & Nitsche, 2011). Minimal increases in calcium ions post-synaptically result in long-term depression (LTD), large calcium influxes result in long-term potentiation (LTP) changes, and a moderate level of influxes result in no changes (Stagg & Nitsche, 2011). Once calcium has entered the cell, downstream signalling occurs. Calcium/Calmodulin dependent kinase (CAMK) and cyclic adenosine monophosphate response binding protein (CREB) undergo phosphorylation, required to trigger genetic transcription required for LTP (Silva, 2003). To summarize, LTP processes may act as a protective mediator, whereas LTD may share processes seen in neurodegeneration (Sheng & Erturk, 2014). LTP and LTD processes may be altered by NMDA modulation using tDCS and may be beneficial in both healthy and pathological cognitive aging.

## 2.4 tDCS Applications to Improve Cognitive Processing Across the Lifespan

### *2.4.1 Single Session tDCS Applications in Young Adults.*

Numerous studies have implemented single-session tDCS protocols in young adults. In the majority of studies applying anodal tDCS specific to WM in younger adults, it is reported that WM enhancement can be achieved during (online) and after (offline) tDCS stimulation (Hurley & Machado, 2018). Fregni and colleagues (2005) investigated the effects of 1mA anodal tDCS over the left DLPFC on a WM 3-back task in fifteen healthy young adults aged 19-22 years old (of which, $n = 7$ repeated the study with cathodal tDCS). Anodal stimulation resulted in increased WM accuracy on the 3-back task, while cathodal stimulation resulted in no significant changes (Fregni et al., 2005). In line with Fregni and colleagues (2005), a separate study investigated the temporal after-effects of 1mA anodal tDCS over the left DLPFC on the 3-back

task; again, it was found that 3-back accuracy was increased with anodal tDCS, with performance gains lasting at least 30 minutes after stimulation (Ohn et al., 2008). Offline improvements were increased by electrical current coverage involving the DLPFC (Kim et al., 2014).

While the majority of studies investigating tDCS on cognitive processing have targeted the left DLPFC with anodal tDCS, WM improvements have also been noted with other electrode montages, such as right DLPFC stimulation (Hurley & Machado, 2018). Another key consideration is the dosage of electrical current. Previous evidence suggests that 2mA of current may elicit a higher performance during online tasks, while 1mA may target offline performance (Hurley & Machado, 2018). In a combined tDCS-EEG study targeting WM and the temporal aftereffects of stimulation, significant improvements in reaction time on the 2-back span were reported; interestingly, it was found that those receiving a 1mA current (20 minutes, anode over the left DLPFC) resulted in the most significant results and that higher doses did not increase cognitive performance nor the temporal after-effects of tDCS stimulation (Hoy et al., 2013). Results of anodal stimulation in other variations of the *n*-back task and the Digit span forward task remain consistent with these findings of improved cognitive performance (Martin et al., 2014; Andrews et al., 2011).

Several meta-analyses of the effects of tDCS on WM in healthy and clinical populations have been conducted. Hill, Fitzgerald, & Hoy (2016) report a small yet significant effect size favouring the use of anodal tDCS to increase WM; however, a separate meta-analysis reports no clear effect of tDCS on WM (Horvath, Forte, & Carter, 2015). In a third meta-analysis, Brunoni & Vanderhasselt (2014) report that tDCS only improved reaction times during WM tasks. Some of the disagreement between findings may be due to differences in meta-analytic designs,

inclusion criteria, publication bias, and repeated inclusion of overlapping samples potentially skewing the pooled effect size. With such variability, it is still unclear whether tDCS increases WM performance based solely on cognitive metrics, with meta-analytic reviews suggesting no or limited augmentation (Mancuso et al., 2016; Medina & Cason 2017). Thus, when exploring the effects of tDCS on WM, it may be of value to pair other metrics (such as neuroimaging) to complement the inconsistent WM cognitive performance metrics.

### *2.4.2 tDCS Applications in Older Adults.*

tDCS may be a valuable tool to augment cognitive performance across ages, including in older adult populations (Stephens & Berryhill, 2016; Di Rosa et al., 2019; Park et al., 2014; Boggio et al., 2011). tDCS may alter cognitive and behavioural domains, making tDCS a potential non-pharmaceutical tool for the management of disordered cognitive aging (Cruz Gonzalez et al., 2018; Meinzer et al., 2013; Manenti et al., 2016). Although promising studies are being reported, there are no current recommendations for the use of tDCS in the cognitive enhancement in aging-related cognitive impairment.

Summers and colleagues (2016) have previously conducted a meta-analysis examining the effects of tDCS in middle and older adults in both cognitive and motor functioning. From their moderator variable analyses (consisting of cognitive and motor processes, effects of tDCS on the DLPFC compared to other regions on cognition, cognitive domains, the timing of stimulation on cognitive performance, and timing of stimulation on motor performance), they report a significant medium effect size of 0.45 in cognitive functioning, and further report a cognitive effect size specific to the DLPFC of 0.39. Furthermore, when the moderating variable of cognitive domain is accounted for in a subanalysis, a significant moderate effect size of 0.45 was reported for the impact of tDCS on WM functioning (Summers et al., 2016). A separate

meta-analysis conducted by Indahlastari and colleagues (2021) investigated the effects of tDCS-induced cognitive enhancement in older adults over the age of 65, specifically exploring the timing of tDCS delivery and stimulation parameters. They reported an effect size of $g = 0.48$ on WM tasks approaching significance ($k = 6$; $p = 0.10$). In addition, a meta-regression found that none of the tDCS parameters of current dosage, charge, timing, density, intensity, and laterality impacted the effect size measures, except the variable of age ($F[1,15] = 10.25$, $p = 0.006$; Indahlastari et al., 2021) However, across the two discussed meta-analyses, age was limited to a sample of young-old and middle-old; therefore, results may differ in the oldest-old age group.

When examining the effects of tDCS in aging-related cognitive disorders, including in Mild Cognitive Impairment and dementia, effect sizes reported in meta-analyses continue to show promising results. Cai and colleagues (2019) report significant cognitive enhancement following tDCS protocols applied to individuals with mild to moderate Alzheimer's dementia (SMD = 0.38); one major limitation, however, is that the included studies were pooled together without a subgroup analysis to further explore the effects within cognitive domains or cognitive tasks. In a separate meta-analysis that included four randomized controlled trials examining the effect of tDCS on memory (subtype unspecified) augmentation in MCI and dementia, tDCS was found to have a moderate immediate effect on increasing memory ($d = 0.39$, $p = 0.04$), however, long-term effects were minimal (Cruz-Gonzalez et al., 2018). In a more recently published systematic review and meta-analysis focusing on AD samples, tDCS was reported to have significant effects on general cognitive measures as well as on memory (including general, visual, recognition, verbal, and working memories), however, not in attention (Majdi et al., 2022). However, the reported findings should be interpreted with caution, with a limited literature base and varying degrees of heterogeneity across studies.

In addition to MCI and dementia, mental health disorders including depression and anxiety can have significant impacts on cognition in older adults; further, depression is a risk factor doubling the risk of dementia progression later on in life (Morimoto & Alexopoulos, 2013). Although there appears to be a relationship between depression and dementia, it remains up to debate whether depression is a prodromal phase or a risk factor for dementia (Steffens & Potter, 2007). The presence of depression can impair multiple cognitive domains, including working memory (Nebes et al., 2000; Dumas & Newhouse, 2015). In addition to the role of the DLPFC in executive functioning (including WM) as previously discussed, the DLPFC has also been consistently demonstrated to be implicated in both depression and anxiety (Kennedy et al., 1997; Grimm et al., 2008; Chang et al., 2011; Moon et al., 2015; Balderston et al., 2017; Meyer et al., 2019). Thus, the DLPFC may be a valuable target for tDCS stimulation to increase executive functioning including WM in older adults with depression and/or anxiety.

### *2.4.3 Unique tDCS Considerations in Aged Adults.*

Several factors impacting tDCS efficacy have been reported in the discussed meta-analyses, including current densities and the number of sessions. In line with Hoy and colleagues (2013), Cai and colleagues (2019) reported that lower tDCS currents significantly improved cognitive performance in a sample of mild-to-moderate Alzheimer's dementia patients, whereas higher current densities did not. Cai et al. further reported that single session tDCS protocols were effective in increasing cognition, with this effect being lost in multi-session tDCS designs. This finding was also reported in a separate meta-analysis examining the effects of multisession tDCS protocols in AD and MCI (Inagawa et al., 2019). Other factors, including cognitive reserve, the severity of dementia, region of stimulation, and level of education, may also alter the effectiveness of tDCS stimulation on cognition (Cai et al., 2019; Elder & Taylor, 2014). The

effects of pairing tDCS with cognitive training in older adults remain up for debate with inconsistent findings being reported (Cruz-Gonzalez et al., 2018; Byeon, 2020).

Ageing-related considerations should be taken into account when designing tDCS protocols. In addition to neuropsychological differences in aging, neurophysiological and neuroanatomical differences exist, including lower synaptic densities, changes of the action potential threshold, widening of the refractory period of the action potential, global cerebral atrophy, and cerebrospinal fluid changes (see Habich et al., 2020, for a detailed discussion on these factors). Further, other biomedical-related factors may impact tDCS efficacy. It is well known that older adults are at higher risk of impaired electrolyte disturbances under increased stress; for instance, eleven percent of older adults in the community setting were found to be hyponatremic (i.e., low sodium concentrations; Schlanger et al., 2010). These aging-specific factors may potentially impact the effects of tDCS on downstream cognition and cerebral oxygenation hemodynamics, in addition to impacting baseline neuronal functions.

Pharmacological agents used by older adults should also be considered in tDCS paradigms. As sodium is one of the major ions involved in neuronal action potentials and conduction, some sodium channel blocker drugs that cross the blood-brain barrier can alter multiple neurotransmitters and receptors, including GABA, serotonin, and noradrenaline (Dokken & Fairley, 2021). Sodium channel blockers can be used as antiarrhythmics (Procainamide, used to treat abnormal cardiac rhythms), prescribed for neuropathic pain (Tricyclic antidepressants, including amitriptyline), or used as anticonvulsants (Phenytoin, Lamotrigine). Furthermore, drugs that can potentially alter cognition may increase the risk of adverse cognitive effects in older adults, including sedative-hypnotics, anticholinergic agents, antipsychotics, and opiates (Lee et al., 2018). Lastly, care should be taken to thoroughly assess

tDCS exclusion criteria that may be more prevalent in older adults (e.g., presence of cardiac pacemakers, because of the hypothetical risk of tDCS interference on the pacemaker; Bikson et al., 2016).

### *2.4.4 tDCS & Cerebral Perfusion.*

Perfusion, the flow of blood in the body, largely depends on the heart, lungs, vasculature, and body tissues. As body tissues (especially the brain) require oxygen to function, the heart, lungs, and nervous system compensate to meet oxygenation demands. If tissue requires additional oxygen and nutrients (such as glucose) to function, then blood flow to the region tends to increase (Willie et al., 2014). This perfusional principle remains true in the brain.

Normal and pathological changes to vasculature across aging occur systemically, as well as regionally in the brain. The amyloid cascade hypothesis quantifies the pathological progression in AD, yet fails to answer the root cause of amyloid-beta deposition. Factors present earlier within the lifespan, such as perfusional changes may also alter downstream processes in the future. In a study examining spatial relationships between perfusion and amyloid deposition, Meier et al. (2020) found that regions with increased perfusion in young adults may be at increased risk of amyloid-beta plaques later in life. In contrast to these results, others have reported that chronic cerebral hypoperfusion in older adults may increase the risk of accelerating cognitive decline and dementia (Wolters et al., 2017; De La Torre, 2017). However, regions of hyperperfusion have been reported in the bilateral frontal lobes in MCI (Ding, Fu, & Lee., 2014). The question of whether these perfusional changes occur as a result of neuronal neurodegeneration, or as a compensatory mechanism remains unclear. Yet, it appears that perfusional changes occur across the lifespan, and can impact cognitive performance later in life.

The application of tDCS can result in a shift in neuronal polarities (Woods et al., 2016). By doing so, downstream processes in the neurovascular unit may also shift. If anodal tDCS excites resting membrane potentials, it may be possible to capture changes in cerebral perfusion (an indirect measure of the cerebral metabolic rate of oxygen, $CMRO_2$) using several types of neuroimaging. A recently developed type of neuroimaging, which measures hemoglobin-related hemodynamics, is functional near-infrared spectroscopy (fNIRS).

**2.5 Fundamentals of fNIRS**

fNIRS is a novel application in cognitive research and has been gaining popularity as a neuroimaging approach in research settings. fNIRS involves applying near-infrared light on the scalp over a cortical region of interest. This high-intensity light can penetrate the outer cerebral cortical layers, causing refraction on specific tissues at specific wavelengths. The returning refracted light is then measured using detectors (Wilcox & Biondi, 2015). fNIRS devices tend to be more cost-efficient than fMRI or electroencephalography (EEG), increasingly portable (with lightweight wireless options that can be paired using Bluetooth technology), and user-friendly. In specific instances, fNIRS applications may be more favourable than fMRI. For instance, fNIRS is beneficial in developmental studies with infants while controlling for spontaneous movement (which may also be beneficial in certain situations in older adults with dementia who may be restless or agitated) or applied to individuals for whom MRI is contraindicated (Obrig, 2014; Almajidy et al., 2020).

Although the temporal resolution of fNIRS is significantly higher than fMRI, spatial resolution is limited to the superficial layers of the cortex (Obrig, 2014; Almajidy, 2020). Despite this reduced spatial resolution, the hemodynamic oxyhemoglobin (HbO) and total hemoglobin (HbT) response signals obtained by fNIRS are highly correlated to the fMRI blood-

oxygen-level dependent (BOLD) signal (Huppert et al., 2006). Due to these advantages, fNIRS has been increasingly applied in varying protocols, advancing the ability of cognitive neuroscientists to conduct research across the lifespan.

### *2.5.1 fNIRS, tDCS, and Cognition: The Neurovascular Unit.*

On a theoretical basis, the central theory merging cognition, tDCS, and fNIRS is based on neurovascular coupling (NVC) which occurs within the neurovascular unit. As neurons become activated at the cellular level, increased oxidative phosphorylation metabolism occurs, resulting in the need for glucose and oxygen to form adenosine triphosphate (i.e., cellular energy; Phillips et al., 2016). Similar neuronal metabolic increases may be invoked with tDCS (Rae et al., 2013). Downstream, glutamate in the synaptic cleft binds to astrocytes within the neurovascular unit, invoking calcium-mediated signalling, which ultimately causes regional vasodilation (Krainik et al., 2013). An influx of blood to the region occurs to support this demand, usually with excess nutrients (Villringer & Dirnagl, 1995).

Hemoglobin, a component of whole blood, is the primary carrier of oxygen contained in the vasculature. In the capillary bed within the neurovascular unit after neuronal activation, the oxygen-carrying HbO is exchanged to the neurons and becomes deoxyhemoglobin (HbR). Together, the total amount of HbO and HbR at an instantaneous time point results in HbT. HbO and HbR have slightly different optical properties, known as chromophores. These chromophores require different wavelengths of light to be detected and quantified into concentrations.

Neuromodulation achieved with tDCS is thought to alter cerebral perfusion. In animal models, it has been demonstrated that tDCS-invoked modulation results in perfusional alterations cerebrally (Wachter et al., 2011). Further research has reported increased vasodilatory responses

in animals, increasing cerebral blood flow after anodal tDCS (Bragina et al., 2018). In humans, tDCS has been demonstrated to alter cerebral perfusion, dependent on tDCS montage (i.e., anodal and cathodal; Stagg et al., 2013). Specific to working memory, anodal tDCS returned working memory processes to a youthful-like state in primates (Wang et al., 2011). In vivo, tDCS studies paired with neuroimaging have confirmed significant changes in cerebral hemodynamics after anodal tDCS montages (Zheng et al., 2011). tDCS invoked neurovascular modulation may be a result of numerous components within the NVU, including the perivascular nerves, endothelial lining, astrocytes, neurons, as well as vessel properties (Bahr-Hosseini & Bikson, 2021). Thus, exhibited changes in cerebral hemodynamics achieved with tDCS can be successfully quantified with fNIRS (Figeys, Zeeman, & Kim, 2021).

This principle is often extended into cognitive domains including neurodegenerative disorders (Yu, Ji, Shao, 2020; Beishon & Panerai, 2021), where it is hypothesized that increasing cognitive demands results in increased neuronal activity, which in turn increases cerebral blood flow regionally. By further augmenting neuronal resting membrane potentials with tDCS, it may be possible to increase neuronal activity, which can result in a regional influx of blood. If so, then these changes can be captured on the cortical surfaces of the brain with fNIRS.

### *2.5.2 Working Memory, tDCS, and fNIRS: Considerations Across the Lifespan.*

When considering age-specific neurophysiological changes, there appears to be a temporal delay between neuronal response and cerebral perfusion, which increases across aging (Fabiani et al., 2014). Thus, fNIRS temporal lags may increase with aging, reflecting changes in the neurovascular unit and neuronal metabolic processes. Further, physiological processes such as increased vascular resistance and other vascular changes seen in aging may decrease the amount of regional vasodilation, dampening obtained fNIRS amplitudes.

Neurophysiological changes across aging may impact cognitive performance. When examining the effects of tDCS on cognitive performance paired with fNIRS, four studies targeting young adults each report no significant cognitive gain, however, it appears that tDCS increases cerebral HbO (Figeys, Zeeman, & Kim, 2021). In contrast, two studies in older adults reported a significant increase in cognitive performance due to tDCS (Stephens & Berryhill, 2016; Di Rosa, 2019). Thus, these findings suggest that tDCS may increase cerebral oxygen hemodynamics across aging; however, neurally-mediated cognitive performance gains have not been found in younger adults. This result may be because of a potential cognitive ceiling effect, which declines with age, in line with the previously discussed CRUNCH and HAROLD models. Although this review reflects a small number of studies and the generalizability of these findings may be limited due to different study designs and protocols, this data suggest tDCS can enhance cognitive performance in older adults, and associated increases in blood oxygenation can be detected using fNIRS (Figeys et al., 2021).

# Chapter 3: Methods Surrounding tDCS & fNIRS

With tDCS and fNIRS now introduced, this chapter will continue to expand on these topics specifically surrounding methods, including procedures and analyses. Discussion surrounding tDCS will largely focus on how to plan and administer protocols safely and effectively. In addition, specific details on fNIRS, including design considerations, signal processing, and statistical approaches will be elaborated on. A brief overview of the methods utilized in the presented studies will be presented, which will be discussed in more detail within each study.

## 3.1 tDCS Methods

Care should be taken when designing tDCS studies, especially when targeting clinical populations; this includes screening for absolute contraindications, determining tDCS parameters and regions of stimulation, and effective tDCS administration to optimize the current being delivered.

### *3.1.1 tDCS Participant Screening*

Although tDCS is well-tolerated, several factors should be considered when designing and implementing a tDCS study. As numerous medical conditions may be impacted by the delivery of exogenous electrical currents, the implementation of tDCS could increase the overall risk of an adverse effect. For instance, the presence of implants (such as cardiac pacemakers and deep brain stimulators), neurological and psychiatric conditions, headache disorders, and neuropsychotropic drugs (as these can alter brain plasticity, neurotransmitters, and resting-membrane thresholds) can impact tDCS current delivery (for an in-depth discussion of tDCS safety screening, refer to Bornheim et al., 2019; Thair et al., 2017).

Age alone is not a contraindication for tDCS stimulation (Hindle, 2010). However, other aging-related considerations may impact tDCS. However, aging is associated with an increased risk factor of cancer, cardiovascular disease, and neurodegeneration (Niccoli & Partridge, 2012); the presentation, management, and potentially associated comorbidities with these diseases may be risk factors for tDCS delivery. Additionally, older adults are more likely to utilize prescription drugs, with numerous agents impacting cognition. In a survey of 2206 older adults living in the community, 87% utilized one prescription drug, whereas 36% utilized more than five different drugs (Qato et al., 2016). Furthermore, prescribed drugs may be altered when patients are hospitalized (such as the addition of other drugs, dosage changes, etc…). In a review examining the safety of tDCS, no major side-effects were reported in 40 studies applying tDCS to over 600 participants (Bikson et al., 2016). Therefore, additional consideration should be given to older-aged adults due to the increased risk of factors that may impact tDCS delivery and efficacy, however, age alone is not contraindicated.

### *3.1.2 Determining Electrode Targets & Landmarking*

Firstly, a target location of where to place the electrodes should be determined. This should be developed with a theoretical (such as a task or specific research question of interest) or a clinical underpinning. An alternative is using individualized neuroimaging data, which may be beneficial in certain tDCS designs (such as individualizing tDCS delivery in those with neurological disorders). Lastly, computational and machine learning mechanisms can be applied to model tDCS electrical delivery across the brain to optimize electrode locations (Huang et al., 2019).

With a target location in mind, desired regions of stimulation (such as the DLPFC) can be then extracephallically determined. A few approaches can be used to identify target regions, such

as the 10:20 EEG system (Klem et al., 1999), utilizing structural neuroimaging (potentially paired with a 3D digitizer), or determining physiological responses can guide electrode placement (i.e., using TMS to find the motor cortex by invoking motor evoked potentials, Nitsche & Paulus, 2000; or utilizing electroencephalographic data; Rich et al., 2017).

### *3.1.3 Selecting tDCS Parameters.*

Once a location has been identified, tDCS parameters should be developed. The most common tDCS electrode sizes are rectangular 5cm x 5cm or 5cm x 7cm pads (Utz et al., 2010), although other tDCS electrode sizes exist, including round electrodes (Minhas, Datta, & Bikson, 2011). Current intensity may be based on previous studies; typically, 1-2mA of current is applied between 5-30 minutes (Iyer, 2005; Bikson et al., 2009; Thair et al., 2017). It should be noted however that a higher dosage does not necessarily mean a greater invoked response (Hoy et al., 2013), and the potential dose-effect relationship remains poorly understood. As previously mentioned, anodal tDCS is generally thought to induce neuronal hypopolarization, whereas cathodal tDCS is thought to induce a hyperpolarized state; however, dosage and length of current application may result in counter-regulatory mechanism activation resulting in a reversal of effects (Das et al., 2016; Hassanzahraee et al., 2020).

### *3.1.4 Placebo-Controlled Stimulation Group (Sham).*

To create a control group, a blinding method known as sham stimulation can be implemented. Sham stimulation involves the delivery of a tDCS current that is ramped up for several seconds, then a tapering down of the current for several seconds until there is no current being delivered (Gandiga, Hummel, & Cohen, 2006; Thair et al., 2017). This blinding method creates a cutaneous electrical stimulation sensation; individuals acclimate to this electrical "prickling" sensation in active stimulation after approximately 1 minute, which makes the ramp-

up/ramp-down blinding protocol effective (Ambrus et al., 2012; Thair et al., 2017). With the current being delivered for such a short period, it is believed that it does not induce neuromodulatory effects (Nitsche et al., 2008). This tDCS blinding technique is suitable for those new to or familiar with tDCS (Ambrus et al., 2012).

### *3.1.5 Implementation.*

Prior to placing the tDCS electrodes in the determined locations in the presented studies, electrodes were placed in electrode sponges, which were saturated in an electrolytic solution (0.9% normal saline). The electrolytic solution is necessary to increase the electrical conductance of the current, but care should be taken to avoid oversaturation, which can result in skin injuries (Woods et al., 2016). These electrodes were then placed on the marked regions, and a non-conductive securing device was used to hold the electrodes in place (in these studies, a snuggly fitted hairnet). From here, the device may be turned on and the current can be delivered while assessing the participant to ensure no immediate adverse effects. In addition, in the case of the tDCS devices used in these studies (using HDC MagStim tDCS Devices), an error message will occur if the impedance is too high. One common reason for this is poor tDCS electrode contact with the scalp, such as in the case when there is a significant amount of hair in the way; thus, it is important to assess both the participant and the device throughout the stimulation protocol to ensure safety and the adequate delivery of the electrical current.

### *3.1.6 General Methodological Considerations Across Presented Studies.*

In this thesis, all participants underwent screenings for tDCS contraindications. The DLPFC was targeted with tDCS as it is a region highly associated with executive functioning including WM, in addition to depression and anxiety (refer to Chapter 2 for more details). In the two randomized controlled trials presented (Chapters 5 & 6), the 10:20 system EEG coordinate

system was utilized to determine tDCS electrode placement. This involves taking measurements over the scalp, to locate corresponding regions in the brain. In the presented studies, F3 (left DLPFC) was stimulated with anodal tDCS stimulation with the cathode on the right supraorbital region (Chapter 4). In Chapter 5 (the combined tDCS-fNIRS study in younger adults), F4 (right DLPFC) was targeted with anodal stimulation, with the cathode placed over the left deltoid muscle. Due to the potential of reversal effects in prolonged stimulation methods, a 1.5mA current for 20 minutes was applied in both of the presented randomized controlled trials (Chapters 5 & 6). Blinding was achieved using the ramp-up/ramp-down approach over 1 minute (Ambrus et al., 2012). Electrodes were placed in electrode sponges, and saturated in normal saline.

### *3.1.7 Pairing tDCS & fNIRS.*

tDCS can easily be paired with fNIRS devices (with dual-integrated commercial devices increasingly available, such as the Artinis Starstim fNIRS device). In consultation with the manufacturer of the fNIRS device used in the study presented in Chapter 5 (Brite24 fNIRS device, Artinis Medical Systems), we were instructed to have the fNIRS device off when delivering tDCS, eliminating the potential of a concurrent tDCS-fNIRS protocol; thus, a sequential design was implemented. In the first systematic review examining tDCS and fNIRS protocols, Patel and colleagues (2020) report a total of 28 included studies, of which 20 administered tDCS and fNIRS concurrently. Of the 28 studies, $k = 7$ studies focused on cognition, and $k = 6$ were conducted in clinical populations. Patel and colleagues reported a general trend in support of online stimulation in cognitive protocols, where prefrontal tDCS stimulation increased oxyhemoglobin concentrations (Patel et al., 2020). The interaction between

cognitive performance and fNIRS signals across aging is the focus of the scoping review presented in Chapter 4.

## 3.2 fNIRS Methods

### *3.2.1 Brite24 Device & fNIRS Fundamentals.*

The parameters behind fNIRS devices, such as wavelengths, near-infrared sources, recording frequencies, and portability can vary across manufacturers; using the Brite24 continuous-wave fNIRS system (Artinis Medical Systems), specific fNIRS montages can be customized to regions of interest. In addition, this device is highly portable and can connect to any computer or laptop with Bluetooth connectivity. Near-infrared LED photon emitters (sources) emit high-intensity light at known wavelengths near the infrared spectrum; this light goes through the skull, penetrating through the first few centimetres of cortical tissue, and returning through the skull (i.e., a banana-shaped arc; Delpy & Okada, 2003); the remaining photons are detected using photon receivers (detectors). Using optical properties, concentrations can be determined. The combination of a source and detector is referred to as a channel (Patil et al., 2011). Different fNIRS arrays can be selected, resulting in a varying number of channels.

### *3.2.2 Channel Distances and Optode Placement.*

Typically, a 30mm distance is used between sources and detectors in adults (Pinti et al., 2019). A more novel approach is to utilize a short-channel, distanced at 8mm apart, which is believed to measure non-cerebral (scalp) signals which can then be regressed out of the long-channel (scalp + brain) signals (Brigadoi & Cooper, 2015; Wyser et al., 2020). Monte Carlo based photon transport modeling can be implemented to optimize fNIRS signal response to targeted brain specificity (Brigadoi & Cooper, 2015; Zimeo Morais et al., 2018), or 10:20 EEG coordinate system placement can be utilized, and preferably co-registered with MRI structural

data or 3D-digitized if possible (Herold et al., 2018). Typically, the fNIRS optodes for the montage are placed and secured using a snuggly fitted cap, similar to an EEG cap, and aligned to the participant's head.

### *3.2.3 fNIRS Recordings.*

Several different software applications are available to facilitate fNIRS recordings. In the study presented in Chapter 5, Oxysoft (Artinis Medical Systems) was utilized as it is specific to Artinis devices, including the Brite24 fNIRS device. fNIRS recordings typically occur at a temporal resolution between 1-100 Hz (Pinti et al., 2018; the Brite24 device has a sampling rate up to 50Hz). One advantage of higher sampling rates (e.g., 10+ Hz) is that the presence of a cardiac heartbeat (~1Hz) can be utilized as an indicator of adequate fNIRS contact to the scalp, and control to ensure a high-quality fNIRS signal (Yücel et al., 2021).

### *3.2.4 From Optical Properties to Concentrations.*

Near-infrared light in the range of 650-925nm can penetrate most biological tissues, while hemoglobin chromophores absorb light in this range; oxyhemoglobin better absorbs wavelengths above 790 nm, whereas deoxyhemoglobin absorption is stronger below 790 nm. The photons that are not absorbed by the hemoglobin chromophores follow a “banana-shaped arc” and are returned to a detector (Gratton et al., 1994). The modified Beer-Lambert Law is then used to convert raw optical signals to concentrations; optical density (OD) is equal to the -log of the returned light intensity (I) over the initial light intensity, at time (t) and wavelength (lambda). This is equal to the molar extinction coefficient multiplied by the hemoglobin concentration c, multiplied by the differential pathlength factor (DPF; the distance photons migrate in light scatter in the medium), multiplied by the distance (d). G represents a term for signal loss, see Equation 1. This is done for both wavelengths emitted to calculate HbO and HbR.

Eq. 1 $$OD = -log \frac{I(t,\lambda)}{I_0(t,\lambda)} = \varepsilon \times c_i \times DPF \times d + G$$

### *3.2.5 Pre-Processing.*

Currently, there are no standardized procedures for fNIRS data preprocessing (Herold et al., 2018). Numerous filters exist in fNIRS signal analysis; wavelet filtering and hybrid models can be used to remove motion artifacts, short-channel regression can be used to remove extracerebral components of the long-channel signals, as well as band-pass filters, spline interpolation, and principal component analysis (Herold et al., 2018; Huppert et al., 2009; Scholkmann et al., 2010). In addition to motion artifacts, fNIRS signals have serially correlated noise from physiological signals (cardiac, blood pressure, respiratory, and superficial noise), which violate the statistical assumption of independence (Barker, Aarabi, & Huppert, 2013). Thus, autoregressive-based general linear models can reduce these noise inputs into the fNIRS cerebral signal and have been demonstrated to significantly reduce type 1 error compared to other filtering approaches (Barker et al., 2013; Meidenbauer et al., 2021).

### *3.2.6 fNIRS Analysis.*

Like the fNIRS preprocessing step, there is no standardized method to analyze fNIRS data statistically (Herold et al., 2018). Commonly utilized approaches include ANOVA, General Linear Models, block averaging, t-tests, F-tests, and linear mixed-effect modeling (Herold et al., 2018; Tak & Ye, 2014). In the fNIRS analysis implemented in Chapter 5, a linear mixed-effect model was implemented; similar to a general linear model, the key assumption is that the time-series fNIRS data is a linear combination made up of regressors. One notable difference is the linear mixed-effects model incorporates a random effects term accounting for sources of variability within and between subjects (Yücel et al., 2021). This allows for additional inference making about the population under study (Yücel et al., 2021).

With numerous channels, all convoluted in a time-series (consisting of each channel, HbO and HbR values per signal, across the recorded time), there is a high risk of type 1 error (false positive); this should be taken into consideration when examining significance on channels or region of interest approaches (such as the F-statistic; Yücel et al., 2021). This can include the more commonly known Bonferroni corrections utilized in traditional statistics, however, which may be too conservative in neuroimaging (Singh & Dan, 2006; Yücel et al., 2021). An alternative, the *false discovery rate* (Benjamini & Hochberg, 1995), provides a better control between specificity and power, which has been demonstrated to have 52% more power than the traditional Bonferroni correction in multichannel near-infrared spectroscopy (Singh & Dan, 2006).

In the analysis presented in Chapter 5, an autoregressive model was implemented at the subject level statistics, followed by a linear mixed effect model to determine group effects. To compare between groups, t-tests were implemented and corrected using the Benjamini-Hochberg false discovery rate adjustment. Without a "gold standard" approach to fNIRS signal processing and analysis, the use of an autoregressive model was selected as it has a lower risk of type 1 error.

## Chapter 4: Effects of Transcranial Direct Current Stimulation (tDCS) on Cognitive Performance and Cerebral Oxygen Hemodynamics: A Systematic Review[1]


### Abstract

**Background.** There is increasing evidence to support the efficacy of transcranial direct current stimulation (tDCS) applications in cognitive augmentation and rehabilitation. Neuromodulation achieved with tDCS may further regulate regional cerebral perfusion affiliated through the neurovascular unit; however, components of cerebral perfusion decrease across aging. A novel neuroimaging approach, functional near-infrared spectroscopy (fNIRS), can aid in quantifying these regional perfusional changes. To date, the interaction of the effects of tDCS on cognitive performance across the lifespan and obtained fNIRS hemodynamic responses remain unknown.

**Objective.** This review aims to examine the effects of tDCS on cognitive performance and fNIRS hemodynamic responses within the context of cognitive aging.

**Methods.** Six databases were searched for studies. Quality appraisal and data extraction were conducted by two independent reviewers. Meta-analysis was carried out to determine overall and subgroup effect sizes.

**Results.** Eight studies met inclusion criteria. The overall effect size demonstrates that tDCS can alter cognitive performance and fNIRS signals, with aging being a potential intermediary in tDCS efficacy.

**Conclusion.** From the studies included, tDCS efficacy on cognitive performance and fNIRS metrics appear to be preeminent in young healthy adults with a potential decline in aging. Given the small number of studies included in this review further investigation is recommended.


[1] This paper has been published: Figeys, M., Zeeman, M., & Kim, E.S. (2021). Effects of Transcranial Direct Current Stimulation (tDCS) on Cognitive Performance and Cerebral Oxygen Hemodynamics: A Systematic Review. *Frontiers in Human Neuroscience, 15*. https://doi.org/10.3389/fnhum.2021.623315

**Keywords:** Transcranial direct current stimulation, cognition, functional near-infrared spectroscopy, aging, tDCS, fNIRS

# 1. Introduction

Interventions to enhance cognitive functioning are increasingly being used as a potential avenue to combat the effects of dementia and age-related cognitive decline. These range from behavioural training programs to non-invasive brain stimulation.[1–4] Transcranial direct current stimulation (tDCS), one type of non-invasive brain stimulation, involves the application of a low-dose electrical current across the brain. tDCS is often paired with behavioural training protocols and is hypothesized to alter the efficacy of training-induced cognitive performance. Increasing evidence suggests that tDCS acts beyond neuronal structures and may modulate cerebral perfusion.[5] The relationships between the mechanisms of cognition, cerebral perfusion, and neuronal activity remain poorly understood, especially when considering healthy and pathological cognitive aging. With the use of functional near-infrared spectroscopy (fNIRS) to measure key factors in perfusion, as well as cognitive performance metrics, the impact of aging on these mechanisms can be explored. The purpose of this systematic review is to begin to explore the effects of tDCS on cognitive performance and fNIRS signals, with an emphasis on how these may differ across age.

## *1.1 Non-Invasive Electrical Brain Stimulation*

Among available transcranial electrical current stimulation modalities, tDCS and transcranial alternating current stimulation (tACS) are the most commonly reported techniques within the literature.[6] Direct current (DC) stimulation is utilized in tDCS, compared to an oscillating sinusoidal-current at a set frequency used in tACS. The physiological effects of tACS neuromodulation are thought to target specific neuronal frequency bands,[6] compared to neural polarity modulation involving voltage-dependent ion channels in tDCS.[7] These differences in electrical properties may result in different neurophysiological responses. In this review, we

focus on the cognitive and cerebral perfusion effects of tDCS, in combined tDCS and fNIRS protocols.

### *1.2 Transcranial Direct Current Stimulation*

Transcranial direct current stimulation (tDCS) is one form of non-invasive brain stimulation that has been used in numerous healthy and clinical populations.[8–15] Low-dose direct current applied to the brain is thought to modulate resting membrane threshold with application-dependent stimulation montages producing a differential increase or decrease in neuronal excitability.[16–19] The effects of tDCS are often examined using behavioural task metrics but reported results have been variable.[8,12,20,21]

Neuronal modulation induced by tDCS works in a summative fashion across neurons. Anodal tDCS is believed to invoke hypopolarization without reaching the depolarization threshold, whereas cathodal stimulation is thought to further shift the neuron into a hyperpolarized state.[19] These effects have proven beneficial in cognitive studies across aging and clinical populations; anodal tDCS has been demonstrated to increase performance on working memory,[22] cognitive control,[23] and language.[24] In contrast, cathodal stimulation has been demonstrated to decrease cognitive control.[25] Thus, the potential clinical utility of tDCS targeting cognitive augmentation in aging and in cognitive disorders such as Mild Cognitive Impairment (MCI) may be of significant value.

tDCS can be easily paired with other treatment modalities, including cognitive rehabilitation protocols. For instance, researchers have reported that anodal-tDCS paired with cognitive training in young adults resulted in higher performance on a working memory task compared to the sham condition.[9] Although these findings are promising, wide variability in terms of results and effect sizes exists within the tDCS literature. Numerous methodological

variables including tDCS dosage, location, and length of stimulation, as well as population parameters such as age, education, and health status, may impact reported results. Overall, a consensus seems to be emerging that there is no clear advantage of adding tDCS to cognitive protocols.[26] Even with this uncertainty, the use of tDCS has been demonstrated to increase regional blood flow in those receiving tDCS paired with cognitive training.[27] Therefore, tDCS may potentially evoke other physiological and neurological mechanisms beyond behavioural responses.

Working memory is a cognitive function, which has been shown to be affected by age-related changes.[28] In turn, aging may impact the efficacy of tDCS during working memory tasks. In a meta-analysis specifically examining the effects of tDCS on working memory in healthy young adults, no significant differences in performance were reported.[29] However, when tDCS was paired with cognitive training, a small yet significant effect size was observed on working memory performance.[29] A separate study investigating the effects of tDCS on working memory in older adults reported increased functional connectivity in the group receiving active anodal stimulation compared to the sham stimulation group during an *n*-back task.[30] Despite the increase in functional connectivity in the anodal group, no significant differences in performance were noted on the *n*-back task.[30]

Age and disease status may play a pivotal role in tDCS outcomes, including aging-related cognitive disorders. A meta-analysis conducted by Hsu and colleagues[31] examined the effects of non-invasive brain stimulation, including tDCS, on cognitive function in healthy older adults and those with Alzheimer's dementia. A small effect size was reported in healthy older adults, and a large effect size was found in older adults with Alzheimer's.[31] Similar results in healthy older adults were reported by Summers and colleagues[32] with a moderate effect size. When examining

effect sizes obtained across studies, there appears to be a trend of tDCS augmenting performance to a greater degree in those with lower cognitive functioning. That is, older adults with cognitive impairment seem to receive a greater benefit than healthy older adults, who in turn receive a greater benefit than young healthy adults.[29-33] This finding should be interpreted with caution, however, as methodological and population variability is present across studies included within the published literature.

### *1.3 Cerebrovascular Perfusion Changes Across Aging & tDCS Considerations*

In addition to neuro-cognitive modulation, tDCS may invoke cerebroperfusional modulation associated with cortical hemodynamic functions.[34–36] However, the interaction between tDCS induced effects on cognition and cerebral perfusion across aging remains widely unknown. Post-tDCS cerebral perfusion changes have been measured using neuroimaging techniques such as functional magnetic resonance imaging (fMRI)[37] and functional near-infrared spectroscopy (fNIRS).[38] Widespread decreases in cerebral perfusion after cathodal and anodal tDCS have been reported using arterial spin labelling.[5] Furthermore, regional decreases in blood-oxygen-level-dependent signals have been reported beyond, but not within, the region of stimulation.[37] Regarding fNIRS, significant interindividual and methodological variability on reported tDCS effects exists in tDCS-fNIRS study designs.[38] However, increases in cortical activation are reported during resting state; interestingly, a decreased level of cortical activation has also been reported during online tasks.[38]

Changes in cerebral blood flow and cerebrovascular structure such as plaque formation, rarefaction, and vascular-wall connectivity appear to be aging dependent (see Sonntag and colleagues[39] for an overview). Moreover, disorders impacting both systemic and cerebral vasculature are associated with pathological age-related cognitive decline.[40–42] Current evidence

suggests a decrease in cerebral blood flow occurs in individuals with MCI beyond the extent of normal cognitive aging,[43–46] yet it remains unclear whether this is an accompanying or a causal factor. Consequently, normal and pathological vascular changes may impact tDCS-evoked neuromodulation and cerebral perfusion modulation in older adults relative to young adults. Ultimately, when considering the potential effects of tDCS on cognitive performance and cerebral perfusion, different responses may occur across age and disease status.

It is important to consider structures and mechanisms beyond the neuron and their potential impacts on cognition, such as the neurovascular unit. The neurovascular unit comprises a dynamic interaction between the neuron, vasculature, and glial cells[47]; the mechanism in which tDCS directly acts upon the neurovascular unit beyond the neuron itself remains unclear. Applied stimulation appears to alter vessel diameter to accommodate for the regional increase in neuronal metabolism.[48] tDCS may also alter astrocytic mediated responses resulting in downstream vascular responses.[49] tDCS induced perfusional modulation occurs across cortical and subcortical structures.[5] Thus, perfusion changes may underlie behavioural-induced tDCS effects,[5] potentially through neurovascular coupling.

Investigating the interaction of cerebral perfusion and cognition, total cerebral blood flow appears to decrease across healthy aging. In an investigation of cerebral perfusion and cognitive aging, Catchlove and colleagues report a cerebral blood flow difference of roughly 84.15 mL $min^{-1}$ between the younger and older adult groups.[50] Interestingly, the investigators reported an interaction between total cerebral blood flow and attention in older adults, but not in younger adults. This interaction between cognitive performance and cerebral blood flow in older adults demonstrates an unexpected inverse relationship, with increased performance associated with a decrease in cerebral blood flow, potentially suggesting higher neural efficiency mechanisms.[50]

There appears to be a trend towards declining cerebral blood flow in older adults with pathological cognitive impairment. Kitagawa and colleagues report a statistically significant lower cerebral blood volume in older adults with cognitive impairment compared to cognitively healthy age-matched controls.[51] In addition to certain subcortical structures, significant differences in frontal, temporal, parietal, and occipital cortices were all present between groups differing in cognitive status.[51] Similarly, significantly lower cerebral blood flow was reported in older adults with Alzheimer's dementia compared to those with subjective cognitive impairment.[52]

Again, a general trend may be arising from the literature, suggesting that the greatest tDCS modulation of cerebral blood flow occurs in healthy young adults, followed by healthy older adults, and finally older adults with cognitive impairment. Note, this is in the opposite direction of the previously hypothesized trend of tDCS impacting behavioural performance to a greater degree in those with cognitive impairments. To summarize, the neurophysiological mechanisms of tDCS may act downstream on the neurovascular unit. When tDCS is applied, both neuronal and perfusional modulation occurs. As vasodilation results in a localized influx of blood, these perfusional changes may be quantified using fNIRS.

### *1.4 Functional Near-Infrared Spectroscopy*

fNIRS is a novel functional neuroimaging technique that utilizes near-infrared light to measure hemoglobin chromophores (oxyhemoglobin; HbO, deoxyhemoglobin; HbR, and total hemoglobin; HbT).[53] Concentrations of each chromophore can be calculated by applying the measured optical properties in a modified Beer-Lambert equation.[53] Under normal circumstances, cortical activation increases oxyhemoglobin concentration with an associated decrease in deoxyhemoglobin concentration.[53] These concentrations can quantify local

perfusion changes within the first few centimetres of the brain cortex and has been previously correlated with fMRI BOLD signals.[54] fNIRS has been used increasingly within cognitive neuroscience research, and signal responses are sensitive to both cognitive load and cognitive state.[55] As fNIRS primarily measures the superficial cerebral structures composed of grey matter[56,57] it can be a useful neuroimaging tool for examining the effects of tDCS.

fNIRS has several advantages over other neuroimaging methods. fNIRS devices tend to be more cost-efficient than an fMRI or EEG, user-friendly, and increasingly portable (with lightweight wireless options that can pair over Bluetooth). fNIRS is advantageous in that it can control for movement and be applied to individuals who have contraindications for MRI,[58,59] and may be better tolerated by older adults.[71] While the temporal resolution is significantly higher than fMRI, spatial resolution is limited to the superficial layers of the cortex.[58,59] Given this expanding area of research, further discussion regarding the utility of fNIRS in cognitive paradigms as a function of aging is required.

### *1.5 Purpose*

Previous studies have successfully utilized fMRI with tDCS during cognitive tasks, though only a handful have implemented fNIRS with tDCS (see Patel and colleagues[38] for a review). As methodological and perfusional considerations differ between fNIRS protocols and other types of neuroimaging, this study will solely review tDCS-fNIRS protocols targeting cognition. Specifically, the purpose of this systematic review is to explore the neuromodulatory effects of tDCS delivery on cognitive performance and oxygen hemodynamics. Furthermore, the variable of age will be explored across reported metrics. The proposed research questions are as follows:

1. *Does tDCS alter cognitive performance and regional oxygenation during cognitive tasks as measured by fNIRS?*
2. *Does aging impact the efficacy of tDCS on cognitive performance and fNIRS signals?*

Based on the literature, it is hypothesized that tDCS effects on cognitive performance will be greater in older adults compared to younger adults. Regarding fNIRS metrics, we hypothesize young adults will experience greater perfusional change than older adults due to decreasing cerebral blood flow rates in aging.

## 2. Methods

### *2.1 Search Strategy*

Electronic searches were conducted using the following databases: CINAHL, Embase, Medline, PsychInfo, Pubmed, Scopus, and Web of Science using Boolean operators in consultation with a research librarian. Search terms included (transcranial direct current stimulation OR tDCS) AND (near-infrared spectroscopy OR functional near-infrared spectroscopy OR fNIRS). This search method resulted in all available tDCS and fNIRS articles; cognitive-orientated studies were then manually extracted. Database searches were conducted on February 19, 2020, and updated on December 27, 2020. No date restrictions were placed on the literature search. Compiled results were imported into Covidence (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia), where inclusion and exclusion criteria were applied.

### *2.2 Inclusion and Exclusion Criteria*

Full-text journal articles published in English were included if they applied tDCS (either concurrent or sequential) and fNIRS to a cognitive paradigm. Non-cognitive study protocols (such as motor function) and review articles were excluded. Further, articles were included if

they reported baseline and post-tDCS stimulation metrics on both cognitive performance and recorded fNIRS signals. To compare the efficacy of tDCS, studies were included if they reported a control (sham) and treatment group, or a crossover design study. No restrictions were placed on tDCS type, duration, current intensity, or time of stimulation. Other non-invasive brain stimulation methods such as transcranial magnetic stimulation and transcranial alternating current stimulation were excluded as physiological effects may differ from tDCS. Within this review focusing on cognition, articles reporting healthy adults, or older adults with MCI or dementia were included, with no boundaries on age limits. All other medical diagnoses and mental health disorders were excluded. If studies reported additional metrics in addition to a cognitive paradigm, only the reported interaction between tDCS on performance and fNIRS recordings within the context of the cognitive domain was included within the analysis.

### *2.3 Quality Assessment*

Each article was reviewed and underwent quality appraisal by two independent reviewers. Six articles were found in the initial search, and two additional articles were included in the updated literature search. Appraisal checklists were selected according to study design using The Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials[60] or the Ding and colleagues checklist for crossover design.[61] Traditional quality appraisal tools may bias crossover research designs, hence to minimize bias, the proposed checklist outlined in Ding and colleagues was applied.[61] Quality assessment tools for other study designs were not required for the final selection of articles due to a relative homogeneity in study designs. Discrepancies in the quality assessment were discussed and resolved. Scores were assigned to each study according to checklist criteria to allow for comparison. Fleiss's kappa was

calculated in SPSS Version 26 (IBM Corporation, Armonk, NY, USA) to determine the initial inter-reliability between the reviewers.

### *2.4 Meta-Analysis*

Appropriate statistical values for effect size calculations (including: means, medians, standard deviations, standard errors, *p*-values, F-Values, and regression coefficients) in addition to sample sizes were extracted from the identified articles. Data was extrapolated from reported figures when necessary. Cohen's *d* effect sizes were calculated for the changes in cognitive performance and fNIRS signals reported within each study. If regression-based beta-estimates were reported without an r value, an estimated r value was calculated using the criteria outlined by Peterson and Brown.[62] This imputed r value was then utilized within the conventional effect size analysis outlined by Cohen.[63] Effect sizes were interpreted as: small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$).

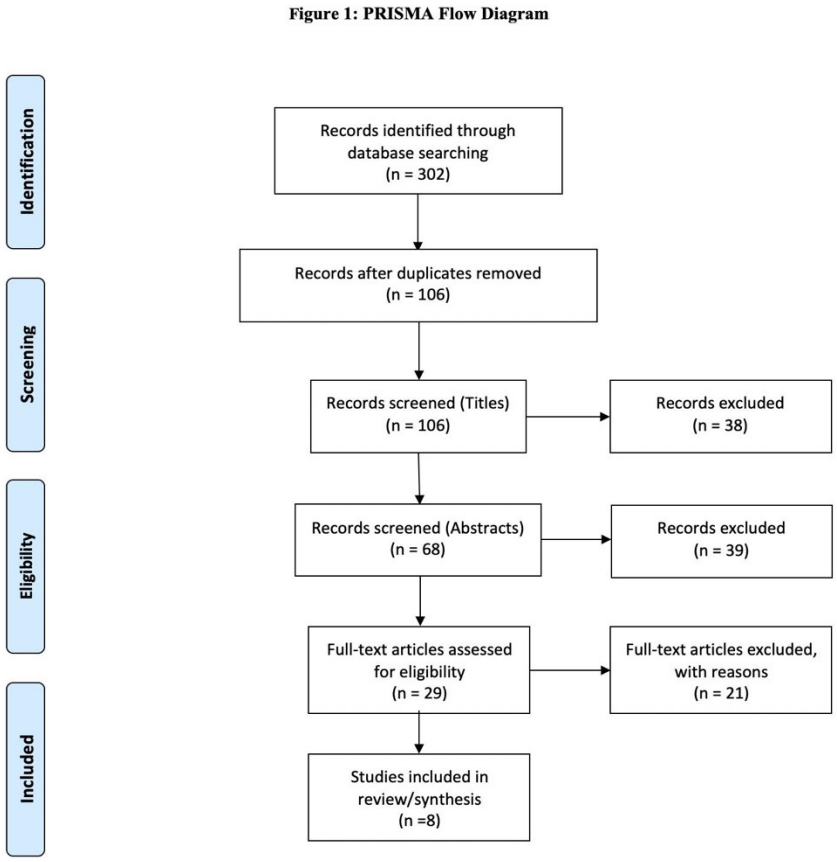
These effect sizes were then imported into Stata (Version 16; StataCorp, College Station, TX, USA) to further process and run the meta-analysis. To investigate the variable of age, a subgroup meta-analysis was performed. A random-effects model using restricted maximum likelihood was utilized to conduct the meta-analysis. REML minimizes bias while reducing mean squared error compared to other meta-analysis approaches.[64] It should be noted that with the small number of studies present with varying protocols, a high level of heterogeneity is suspected. We will report overall heterogeneity $I^2$ statistics, however, REML derived point-heterogeneity in limited meta-analysis sample sizes should be interpreted with caution and reported with confidence intervals.[64,65]

# 3. Results

## *3.1 Study Selection*

Of the three hundred and two references identified during the initial database search, one hundred and ninety-six duplicates were removed. One hundred and six studies were screened, twenty-nine of which underwent full-text review. Twenty-one articles were excluded for the following reasons: lacking a cognitive protocol (n = 9), wrong patient population of interest (n = 4), not an empirical research study (n = 4), lacking a fNIRS protocol (n = 2), lacking application of tDCS (n = 1), and lacking cognitive task measures with fNIRS (n = 1) resulting in eight studies suitable to be included within the review.[66–73] Please refer to the PRISMA diagram in Figure 4.1 for details. Table 4.1 describes the participant demographics across all included studies.

**Figure 4.1: PRISMA Flow Diagram**






*Modified from:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

**Table 4.1: Characteristics of Participants**

| Reference | Population | Exclusion Criteria | Sex | Mean Age (SD if reported) | Mean Education (SD) |
|---|---|---|---|---|---|
| [66] | Healthy young adults (n = 22; 20 in final sample) | Bad sleep quality; moderate-high usual CF (cognitive fatigue), excessive sleepiness, excessive anxiety/depression | 8M, 14F | 23 (2.28) | NR |
| [67] | Healthy older adults (60-80yrs) (n = 21 in final sample)<br><br>(*Experiment 1) | Hx of neurological/ psychiatric illness, contraindications to tDCS, left-handed | 9M, 12F | 69.7 (5.1) | 14.1 (3.3) years |
| [68] | Healthy young adults; (Group 1 n = 23; Group 2 n = 23) | Left-handed, history of mental/neurologic disorders, contraindications to tDCS | 1: 9M, 14F<br><br>2: 12M, 11F | 1: 32.1 (10.5)<br>2: 24.3 (2.4) | NR |
| [69] | Healthy young adults (n = 24)<br><br>(*Experiment 1) | Neurological/psych iatric symptoms or head injuries; medications | 12M, 12F | 23.8 (3.7) | NR; University students |
| [70] | Healthy young adults (n = 61) | Mental, neurological, or psychiatric illness; current use of psychopharmaceut-icals, contraindications to tDCS | 31M, 30F | 24.3 | NR;<br>55 College students; 6 with 10 years school education |
| [71] | Healthy older adults (n = 90; 30 in each group Sham, Active1 - 1mA, Active2 - 2mA) | Neurologic/psychia -tric diseases, contraindications to tDCS, seizure disorders, medications, MMSE < 22 | **Sham:** 14M, 16F; **Active1:** 14M, 16F; **Active2:** 13M, 17F | **Sham:** 69.9<br>**Active1:** 68.6<br>**Active2:** 68.6 | **Sham:** 15.2 years<br>**Active1**: 15.8 years<br>**Active2:** 15.7 years |
| [72] | Healthy adults (n = 32) | Poor visual acuity, | M: 31 | **DLPFC Stim:** | NR |

| | | | | | |
|---|---|---|---|---|---|
| | DLPFC Active: n = 7<br>DLPFC Sham: n = 7<br>M1 Active: 10<br>M1 Sham: 8 | history of epileptic seizures, history of known neurological disorders, pregnancy (or likely to become pregnant during the study) | F: 1 | 35 (11)<br>**DLPFC Sham:** 42 (13)<br>**M1Stim:** 41 (16)<br>**M1Sham:** 31 (5) | |
| [73] | Cognitively healthy young adults (Sham: n= 10; Active: n= 11) | Current use of psychopharmaceutical agents | M: 10<br>F: 11 | 20.3 | NR; University students |

NR: Not Reported, M: Male, F: Female, MMSE: Mini-Mental State Examination

### *3.2 Quality Assessment*

Quality scores ranged widely depending on the appraisal tool used. Four articles were appraised using the Ding and colleagues crossover study checklist,[61] and each had a total score of 3/9, though the scoring of individual items varied (see Table 4.2).[66–69] Four articles were appraised using the JBI Critical Appraisal Checklist for Randomized Controlled Trials[60] with a mean score of 10/13.[70–73] The mean quality percent score of all articles was 57.5% with a range of 33.3 to 84.6%. Descriptions of the individual items and corresponding scores are described in Table 4.2 and Table 4.3. Inter-rater reliability was considered strong with a Fleiss' κ of 0.851.

**Table 4.2: Quality Assessment - Crossover Studies**

| Reference | Checklist from Ding et al. [20] for Cross-Over Studies | | | | | | | | | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | |
| [66] | 1 | -1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 3/9 |
| [67] | 1 | -1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 3/9 |
| [68] | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 3/9 |
| [69] | 1 | -1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 3/9 |
| **Total Item Score** | 4/4 | -3/4 | 0/4 | 0/4 | 1/4 | 4/4 | 3/4 | 3/4 | 0/4 | |

Each item was scored according to risk of bias: 1 low risk, 0 unclear, -1 high risk
**1** Appropriate crossover design. **2** Randomized treatment order. **3** Carry over effect. **4** Unbiased data. **5** Allocation concealment. **6** Blinding. **7** Incomplete outcome data. **8** Selective outcome reporting. **9** Other bias

**Table 4.3: Quality Assessment – Randomized Controlled Trials**

| Reference | JBI Critical Appraisal Checklist for Randomized Controlled Trials [19] | | | | | | | | | | | | | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | |
| [70] | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11/13 |
| [71] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10/13 |
| [72] | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10/13 |
| [73] | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9/13 |
| **Total Item Score** | 4/4 | 0/4 | 1/4 | 4/4 | 2/4 | 1/4 | 4/4 | 4/4 | 4/4 | 4/4 | 4/4 | 4/4 | 4/4 | |

Each item was scored according to answer: 1 yes, 0 unclear or N/A, -1 no

**1** Was true randomization used for assignment of participants to treatment groups? **2** Was allocation to treatment groups concealed? **3** Were treatment groups similar at baseline? **4** Were participants blind to treatment assignment? **5** Were those delivering treatment blind to treatment assignment? **6** Were outcomes assessors blind to treatment assignment? **7** Were treatment groups treated identically other than the intervention of interest? **8** Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? **9** Were participants analyzed in the groups to which they were randomized? **10** Were outcomes measured in the same way for treatment groups? **11** Were outcomes measured in a reliable way? **12** Was appropriate statistical analysis used? **13** Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

### *3.3 Impact of tDCS on Cognitive Task Outcomes*

All eight studies reviewed investigated anodal tDCS compared to sham stimulation, with two of these studies also including a cathodal tDCS stimulation condition.[68,70] Only two articles reported an increase in immediate cognitive performance.[67,73] A third study reported no increase in cognitive performance, however, an increase in an untrained task at one-month follow-up was evident, dependent on dose (i.e., the greatest increase in those receiving 2mA, followed by 1mA, compared to sham).[71] There were no reported effects of tDCS on verbal fluency task performance. The two studies which included older adult participants[67,71] both reported improvements in cognitive performance. Only one of the six studies with young adult participants reported an increase in accuracy and precision on a spatial memory task.[73] tDCS parameters and cognitive effects are presented in Table 4.4.

**Table 4.4: tDCS Parameters and Effects on Cognition**

| Reference | Montage | Participant Grouping | Age (SD) | # tDCS Sessions | Active tDCS Parameters | Region Stimulated | tDCS Administration (Online/Offline to Cognitive Task) | Significant Changes in Cognitive Performance? |
|---|---|---|---|---|---|---|---|---|
| [66] | Anodal/ Sham | Within Subject | 23 (2.28) | 1 Active/ 1 Sham | 1.5mA for 25 minutes | Anode: left dorsolateral prefrontal cortex (F3) cathode: right forearm | Online | No |
| [67] | Anodal/ Sham | Within Subject | 69.7 (5.1) | 1 Active/ 1 Sham | 1.5mA for 26 minutes | Left PFC between F3 & F7; reference on contralateral shoulder | Online | Yes: Anodal tDCS with reward motivation increased WM performance (Baseline WM as a modulator) |
| [68] | Anodal/ Sham, Cathodal/ Sham | Within Subject | **1**: 32.1 (10.5) **2:** 24.3 (2.4) | 1 Active/ 1 Sham | 1mA for 20 minutes | Broca's area (between C3, F3, F7); reference on contralateral supraorbital region | Offline to VFT | No |
| [69] | Anodal/ Sham | Within Subject | 23.8, (3.7) | 1 Active/ 1 Sham | 1.5 mA for 10 minutes | Anode over left prefrontal cortex (between F3 and F7); cathode over the contralateral cheek | Offline | No |
| [70] | Anodal, Sham, | Between Group | 24.3 (NR) | 1 | 1.5mA for 26 minutes | Bilateral Prefrontal Cortex | Online | No |

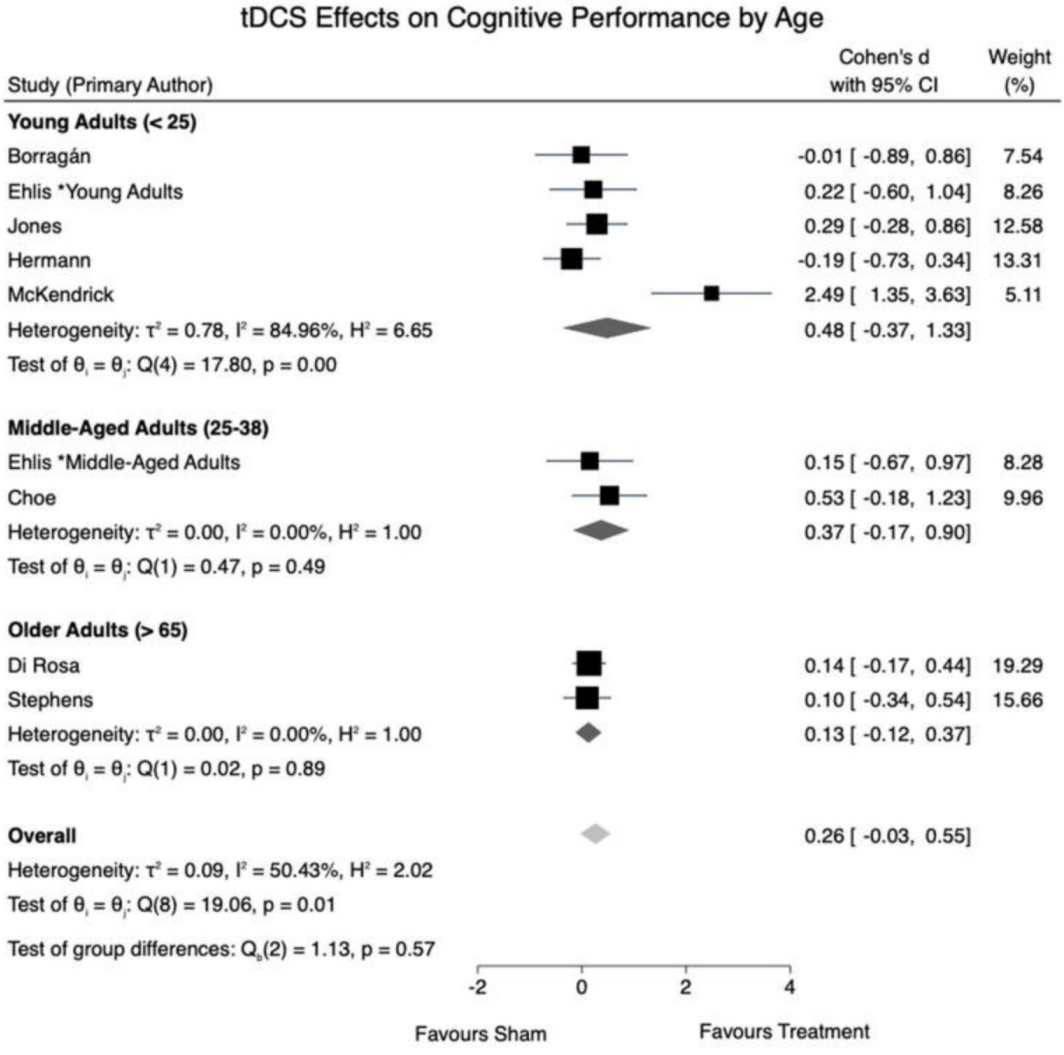
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cathodal | | | | | | | |
| [71] | Anodal/ Sham | Between Group | **Sham:** 69.9 (NR) **Active1:** 68.6 (NR) **Active2:** 68.6 (NR) | 5 | 1 or 2 mA (two separate groups) for 15 minutes | Anode over F4; reference on contralateral cheek | Offline (tDCS was paired with WM training) | *n*-back: No significant differences, however a trend was seen in the Active2 group of increased benefit. *2mA tDCS did significantly increase far transfer tasks after one month |
| [72] | Anodal/ Sham | Between Group | **DLPFC Stim:** 35 (11) **DLPFC Sham:** 42 (13) **M1Stim:** 41 (16) **M1Sham :** 31 (5) | 4 | 2mA for 60 minutes | **Right dorsolateral prefrontal cortex** Anodes: F6 & FC6 Cathodes: Fp2, AF4, AF8<br><br>**Left Motor Cortex** Anodes:CP1 & CP3 Cathodes :Fp1, F9, F8 | Online (motor finger tapping task done prior) | *n*-Back: No significant differences between DLPFC stimulation condition as well as M1 stimulation conditions on accuracy. * Reduced variability within individual learning rates with DLPFC stimulation, however trend appears to be minimal with M1 stimulation. |
| [73] | Anodal/ Sham | Within Subject & Between Group | 20.3 (NR) | 2 **Control:** Sham & Sham. **Active:** Sham & | 1mA for 15 minutes | Right ventrolateral prefrontal cortex: Anode over F10; cathode over F2 | Online | Yes: Anodal tDCS increased spatial memory task performance |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Anodal | | | | |

NR: Not Reported, WM: Working Memory, VFT: Verbal Fluency Task, DLPFC: Dorsolateral prefrontal cortex

All eight studies were eligible to be included in the cognitive performance meta-analysis. A moderate level of overall heterogeneity was observed ($I^2$ = 50.43%, $\chi^2(8)$ = 19.06, $p$ =0.01). An overall effect size for tDCS effects on cognitive performance of $d$ = 0.26 (95% CI -0.03 to 0.55, $p$ = 0.077) was obtained. A non-significant trend-wise decrease in the effects of tDCS on cognition was seen in the pooled effect sizes of tDCS as age increased. Figure 4.2 provides a summary of the calculated tDCS effect sizes on cognitive performance.

**Figure 4.2: tDCS Effect on Cognitive Performance by Age**



### *3.4 Impact of tDCS on fNIRS Outcomes*

Studies differed in reported fNIRS measures (HbO, HbR, HbT, and calculated oxygenation metrics). Within the context of a cognitive task, three studies reported no effects of anodal tDCS on HbO.[70–72] Three studies reported an increase in HbO signals following anodal tDCS,[67–69]one study reported a trend-wise decrease in HbO signals following cathodal stimulation,[68] and another study reported no cathodal tDCS effects.[70] When considering HbR, one study reported an increase in HbR concentration within the frontotemporal cortex following anodal stimulation.[70] Hemispheric differences were reported in two studies.[66,67] Lastly, when examining oxygenation-derived values from HbO and HbR signals, two articles report decreases in regional oxygenation hemodynamic responses with anodal stimulation compared to sham.[66,73] fNIRS parameters are highlighted in Table 4.5 below.

All eight articles were eligible for inclusion within the fNIRS meta-analysis. A moderate level of heterogeneity remained present when examining the overall effects of tDCS on obtained fNIRS signals ($I^2 = 44.63\%$, $\chi^2(8) = 13.71$, $p = 0.09$). Effect sizes were calculated, however consideration of the signal directionality (i.e., if the effect size corresponds to an increase or decrease of an fNIRS signal) in the overall meta-analysis model was not taken into account. An overall effect size of $d = 0.63$ (95% CI 0.32 to 0.94, $p < 0.001$) was obtained. Further, a statistically significant effect size of $d = 0.82$ (95% CI 0.48 to 1.16, $p < 0.001$) was present in young adults, whereas non-significant effect sizes of 0.48 (95% CI -0.47 to 1.43) and 0.53 (95% CI -0.28 to 1.34) were determined in the middle-aged adult and older-aged adult groups respectively. Figure 4.3 provides a forest plot of the included studies and their respective calculated effect sizes.

**Table 4.5 fNIRS Parameters**

| Reference | fNIRS Optode Placement | Concurrent /Sequential to tDCS | Signals Reported | Recording Parameters | Signal Processing and Analysis | Cognitive Task Measured with fNIRS |
|---|---|---|---|---|---|---|
| [66] | Bilateral Superior Frontal Cortex | Concurrent | COE (HbR- HbO) | **Channels:** 24 channels<br>SDD: 3cm<br>***Λ***: 685 & 830nm<br>**Sampling Rate:** 20Hz<br>**Other**: Triggered to event onset/offset of TloadDback task | **Software:** HomER<br>**Filter:** Low pass (0.009-0.08Hz)<br>**Analysis:**<br>Grand averaging of COE by 4min blocks, ANOVA | TLoadDBack |
| [67] | Inferior and Midfrontal Gyri, Supplementary motor area, intraparietal sulcus | Concurrent | HbO, HbR | **Channels:** 4 laser diodes and 8 photo-multiplier tubes. 38 channels, 2 short channels<br>***Λ***: 690 nm & 83 nm<br>**SDD:** 3cm, Short channels: 0.8cm<br>**Sampling Rate:** 7.8Hz | **Software:** HomER2<br>**Filter:** Band pass filter (0.01 and 3Hz);<br>**Corrections:** Removal of signal-noise ratio <2 and motion artifacts. Age dependent DPF.<br>**Consolidation:**<br>GLM approach of hemodynamic modelling with gaussian functions. Mean HbO, mean HbR, mean hemodynamic responses in interval 5-11s after stimulus onset.<br>**Analysis:**<br>ROI, ANOVA | Visuospatial WM task, reward incentives |
| [68] | Bilateral frontotemporal | Sequential | HbO, HbR | **Channels:** 44 channels (2x22) in two 3x5 | **Software:** MATLAB;<br>**Filter:** Low pass (0.3Hz); | Verbal Fluency Test |

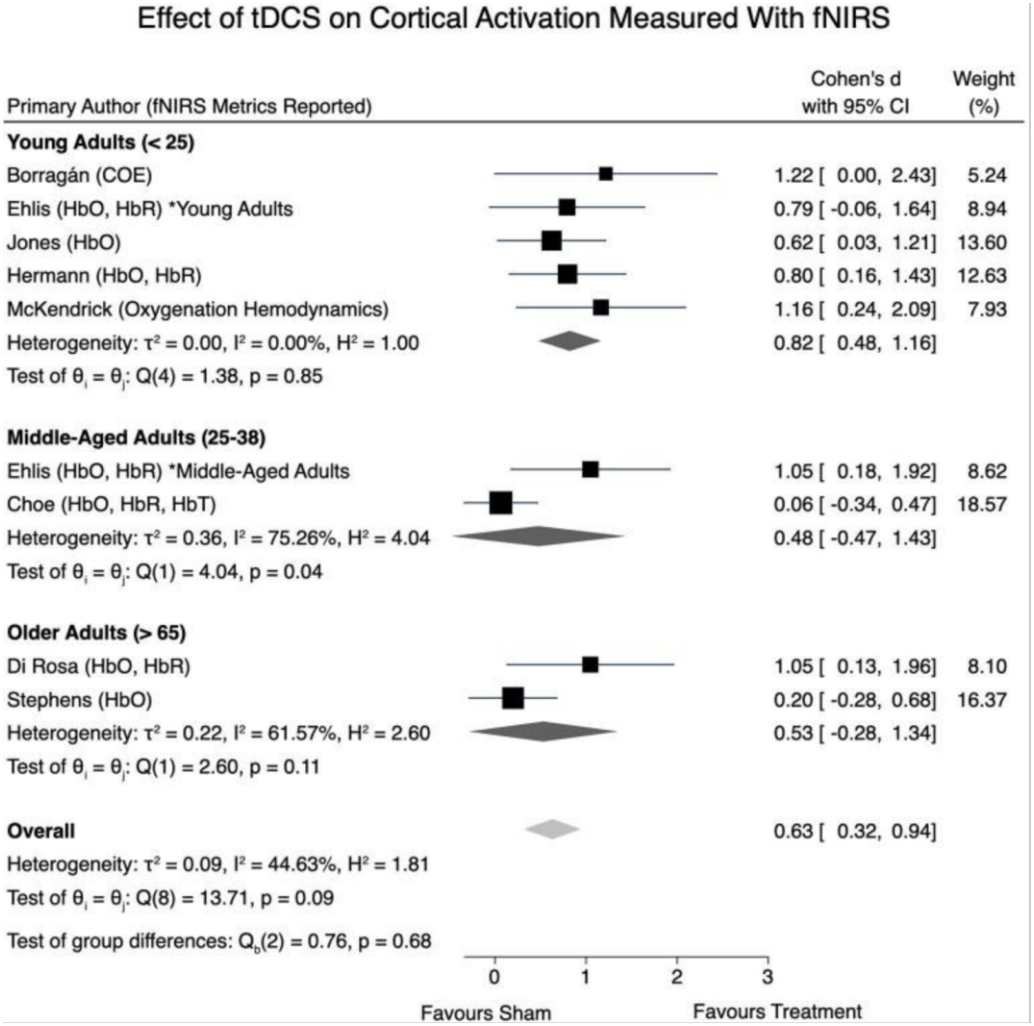
| | | | | | | |
|---|---|---|---|---|---|---|
| | regions | | | optode arrays.<br>***λ:*** 695 ± 20 nm & 830 ± 20 nm<br>**Sampling Rate:** 10Hz | **Corrections**: Linear fit function (10s baseline, last 10s of rest), noise correction by interpolation of mean adjacent channel signals<br>**Analysis**:<br>Means of the last 20 s of individual averaged activation was calculated (across each individual, condition, tDCS stimulation session, and channel).<br>Channel wise t-maps, ROI Analysis, ANOVA | |
| [69] | Left prefrontal cortex | Sequential | HbO | **Channels:** 3 channels<br>***λ:*** 690 & 830nm<br>**SDD:** 2.6cm<br>**Sampling Rate:** 50Hz | **Software:** HomeER2<br>**Filter**: Low pass filter (0.5Hz)<br>**Corrections:** Removal of first 5s of each 25s block and motion artifacts.<br>**Consolidation:**<br>Mean HbO per condition; recorded over final 20s of each 25s block.<br>Normalization of HbO difference scores.<br>**Analysis**:<br>ANOVA | WM Change Detection Task |
| [70] | Bilateral prefrontal cortices | Concurrent | HbO, HbR | **Channels:** 52; Three rows (each with 11 optodes, SSD 3cm). 33 optodes (17 laser diodes | **Software:** MATLAB;<br>**Filter**: Low pass (0.5Hz) and discrete cosine filters;<br>**Corrections**: Removal of high- | Verbal Fluency Test |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | and 16 photodetectors)<br>**SDD:** 3cm<br>**Sampling Rate:** 10Hz | frequency artifacts using 5s moving average, common average reference to remove physiological noise, DPF<br>**Analysis:**<br>Effect size (baseline to task performance), t-maps, ROI, ANOVA | |
| [71] | Bilateral prefrontal cortices | Sequential | HbO | **Channels:** 14<br>**Sampling Rate:** 50Hz | **Software:** HomER2<br>**Filter:** Low pass filter (0.5Hz);<br>**Corrections:** Removal of motion artifacts. Normalization of each channel<br>**Analysis**:<br>Peak HbO amplitude per channel standardized per participant across time, transformed into overall percentage of channels with decrease activation across time. | *n*-Back Task |
| [72] | M1, Right dorsolateral prefrontal cortex | Concurrent | HbO, HbR, HbT | **Channels:** 20 channels (10 channels over M1; 10 channels over the right dorsolateral prefrontal cortex).<br>**SDD:** < 3.5cm<br>**Sampling Rate:** 8Hz | **Software:** nirsLab, SPM<br>**Filter:** Band-pass filter (0.01 Hz – 0.2 Hz)<br>**Corrections:** Inter-trial signals removed from time-series. Average baseline concentration subtracted from task-evoked concentration changes<br>**Analysis:** HbO, HbR, HbT | *n*-Back Task |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | average concentrations ran for each channel, participant, task, and time. Concentrations were averages within time (days) across all *n*-back trials. Concentrations were further region and grouped averaged across the total time difference. General linear model-based SPM was performed, multiple comparison correction of channels. | |
| [73] | Bilateral prefrontal cortices (Anterior and dorsolateral prefrontal cortices, Pars Triangularis, Pars Opercularis) | Concurrent | HbO, HbR, Oxygenation (HbO - HbR) | **Channels:** 16<br>***Λ***: 730nm & 850nm<br>**SDD:** 2.5cm<br>**Sampling Rate:** 2Hz | **Software:** COBI Studio software;<br>**Filter:** Low pass filtered (0.1 Hz)<br>**Corrections:** Motion artifact assessment<br>**Analysis:**<br>Temporal hemodynamic function temporally group averaged. Linear mixed effect modelling with restricted maximum likelihood. Bayesian information criterion to determine random and fixed effects. False discover rate corrections. | Spatial memory task |

COE: Cerebral Oxygen Exchange, HbO: Oxyhemoglobin, HbR: Deoxyhemoglobin, HbT: Total Hemoglobin, ROI: Region of Interest, ANOVA: Analysis of Variance, SDD: Source-Detector Distance, DPF: Differential Pathlength Factor, *Λ: Wavelength*

**Figure 4.3: Effect of tDCS on Cortical Activation Measured with fNIRS**




## 4. Discussion

In this systematic review, we explored the effects of tDCS on cognitive performance and fNIRS-based hemodynamics. A secondary question explored how these measures are affected by aging. The studies reviewed included RCTs (n = 4) and within-subject crossover designs (n = 4). Four studies included young adults (mean age less than 25),[66,69,70,73] two included older adults (mean age greater than 65 years old),[67,71] one included middle-aged adults (mean age between 25-38 years old),[72] and one study had both a young-adult and middle-adult group as

participants.[68] Based on the studies included in this review, tDCS does have an impact on cognitive performance and cerebral hemodynamics, as measured by fNIRS metrics. Further, as expected, aging processes appeared to alter the effectiveness of tDCS applications.

Five studies, all of which included young adults, reported no cognitive performance gains following anodal stimulation when compared to sham. Interestingly, in the subgroup meta-analysis, the pooled effect size was greatest in young adults under the age of 25 ($d$ = 0.48), followed by middle-aged adults aged 25-38 ($d$ = 0.37*),* and older adults over 65 ($d$ = 0.13). This trend was in the opposite direction from our initial hypothesis, which was based on previous reports of tDCS effects being greater in studies with older or cognitively impaired participants.[9,30,32,33] Nonetheless, there are other reports of aging-related resistance to tDCS effects. For instance, Leach and colleagues reported tDCS-evoked cognitive gains in associative memory in young adults, which was absent in older adults in the same study.[74] This is further in line with a previous tDCS meta-analysis specific to older adults, where no significant gains were reported in any cognitive domain.[75] Yet others have proposed that factors such as baseline performance or education level, as opposed to age, may modulate tDCS efficacy in older adults.[76,77] Clearly, this is an area that warrants further study, and may even require tDCS protocols that are adapted to address the structural and neuroanatomical changes associated with aging brains.[78]

For the purposes of the specific questions in this review, we included studies that explored the effect of tDCS on some aspect of cognition. Undoubtedly, there was much variability in the cognitive tasks used in the studies, including verbal fluency tasks (n = 2),[68,70] spatial memory tasks (n = 1),[73] and working memory tasks (n = 5).[66,67,69,71,72] Within this latter category, there was a large amount of procedural variability. One WM task was a modification of

the *n*-back task called T-load D-back, which incorporates both the *n*-back and a number decision task into one process.[66] Another was a novel visuospatial task that required both identification and location memory of pictures and letters.[67] A third study utilized an operation span task while another conducted a battery of *n*-back and letter span tasks.[69] This heterogeneity in the behavioural assessment of WM introduces a potential reason/confound for the variability of tDCS effects. Though not within the scope of this review, two of the included studies further assessed the role of motivation on tDCS efficacy, both of which found that higher motivation via financial incentive augmented behavioural performance to a greater extent in anodal tDCS groups.[67,69] Further, one tDCS and fNIRS study examined additional variables related to flight simulation, however only the cognitive component was included in this review.[72] It is possible the variation in effect sizes reported in this review is reflective of the differences in cognitive tasks used across the various studies.

The majority of articles reviewed utilized a working memory paradigm as the cognitive measure. The impact of tDCS on enhancing working memory task performance in younger adults has previously been reported.[79] However, tDCS effect sizes within the cognitive domain of working memory also appear to differ across adulthood, and in older adults with mild cognitive impairment or dementia.[29,32,33,67,71] Although our search did not yield any studies of tDCS and fNIRS in individuals with cognitive impairments, this is a population in which further study could be illuminative of the impact of tDCS on cognitive performance and cerebral perfusion. Future investigations based on theoretical models of cognitive aging, such as the Hemispheric-Asymmetry Reduction in Older Adults (HAROLD),[80] Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH),[81] and the Scaffolding Theory of Aging and Cognition (STAC)[82] may provide useful frameworks for further inquiry.

The studies reviewed lacked a standardized metric of cerebral oxygenation, reflected in the variety of fNIRS signals reported (Table 4.5). Even within studies reporting the same metric however, effects of tDCS on cerebral oxygenation were mixed. For instance, three studies reported increases in HbO following tDCS stimulation[67-69] while three studies reported no significant changes. [70–72] One study reported an increase in HbR following anodal stimulation[70] and another two studies reported decreases in oxygenation when estimated as a function of HbO and HbR.[66,73] As there is little consensus on the downstream cognitive effects of changes in HbO and HbR concentration, this is an area where future studies may help to further elucidate the mechanisms underlying tDCS-induced cognitive enhancement.

In the studies reviewed, tDCS was found to impact cerebral perfusion as measured by fNIRS, demonstrated by our overall statistically significant moderate effect size of $d = 0.63$. We hypothesized that young adults would exhibit greater perfusional change relative to older adults following tDCS, as measured by fNIRS metrics. This hypothesis was supported by our subgroup analysis. A statistically significant effect size of $d = 0.82$ was present within the younger adults, whereas non-significant effect sizes were reported for middle-aged and older adults. It is possible that the large effect sizes calculated for the studies reporting decreased oxygenation[66,73] may have skewed the overall effect size, therefore these results should be interpreted with caution due to the limited number of studies and level of heterogeneity present.

The theoretical grounding of this review is based on the premise that the interaction between the neuron (when modulated by tDCS) and associated cerebral perfusion at the neurovascular unit impacts cognitive performance. However, other changes beyond the level of the neurovascular unit, such as cerebral atrophy should be considered. In a study investigating cerebral blood flow changes across aging, Meltzer and colleagues[83] noted there were no age-

related cerebral perfusion differences using positron emission tomography (PET), after correcting for brain volume.[83] This suggests that cerebral atrophy, not cerebral blood flow, may underlie functional deterioration, Conversely, another study using arterial spin labelling found that cerebral perfusion was significantly correlated with cortical thickness and total brain volume, as well as performance on executive function tasks.[84] However, there was no direct association between brain volume and cortical thickness with cognitive function. Another study using PET in participants with hypertension with lacunar infarcts, or white matter lesions, reported that lower cerebral blood flow precedes cognitive decline three years later, measured using the Mini-Mental State Examination tool.[51] From these findings, it appears possible that cerebral blood flow underlies a common mechanism present in both cognitive decline and cerebral atrophy.

No articles with individuals with MCI or dementia were identified in our search, demonstrating the need for cognitive-based tDCS and fNIRS research protocols with these populations. Significant effects of tDCS on cognitive performance have previously been reported in the literature, [26] and there is evidence the effectiveness of non-invasive brain stimulation may vary among older adults with MCI.[85] Further research is needed to investigate potential age-related changes in cognitive mechanisms to explain this variability.

### *4.1 Limitations & Future Directions*

With the limited number of articles suitable for review, studies were grouped by age despite having varying cognitive tasks. Although spatial memory and working memory may represent similar cognitive mechanisms, verbal fluency tasks may be grounded in an alternative cognitive domain altogether. The studies using verbal fluency tasks were conducted in younger adults, which potentially impacted the effect sizes reported (Figure 4.2). Nonetheless, studies

employing working memory tasks were included across all subgroups included in effect size calculations. With ongoing research in the field, it is recommended that future reviews conduct an analysis accounting for the different cognitive tasks utilized in addition to age.

Research investigating aging-related differences in tDCS and cognition as it relates to cerebral perfusion yields meaningful insight into the current understanding of these cognitive processes and the ability for neuromodulation. Future directions should also aim to investigate populations with microvascular changes (such as diabetes and chronic hypertension) in addition to larger vascular changes (such as aortic and carotid stenosis), using a cognitive-orientated tDCS and fNIRS paradigm to further assess the role of cerebral blood flow and vascular health in cognitive task performance.

There exists a possibility in which repeated tDCS sessions might induce different physiological changes within and beyond the stimulated brain region, and this should further be assessed within the context of cognitive aging. In addition to tDCS stimulation frequency, the effects of current intensity, time, regions of stimulation, and montage (anodal or cathodal) require further investigation regarding cognitive performance across normal and pathological cognitive aging. tDCS effects and direction of change (i.e., increases or decreases) of specific chromophores (HbO, HbR, HbT) or oxygenation is yet to be determined. With the limited number of cognitive-oriented tDCS and fNIRS studies, it is recommended that additional studies be conducted before establishing the directionality of these unknown variables in meta-analysis. With interindividual differences, it is recommended to perform electric field modelling using structural neuroimaging of each participant if available to assist in optimizing tDCS parameters and regions of stimulation. Lastly, to the author's knowledge, no widely available graphical user interface or software is available to model the effects of tDCS current on cerebral perfusion,

which is an avenue to explore in the future using perfusional neuroimaging methods including fNIRS.

### *4.2 Conclusion*

With the eight included tDCS and fNIRS studies on cognition, we report significant overall effect sizes on cognitive performance and fNIRS signals due to tDCS-evoked neuromodulation. Further, age-related differences appear to alter the efficacy of tDCS effects. With the limited number of studies and heterogeneity in combined tDCS, fNIRS, and cognitive testing parameters, further research is required to test the efficacy and directionality of fNIRS signals. Confounding variables such as baseline performance, education, health status, and factors impacting cerebral blood flow should further be investigated and included in future study designs. In conclusion, tDCS may be a promising tool for neuromodulation and cerebral perfusion modulation, however, significant research is still needed to determine which groups are more susceptible to tDCS-evoked effects.

**s**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# Chapter 5: Transcranial Direct Current Stimulation Over the Right Dorsolateral Prefrontal Cortex Increases Oxyhemoglobin Concentration and Cognitive Performance Dependent on Cognitive Load[2]


## Abstract

Transcranial direct current stimulation (tDCS) has been explored as a potential method for cognitive enhancement. tDCS may induce a cascade of neurophysiological changes, including alterations in cerebral oxygenation. The purpose of this study was to investigate the effects of tDCS on working memory performance and cerebral oxygenation concentrations in bilateral dorsolateral prefrontal cortices (DLPFC) measured with functional near-infrared spectroscopy (fNIRS), while controlling for individual variation in oxygenation variability using baseline resting-state measurements. Baseline cerebral oxygenation during resting-state and during the Toulouse *n*-back task was measured using fNIRS in thirty-three healthy young adults. tDCS was then administered with participants receiving either anodal or sham tDCS over the right DLPFC. After tDCS, a post-Toulouse *n*-back task was then re-administered paired with fNIRS. With individual oxygenation controlled for, anodal tDCS was found to increase oxyhemoglobin concentrations over the stimulated right DLPFC, during the 2-back ($q = 0.015$) and 3-back ($q = 0.008$) conditions. Additionally, anodal tDCS was found to improve accuracy


**Explanatory Note:** Due to COVID-19, the conceptualization of this study was changed to accommodate for clinical and research restrictions. Prior to COVID-19, it was initially proposed to conduct this study at the Glenrose Rehabilitation Hospital using a sample of older adults with Mild Cognitive Impairment as an extension of the third study (presented in Chapter 6). However, this study design was changed to a single-session intervention to limit contact and exposure, using a sample of healthy younger adults. A sample of younger adults was selected as they are at a lower-risk of COVID-19 related complications, compared to older adults in clinical-care settings. Therefore, generalizability of this study is specific to younger adults, however, serves as a fundamental basis for similar protocols using older adults in the future.

[2] Manuscript in preparation for submission as: Figeys, M., Loucks, T., Leung, A., Kim, E.S. Transcranial Direct Current Stimulation Over the Right Dorsolateral Prefrontal Cortex Increases Oxyhemoglobin Concentration and Cognitive Performance Dependent on Cognitive Load.

during the 3-back task by 13.4% ($p$ = .028) and decrease latency by 250 ms ($p$ = 0.013). Taken together, anodal tDCS over the right DLPFC was found to regionally increase oxyhemoglobin concentrations, as well as working memory performance, in higher cognitive load conditions. Using baseline resting-state fNIRS metrics to control for interindividual oxygen hemodynamics may be of value when comparing across healthy and clinical samples; further studies are warranted to explore this finding in other populations.

**Keywords**: Transcranial Direct Current Stimulation, Functional Near-Infrared Spectroscopy, Dorsolateral Prefrontal Cortex, Cerebral Oxygenation, Cognition, Working Memory

# 1. Introduction

Cognitive augmentation and rehabilitation are of increasing interest across numerous healthy and clinical populations, respectively. In the past decade, the use of non-invasive brain stimulation, including transcranial direct current stimulation (tDCS), has been investigated as a means of cognitive enhancement [1]. tDCS may be a promising intervention to modulate cognitive performance, however, the effects of tDCS on cerebral oxygenation hemodynamics and cognitive performance remains poorly understood [2].

To examine the effects of tDCS on cortical cerebral oxygenation, functional near-infrared spectroscopy (fNIRS) can be utilized. Cerebral perfusion and oxygenation, as well as cognitive processing, can change across age and disease status [2–6]. Although previous studies examining the use of tDCS and fNIRS in cognitive research have controlled for age and disease status, to the authors' knowledge, none have controlled for the effects of intersubject variability of cerebral oxygenation. This study begins to investigate how tDCS alters both cognition and cerebral oxygenation while controlling for interindividual cerebral hemodynamic variability within a young healthy adult sample.

## *1.1 Transcranial Direct Current Stimulation, Cognition, & Working Memory*

tDCS involves the administration of a low-dose electrical current delivered across the brain using electrodes placed on the scalp. Typically, currents between 1-2mA are utilized for tDCS applications [7]. These currents are well-tolerated with minimal side effects [8]. Dependent on the stimulation montage, the applied tDCS current is thought to modulate neuronal membrane thresholds, with conventional anodal tDCS inducing neuronal hypopolarization, and cathodal stimulation resulting in neuronal hyperpolarization [9]. In turn, the effect of tDCS can make the neuron easier or harder to achieve an action potential.

tDCS induced neuromodulation may result in downstream cognitive modulation; for instance, tDCS has been demonstrated to augment working memory [10], inhibition [11], and cognitive flexibility [12]. However, results in the literature remain variable and are partially dependent on the effects of age and disease status on cognition and cerebral perfusion [2]. A meta-analysis examining the effects of tDCS on working memory in healthy adults reported a small effect size [13]; yet another meta-analysis looking at the effect of tDCS on cognition in Alzheimer's dementia reported a large effect size [14].

Working memory (WM) is an executive functioning process highly integrated across cognitive domains [6, 15]. WM can be defined as a dynamic function involving the temporary encoding, manipulation, and recall of information [16-17]. WM processes draw on prefrontal structures, including the dorsolateral prefrontal cortex (DLPFC; [18]). Targeting the DLPFC with anodal tDCS appears to have facilitatory effects on WM processes [10, 13]. Previous findings have suggested lateralization differences between the DLPFC on WM; notably that the right DLPFC may be more fluid to broader contextual manipulation including arithmetic and adaptive decision processing [78, 79]. As WM is highly entwined with other cognitive processes, anodal tDCS application over the DLPFC may potentially increase working memory and other cognitive domains. Specifically, this may be of benefit for non-pharmacological treatment of disorders of cognition.

## 1.2 Cerebral Perfusion & Oxygenation

### *1.2.1 Perfusion & Oxygenation.*

The amount of oxygen reaching the brain is largely dependent on cerebral metabolism and glucose, including the cerebral metabolic rate of oxygen [19]. Other factors include the arterial blood concentration of oxygen, as well as cerebral blood flow [19]. Cerebral perfusion,

the passage of blood to the alveolar-capillary beds within the brain, creates a force gradient that assists in the transfer of oxygen to cerebral tissues [20, 21]. Within whole blood, 98% of oxygen is reversibly bound to hemoglobin [22], resulting in two chromophores: oxyhemoglobin and deoxyhemoglobin. When oxyhemoglobin reaches a tissue, diffusion and perfusion assist in driving the oxygen into the tissue per Fick's principle [23]. Once oxyhemoglobin unbinds from oxyhemoglobin, it typically transitions to deoxyhemoglobin.

### *1.2.2 Ageing and Cognition.*

Biopsychosocial factors present in early adulthood may alter cognitive processes in the future [24-26]. Factors impacting cerebral perfusion may also be involved in cognitive ageing and impairment. For instance, amyloid-beta deposition, which has been associated with an increased risk of cognitive impairment, including an increased risk of dementia progression [27] has recently been shown to be related to cerebral perfusion. Specifically, brain regions with increased perfusion in young adulthood may be at increased risk of amyloid-beta plaques later in life [28]. Furthermore, differences in cerebral blood flow were found in young adults carrying APOE4 alleles compared to non-APOE4 carriers, despite similar cognitive performance [29]. In older adults, chronic cerebral hypoperfusion may increase the risk of accelerating cognitive decline and dementia [5, 30]. Whether these perfusional changes are directly due to neurodegenerative processes, or a compensatory-protective mechanism against ongoing decline remains largely unknown.

### *1.2.3 Perfusion and tDCS.*

Neurons are intertwined with cerebral vasculature and glial cells within the neurovascular unit [31]. Anodal tDCS has been demonstrated to increase regional cerebral blood flow during and after stimulation [32, 33]. Increases in oxygenation with a decrease in cerebral blood

velocity in the DLPFC have also been reported after anodal tDCS [34]. The effects of tDCS appear to extend beyond the site of stimulation, with the structures immediately proximal to the stimulating tDCS electrode resulting in perfusional changes that are polarity specific [33, 35, 36]. As Stagg & Nitsche [33] report, anodal tDCS over the left DLPFC induced widespread increases in cerebral perfusion, whereas cathodal stimulation decreased perfusion to the right inferior frontal gyrus and bilateral thalami. Thus, the consideration of tDCS montages should be taken into account when examining the effect of tDCS on the interaction between cerebral perfusion and cognition.

## 1.3 Functional Near-Infrared Spectroscopy (fNIRS)

### *1.3.1 fNIRS Background.*

Cerebral oxygenation, related to adequate cerebral perfusion [37], can be quantified using functional near-infrared spectroscopy (fNIRS). fNIRS, a novel neuroimaging approach, utilizes near-infrared light to measure the differing optical properties between hemoglobin chromophores (oxyhemoglobin, HbO; deoxyhemoglobin, HbR). Raw optical signals can be converted into concentrations using a modified Beer-Lambert equation [38, 39]. fNIRS is highly correlated to the fMRI bold signal [40] while having a higher temporal resolution; however, spatial resolution is limited to superficial cortical regions. In addition to having a higher temporal resolution, fNIRS is better suited to accommodate motion artifacts, can be portable and wireless, be applied in populations contraindicated to MRI or in studies where obtaining an MRI may be difficult. Specific to cognition, fNIRS signals have previously been determined to be sensitive to varying cognitive states and loads [41].

### *1.3.2 fNIRS & tDCS Applications Targeting Cognition.*

It is thought that activation of a cortical area increases HbO concentration with an associated decrease in HbR concentrations [42]. Recent meta-analyses examining the effects of tDCS on cognition and cerebral oxygen hemodynamics found that tDCS does indeed alter cerebral oxygenation and cognitive performance; however, ageing and disease status are potential factors impacting the effectiveness of tDCS on HbO, HbR, and cognitive performance [2, 35]. Further, the interaction effect of tDCS on the directionality of HbO and HbR signals with cognitive performance remains unclear [2]. McKendrick and colleagues [43] report that tDCS increases cognitive performance while reducing cerebral oxygenation, suggesting the potential for increased neuronal efficiency. This is in contrast to a separate study that reports an increase in cognition with an increase in HbO [44]. In addition, studies have reported no cognitive enhancement after receiving tDCS despite increases in HbO with anodal stimulation [45] or interhemispheric oxygenation shifts [46]. To summarize, the overall effect of tDCS on fNIRS metrics and cognition remains largely unknown due to varying study protocols and variability of reported results.

### *1.3.3 Neuronal Variability, Cognition, & fNIRS Considerations.*

Neuronal variability is often regarded as a normal signal component within a healthy nervous system [47, 48]. Neuronal variability has previously been defined as within-subject signal variations in cerebral functional activity, primarily measured with fMRI and EEG approaches [48]. Additionally, neuronal variability has been compared to as an inverted U-shape across ageing; during infancy neuronal variability is limited, which then increases early in the lifespan into younger adults, plateaus, and declines across age [47]. It has been proposed that neuronal variability contributes to a more diverse nervous system [47, 49].

Neuronal variability has previously been demonstrated to be higher in healthy young adults, who performed better in cognitive tasks when compared to healthy older adults [49, 50], Moreover, young adults demonstrated greater increases in neuronal variability under increasing cognitive loads, while older adults presented with less robust changes present and slower performance; thus, increased variability may allow adults to process stimuli information more efficiently [49].

The hemo-neural hypothesis [51] suggests that in addition to neural responses, direct and indirect mechanisms can alter cerebral hemodynamics. The hemodynamic response associated with neuronal variability can be measured with fNIRS [48]. As factors related to ageing, health, and disease status may impact the hemodynamic response functions obtained with fNIRS [2, 52, 53], these factors may need to be controlled for, depending on the design of the study as well as study objectives. Furthermore, it may be of benefit to control for baseline resting-state variability quantified with fNIRS when examining the effects of an intervention across ageing, or between healthy and clinical populations. Although processing methods allow the comparison between baseline and task-evoked responses [52–55], the addition of resting-state measurements in more robust fNIRS processing models may assist in controlling for these differences in neuronal and vascular variability by personalizing the dataset for physiological differences which may impact the obtained fNIRS responses.

### *1.4 Purpose & Hypothesis*

The purpose of this study was to investigate the effects of anodal tDCS over the right DLPFC on cognitive performance and concentrations of HbO and HbR as measured by fNIRS, controlling for the effect of individualized resting-state baseline oxygenation. Two research questions were developed: *1) What are the effects of anodal tDCS over the right DLPFC on*

*performance (accuracy, reaction time) across increasing spans on a modified n-back task? 2) What are the effects of anodal tDCS over the right DLPFC on cerebral oxygen hemodynamics while accounting for individualized resting-state variability as working memory load increases?* Due to the potential of tDCS induced hemispheric-perfusional shifts, bilateral DLPFC activity was recorded using fNIRS. It was hypothesized that anodal tDCS over the right DLPFC would regionally increase HbO concentrations while augmenting cognitive performance on a working memory task.

## 2. Material and Methods

A double-blinded randomized control trial was conducted in a university research laboratory. Eligible participants completed a remotely delivered memory assessment (through CogniFit$^{TM}$; CogniFit Ltd, New York, USA) before conducting the in-person phase of the study. In the laboratory, resting-state baseline activity was first recorded using fNIRS, followed by the administration of a computer-delivered modified *n*-back task concurrent with fNIRS. After the baseline measurements, anodal or sham tDCS was administered, followed by a post-stimulation modified *n*-back task paired with fNIRS. After completing the modified *n*-back task, post-resting state fNIRS measurements were taken, then a post-tDCS CogniFit battery. See Figure 5.1. This study was approved by the University of Alberta Research Ethics Board (Pro00106123). Participants were given a $10.00 gift card.

**Figure 5.1: Procedure**

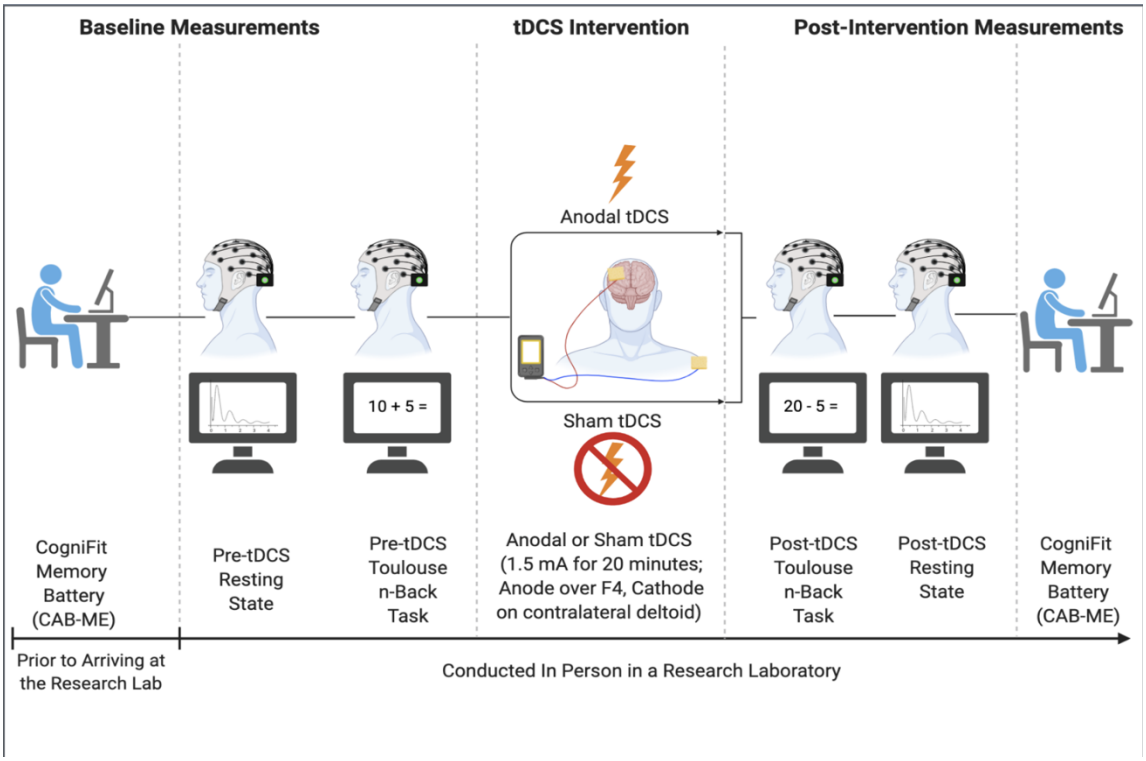



**Figure 5.1 Caption:** Participants completed a remotely delivered computerized cognitive assessment prior to coming into the laboratory. During the in-person session, baseline resting-state fNIRS recordings were taken over bilateral DLPFC, followed by the initial Toulouse *n*-back task paired with fNIRS recordings. Immediately afterwards, 1.5 mA tDCS (anodal or sham) was delivered for 20 minutes. After tDCS, a post-Toulouse *n*-back paired with concurrent fNIRS measurements were taken, followed by a final resting-state measurement. Participants were then asked to complete a computerized cognitive battery.

### *2.1 Participants*

A total of 33 young adults were recruited using poster, email, and word-of-mouth referrals. Inclusion criteria included: healthy young adults aged 18-40, speak English proficiently, pass screenings of vision and hearing, and be able to provide informed consent.

Exclusion criteria included the presence of a diagnosed neurological, psychiatric, or cognitive disorder, the use of prescription neuropsychiatric drugs within the past three months (such as antidepressants and antipsychotics), known seizure disorder, and any tDCS contraindications as outlined by Thair and colleagues [8]. One participant was dropped due to the exclusion criteria.

**Table 5.1: Participant Demographics**

| | **Anodal (*n* = 16)** | **Sham (*n* = 16)** |
|---|---|---|
| Age (Years) | 24.56 ± 5.77 | 25.19 ± 6.08 |
| Biological Sex (Male/Female) | 6/10 | 6/10 |
| Education (Years) | 15.25 ± 2.35 | 16.38 ± 2.90 |
| Handedness (Right/Left) | 16/0 | 14/2 |

### *2.2 Cognitive Battery*

To examine the potential generalizability of tDCS across other memory and executive functioning domains, a computer-delivered memory cognitive battery (CAB-ME) through CogniFit was implemented. Recruited participants were administered the CAB-ME to complete prior to arriving for the in-person component of the study. This battery assesses visual short-term memory, working memory, response time, planning, processing speed, response time, inhibition, contextual memory, non-verbal memory, naming, and visual perception. The CAB-ME was then re-administered in the laboratory after completing the tDCS and fNIRS components of the study (see Figure 5.1). For additional details on the implemented cognitive battery, refer to the supplementary materials.

### *2.3 fNIRS*

An Artinis Brite24 continuous-wave fNIRS device (Artinis Medical Systems; Elst, Netherlands) measuring HbO and HbR raw light intensities at a frequency of 25Hz and

hemoglobin chromophores using emitted wavelengths of 760 nm and 850 nm was used in this study. 10:20 EEG landmarking was utilized to locate Cz for cap alignment. F3 and F4 were utilized to orient a 2 x 11 channel array; hair was moved to allow direct optode contact on the scalp. Sources and detectors were kept 3cm apart. As this array extends inferiorly and posteriorly beyond the region of interest, only channels over bilateral DLPFC will be reported as this is a critical region of interest involved in WM. Thus, a total of eight channels are included for analysis, evenly distributed between bilateral DLPFC regions. Refer to Figure 5.2.

**Figure 5.2: fNIRS Montage**

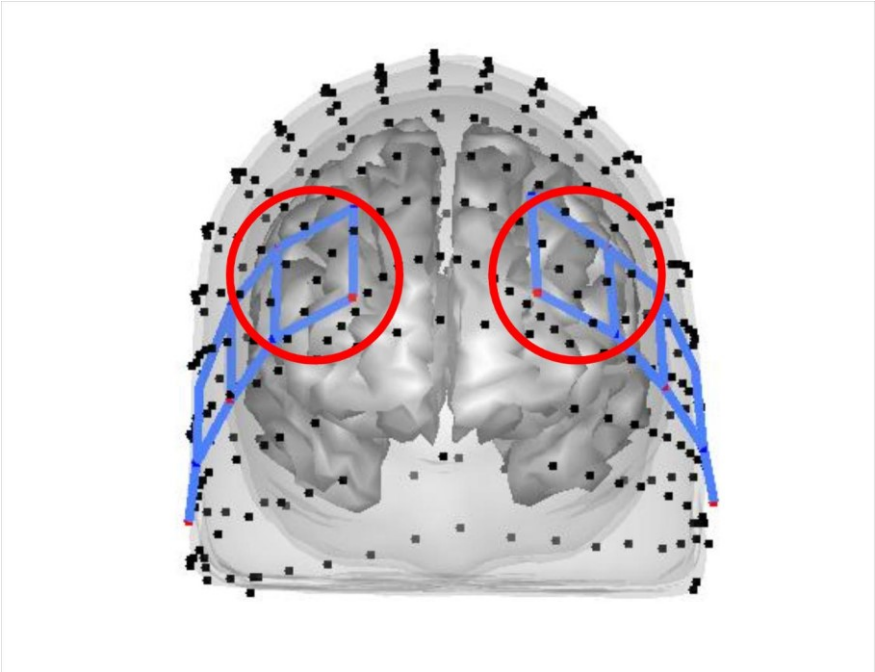


**Figure 5.2 Caption:** A 2x11 channel array was placed over bilateral frontal and temporal regions. Red dots represent emitters, and blue dots represent detectors, together forming a single channel. The channels included in the red circles (F3 - Left DLPFC; F4 - Right DLPFC) were utilized in the analysis as the DLPFC is highly involved in working memory processes. The fNIRS montage was registered to the Colin27 Atlas.

Oxysoft (Artinis Medical Systems, Elst, Netherlands) was utilized to record fNIRS data, which received the raw fNIRS signals through Bluetooth. Live signals over bilateral DLPFC were assessed to ensure quality by determining the presence of a cardiac signal [53] as well as adequate impedance values automatically detected in Oxysoft to ensure optimized channel recordings; if channels were not adequate, hair was repositioned, and the optodes were realigned to ensure scalp contact before proceeding. Resting-state fNIRS recordings were conducted before the initial *n*-Back task and after the final *n*-back task. During resting-state recordings, participants were instructed to sit still with their eyes closed for 120 seconds in a quiet space and told to avoid extraneous thinking. fNIRS was administered concurrently with the Toulouse *n*-back tasks, highlighted below.

### *2.4 Toulouse n-Back Task*

The Toulouse *n*-back task (described in Causse and colleagues, [56]) was administered in conjunction with fNIRS, before (Pre-Toulouse) and after (Post-Toulouse) the tDCS protocol. This task requires participants to solve a presented math equation and determine if the solution is a match to a previous solution *n*-turns previously. *n*-back spans of 1-3 were tested, with 10 trials per span during each of the Pre-Toulouse and Post-Toulouse *n*-back. In each span, 50% of trials were matched to previous stimuli. Participants were instructed to press the '1' key if the solution to the presented equation matched the solution n-turns previously, or the '2' key if it was not a match. Math equations presented were in addends or subtrahends of 5 between 0-100, with solutions < 100. Equations presented consisted of only addition or subtraction operations, and the equations given between the Pre-Toulouse and Post-Toulouse tasks differed to minimize learning. Prior to conducting the Pre-Toulouse *n*-back task, participants were given instructions

as well as 5 trials of each span with live accuracy feedback for practice to ensure comprehension of the task.

The Toulouse *n*-back task was programmed in E-Prime (Version 3.0; Psychology Software Tools, Pittsburgh, PA). A customized InLine E-Prime script sent stimulus onset and offset time markers to Oxysoft, allowing for fNIRS recording to run concurrently with the Toulouse *n*-back task. Stimuli were presented for 3000ms, with a 15000 ms inter-stimulus delay using a fixed cross in the middle of the screen. This delay was programmed to allow adequate recovery of the hemodynamic response, in addition to allowing a period of activity recording before the stimuli presentations.

**Table 5.2: Pre-Toulouse & Post-Toulouse Mean Accuracy and Reaction Time by Span and tDCS Condition**

| **tDCS** | **Span** | ***Pre-Toulouse n-back*** | | ***Post-Toulouse n-back*** | |
|---|---|---|---|---|---|
| | | Mean Accuracy (% ± SE) | Mean Reaction Time (ms ± SE) | Mean Accuracy (% ± SE) | Mean Reaction Time (ms ± SE) |
| **Anodal (*n*=16)** | 1 | 89.58 ± 2.56 | 1444.34 ± 40.53 | 85.41 ± 2.95 | 1464.69 ± 50.51 |
| | 2 | 89.06 ± 2.76 | 1536.12 ± 46.50 | 94.53 ± 2.01 | 1317.90 ± 40.97 |
| | 3 | 82.14 ± 3.64 | 1496.35 ± 62.72 | 82.14 ± 3.64 | 1320.75 ± 51.05 |
| **Sham (*n*=16)** | 1 | 95.83 ± 1.69 | 1580.84 ± 40.77 | 86.11 ± 1.68 | 1566.11 ± 42.24 |
| | 2 | 91.40 ± 1.95 | 1678.54 ± 44.99 | 90.60 ± 2.48 | 1488.96 ± 45.98 |
| | 3 | 84.82 ± 1.72 | 1594.75 ± 59.87 | 71.42 ± 3.40 | 1513.18 ± 52.34 |

SE: Standard Error, ms: milliseconds

### *2.5 tDCS*

The right DLPFC was selected as the target of stimulation based on previously proposed literature on the right DLPFC involvement in arithmetic manipulation and WM processing, which are both involved in the Toulouse *n*-back task [56, 79]. tDCS was administered using an

HDC MagStim device, with the anode over the right DLPFC (marked at F4 referring to 10:20 coordinates), at a current of 1.5mA for 20 minutes. The cathode was placed on the contralateral deltoid. Current was delivered using 5cm x 7cm x 0.5cm electrode sponges, saturated with 10mL normal saline solution. The electrical current was ramped up and down over 15 seconds. In the sham condition, the current was ramped up for 15 seconds, a 1.5 mA current was delivered for 30 seconds, then ramped down for 15 seconds; this blinding method was utilized to achieve the cutaneous sensation of electrical stimulation as a blinding protocol [8, 57]. The tDCS devices were programmed to deliver the real or sham current by an individual outside of data collection, with concealment kept by the individual until data analysis was completed. Refer to the tDCS intervention in Figure 5.1 for a visualization of the tDCS montage.

## 2.6 Analyses

### *2.6.1 Cognitive Data.*

Toulouse *n*-Back Task E-Prime files were first cleaned of practice trials and the corresponding *n* stimuli without a match were removed (e.g., the first two presentations on the 2-Back condition). Differences (Δ's) between the Post-Toulouse and Pre-Toulouse *n*-backs were calculated in SPSS (Version 28; IBM Corp., Armonk, NY). To calculate ΔAccuracy, all eligible cleaned runs were included. For ΔReaction Time, only correct responses were utilized. A MANOVA on the variables ΔAccuracy and ΔReaction Time was utilized, using tDCS Group (Anodal, Sham) and *n*-Back Span (1-, 2-, 3-Back conditions) as between-group factors. Significance was determined at $p < 0.05$. A Bonferroni post hoc correction was performed where applicable.

A similar method was used to analyze the CogniFit Results. Differences were calculated between post-tDCS and pre-tDCS for each of the tests included on the CAB-ME battery and

used to calculate a MANOVA and associated univariate ANOVAs for each test. tDCS group was included as a between-subject factor, and time since the baseline CogniFit test was included as a covariate. Bonferroni post hoc analysis was performed to correct for multiple comparisons.

### *2.6.2 fNIRS.*

The fNIRS analysis followed similar methods to a previous study examining the effects of cognitive load on fNIRS activity and cognitive performance [58]. First, the OXY4 fNIRS files were converted to NIRS files using *Oxysoft2Matlab*, a Matlab-based conversion software developed by the fNIRS device manufacturer (Artinis Medical Systems). NIRS files were then imported into Homer2 [54], and the channels over bilateral DLPFC were examined for the presence of significant artifact and a cardiac signal at approximately 1 Hz using power spectral densities; this was utilized as a signal quality assessment [58, 59]. As each participant underwent two rounds of fNIRS recordings paired with the Toulouse *n*-back task before and after tDCS (Pre-Toulouse and Post-Toulouse), participants were excluded from the fNIRS analysis if either file failed to demonstrate the presence of a cardiac signal.

fNIRS raw light intensity data was imported into the Brain AnalyzIR Toolbox [60], which was run in Matlab version 2019b (The MathWorks Inc, Natick, MA). Files were downsampled to 5Hz, converted to optical densities, and then converted into oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations by applying a modified Beer-Lambert law across the time series. Baseline resting-state HbO concentrations were averaged across the 120-second time series from the four channels over each DLPFC per individual, using a customized Matlab code. Individualized and hemispheric specific baseline resting-state HbO concentrations were then added to the Toulouse *n*-back hemodynamic statistics described below.

Subject level statistics were applied to the HbO and HbR concentrations. As described in Meidenbauer and colleagues [58], the presence of autocorrelation due to oversampling as well as noise increases the risk of type-1 error [55, 58]. To account for this, pre-whitening using an autoregressive filter present in an autoregressive iteratively reweighted least-squares model (AR-IRLS) was employed for the subject-level statistics (see Meidenhauer and colleagues [58] for additional details).

No participants were excluded from the dataset after calculating leverage and outliers ($p < 0.05$). Group-level statistics were then calculated, utilizing a linear mixed-effects model. As baseline resting-state HbO concentration was a variable of interest, it was included as a covariate in the model. To examine the effect of tDCS between groups (Anodal and Sham tDCS), contrasts were conducted using a t-test and corrected for multiple comparisons using the Benjamini-Hochberg false-discovery rate. As each fNIRS channel represents a limited region, the four channels over each DLPFC were then combined in a Region of Interest (ROI) Analysis; adjusted $p$-values, reported as $q$-values, will be utilized to determine significance at $q < 0.05$.

fNIRS depth maps were further developed in Brain AnalyzIR [60], which can determine the region of interests and depths achieved using the applied fNIRS montage. The depth map function utilizes Talairach daemon parcellation from the Colin27 brain [61], in addition to fNIRS montage spatial data, to determine the distances between fNIRS probes and specified target regions [58, 60]. In this study, depth maps for bilateral Brodmann Area 46 were computed. As current fNIRS applications generally have light penetration of up to 30mm, regions extending beyond 30mm do not reach the physiological responses of the specified ROI (i.e., the channels mapped over yellow regions, see Figure 5.4).

### *2.6.3 tDCS Modeling.*

tDCS electrical field modeling was conducted using the realistic volumetric approach to simulate transcranial electric stimulation (ROAST; [62]), using MatLab (Version 2019b), on the T1-weighted Colin27 atlas [61]. tDCS parameters, including current intensity, electrode size, and electrode montage were specified in the model.

## 3. Results

### *3.1 Participants*

From the 33 participants, 1 individual was dropped as they were actively taking a selective-serotonin reuptake inhibitor. Of the 32 participants eligible for analysis, 7 were excluded from the fNIRS analysis due to poor signal quality; however, all 32 participants were included in the cognitive analysis. There were no significant differences between the anodal or sham group on the variables of age ($p$ = .768), years of education ($p$ = 0.237), and baseline resting-state HbO concentrations ($p$ = 0.301). There was a 12:20 male to female ratio, evenly distributed between the tDCS groups.

### *3.2 Cognitive Results*

#### 3.2.1 Toulouse n-Back Task.

The MANOVA revealed a significant effect of the *n*-Back span, for both accuracy and reaction time ($\Lambda$ = 0.965, F = 6.885, $p$ < 0.001). Additionally, a significant effect of the tDCS group (Anodal, Sham) was observed ($\Lambda$ = 0.998, F = 4.700, $p$ = 0.009). The *n*-back span x tDCS group interaction was non-significant on the multivariate model; between-group effects on tDCS allocation revealed significant differences in accuracy (F = 6.506, p = 0.011) but not on reaction time (F = 1.769, $p$ = .184).

Univariate contrasts on mean difference reaction times were non-significant (using Bonferroni corrections) on the 1- and 2-back spans. However, there was a significant mean difference of -250.70 ms between the anodal and sham stimulation conditions on the 3-back span ($p$ = 0.013, 95% CI: 53.55, 447.84). Similarly, the mean differences in accuracy across the 1- and 2-back were non-significant. Again, a significant mean difference of 13.4% between the anodal and sham tDCS groups was noted on the 3-back span ($p$ = 0.028, 95% CI = 0.15, 0.253). Thus, a significant increase in WM processing occurred in the anodal group during the 3-back after receiving the tDCS stimulation; refer to Table 5.3 and Figure 5.3.

**Table 5.3: Toulouse *n*-Back Task Results Between Anodal & Sham Stimulation Conditions**

| Dependent Variable | *n*-Back Span | Mean Difference (Anodal-Sham) | Std. Error | Sig.[a] | 95% Confidence Interval for Difference[a] | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound |
| Δ Reaction Time (ms) | 1Back | 49.813 | 88.567 | .574 | -124.052 | 223.677 |
| | 2Back | -16.648 | 93.939 | .859 | -201.059 | 167.762 |
| | **3Back** | **-250.696*** | **100.425** | **.013** | **-447.840** | **-53.553** |
| Δ Accuracy | 1Back | .056 | .053 | .299 | -.049 | .161 |
| | 2Back | .063 | .057 | .271 | -.049 | .174 |
| | **3Back** | **.134*** | **.061** | **.028** | **.015** | **.253** |

a. Corrected Bonferroni *p*-values for multiple comparisons. Mean differences in Δ Accuracy are decimal transformed percentages.

**Figure 5.3: Estimated Marginal Means of Δ Reaction Time (ms) and Δ Accuracy (%)**

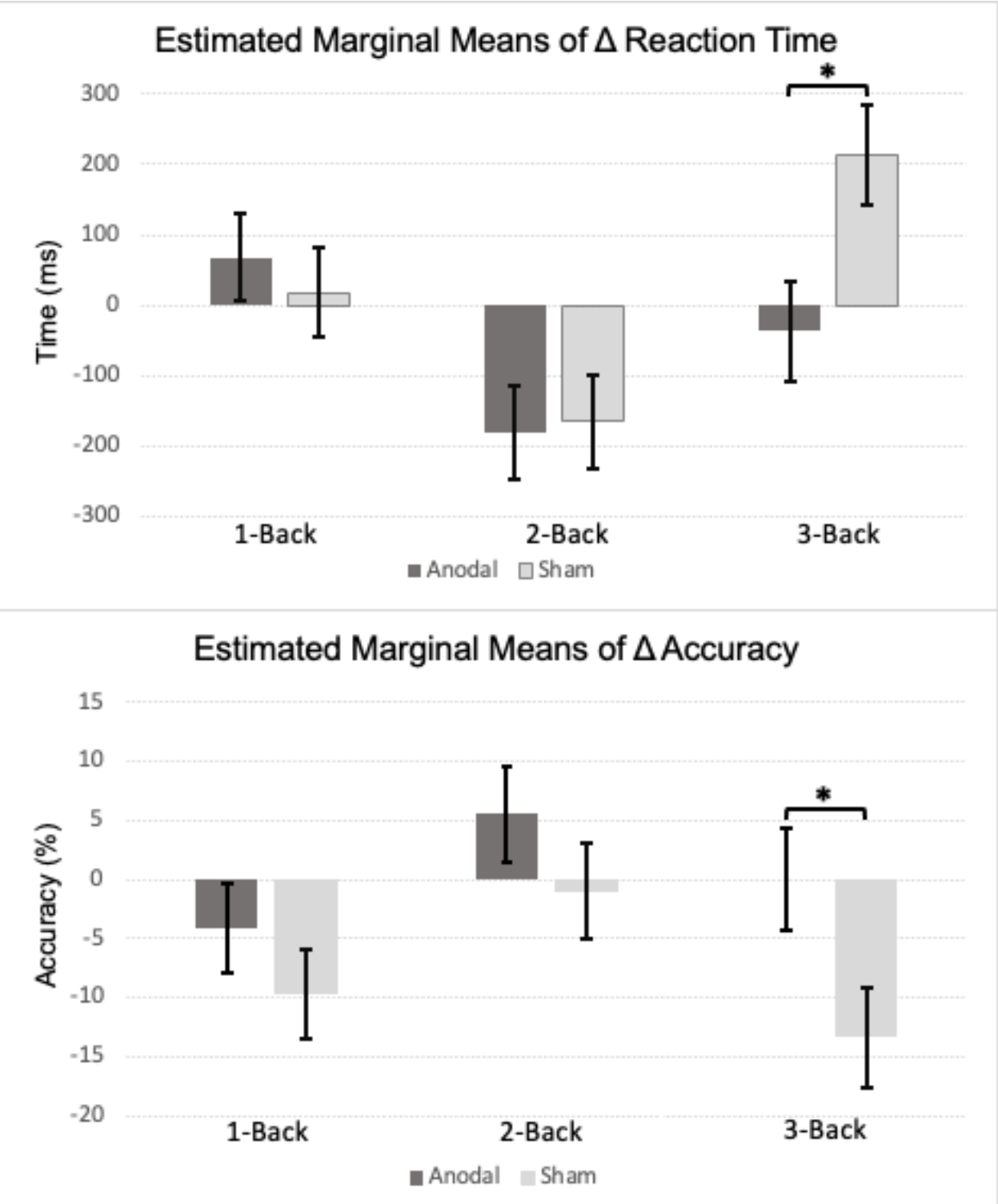



**Figure 5.3 Caption:** Estimated marginal means. Note: Error bars represent standard error.

### 3.2.2 Cognifit.

No significant differences were found between tDCS groups across the cognitive domains tested across the CAB-ME battery on the multivariate analysis as well as on univariate ANOVA's. Refer to table 5.4.

**Table 5.4: Cognifit Memory (CAB-ME) Battery Results Between Anodal & Sham Stimulation Conditions**

| Dependent Variable | Cognitive Process | Mean Difference (Anodal-Sham) | Std. Error | Sig.[a] | 95% Confidence Interval for Difference[a] | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound |
| **Glowing Circles Task** | | | | | | |
| Δ Average Span | Visual Short-term memory | .329 | .423 | .443 | -.538 | 1.197 |
| Δ Average RT (Stimuli) | Response Time | -42.936 | 82.645 | .608 | -212.510 | 126.638 |
| Δ Average RT (Series) | Planning | 109.155 | 353.636 | .760 | -616.445 | 834.756 |
| Δ Max Sequence Length | Visual short-term memory, planning | .694 | .599 | .257 | -.536 | 1.924 |
| Δ Sequence Length (with interference delay) | Visual short-term memory, planning | -.035 | .546 | .949 | -1.155 | 1.084 |
| **Objects Seen or Heard Before** | | | | | | |
| Δ RT (All Stimuli) | Contextual memory | -10.882 | 77.832 | .890 | -170.580 | 148.817 |
| Δ RT (Correct Pictures) | Non-verbal memory | -33.735 | 75.439 | .658 | -188.524 | 121.054 |
| Δ RT (All Correct) | Contextual memory | -44.426 | 73.779 | .552 | -195.807 | 106.956 |

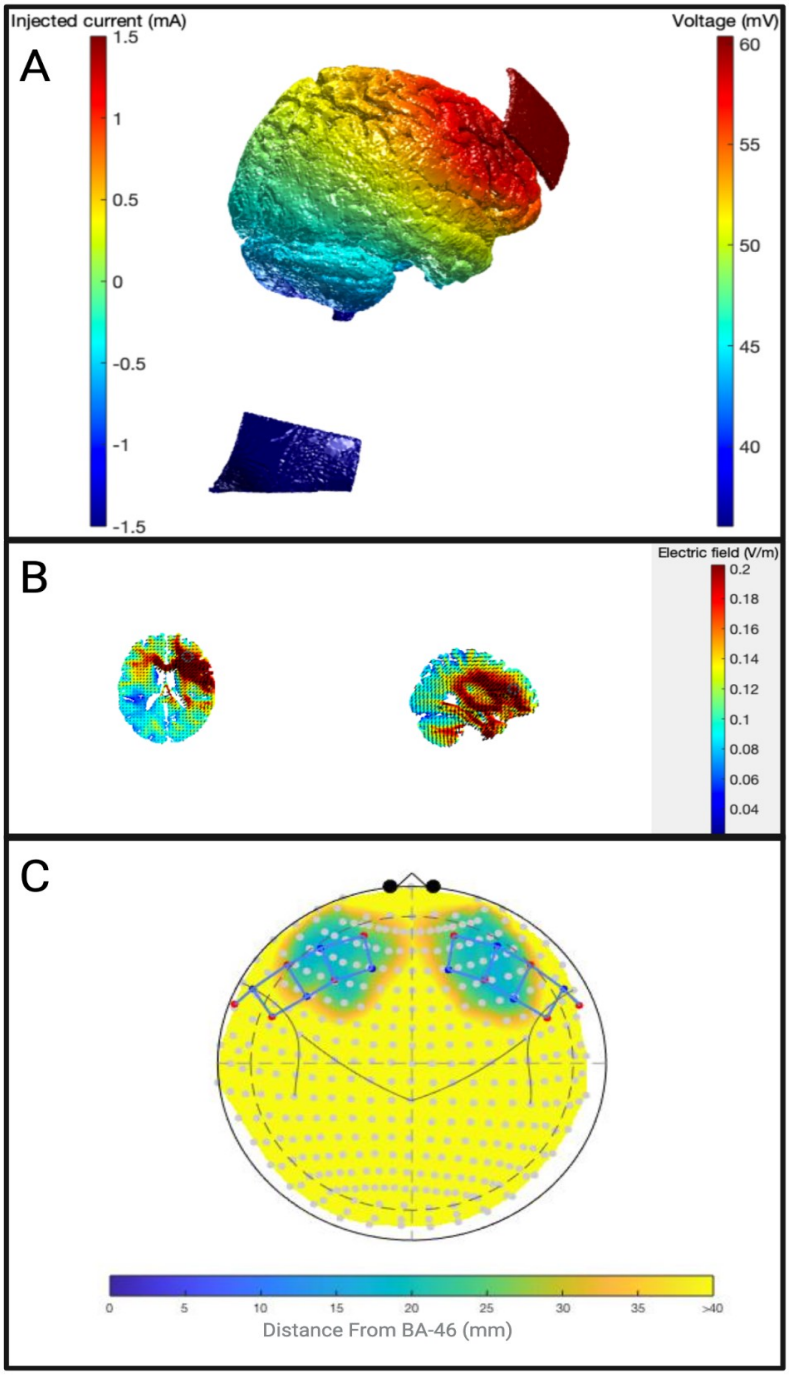
| | | | | | | |
|---|---|---|---|---|---|---|
| **Letter Task** | | | | | | |
| Δ RT (Correct) | Naming, visual perception | 100.656 | 119.066 | .405 | -143.646 | 344.958 |
| **Number Task** | | | | | | |
| Δ Average RT (Stimuli) | Response time | -77.439 | 79.815 | .341 | -241.206 | 86.328 |
| Δ Average RT (Series) | Planning | -155.742 | 546.430 | .778 | -1276.923 | 965.439 |
| **Colors & Words Task** | | | | | | |
| Δ Average RT (Correct) | Inhibition | -604.118 | 479.060 | .218 | -1587.068 | 378.833 |

a. Adjustment for multiple comparisons: Bonferroni. RT: Reaction Time. Refer to the supplementary materials for additional details of the tasks and variables.

### *3.3 tDCS Modeling and fNIRS Depth Maps.*

Results from the tDCS modeling from ROAST using the Colin27 atlas indicate that the tDCS electrical current increased the electric field density in the right DLPFC. In addition to targeting the right DLPFC, the applied current appears to reach deeper subcortical structures, extending into the contralateral hemisphere including regions surrounding the unstimulated left DLPFC. Gross ROI depth maps of bilateral Brodmann Area 46 regions support that the fNIRS hemodynamic signals can measure cortical structures that were targeted with tDCS (see Figure 5.4).

**Figure 5.4: tDCS Distribution Modeling and DLPFC Depth Map**




3A: Modeled tDCS current and voltage (modeled using the Colin27 Atlas) over the stimulated right DLPFC (Anode - Red Rectangle; Cathode - Blue Rectangle placed on the left deltoid).

3B: Electric field density (V/m) demonstrating the dispersion of tDCS stimulation, with the anode at F4 and cathode on the contralateral deltoid.

3C: Modeled depth map of the fNIRS montage over bilateral DLPFC (registered to the Colin27 Atlas). Note: fNIRS has a typical depth of up to 30mm, thus anything greater (in orange and yellow) are out of the range of conventional fNIRS devices.

### *3.4 fNIRS Results*

Between-group contrasts on the group (Anodal, Sham) x time (Post-Toulouse, Pre-Toulouse tasks) interaction with interindividual baseline resting-state HbO concentrations controlled in a linear mixed effect model found significant increases in HbO in the right DLPFC region within the anodal group compared to sham. When conducting an ROI analysis in each of the left and right DLPFC, HbO concentrations were found to be significantly higher in those receiving anodal tDCS compared to the sham control (t = 2.77, DF = 129, $q$ = 0.025). No significant differences were found between groups in right-DLPFC HbR concentrations. Lastly, no significant differences are noted in HbO or HbR in the left DLPFC between groups relative to baseline.

**Figure 5.5: fNIRS Results Per Channel (Across All *n*-Back Spans)**

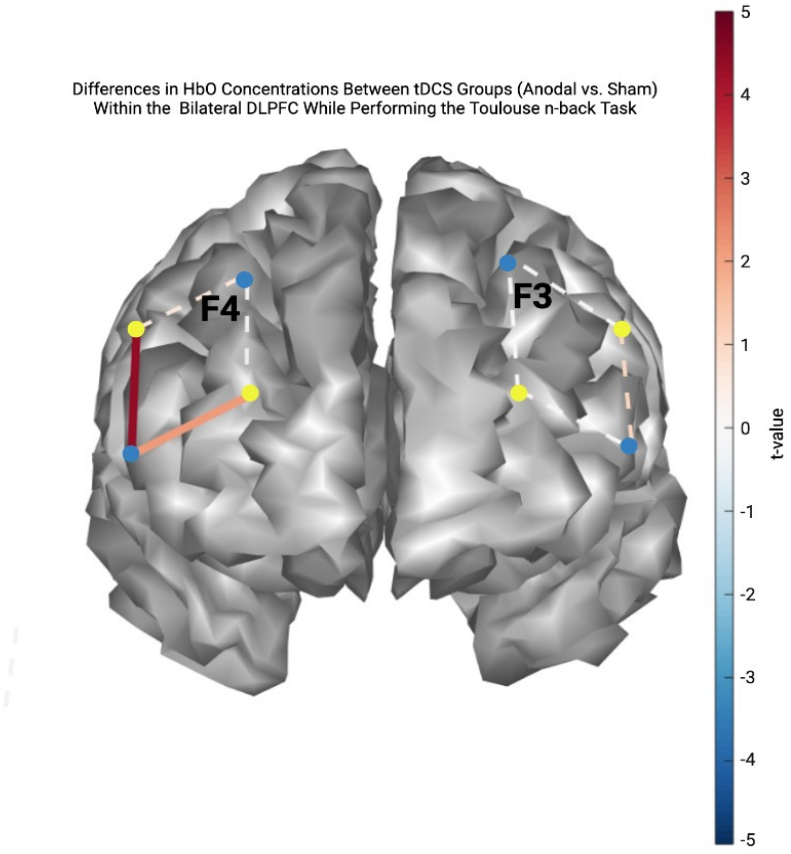


**Figure 5.5 Caption:** Differences (Post-Toulouse - Pre-Toulouse Tasks) in HbO concentrations across all the *n*-back span trials. Yellow circles represent LED sources, blue circles represent detectors; the pair of which form a channel. Solid lines represent significant differences in the channel between the anodal and sham stimulation groups. The tDCS anode was placed over F4. Registered to the Colin27 Atlas.

When examining the group x time x *n*-back condition between groups, ROI results were dependent on the *n*-back span. During the 1-back, no significant differences were found between groups in either HbO or HbR across bilateral DLPFC; however, increases in HbO concentration in the anodal group were found ($t = 2.15$, $DF = 125$, $q = 0.067$). During the 2-back, a significant increase in the HbO concentration was observed in the anodal group compared to the sham group solely in the right DLPFC ($t = 2.95$, $DF = 125$, $q = 0.015$) after the resting state correction. This significant difference further increased in the 3-back condition between groups ($t = 3.17$, $DF = 125$, $q = 0.0077$). In the 2-back and 3-back conditions, no significant differences were found in HbO in the left DLPFC, as well as HbR bilaterally.

**Table 5.5: Between Group fNIRS Contrasts (Anodal-Sham) Across *n*-Back Spans**

| Span | ROI | Chromophore | Beta | SE | DF | T | p | *q* |
|---|---|---|---|---|---|---|---|---|
| **Overall** | **Right DLPFC** | **HbO** | **4.634** | **1.672** | **129** | **2.772** | **0.0006** | **0.0256** |
| | | HbR | 1.032 | 0.603 | 129 | 1.711 | 0.089 | 0.179 |
| | Left DLPFC | HbO | 0.744 | 1.535 | 129 | 0.485 | 0.627 | 0.629 |
| | | HbR | -0.528 | 0.641 | 129 | -0.824 | 0.412 | 0.549 |
| `1-Back | Right DLPFC | HbO | 4.201 | 1.956 | 125 | 2.148 | 0.034 | 0.067 |
| | | HbR | -0.566 | 0.789 | 125 | -0.718 | 0.474 | 0.632 |
| | Left DLPFC | HbO | -0.117 | 2.051 | 125 | -0.057 | 0.955 | 0.955 |
| | | HbR | -0.190 | 0.845 | 125 | -2.255 | 0.026 | 0.067 |
| **2-Back** | **Right DLPFC** | **HbO** | **5.59** | **1.894** | **125** | **2.952** | **0.004** | **0.015** |
| | | HbR | 1.528 | 0.788 | 125 | 1.940 | 0.055 | 0.109 |
| | Left DLPFC | HbO | 0.380 | 2.026 | 125 | 0.188 | 0.851 | 0.851 |
| | | HbR | 0.358 | 0.840 | 125 | 0.426 | 0.671 | 0.851 |
| **3-Back** | **Right DLPFC** | **HbO** | **5.99** | **1.89** | **125** | **3.169** | **0.00192** | **0.00770** |
| | | HbR | 0.979 | 0.791 | 125 | 1.238 | 0.218 | 0.369 |
| | Left DLPFC | HbO | 0.317 | 2.03 | 125 | 0.156 | 0.876 | 0.876 |
| | | HbR | 0.917 | 0.841 | 125 | 1.090 | 0.277 | 0.369 |

ROI: Region of Interest, HbO: Oxyhemoglobin, HbR: Deoxyhemoglobin, SE: Standard Error, DF: Degrees of Freedom, q: False discovery rate *p*-value corrections for multiple comparisons. Bolded values indicate significant differences.

## 4. Discussion

The purpose of this study was to explore the effects of anodal tDCS over the right DLPFC on working memory performance and regional cerebral oxygenation concentrations on the Toulouse *n*-back task. In addition, by incorporating resting-state baseline fNIRS metrics into statistical modeling, personalization of the hemodynamic responses allowed for controls within group-level and between-group comparisons.

We hypothesized that anodal tDCS at 1.5mA for 20 minutes over the right DLPFC in young healthy adults would increase working memory performance with an associated increase in oxyhemoglobin concentrations. Overall, the results are in line with our initial hypothesis; HbO concentrations and working memory performance were found to be significantly higher in the anodal tDCS group compared to sham, however, this effect was only noted in higher-load conditions.

### *4.1 Impact of tDCS on Cognition*

To our knowledge, this is the first study utilizing the Toulouse *n*-back task in a tDCS-fNIRS protocol. The addition of mathematical manipulation in the *n*-back task is thought to invoke a higher multidimensional cognitive workload compared to traditional *n*-back paradigms [56]. This may partially explain observed differences from previous tDCS-fNIRS studies using *n*-back tasks (see Figeys and colleagues [2] for a review). Specific to other *n*-back tasks employed in cognitive tDCS-fNIRS protocols, Borragán and colleagues [46] report that tDCS did not improve performance on the TLoadDBack task, which involves a combination of a

numeric decision-making task paired with a traditional *n*-back task [46, 63]. Similarly, tDCS did not increase accuracy on a visuospatial *n*-back task, however, learning variability was decreased in those receiving tDCS stimulation [64]. In older adults, null tDCS effects have also been reported on a visual *n*-back task, although these individuals did improve significantly on far-transfer tasks [65]. As the Toulouse *n*-back task may be more cognitively taxing, greater differences in cerebral oxygenation may occur as a result of varying neuronal activation and metabolic processes compared to traditional *n*-back paradigms.

To explore the effects of generalizability of tDCS effects into other cognitive domains, a standardized cognitive battery was implemented using CogniFit. We report no significant differences between the anodal and sham stimulation groups across all the cognitive domains tested using the computer-delivered memory battery. Again, this finding may be dependent on the difficulty of the cognitive task, as well as the nature of the cognitive task itself. The tDCS montage implemented targeted the DLPFC, as it is highly integrated with WM processes (see Owen et al., [18] for a review); thus, the tDCS montage may have not been optimized for the cognitive tasks [66] utilized within the CogniFit battery.

### *4.2 Cerebral Oxygenation & Working Memory Interaction*

The impact of tDCS on HbO concentration was prevalent as the cognitive load on the Toulouse *n*-back task increased. Specifically, individuals in the anodal group demonstrated increased accuracy and latency on higher span conditions, with an associated increase in regional HbO concentration within the stimulated right DLPFC. Our results suggest that tDCS augmented regional oxyhemoglobin concentrations as well as cognitive performance. However, given the varying reported effects of tDCS on cognition and cerebral oxygenation hemodynamics [2, 35], results may be task and load-dependent. The effects of increasing WM load on fNIRS signals

have also recently been reported by Meidenbauer and colleagues [58], who report potential metabolic activation variability based on both cognitive task and load. Therefore, the effects of tDCS on the interaction between cognitive performance and cerebral oxygenation hemodynamics should be considered in the context of the task, cognitive load, and cognitive domain.

Although it was found that tDCS increases cognitive performance and cerebral oxygenation in a load-dependent manner, the interaction between cognition and cerebral oxygenation remains less clear. During the 1-back condition, there were no significant differences in fNIRS signals or cognitive performance between groups. During the 2-back condition, a significant increase in HbO concentration was observed for the anodal group, without improvements in cognitive performance. However, on the 3-back, an increase in HbO was present with increased accuracy and decreased reaction time on the Toulouse *n*-back task. Thus, it is possible that tDCS modulates the neural-hemodynamic interaction prior to the effects being observed in cognitive domains; this may be impacted by individual cognitive factors including cognitive capacity and reserve.

fNIRS has been previously used to investigate cerebral oxygenation changes during the Toulouse *n*-back task. Causse and colleagues [56], [67] reported a decline in WM performance on the Toulouse *n*-back task as cognitive load increased, with an associated increase in prefrontal oxygenation, and increases in pupillary size indicative of greater cognitive processing demands [56, 67]. Our results suggest that tDCS neuromodulation may increase prefrontal oxyhemoglobin concentration in each WM condition while augmenting cognitive performance in higher-load processing.

To better control for interindividual neuronal variability, individualized resting-state oxygenation was controlled for in the fNIRS modeling. In addition, as changes within the

neurovascular unit can occur across ageing and disease, controlling for such neurovascular variability may allow for a more accurate representation of fNIRS responses. However, other neurophysiological factors can contribute to the efficiency of neuronal engagement [68]. For instance, automaticity may have been a modulating factor in neuronal activation measured with fNIRS during the lower span tasks, in line with the neuronal efficiency hypothesis [58, 69–71]. Regarding neuronal efficiency, it is hypothesized that those with more efficient cognitive processing, compared to those with lower processing strategies, will display lower activation patterns during easier cognitive tasks, and greater neuronal activation during higher cognitive demands [58, 69–71].

Overlapping with the neuronal hemo-neural hypothesis [51], which suggests that direct and indirect mechanisms can alter the hemodynamic-neural interaction, the varying neuronal activation patterns proposed in the neuronal efficiency hypothesis may have resulted in downstream hemodynamic differences including changes in cerebral oxygenation, dependent on neuronal and cognitive efficiency. If tDCS augments neuronal efficiency, changes in neuronal metabolism resulting in reductions of HbO concentrations may occur after stimulation (i.e., more efficient neuronal metabolic processes may already have adequate oxygenation from baseline perfusional factors when engaging in cognitive demands or possibly require less oxygen). In line with this merged hypothesis, increased neuronal efficiency, improvements in cognitive performance, and declines in cerebral oxygenation after tDCS stimulation have been previously reported by McKendrick and colleagues [43].

tDCS modeling found that the applied current reached the contralateral prefrontal cortex with a significant current density and electric field crossing the corpus callosum (Figure 5.4B). By complementing the obtained results with this tDCS current modeling, tDCS may have

resulted in hemispheric-specific modulation by altering neuronal efficiency in the left DLPFC and increased neuronal metabolic processes and activation over the stimulated right DLPFC. Future research is required to determine the impact of tDCS on neuronal efficiency and neuronal activation, interactions, trade-offs, and potential hemispheric shifts.

### *4.3 Limitations & Future Directions*

Several limitations exist in this study. First, although levels of education were similar between groups, the high levels of education in the recruited sample may not reflect the general population. Second, we implemented a single tDCS session over the right DLPFC; although we report significant HbO concentration and cognitive performance changes, future studies should explore the effect of multi-session tDCS on these variables, as well as different montages and doses [10, 66, 72–74]. Although this study controlled for interindividual resting-state HbO, additional factors including WM strategy, motivation, individual WM capacity, age, and education may have impacted the results [2, 35, 43, 44, 75]. Furthermore, task difficulty has been demonstrated to modulate lateralization of activation measured with fNIRS [76]. This study is limited to younger adults, although similar results have been reported in older adults [44]. Additionally, healthy adults were recruited in this study; numerous diseases and ageing-related factors on cognition and microvascular changes may impact both performance and fNIRS signals [2] warranting future research drawing from clinical populations .

Ongoing research examining the effect of tDCS on cerebral perfusion, cerebral oxygenation, and cognition is necessary. As fNIRS is only able to quantify hemoglobin chromophore concentrations in cortical regions, it would be advantageous to complement fNIRS with other perfusional neuroimaging approaches such as single-photon emission computed tomography, positron emission tomography, or arterial spin labeling (ASL). Previous studies

have demonstrated that tDCS over the DLPFC resulted in increased perfusion in structurally related regions using ASL in healthy adults [33]. In addition, a recent study examining the effect of tDCS and cognitive training on cerebral perfusion and cognitive performance in participants with traumatic brain injuries report that anodal tDCS over the left DLPFC resulted in the maintenance or increased cerebral blood flow in the right inferior frontal gyrus; cognitive performance was not impacted by this perfusional change [77]. Future research is required to determine perfusional-cognitive effects of tDCS across healthy and clinical populations, as well as cognitive ageing, utilizing varying tDCS parameters and cognitive protocols. Lastly, as neuronal variability can extend to the neurovascular unit impacting cerebral perfusion and oxygenation, future research should continue to develop methods to control for such variability measured using fNIRS, as well as controlling for oxygenation variability in other populations of interest.

## 5. Conclusion

This study examined the effects of tDCS on cerebral oxygenation measured with fNIRS signals and cognitive performance while controlling for perfusional individual variability. tDCS was a well-tolerated intervention across participants, with a mild pins and needles sensation under one or both electrodes frequently being reported; we report no significant adverse tDCS effects. The results of this study suggest that single session tDCS over the right DLPFC in healthy young adults can locally increase HbO concentrations and enhance working memory in higher cognitive processing conditions. Controlling for individual neurohemodynamic variability may provide further insights into tDCS effects on brain-behaviour interactions in basic and clinical populations. Further research is required to corroborate these findings in other populations and explore other potential moderating factors.

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# Chapter 6: tDCS Over the Left Prefrontal Cortex Improves Mental Flexibility and Inhibition in Geriatric Inpatients with Symptoms of Depression or Anxiety: A Pilot Randomized Controlled Trial[3]


## Abstract

**Background:** Patients with depression and/or anxiety are commonly seen in inpatient geriatric settings. Both disorders are associated with an increased risk of cognitive impairments, notably in the domain of executive functioning. Transcranial direct current stimulation (tDCS), a type of non-invasive brain stimulation, involves the administration of a low-dose electrical current to induce neuromodulation which ultimately may act on downstream cognitive processing.

**Objective:** The purpose of this study was to determine the effects of tDCS on executive functioning in geriatric inpatients with symptoms of depression and/or anxiety.

**Methods:** Thirty older-aged adults underwent ten-to-fifteen sessions of 1.5 mA anodal or sham tDCS over the left dorsolateral prefrontal cortex; cognitive assessments were administered at baseline and following the tDCS protocol. Analysis was based on 20 participants, comparing the effects of tDCS on cognitive performance between groups following the tDCS protocol.

**Findings:** tDCS was found to increase inhibitory processing and cognitive flexibility in the anodal group, as measured by significant changes on the Stroop test and Trail Making Test (Part B), respectively. No significant changes were observed on measures of attention or working memory.


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**Explanatory Note:** The emergence of SARS-2-COV (COVID-19) at the beginning of 2020 directly impacted this study. As this study utilized a sample of hospitalized older adults, recruitment and data collection was terminated early to protect the health and well-being of participants and patients. By doing so, a final sample of 20 older adults were included in the analysis, which resulted in a change of conceptualization to a pilot study design.

[3] This paper is in preparation for submission as: Figeys, M., Villarey, S., Leung, A., Raso, J., Buchan, S., Kammerer, H., Rawani, D., & Kohls-Wiebe, M, Kim, E.S.. tDCS over the left prefrontal cortex improves mental flexibility and inhibition in geriatric inpatients with symptoms of depression or anxiety: A pilot randomized controlled trial.

**Interpretation:** These results provide preliminary evidence that tDCS-induced neuromodulation may selectively improve cognitive processing in older adults with symptoms of depression and/or anxiety.

**Clinical Trials Registration:** www.clinicaltrials.gov, NCT04558177

**Funding Information:** Centre for Aging and Brain Health Innovation, Glenrose Rehabilitation Foundation.

**Keywords:** Transcranial Direct Current Stimulation, Executive Functioning, Depression, Anxiety, Geriatric

**Disclosure Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author, MF, upon reasonable request.

## 1. Introduction

Older adults admitted for rehabilitation often present with concomitant depression and/or anxiety (Shah, Evans, & King, 2000; Sayers et al., 2007; Yohannes et al., 2008). Multi-morbidity as well as cognitive impairment may be synergistically coupled with depression and anxiety in older adults (Read et al., 2017; Gould et al., 2016). Additionally, depression and anxiety are often comorbid psychiatric disorders (Kalin, 2020; Beekman et al., 2000). In older adults, the severity of depression often increases when an anxiety disorder comorbidity is present (Fiske, Wetherell, & Gatz, 2009; Andreescu et al., 2007). Furthermore, depression and/or anxiety may impair processes related to successful rehabilitation and are associated with increased length of hospital stay, increased utilization of inpatient resources, and a higher rate of inpatient mortality (Sayers et al., 2007; Prina et al., 2012; Sugawara et al., 2015).

Executive functioning (EF) is a key mediating factor associated with functional status in older adults (Grigsby et al., 1998). EF is often discussed in terms of three subdomains required to perform daily activities: inhibition, working memory, and cognitive flexibility (Diamond, 2013). Although EF naturally declines across normal cognitive aging (Etienne et al., 2008; Harada et al., 2013; Fjell et al., 2017), numerous underlying etiologies including mild cognitive impairment (MCI) and dementia can impair EF beyond the extent seen across normal cognitive aging (Kirova et al., 2015). Cognitive changes in EF have been observed in older adults with neurocognitive and psychiatric disorders, including depression, anxiety, MCI, and dementia (Lockwood et al., 2002; Alexopoulos et al., 2011; Pantzar et al., 2014; Brandt et al., 2009; Duong et al., 2006; Clark et al., 2012; Guarino et al., 2018; Kassem et al., 2017; Yochim et al., 2013). Therefore, interventions aimed at improving EF may lead to improved functional outcomes in older adults (See Karr and colleagues, 2014, for a review).

Experimental use of transcranial direct current stimulation (tDCS) has been increasingly explored as a cognitive enhancement technique, including within older adult populations (Huo et al., 2019; Indahlastari et al., 2021; Lee, Lee, & Kang, 2021). tDCS is an emerging method of non-invasive brain stimulation, where neuromodulation is achieved by altering neuronal polarities through the administration of a low-dose electrical current applied across the scalp to target brain structures. Although transcranial magnetic stimulation (TMS) has been approved for clinical applications such as treatment-resistant depression in a wide number of countries, tDCS approval currently remains primarily for research purposes in most nations (Fregni et al., 2015).

Previous studies have demonstrated that tDCS can result in improvements in cognition, as well as modulating symptoms associated with depression, MCI, and dementia (Kalu et al., 2012; Meinzer et al., 2015; Cruz Gonzelez et al., 2018). Several of these studies explored the effects of tDCS on the dorsolateral prefrontal cortex (DLPFC; Kalu et al., 2012; Cruz Gonzelez et al., 2018). The DLPFC has also been established as a neural region involved in mediating cognitive processes underlying EF, including attention (Kane & Engle, 2002), cognitive flexibility (the ability to switch across multiple different concepts in a context dependent manner; Kim et al., 2011; Uddin, 2021) and higher-order cognition (MacPherson et al., 2002; Tremblay et al., 2014). Further, neuroimaging has consistently demonstrated that the DLPFC is implicated in depression and anxiety (Kennedy et al., 1997; Grimm et al., 2008; Chang et al., 2011; Moon et al., 2015; Balderston et al., 2017; Meyer et al., 2019).

The purpose of this study was to explore the effects of tDCS on the DLPFC-associated cognitive domains of EF, attention, and cognitive flexibility in older adult inpatients with symptoms of depression and/or anxiety. The following research question was of interest: *What are the effects of multi-session anodal tDCS over the left DLPFC on executive functioning in*

*older adult inpatients with symptoms of depression and/or anxiety compared to those receiving sham stimulation?* It was hypothesized that anodal tDCS would augment performance across executive functioning processes compared to sham stimulation.

## 2. Materials and Methods

To answer the research question, a double-blinded parallel, sham-controlled, single-centre randomized control trial was conducted at the Glenrose Rehabilitation Hospital (Alberta Health Services, Edmonton, Canada). Ethics was approved by the University of Alberta Research Ethics Board (Pro00078317). The study protocol was registered with the National Institute of Health (NCT04558177).

### *2.1 Participants*

A subset of patients taking part in a larger study examining the effects of tDCS in geriatric depression and anxiety were recruited to undergo additional cognitive assessments before and after tDCS stimulation. These participants were recruited from Specialized Geriatric Rehabilitation inpatient wards at the Glenrose Rehabilitation Hospital (Alberta Health Services, Edmonton, Canada). All patients underwent depression and anxiety screenings upon admission using the (GDS; Sheikh & Yesavage, 1986) and Geriatric Anxiety Inventory (GAI; Pachana et al., 2007). These screening tests were administered by Occupational Therapists on the geriatric wards. Inclusion criteria were defined as: being over the age of 65 years old, GDS $\geq 5$, GAI $\geq 8$, proficiency in English, ability to provide informed consent, and the absence of dementia. If eligible for participation, patients were referred to the research team by the Occupational Therapists or Physicians for recruitment. Signed informed consent was obtained from patients who agreed to participate in the study, or their respective powers of attorney. Exclusion criteria included: active infection, implanted medical devices (e.g., cardiac pacemakers, deep brain

stimulators), history of seizures, metallic implants in the head, or history of severe neurological illness. Participation in the study was in addition to usual routine clinical care, and participants did not receive compensation.

### *2.2 Clinical Care*

Multi-disciplinary clinical care varied across patients; however, all patients received a combination of geriatric orientated physical and occupational therapy, in addition to medical and nursing care. As routine clinical care remained the primary focus for these patients, tDCS sessions were occasionally skipped if required to accommodate standard patient care. Therefore, not all individuals were able to complete all fifteen tDCS sessions; participants who completed at least 10 tDCS sessions were included for analysis.

### *2.3 Cognitive Assessments*

Participants underwent paper-based cognitive assessments administered by the primary author, with a battery of tasks largely assessing executive functioning, including: inhibitory control, working memory, attention, processing speed, and cognitive flexibility (see Table 6.1 for an overview of the cognitive battery administered). Instructions and practice trials of the assessments were given to ensure participant comprehension; errors were immediately corrected during the trial runs. To minimize potential physiological and circadian confounds relating to cognitive fatigue, cognitive assessments and tDCS sessions were administered between 15:00 - 17:30 daily based on the participant's availability around their clinical care routine. Cognitive testing and tDCS sessions were delivered in participants' hospital rooms with distractions minimized (e.g., lights on, television off, door closed).

**Table 6.1: Overview of the Cognitive Battery Administered**

| Cognitive Assessment | Domains Targeted | Task Description | Scoring |
|---|---|---|---|
| **SDMT** (Smith, 1982) | Processing Speed, attention | Participants matched a series of symbols to a numbered answer key | Number of correct responses divided by the number of total responses in a 90 second period |
| **TMT-A** (Reitan, 1955) | Processing speed, visuospatial attention | Participants connected a series of circled numbers ranging from 1-25 scattered randomly across the page by drawing a line in sequential order | Total amount of time (seconds) |
| **TMT-B** (Reitan, 1955) | Cognitive flexibility, task switching processing speed, visuospatial attention | Starting at 1, participants connected a series of circled numbers to the corresponding circled letter by drawing a line in sequential order. (e.g.: 1-A-2-B-3-C…) | |
| **Digit Span-Forwards** (Wechsler, 2008) | Short-term memory | Participants were verbally presented with a sequence of numbers and asked to repeat the sequence, with each successive attempt requiring a longer sequence of numbers (Two attempts per sequence) | If a participant was correct the first time, one point is awarded; if a participant was wrong on the first attempt but was correct on the second attempt, a score of zero was awarded. The test was discontinued once two wrong attempts on the same sequence occurred. |
| **Digit Span-Backwards** (Wechsler, 2008) | Working Memory | Participants were verbally presented with a sequence of numbers, and asked to repeat the sequence in reverse order, with each successive attempt requiring a longer sequence of numbers (Two attempts per sequence) | |
| **Stroop Task-Interference Scores** (Stroop, 1935) | Executive function-inhibitory control | A standardized Stroop test was administered. It is thought that interference scores provide information about processing speed and inhibitory control (Stroop, 1935) | The participant was given 45 seconds to complete each Stroop subtest. Interference scores were calculated, given by: $I = CW - \frac{(W \times C)}{(W + C)}$ |

SDMT: Symbol Digit Modalities Test, TMT-A: Trail Making Test (Part A), TMT-B: Trail Making Test (Part B). I: Interference, C: Colour, W: Word, CW: Colour-Word

### *2.4 tDCS Randomization & Parameters*

To maintain double-blinding, six HDCStim tDCS devices (Newronika, Italy) were programmed to deliver anodal (n = 3) or sham (n = 3) stimulation by an individual not involved in the study. Participants, researchers, and clinicians remained blinded to the intervention. Recruited participants were allocated a specific tDCS device for the study in a 1:1 allocation ratio. Simple randomization was performed, dependent on the programming of the tDCS to deliver an active anodal or sham stimulation.

tDCS sessions were delivered daily, based on the participants' availability around routine clinical care, with participants receiving 10 -15 consecutive sessions (including weekends). tDCS parameters were based on previously established safety parameters (refer to Thair et al., 2017). Electrodes were placed in 5cm x 7cm (35cm$^2$) electrode sponges and saturated with 10mL 0.9% NaCl solution and secured to the scalp using a snuggly fitting hairnet. Using the 10:20 EEG system, the anode was placed over F3 (the left DLPFC) and the cathode over the contralateral (right) supraorbital region, in line with Liao and colleagues (2021). A 1.5mA current was applied for 20 minutes per session. The current was ramped over 1 minute until reaching 1.5 mA (Thair et al., 2017).

**Figure 6.1: tDCS Electrode Placement**

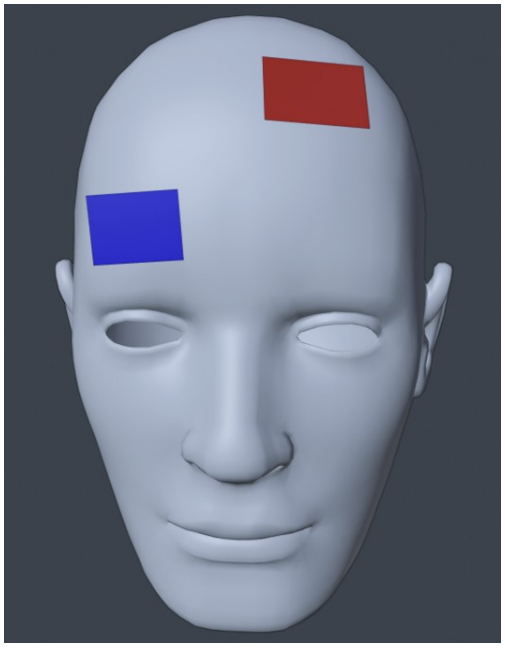


Figure 6.1: tDCS electrode placement; the anode (red) was placed over F3, the cathode (blue) was placed over the right supraorbital region.

The sham group received 1.5 mA of electrical stimulation for one minute: ramping up over 15 seconds, steady for 30 seconds and ramping down for 15 seconds. This blinding technique involves the replication of a cutaneous electrical sensation used to mask participants' group allocation (Ambrus et al., 2012; Thair et al., 2017). Participants were free to participate in any task during tDCS sessions; most participants remained in bed or watched television. tDCS sessions were administered by the primary author as well as three other research assistants, who all received training from the same rehabilitation engineer familiar with tDCS.

Once data collection was stopped, stimulator assignment and group allocation (anodal, sham) were revealed by the individual outside of the study.

***2.5 Analyses***

The primary outcome was examining the effects of tDCS on cognitive performance in older adults with symptoms of depression or anxiety. Differences between pre-test and post-test scores were calculated for all cognitive assessments (Refer to scoring in Table 6.1 for additional details). Analysis methods were based on a previous randomized control trial using multi-session tDCS using a similar sample size of older adults with MCI (Liao et al., 2021). A two-way mixed ANOVA was performed in SPSS (Version 27, IBM Corp. Armonk, NY) on change scores, with time as a within-subjects factor and treatment condition (anodal or sham) as a between-subject factor. An alpha of 0.05 was set to determine significance, with a Bonferroni correction for multiple comparisons. Significant main effects and main interactions reported in the two-way

mixed ANOVA were followed up using both paired and independent t-tests to determine any significant differences. Analysis was conducted based on the tDCS group assignment.

**Figure 6.2: Implemented Protocol**

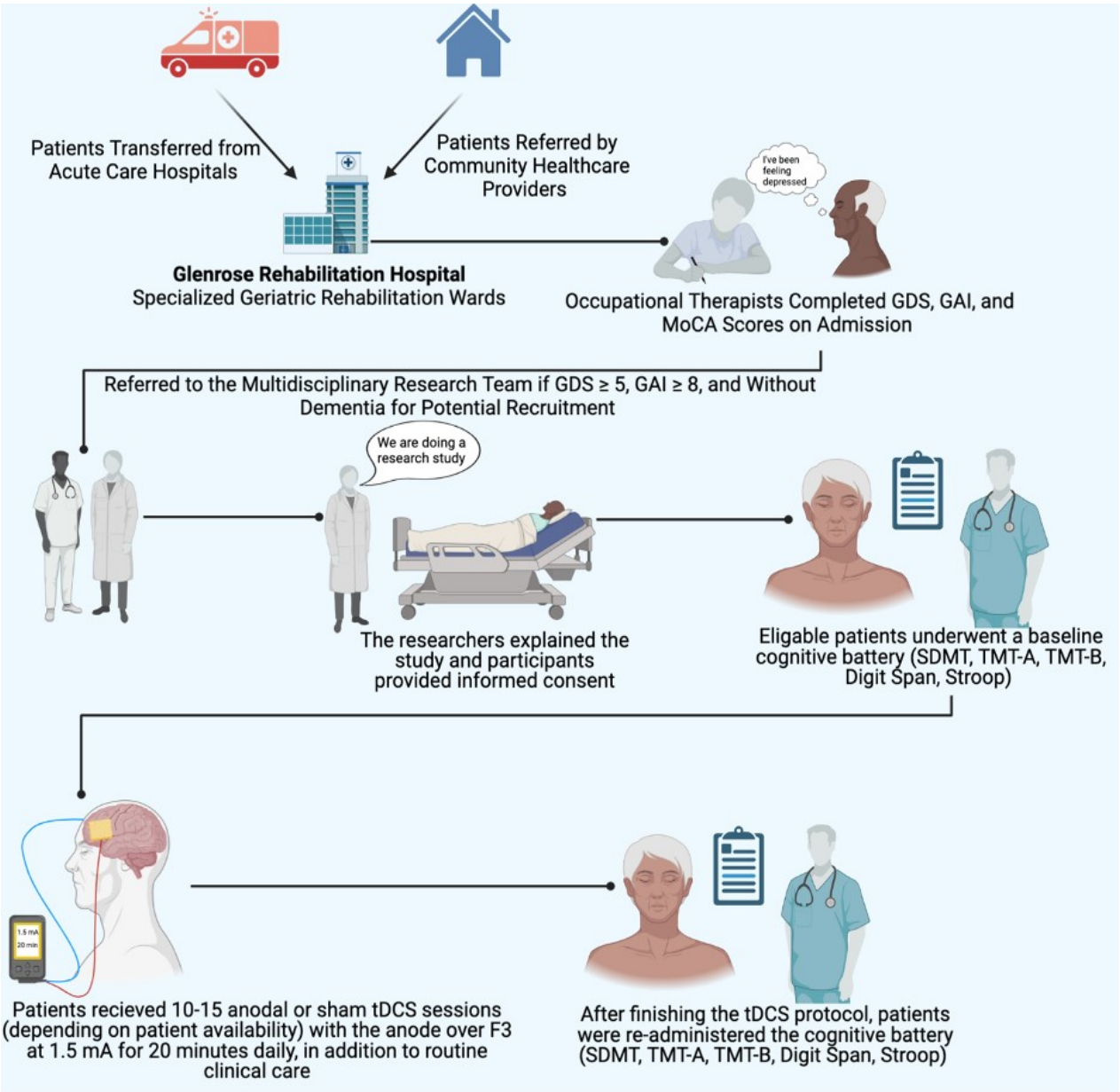



**Figure 6.2:** Study protocol implemented illustrating participant recruitment, consent, assessment, and tDCS procedures. SDMT: symbol digit modalities test; TMT A: Trail Making Test Part A; TMT B: Trail Making Test Part B; MoCA: Montreal Cognitive Assessment.

## 3. Results

### *3.1 Participants*

Twenty eligible participants were included in the final sample (n = 10 in each group), consistent with similar sample sizes of older adults with multi-session tDCS interventions in MCI (Liao et al., 2021) and depression (Brooks et al., 2021). Participant recruitment and data collection were stopped early because of the emergence of SARS-CoV-2. Figure 6.3 highlights the recruitment process. Admitting diagnoses included: decreased functional mobility and weakness, falls, cognitive decline, depression, anxiety, cancer, congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction, and cerebrovascular accidents.

**Figure 6.3: CONSORT Flow Diagram**

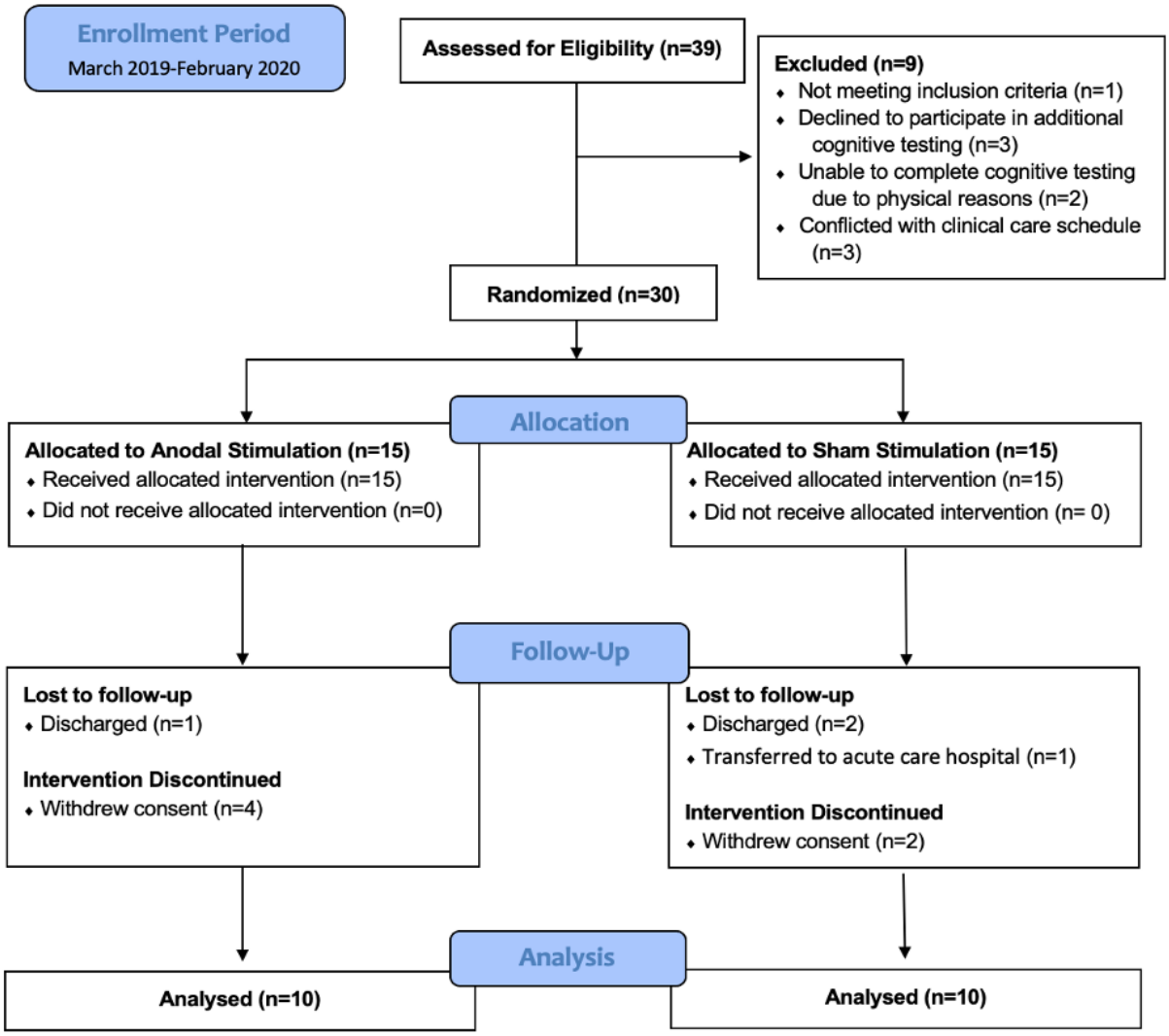


Figure 6.3: Adapted from the CONSORT 2010 Statement (Schulz et al., 2010)

No significant differences were found between those who received 10-14 tDCS sessions and those who completed all 15 sessions, as well as on age, education, baseline MoCA, GDS, and GAI scores. Hence, we combined the results of those receiving 10-15 tDCS sessions and report them together, respective to their tDCS group allocation. An independent t-test found no significant differences between the active and sham groups on the variables of age, years of education, baseline MoCA, GDS, and GAI (all $p$'s $> 0.05$; Refer to Table 6.2).

**Table 6.2: Demographics & Cognitive Battery Performance**

| **Assessment** | ***Pre-tDCS* (Mean ± SD)** | | | ***Post-tDCS* (Mean ± SD)** | | | | |
|---|---|---|---|---|---|---|---|---|
| | Anodal | Sham | *p*-value | Anodal | Sham | *p*-value | | |
| ***Participant Demographics*** | | | | | | | | |
| Age (Years) | 77.10 ± 6.98 | 72.50 ± 7.46 | 0.172 | | | | | |
| Education (Years) | 11.60 ± 2.01 | 12.70 ± 3.97 | 0.445 | | | | | |
| Biological Sex (Males/Females) | 6/4 | 4/6 | | | | | | |
| ***Baseline Screenings*** | | | | | | | ***Psychometrics*** | |
| Baseline GDS | 7.70 ± 2.98 | 9.20 ± 3.52 | 0.404 | | | | Normal: 0-4<br>Mild: 5-9<br>Moderate-to-Severe: 10+ | |
| Baseline GAI | 11.70 ± 5.19 | 8.40 ± 6.43 | 0.158 | | | | Normal: 0-7<br>Query Anxiety: 8+ | |
| Baseline MoCA | 22.20 ± 3.36 | 23.30 ± 4.06 | 0.518 | | | | Normal: 26+<br>Cognitive Impairment<br>Mild: 18-25<br>Moderate: 10-17<br>Severe: < 10 | |
| Baseline OPQoL | 115.33 ± 16.8 | 113.30 ± 11.48 | 0.403 | | | | Range: 35 – 175<br>*Lower scores indicative of lower quality of life | |
| ***Cognitive Battery*** | | | | | | | ***Normative Data (Mean ± SD)*** | |
| SDMT (Items Correct) | ***18.40 ± 2.84*** | ***29.40 ± 14.95**** | **0.035** | 23.30 ± 5.01 | 30.60 ± 16.24 | 0.191 | Anodal | 29.76 ± 10.65 |
| | | | | | | | Sham | 34.79 ± 10.54 |
| Trail Making Test Part A (Seconds) | 88.90 ± 27.79 | 66.00 ± 25.69 | 0.072 | 75.20 ± 21.76 | 61.40 ± 24.15 | 0.196 | Anodal | 50.81 ± 17.44 |
| | | | | | | | Sham | 40.13 ± 14.48 |
| Trail Making Test Part B (Seconds) | 202.70 ± 72.68 | 159.70 ± 83.88 | 0.236 | 156.60 ± 40.06 | 149.70 ± 83.59 | 0.410 | Anodal | 130.61 ± 45.74 |
| | | | | | | | Sham | 86.27 ± 24.07 |
| Digit Span-Forward (Span) | 8.60 ± 2.76 | 10.80 ± 3.16 | 0.114 | 9.50 ± 2.22 | 10.70 ± 3.34 | 0.178 | Anodal | 4.98 ± *0.97* |
| | | | | | | | Sham | 5.39 ± 1.07 |
| Digit Span-Backward (Span) | 6.60 ± 2.46 | 7.50 ± 2.95 | 0.468 | 6.70 ± 2.21 | 7.50 ± 2.67 | 0.238 | Anodal | 3.46 ± *0.99* |
| | | | | | | | Sham | 3.80 ± *1.08* |
| Stroop (Interference) | -5.67 ± 4.24 | -6.01 ± 4.49 | 0.861 | -3.86 ± 3.90 | -6.65 ± 3.98 | 0.131 | Anodal | * |
| | | | | | | | Sham | |

Note: *p*-values obtained from two-tailed independent t-tests; Baseline SDMT: Significant between groups at $p < 0.005$. MoCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; GAI: Geriatric Anxiety Inventory; SD: Standard Deviation. Normative data was obtained from: SDMT (Kiely et al., 2014); Trail Making Test Parts A & B (Tombaugh, 2004); Digit Span

(Grégoire & Van Der Linden, 1997), Stroop*: Negative interference suggests a pathological impairment of inhibition; lower scores indicate greater impairment (Scarpina & Tagini, 2017). Age and education adjusted normative data is reported. Psychometric data taken from: GDS (Conradsson et al., 2013); GAI (Pachana et al., 2007); MoCA (Nasreddine, 2005); OPQoL (Bilotta et al., 2011)

### *3.2 Symbol Digits Modality Test (SDMT)*

A non-significant main effect of time (F (1,18) = 3.031, $p = 0.099$, $\eta p^2 = 0.144$) and condition (F (1,18) = 0.53, $p = 0.475$, $\eta p^2 = 0.029$) was found on the SDMT, as well as a non-significant time x condition (anodal or sham) interaction (F (1,18) = 2.82, $p = 0.110$, $\eta p^2 = 0.136$). Paired t-tests demonstrate a significantly higher post-tDCS SDMT score when compared to the baseline scores within the anodal group only, however, no significant group differences were found on the independent t-test.

### *3.3 Trail Making Test A*

Although there was no main effect of condition on TMT-A (F (1,18) = 2.83, $p = 0.110$, $\eta p^2 = 0.136$), there was a significant effect of time (F (1,18) = 15.96, $p < 0.001$, $\eta p^2 = 0.470$). The time x condition interaction for TMT-A was found to be non-significant (F (1,18) = 3.95, $p = 0.062$, $\eta p^2 = 0.180$). Paired t-tests demonstrated significant improvement in TMT-A times within both groups, and an independent t-test found that the change from baseline to post-tDCS was significantly greater in the anodal group relative to the sham group.

### *3.4 Trail Making Test B*

No significant main effect of condition on TMT B completion time was found (F (1,18) = 0.64, $p = 0.435$, $\eta p^2 = 0.034$). The main effect of time on TMT B completion time was significant (F (1,18) = 10.70, $p = 0.004$, $\eta p^2 = 0.373$). The time x condition interaction was determined to be significant (F (1,18) = 4.44, $p = 0.049$, $\eta p^2 = 0.198$). The paired t-test found that only the anodal group demonstrated a significant difference in TMT-B time between baseline and post-tDCS. The independent t-test demonstrated a significant improvement in TMT-B scores within the anodal group.

### *3.5 Digit Span Forward*

No significant main effects of time (F (1,18) = 2.23, $p = 0.152$, $\eta p^2 = 0.110$) and condition (F (1,18) = 1.80, $p = 0.197$, $\eta p^2 = 0.091$) were observed. Interactions between time and condition on digit forward scores (F (1,18) = 3.49, $p = 0.078$, $\eta p^2 = 0.162$) were also non-significant.

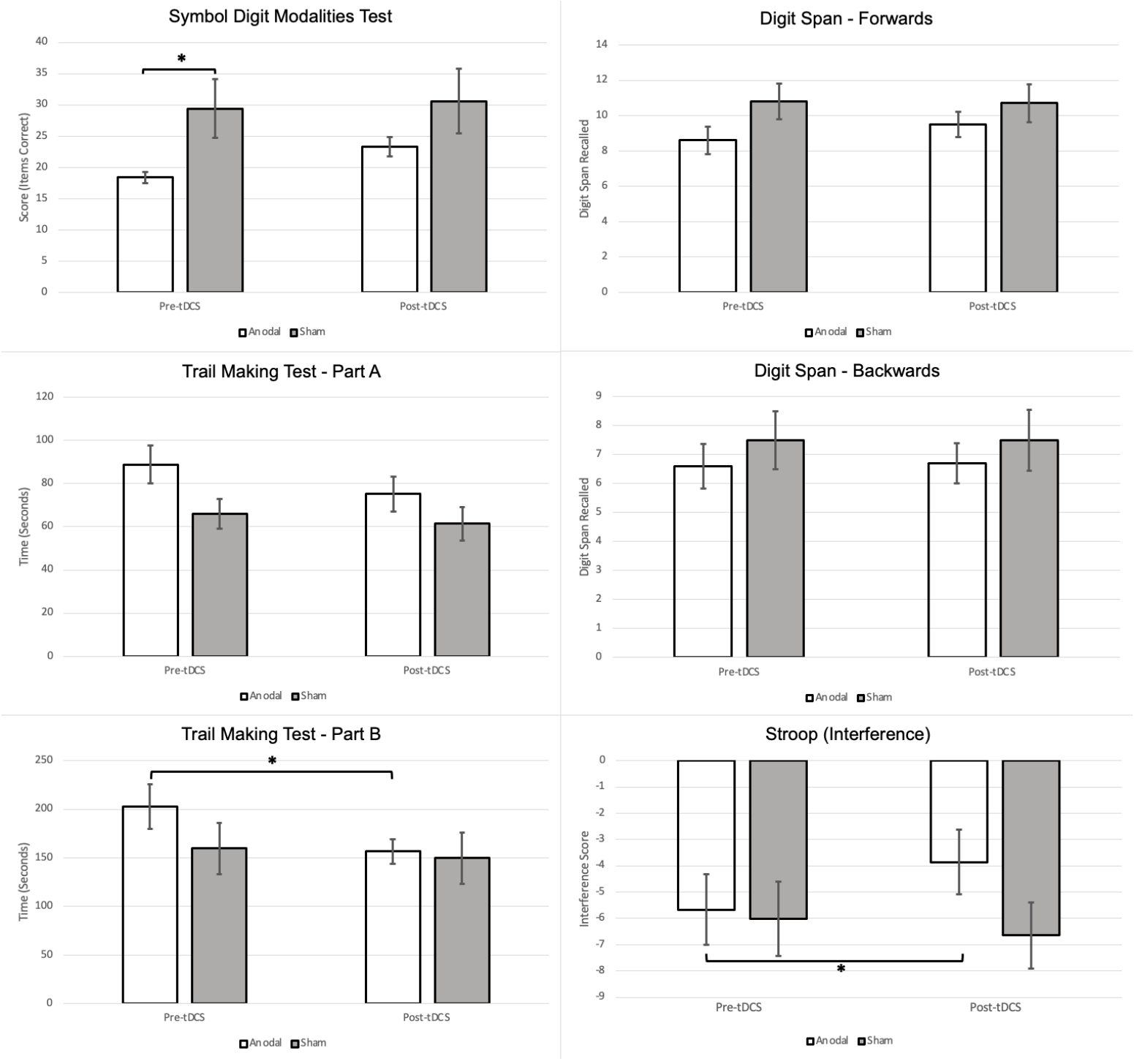
### *3.6 Digit Span Backwards*

No significant main effect of time (F (1,18) = 0.11, $p = 0.747$, $\eta p^2 = 0.006$) or main effect of condition (F (1,18) = 0.64, $p = 0.435$, $\eta p^2 = 0.034$) was found. Like digit span forwards, there was no significant interaction between time and condition (F (1,18) = 0.11, $p = 0.747$, $\eta p^2 = 0.006$). In addition, no significant within-group or between-group differences were noted across t-tests.

### *3.7 Stroop Interference*

A non-significant main effect of time (F (1,18) = 2.93, $p = 0.104$, $\eta p^2 = 0.140$) and a non-significant main effect of condition (F (1,18) = 3.95, $p = 0.062$, $\eta p^2 = 0.180$) was found. A significant time x condition interaction was found on the two-way ANOVA (F (1,18) = 4.77 ηp2, $p = 0.042$, $\eta p^2 = 0.209$); significant increases in Stroop interference scores were found in the paired t-test only within the anodal group. In addition, there was a significant difference between the changes in interference score from pre-tDCS to post-tDCS between the active and sham groups, with the active group demonstrating a greater mean change.

**Figure 6.4: Changes in Performance Between Anodal & Sham Stimulation Groups**




Note: * is significant at $p < 0.05$.

**Table 6.3: Mean Cognitive Test Scores at Baseline, Post-tDCS, and Differences Between Baseline and Post-tDCS**

| Cognitive Assessment | Difference of Scores | | |
|---|---|---|---|
| | Active | Sham | *p*-value |
| | M±SD | M±SD | |
| SDMT | -0.04±0.06 | -0.0007±0.03 | 0.110 |
| TMT A | 13.24±4.18 | 5.87±1.86 | 0.062 |
| **TMT B*** | **-46.20±50.68** | **-10.0±19.61** | **0.049** |
| Digit Forward | -0.90±1.45 | -0.10±0.88 | 0.078 |
| Digit Backward | 0.20±1.62 | 0.00±1.05 | 0.748 |
| **Stroop Test*** | **5.20±7.86** | **-0.63±3.09** | **0.042** |

Note: *p*-values were obtained from independent t-tests; SDMT: symbol digit modalities test; TMT A: Trail Making Test Part A; TMT B: Trail Making Test Part B; * significant time x condition interaction

## 4. Discussion

In this study, 20 older adult inpatients with self-reported symptoms of depression and/or anxiety received 10-15 anodal or sham tDCS sessions delivered over the left DLPFC. We report that the tDCS-protocol provided over the left DLPFC selectively augmented cognitive processing. In line with our hypothesis, we note significant changes in tests involved in higher cognitive processes. However, the effectiveness of tDCS on the domains of attention and working memory was minimal.

The time required to complete the TMT-B decreased in the anodal group, suggestive of increased cognitive flexibility and interference processing. It is generally agreed that the TMT-B has a higher sensitivity to central EF and cognitive flexibility and task-switching compared to TMT-A (Arbuthnott & Frank, 2000; McMorris, 2016). Increased performance on the Stroop task was also evident, suggesting a potential increase in inhibition capacity. tDCS may have modulated the ability to minimize interfering distractors, resulting in more accurate and rapid processing of presented stimuli. In addition, we report null tDCS effects on the other DLPFC-associated cognitive processes of working memory and attention, assessed by the SDMT, TMT-A, and the digit span tests. Cognitive flexibility, working memory, and inhibition are processes highly involved in EF (Diamond, 2013), and necessary in higher-order cognitive processing. Thus, tDCS-induced neuromodulation may have invoked a selective-synergistic interaction in EF domains of cognitive flexibility and interference, increasing performance on tests of higher-order cognition.

These results corroborate previously reported findings. In a similar study design targeting Parkinson's Disease, Doruk and colleagues (2014) report significant improvements on the TMT-B without changes on the TMT-A, with the maintenance of these findings extending to one-

month post-stimulation. Bystad and colleagues (2020) further report significant gains on the TMT-B without improvements in the TMT-A only within a young adult group. In addition, Loftus and colleagues (2015) report reaction time improvements on the Stroop task in young adults after receiving anodal DLPFC stimulation resulting in inhibitory control enhancement; our results continue to support inhibition control enhancement in older aged adults. However, the extent of tDCS effects on cognitive enhancement may vary across the lifespan, which to date remains largely unknown.

We report null tDCS induced cognitive effects on working memory and attention. These findings are in line with Kumar and colleagues (2020), who report a lack of tDCS effects on working memory and global cognition in older adults with depression. Nonetheless, contrasting results are reported by Nissim and colleagues (2019) who reported significant changes in working memory as well as functional connectivity after a two-week tDCS protocol paired with cognitive training in healthy older adults. Again, the pairing of tDCS with working memory training has also been demonstrated to increase digit span performance in older adults (Jones et al., 2015). Although tDCS alone has been demonstrated to selectively modulate working memory within older adults with higher levels of education (Berryhill & Jones, 2012), dual tDCS-cognitive training paradigms may optimize effects on working memory and attention which requires further investigation.

Taken together, these results further contribute to the proposed roles of the DLPFC in higher-order cognition and behaviour (Krawczyk, 2002; Vendetti & Bunge, 2014). However, the role of the DLPFC in lower-order cognition remains unclear. Other frontal lobe structures, including the ventrolateral prefrontal cortex, have been proposed to be engaged in lower-order cognitive processing (Goto et al., 2011). In addition, these results provide additional evidence

that tDCS may selectively increase EF in older adults. Future research is needed to determine who may be optimal candidates for tDCS therapy for EF augmentation, and the effects of tDCS on prefrontal networks.

### *4.1 Limitations and Future Directions*

Across the literature, varying study designs, cognitive protocols, populations of interest, and tDCS parameters exist. The effects of tDCS may be task-specific, cognitive-domain specific, age, and etiology dependent, with varying montages resulting in varying neuro-cognitive modulatory effects. Furthermore, additional factors including multi-morbidity, level of education, and pharmacological agents may all impact neurological and cognitive modulation, which was not accounted for in this study. Taken together, the generalizability of the obtained results to other clinical populations, age groups, tDCS montages, and cognitive domains should be interpreted with caution.

The tDCS montage applied in this study (anode over the left DLPFC; cathode over the contralateral supraorbital region) was similar to a separate randomized control trial using tDCS in older adults with MCI (Liao et al., 2021). However, previous tDCS modelling highlighted the potential of deeper cortical and larger white matter network activation using an extracephalic return electrode (Noetscher et al., 2014), which in turn may alter the efficacy of tDCS and the obtained results. In addition, morphological changes and cerebral atrophy present in MCI may impact tDCS current vectors and electrical field densities (Mahdavi et al., 2018).

The purpose of this study was to investigate whether tDCS influenced cognition within a sample of older adult inpatients with symptoms of depression and/or anxiety. Within this study, participants had an overall mean MoCA of 22.75, which may be indicative of MCI. Furthermore, cognition may have been impaired due to the confounds related to depression and anxiety. With

this study designed as a pilot, our sample may limit the overall power, however, conducting this study within the hospital context contributes towards ecological validity and generalizability of tDCS applications in real-world clinical settings with an interdisciplinary approach.

In this study, we report no major adverse effects from tDCS stimulation. tDCS was found to be well-tolerated by the older-adult participants and did not significantly interfere with clinicians providing routine clinical care. Mild side effects including a tingling sensation under the electrodes, as well as slight discomfort from the snuggly fitted hairnet were reported by some individuals; these side effects are consistent with previous studies (Matsumoto & Ugawa, 2017).

Unique considerations exist when recruiting patients from an inpatient geriatric rehabilitation setting for a tDCS study, including coordination of treatments with routine clinical care, family visits, legal factors, personal values, and comfort. These factors should be taken into consideration and weighed in terms of the feasibility of future studies. Future studies should incorporate larger sample sizes, consider the pairing of tDCS with cognitive or behavioural training, explore other tDCS montages, include a maintenance period, incorporate neuroimaging modalities, and explore effects in other cognitive disorders associated with aging including MCI and dementia. In addition, future studies are encouraged to consider ecological validity to extend the generalizability of cognitive augmentation into real-world settings.

### *4.2 Conclusion*

In this study, multi-session tDCS over the left DLPFC appears to invoke beneficial cognitive augmentation within the domains of inhibition processing, processing speed, and cognitive flexibility in older adult inpatients with symptoms of depression or anxiety. This evidence supports that anodal tDCS-invoked neuromodulation may extend into cognitive modulation, including executive functioning. By examining the effects of anodal tDCS within a

geriatric sample, we contribute to the ongoing investigation of non-invasive brain stimulation targeting cognitive decline in older adults. Future studies should continue to investigate tDCS in normal and pathological cognitive aging, in addition to targeting the optimization of protocols, as well as determining ideal candidates for tDCS interventions. The results of tDCS research are important for assessing its efficacy and practicality for clinical and therapeutic use within geriatric rehabilitation settings.

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## Chapter 7: General Discussion

The overarching purpose of this dissertation was to explore the impact of tDCS applications on the interaction between cognitive processing and cerebral oxygenation hemodynamics measured with fNIRS, with a focus on cognitive enhancement or restoration, across aging and a clinical context. tDCS invoked changes in cognitive processing, as well as cerebral oxygenation hemodynamics measured with fNIRS, were investigated across three separate studies. In this general discussion, the specific research questions will be summarized, followed by a discussion linking the results across the three studies, providing additional theoretical underpinnings, and future directions.

Three research questions, addressed across three studies, were developed. The first research question, *'What are the effect sizes of tDCS on cognition and cerebral oxygenation hemodynamics measured with fNIRS in previously reported studies, taking aging into account?*' was addressed through a scoping review and meta-analysis in Chapter 4. The results showed that tDCS does indeed alter cognition and cerebral oxygenation hemodynamics, with larger effects noted in healthy young adults as compared to older adults. The second research question, *'What are the effects of tDCS on the interaction between working memory performance and cerebral oxygenation measured with fNIRS in healthy younger adults while accounting for individualized cerebral oxygenation?* was addressed in Chapter 5. Results showed that a single-session anodal tDCS applied over the right DLPFC increased working memory accuracy by nearly 13% while decreasing reaction time by approximately 250ms during the 3-back WM task and increased cerebral oxygenation within the right DLPFC during the 2- and 3-back span tasks compared to a sham condition. The third research question, '*What are the effects of tDCS on cognitive functioning in older-adult inpatients with symptoms of depression and/or anxiety?*' was

addressed in Chapter 6. Although the study was limited in sample size as a result of study discontinuation due to COVID-19, results showed that multi-session anodal tDCS applied over the left DLPFC augmented specific cognitive subprocesses within executive functioning (cognitive flexibility, planning, and inhibition), however, did not enhance working memory.

Overall, from the three studies included within this thesis, tDCS appears to alter cognition and cerebral oxygenation hemodynamics in varying populations across ages. Although promising results were found across studies, there is ongoing variability and debate on the effects of tDCS within the field. As discussed within the three studies, determining the exact effects of tDCS on cognition, particularly within a clinical context, is difficult due to varying tDCS protocols, cognitive protocols implemented, and populations being researched. Additionally, changes in oxygenation and cerebral blood flow within the neurovascular unit across age groups may confound the tDCS effects measured with neuroimaging (Ogawa et al., 1993; Csipo et al., 2019; Tarumi & Zhang, 2018). Therefore, the following discussion will be grounded on the results obtained in this dissertation, in the context of the ongoing development of the research on neuromodulation and optical neuroimaging.

### 7.1 Effect of tDCS on Executive Functioning and Working Memory

The three studies included in this thesis have demonstrated that the effects of tDCS may be dependent on numerous underlying biopsychosocial determinants of health, including age and disease. The first study (Chapter 4) reviewed the effects of tDCS on cognition and fNIRS metrics across the lifespan, Chapter 5 examined tDCS effects in healthy young adults, whereas the last study (Chapter 6) examined tDCS on cognitive processing in older adults with symptoms of depression and/or anxiety,

### *7.1.1 Age and disease-dependent effects on cognition.*

As previously discussed, cognition including executive functioning and WM changes across the lifespan; regional and larger neuronal network tDCS modulation may result in different cognitive effects across varying age groups (Harada et al., 2013; Habich et al., 2020). Across the three studies included in this dissertation, executive functioning enhancement was observed across ages, however, WM-specific enhancement was only observed in younger adults (presented in Chapter 5).

Within the older-aged adults with symptoms of depression and/or anxiety (Chapter 6), multiple sessions of tDCS led to a significant increase in inhibitory processing, cognitive flexibility, and planning, without significant differences in WM capacity. However, in healthy young adults, a single tDCS session promoted WM capacity during higher cognitive demands as required for the 3-back Toulouse *n*-back task (Chapter 5). Unlike the older adults with symptoms of depression and/or anxiety, tDCS did not enhance inhibitory processes or cognitive flexibility. In the meta-analysis conducted within the systematic review (Chapter 4), effect sizes of tDCS on cognition were greatest in younger adults and decreased as study populations got older (young adults $d = 0.48$; middle-aged adults $d = 0.37$; older adults $d = 0.13$; Figeys et al., 2021). Although this trend was reported, it is important to keep in mind there was a limited number of studies included in the meta-analysis ($k = 8$).

Cognition in older adults can be impacted by numerous biopsychosocial factors, which were not accounted for. For instance, neuroanatomical changes present in aging (i.e., overall cerebral atrophy) and neurodegenerative processes may alter tDCS current distribution in older adults, as well as in those with varying neuropathologies. Furthermore, pharmacological agents may impact cognition, including those used to manage neurocognitive and psychiatric disorders.

Additionally, cognitive capacities may differ between cognitive disorders (ex. MCI compared to dementia), and between healthy adults. As cognitive impairments are often concomitant with geriatric depression (Steffens & Potter, 2007), reported tDCS results may differ from healthy older adults, as well as those with other cognitive disorders including MCI or dementia. The *Montreal Cognitive Assessment* scores of the older adult patients with underlying depression and/or anxiety in Chapter 6 may be indicative of comorbid MCI in both anodal and sham stimulation groups. However, as the purpose of the study presented in Chapter 6 was to investigate the effects of tDCS specifically on executive functioning in older adult inpatients with underlying depression or anxiety, the effects of tDCS on the symptoms of depression, anxiety, and MCI, were not investigated (however, this data is currently being analyzed with the research team at the Glenrose Rehabilitation Hospital).

In the eight cognitive tDCS-fNIRS studies included in the scoping review (Figeys et al., 2021), none recruited clinical samples, which this dissertation initially set out to examine. The proposed research for this doctoral thesis was to begin to address this gap by investigating the effects of tDCS on the interaction between WM performance and cerebral oxygenation hemodynamics among a sample of older adults with MCI at a tertiary rehabilitation hospital. However, the project was changed to examine younger adults in a laboratory setting due to the research restrictions imposed during COVID-19; this was largely decided to act for the beneficence of older adults as they are at a significantly higher risk of adverse outcomes from COVID-19.

In younger healthy adults, the effects of anodal tDCS over the right DLPFC were found to improve WM accuracy by 13.4% and decrease reaction time by 250 ms, however, only in the most difficult (3-back) condition of the Toulouse *n*-back task (Chapter 5). The effects of tDCS

on WM appear to vary across adulthood and cognitive status, including MCI or dementia (Katsoulaki et al., 2017; Hsu et al., 2015; Mancuso et al., 2016; Stephens & Berryhill, 2016; Summers et al., 2016). Future studies should continue to see if the reported tDCS-WM enhancement on the Toulouse *n*-back task remains present in middle-aged and older-aged adults consisting of both healthy and clinical populations.

### *7.1.2 Cognitive Tasks.*

The three studies included a variety of cognitive tasks used to investigate the effects of tDCS on cognitive processing, with an overlap in the domain of executive functioning. The variety of tasks used to test executive functioning further contributes to the variability of results and inference making. Improvements on the Trail Making Test – Part B and the Stroop Task (cognitive flexibility, planning, and inhibition processing), without improvements on more basic domains of attention or working memory in lower-order component tasks contributing to executive functioning (i.e., SDMT, digit span), were found in the study investigating tDCS on cognition in older adults with symptoms of depression or anxiety (Chapter 6. In the scoping review of cognitive tDCS-fNIRS protocols (Chapter 4), 2 studies utilized verbal fluency tasks, 1 used a spatial memory task, and 5 implemented working memory tasks, with mixed results of tDCS enhancement being reported (Figeys et al., 2021). However, tDCS was found to improve WM on the Toulouse *n*-back task in healthy young adults (Chapter 5). In addition to the factors of age and disease status, generalizability between studies is limited due to these varying cognitive tasks implemented.

It is possible that the effects of tDCS are task-dependent and may be further impacted by the tDCS montage and stimulation parameters. Additionally, effects may be dependent on cognitive load; as seen in Chapter 5, tDCS effects on the Toulouse *n*-back task were prevalent

during higher load WM demands. As WM can vary across individuals and across age, including WM capacity in statistical modeling can provide additional insights. It has been reported that those with higher WM capacities may be more effective at remaining goal-focused through attentional resource control while having higher inhibition processing (Engle & Kane, 2004; Unsworth & Robinson, 2017). Thus, controlling for WM capacity may allow for further inference-making regarding task and load dependency. Lastly, WM capacity may be a valuable covariate to consider in cognitive-aging studies when examining cognition across the lifespan or comparing healthy older adults to those with cognitive impairments.

### 7.2 Effect of tDCS on Cerebral Oxygenation Hemodynamics

The effects of tDCS may act beyond the region of stimulation, as demonstrated in the current modelling conducted in Chapter 5; electrical currents may further act on the neurovascular unit, including astrocytic and vascular-mediated responses (Bahr-Hosseini & Bikson, 2021). Furthermore, tDCS has been demonstrated to alter cerebral perfusion (Stagg et al., 2013). It is well established that aging and numerous disease processes can impact cerebral perfusion and oxygenation (Herrmann et al., 2006; Brassard et al., 2014; Tarumi & Zhang, 2018). Therefore, the effects of tDCS on the neurovascular unit, as well as regional oxygenation, may vary across aging and disease status. The meta-analyses conducted within the scoping review (Figeys et al., 2021) revealed that there may be aging-related influences on how tDCS affects oxygenation hemodynamics, with a general trend of effect sizes decreasing across age.

Again, due to COVID-19, the effect of tDCS on cognition and cerebral oxygenation measured with fNIRS had to be adapted from a clinical sample of older adults to healthy younger adults. As discussed in Chapter 5, the effects of anodal tDCS increased HbO concentrations over the stimulated right DLPFC while performing the Toulouse *n*-back task; notably, anodal tDCS

significantly increased HbO concentrations during the 2- and 3-back spans compared to the sham group. However, no significant differences in HbO were found on the 1-back in the right DLPFC. Additionally, no HbO differences were found in the left DLPFC, and no differences were found in HbR concentrations in bilateral DLPFC.

The results observed in the studies combining tDCS-fNIRS protocols to target cognition, highlighted in Chapter 4 and tested in Chapter 5, may have occurred for several reasons. Firstly, tDCS may have regionally increased processing (increasing the regional cerebral metabolic rate of oxygen), resulting in an influx of HbO. Interestingly, although the effects of tDCS extended into the left hemisphere according to the modeling (presented in Chapter 5), no HbO differences were noted in the left DLPFC. Thus, it is also possible that tDCS effects on cerebral oxygenation are not homogenous across regions and hemispheres (see Stagg et al., 2013, Figure 1). The left DLPFC may have been stimulated by the current increasing the efficiency of neuronal processing with the available resources (largely oxygen and glucose). Similarly, Stagg and colleagues (2013) report increased functional connectivity within the contralateral DLPFC of anodal tDCS stimulation, despite no increases in cerebral perfusion to the region (see Stagg et al., 2013, Figure 2; Keeser et al., 2011). In the future, it may be beneficial to incorporate metabolic-specific neuroimaging such as Magnetic Resonance Spectroscopy or PET to further quantify metabolites (Fuss & Cheng, 2016). Lastly, the generalizability of this finding is largely limited to younger adults. Future studies in older adult samples are required to see if this activation pattern holds true across aging, as cerebral perfusion decreases across age.

### 7.3 Cognition & Cerebral Oxygenation Hemodynamic Interaction

As discussed in Chapter 4, tDCS did appear to have an impact on cerebral oxygenation measured with fNIRS applied in cognitive protocols ($d = 0.63$), however, the directionality (i.e.,

increases or decreases in HbO and HbR) remains unclear, and is further limited by the heterogeneity in reported fNIRS metrics across the included studies. In a subgroup meta-analysis, the effect of tDCS on fNIRS signals during cognitive demands was greatest in younger adults ($d$ = 0.82), however, becomes non-significant in middle and older-aged adults.

The effects of tDCS on the interaction between cerebral oxygenation within the DLPFC and cognitive performance remain less consistent. Although we report increases in cognitive domains across the three presented studies, the effects of HbO and HbR concentrations were found to be variable (Chapters 4 & 5). Within the scoping review (Figeys et al., 2021; Chapter 4), a general trend of declining tDCS effects on both cognition and fNIRS signals was observed as age increased, however, many reported effect sizes were non-significant between the anodal and sham stimulation groups. As mentioned previously, the only statistically significant effect size observed was in healthy young adults on fNIRS signals, which became non-significant in middle and older-aged adults.

Following these meta-analytic findings with a double-blinded sham-controlled randomized control trial in healthy young adults (Chapter 5), similar results are reported. tDCS was found to increase cognitive performance during the 3-back span of the Toulouse *n*-back task and increased HbO concentrations in the stimulated right DLPFC during the 2-back and 3-back. With a sample of healthy younger adults, it is possible that there is a high degree of cognitive reserve, which was enhanced during the higher cognitive load of the 3-back. In addition, during the 2-back, an increase in HbO concentration after anodal tDCS without noted WM improvement may suggest that there are blood oxygenation changes to supply neuronal demands, however, cognitive processing remained “under-control”, possibly due to cognitive reserve and WM capacity as facilitating processes. In the 1-back, no differences in fNIRS signals and WM

performance were noted; thus, the effect of tDCS on the interaction between oxygenation hemodynamics and cognition may partly be cognitive-load dependent.

When considering cognitive aging, the results presented in Chapter 5 are consistent with a separate cognitive tDCS-fNIRS randomized controlled trial using healthy older adults (Di Rosa et al., 2019). When accounting for individual visuospatial WM capacity, Di Rosa and colleagues found significant decreases in reaction times on a visuospatial WM task, as well as HbO increases in bilateral prefrontal cortices. Thus, future studies applying the protocol outlined in Chapter 5 in healthy older adults, as well older adults with cognitive impairment including MCI and dementia, can add to the generalizability of the effects of tDCS on the interaction effects between oxygenation hemodynamics and cognitive performance across normal and maladaptive cognitive aging.

### 7.4 Limitations

Several limitations have been identified to this point which will be elaborated upon, including changes in the protocol (due to COVID-19), differences in both tDCS and fNIRS protocols across studies, the potential of heterogeneity and risk of bias in meta-analytic reporting, limitations in generalizability, as well as neurological and cognitive variability between individuals and across aging.

The effects of tDCS on neuronal modulation and cognitive functioning are dependent on the specific parameters utilized, including current intensity and length of the electrical current application (Gill et al., 2015). Specific to WM, tDCS dosage may influence components underlying performance (Teo et al., 2011). Thus, tDCS montages and stimulation parameters may invoke varying effects regionally and on larger neuronal networks. When considering cognitive aging, the distribution of the electrical current may vary due to changes in the neuron,

neural pathways, as well as global cerebral atrophy (Habich et al., 2020). Lastly, across the studies, the implemented tDCS protocols differed. Although the stimulation parameters remained consistent, the region of stimulation and the number of stimulation sessions varied between the studies.

In addition to neuroanatomical changes, cerebral blood flow declines across aging (Mokhber et al., 2021), with lower blood flow amount being related to cognitive decline in varying diseases (Bangen et al., 2018; Findlay et al., 2019). With the decreasing CBF across aging, cerebral metabolism including oxygen and glucose consumption drop by approximately 5% per decade (Tarumi & Zhang, 2018). With varying differences in cerebral oxygenation, it is necessary to control for individual oxygenation which was done in Chapter 5; however, we are unable to answer the effect of tDCS on the interaction between cognitive processing and cerebral oxygenation hemodynamics measured with fNIRS across aging, as modifications to the study were necessary due to the emergence of the COVID-19 pandemic.

As discussed, tDCS effects may be dependent on cognitive load and cognitive tasks. With varying cognitive domains being assessed using different cognitive tasks between the studies, interpreting results between the presented studies is limited. Additionally, the delivery of tasks differed; for instance, paper-based batteries were implemented in inpatient hospital rooms in Chapter 6, whereas computerized tasks were administered both in-person and remotely in Chapter 5.

Although the fNIRS parameters varied across the studies presented in Chapters 4 and 5, all studies included prefrontal regions of interest. Although tDCS stimulation was applied over the right DLPFC in Chapter 6, with fNIRS recording bilateral DLPFC, the electrical current modeling presented suggests that the current distribution extended well beyond the stimulated

area; thus, it may have been beneficial to examine other regions of interest involved in WM processing with fNIRS.

More specific challenges arose while conducting both randomized controlled trials within this dissertation. Notably, in Chapter 6, participant uptake and recruitment were significantly slower than anticipated. It took over a year to collect data on 20 individuals (who underwent 10-15 tDCS sessions). These individuals were admitted patients at the Glenrose Rehabilitation Hospital (Alberta Health Services) for geriatric-specific rehabilitation for a wide range of varying issues; thus, their primary focus was clinical care, and participation in the study was a voluntary initiative. In addition, some hesitancy was noted surrounding the concept of tDCS from patients, their families, as well as some staff; thus, it may have been of benefit to provide further educational sessions and resources. Although more of a pragmatic randomized control trial, this study adds to the ecological validity of tDCS applications in clinical settings as well as in older-adult populations.

When using fNIRS, it is vital to ensure adequate signal resolution; however, when placing light sources and detectors on the head, it is important to remember that hair may impact fNIRS signals. A significant amount of time was allocated to moving hair; trying to get the hair out of the way of eight channels took 10-20 minutes. In addition, while piloting the protocol prior to data collection, we noted that hair properties, such as colour, thickness, length, and the presence of oils or hair products impacted the signals. In the participants outlined in Chapter 5, the majority were of Caucasian or Asian descent, therefore, impacting generalizability to other ethnic and racial groups. With the risk of bias and generalizability of varying ethnic and racial groups due to hair characteristics (Etienne et al., 2020; Yücel et al., 2021), future studies should explore methods to control for these variables rather than excluding populations. Such

approaches could include braiding hair to allow access to a recording region of interest or relying on developing technologies such as NIRS brush optodes (Khan et al., 2012). With a limited timeframe to complete the protocol, as well as COVID-19 restrictions, it was decided to focus on the eight channels over bilateral DLPFC reported in Chapter 5 instead of ensuring adequate signals for the entire fNIRS array.

### 7.5 Future Directions

Implementing tDCS protocols in geriatric-specific clinical rehabilitation settings was demonstrated to be feasible, however, we did not have the opportunity to implement portable fNIRS recordings within the same context; thus, piloting of combined tDCS-fNIRS protocols in a similar setting is warranted. Despite this limitation, fNIRS has been successfully applied in older adults in traditional laboratory as well as hospital settings (Di Rosa et al., 2019; Blum et al., 2021). Furthermore, future research investigating the effect of tDCS on the interaction between cognition and cerebral oxygenation hemodynamics as presented in Chapter 5 should be extended to older-aged adults in both pre-clinical and clinical settings.

In future clinical studies in older-aged adults, it may be worthwhile to consider alternative research designs. Including older-aged adults in clinical research is necessary, however, unique challenges may arise; thus, exploring pragmatic control trials can address some specific challenges by having more flexibility and sample heterogeneity while being adaptive to clinical care settings. Thus, using a randomized control trial in a pre-clinical setting to continue to investigate tDCS efficacy, followed by pragmatic trial designs in clinical settings to provide real-world ecological data can be of benefit for future studies to consider. Lastly, the inclusion of a multi-centre design will allow for a larger sample pool to recruit from, which may increase the feasibility of obtaining a predetermined sample size of older adults in a shorter time frame.

As discussed, controlling for individual hemodynamic responses, as well as cognitive factors (such as global cognitive scores including the MoCA or MMSE, or WM capacity), may provide further inquiry between groups being compared using fNIRS. For instance, controlling for such factors may allow better control between healthy younger and older adults in tDCS-fNIRS cognitive paradigms.

This thesis was focused on cognitive aging and aging-related cognitive decline; however, it is important to note that many other populations present with cognitive impairments across age groups. For instance, younger adults with depression and/or anxiety may have varying WM deficits, as well as other neurodegenerative disorders which overlap with dementia, including Parkinson's Disease and Amyotrophic Lateral Sclerosis. From the conducted scoping review, no tDCS-fNIRS cognitive protocols have been conducted in clinical samples; thus, varying clinical samples should be explored, as cognition, the neurovascular unit, and cerebral blood flow can be impacted by numerous etiologies.

Transcranial Magnetic Stimulation (TMS), another type of non-invasive brain stimulation, has recently been approved in Canada for the treatment of certain types of depression in clinical practice. Other experimental neuromodulatory stimulation including transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) may result in varying cognitive effects which warrant future investigation across cognitive aging. tDCS and tACS have been demonstrated to alter WM neural networks in different manners (Abellaneda-Pérez et al., 2020). In addition, theta band tACS has been demonstrated to increase associative memory, which was not seen in tDCS delivery (Lang et al., 2019). Thus, the results presented in this dissertation are limited to tDCS protocols, and alternative stimulation approaches should be researched.

In addition to other neurostimulation methods, it is of value to continue to examine the effects of tDCS on the cognitive-hemodynamic relationship using other neuroimaging approaches, such as MRI-based approaches, electroencephalography, or pupillometry. As the field of optical neuroimaging continues to advance, novel devices are being created which can facilitate future research designs. For instance, fNIRS compatible MRI devices are being developed, which could allow concurrent fMRI and fNIRS protocols, as well as the co-analysis of HbO, HbR, BOLD, and structural imaging. Multimodal neuroimaging can especially be of value when oxygenation, blood volume, and cerebral blood flow becomes impaired (Scarapicchia et al., 2017). As technological advances in neuroimaging continue to strive, it can continue to push research innovation across fields including neuromodulation.

### 7.6 Concluding Remarks

There is ongoing variability in the effects of tDCS on cognitive enhancement, which becomes further convoluted when considering age, cognitive status, disease status, and other social determinants of health. Throughout the studies presented within this dissertation, the effects of tDCS may be of benefit for both young and older adults, however, effects may be dependent on the cognitive domain, task, and load. Although HbO increases were found as cognitive performance increased in young adults, future studies to replicate this finding in larger samples are required, in addition to samples consisting of older adults to see if this effect holds true in advancing age. Across studies, tDCS and fNIRS were well tolerated by participants, with minimal side effects being reported; no significant adverse effects occurred. Although we provide some light on the ongoing variability of tDCS studies, ongoing research is required to continue to examine tDCS efficacy and effectiveness in varying populations across aging.

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