Modulating Functional Brain Connectivity using High-Definition Transcranial Direct Current Stimulation (HD-tDCS)

by

Neil Junankar

A Thesis Submitted to the Faculty of Graduate Studies of

The University of Manitoba

In Partial Fulfilment of the Requirements of the Degree of

MASTER OF SCIENCE

Department of Human Anatomy and Cell Science

University of Manitoba

Winnipeg, Manitoba

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive technique for modulating brain activity and is widely used in cognitive neuroscience and clinical research. Conventional tDCS often affects broad cortical regions, limiting its precision when targeting complex regions like the dorsolateral prefrontal cortex (DLPFC). Earlier findings indicated mixed impact of tDCS on brain functional connectivity such that left DLPFC stimulation induced no significant effects, while right DLPFC stimulation increased functional connectivity in the target. High-definition tDCS (HD-tDCS) has been recently developed to improve spatial focality of current delivery, but its effects on functional connectivity have not been systemically investigated.

Rationale: Conventional tDCS is limited by diffuse current spread and suboptimal electrode placement, reducing the specificity of stimulation. This study investigates the effects of HD-tDCS on different targets in the frontoparietal control network: the left DLPFC, right DLPFC, and left inferior parietal lobule (IPL).

Methods: Eighty healthy adults were randomly assigned to one of four groups: HD-tDCS targeting the left DLPFC, right DLPFC, left IPL, or sham. Participants completed cognitive assessments (MoCA, ANAM, BDI-II), followed by structural T1-weighted magnetic resonance imaging (MRI), resting-state functional MRI (rs-fMRI) and pseudo-continuous arterial spin labeling (pCASL). HD-tDCS (2 mA, 20 min) was administered using 9 electrodes positioned to optimize inward current to each target. Rs-fMRI and pCASL were repeated. ANAM was repeated after the scanning session. Functional connectivity and cerebral blood flow were analyzed using region-of-interest (ROI)-based approaches with each target as well as voxel-wise analyses. A 4×2 repeated measures ANOVA assessed time-by-condition interactions.

Results: No significant interaction effects were identified in both behavioral outcomes or ROI-based imaging analyses. In the voxel-wise intrinsic connectivity analysis, significant interaction effects were identified in the cerebellar vermis, and post-hoc ROI analysis suggested that the intrinsic connectivity was significantly increased after the right DLPFC stimulation compared to the sham stimulation.

Conclusion: This study demonstrates asymmetric effects of HD-tDCS where only right DLPFC stimulation produced significant and selective increases in intrinsic connectivity in the cerebellar vermis. These findings underscore the need for further investigation into the mechanisms underlying the asymmetric effects of HD-tDCS and its potential implications for neuromodulation strategies in cognitive and clinical applications.

Keywords

HD-tDCS, DLPFC, IPL, fMRI, pCASL, Intrinsic Connectivity

Acknowledgements

I would like to express my sincere gratitude to my supervisor Dr. Ji Hyun Ko for his invaluable support, advice and unwavering patience throughout this journey. Dr. Ko has been a mentor who has pushed me to become a researcher. His timely feedback and constant availability have been truly appreciated. His guidance and dedication have helped me a lot during my master's program.

Secondly, I would also like to acknowledge and thank my committee members Dr. Alexa Hryniuk and Dr. Jennifer Kornelsen, for their guidance and knowledge, which greatly helped my project. Without their support and feedback, this work wouldn't have been possible.

I would also like to thank members in my lab, because this project wouldn't have been possible without you. Dr. Tiffany Carther-Krone, whose support, patience and unwavering dedication were essential to the success of this project. Your guidance both technically and intellectually was a constant source of clarity and motivation. Quite simply, without you, this would not have been possible. I would like to give a special thanks to Jarrad Perron, who has always been there for me as a colleague and a great friend. Additionally, I would like to acknowledge Eun Choi, our lab research assistant, for her invaluable support in addressing any queries I had regarding the data collection. Although I am far from home, they never made me feel like it.

I am very thankful to my mom, my uncle, brother, sister-in-law and grandparents for their constant support throughout this journey. Their constant support and belief in me made this journey significantly easier and meaningful.

Lastly, I would like to thank the Department of Human Anatomy and Cell Science and PrairieNeuro Research Centre for providing resources and facilities for conducting this research.

Contents

List of Tables

List of Figures

List of Abbreviations

ACC	Anterior Cingulate Cortex
ADHD	Attention-Deficit/Hyperactivity Disorder
ANAM	Automated Neurophysiological Assessments Metrics
BDI-II	Becks Depression Inventory
BDNF	Brain Derived Neurotrophic Factor
BOLD	Blood Oxygen Level Dependent
CBF	Cerebral Blood Flow
CSF	Cerebral Spinal Fluid
DCN	Dynamic Causal Network
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EMG	Electromyography
fMRI	Functional Magnetic Resonance Imaging
FPCN	Fronto-Parietal Control Network
GNS	General Neuropsychological Screening Battery
HD-tDCS	High-Definition Transcranial Direct Current Stimulation
IC	Intrinsic Connectivity
ICN	Intrinsic Connectivity Network
IPL	Inferior Parietal Lobe
IPS	Intra-Parietal Sulcus

LTD	Long-Term Depression
LTP	Long-Term Potentiation
M1	Primary Motor Cortex
MDD	Major Depressive Disorders
MEP	Motor Evoked Potential
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NIBS	Non-Invasive Brain Stimulation
OCD	Obsessive-Compulsive Disorder
pCASL	Pseudo-Continuous Arterial Spin Labeling
PTSD	Post-Traumatic Stress Disorder
ROI	Region Of Interest
rCBF	Regional Cerebral Blood Flow
Rs-FMRI	Resting State Functional Magnetic Resonance Imaging
rTMS	Repetitive Transcranial Magnetic Stimulation
SN	Salience Network
tDCS	Transcranial direct current stimulation
TMS	Transcranial Magnetic Stimulation

1. Chapter 1: Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique (NIBS), allowing for reversible modulation of activity in specific brain regions. The NIBS has become established as a valuable tool for elucidating brain-behavior relationships across a variety of cognitive, motor, social, and affective domains.[1] These methods provide a special ability to alter neuronal excitability, enabling "perturbing and measuring" of brain activity and functions. It has therapeutic potential for a wide range of neurological and psychiatric disorders. Among different NIBS, tDCS is one of the most affordable and safe approaches. The tDCS treatment has been approved by Health Canada for the indication of ameliorating fibromyalgia and migraine. In major depressive disorders, the most common off-label treatment candidates for tDCS application, clinicians typically target the dorsolateral prefrontal cortex (DLPFC), a region crucial for mood regulation, to alleviate depression symptoms and improve emotional wellbeing.[2] Researchers have also demonstrated that tDCS can improve cognitive function in Alzheimer's patients, slowing down cognitive decline and facilitating daily activities.[3]

The neurophysiological mechanisms of tDCS effects are not fully understood, but the fundamental and historical observation is that the neurobehavioral effects of tDCS is realized by tDCS-induced current directly modulating the neuronal membrane potential.[4] In most tDCS applications, two saline soaked sponges (12-80 cm^2) are applied on top of the targeted brain region and on the control site, and a very large brain region between the two sponges are affected indiscriminately. The stimulation time ranges from 7.5 to 30 minutes, with the most common stimulation protocol being 20 minutes long.[5, 6] Anodal stimulation depolarizes the neuronal membrane so that the target neurons become more excitable and spontaneous activity increases.[7] If cathodal stimulation is applied, it hyperpolarizes so that the target neurons become less excitable and spontaneous activity decreases.[7] Its long-lasting effects when applied repeatedly have potentially wide-reaching use as a therapeutic tool for drug-refractory symptoms of many brain disorders.[8]

These “guidelines” about anodal stimulation being excitatory while cathodal stimulation is inhibitory is based on studies conducted on motor cortex where the neuronal excitability can be experimentally measured with electromyography (EMG) and transcranial magnetic stimulation (TMS). However, the most targeted brain region in both research and clinical settings (for cognitive and/or mood disorders) is the left (and less often for the right) dorsolateral prefrontal cortex (DLPFC). To excite the DLPFC for treatment purposes, the anode is typically positioned directly over the target site, while the cathode is commonly placed either over the contralateral supraorbital region or above the contralateral DLPFC. The choice of cathode location depends on the desired current flow direction and the therapeutic objective: placing the cathode over the right supraorbital area produces a unilateral montage that minimizes contralateral cortical inhibition,[7] whereas positioning it over the right DLPFC enables bilateral modulation of prefrontal activity, which may be preferable in cases targeting interhemispheric imbalance, such as in major depressive disorder.[9-11] Accordingly, the left DLPFC activation has been demonstrated to improve depressive symptoms in tDCS studies,[12] while right DLPFC suppression has shown to reduce anxiety and negative emotional processing.

Optimization of treatment protocol requires more accessible readouts than clinical symptoms themselves which take several weeks to observe changes. Unlike the motor cortex, where neurophysiological responses can be measured directly using EMG and TMS the effects of tDCS on the DLPFC cannot be assessed through peripheral physiological signals. As a result, resting-state functional magnetic resonance imaging (rs-fMRI) has become a critical tool for evaluating the effects of tDCS on brain function. rs-fMRI measures spontaneous, low-frequency (<0.1 Hz) fluctuations in the blood-oxygen-level-dependent (BOLD) signal, which reflects changes in local blood oxygenation associated with neural activity.[13] The BOLD signal arises due to differences in magnetic susceptibility between oxygenated and deoxygenated hemoglobin, allowing indirect inference of neuronal activity. In the resting state, when no external task is being performed rs-fMRI enables the examination of intrinsic brain activity and the functional connectivity between regions that co-activate over time. This makes it particularly useful for detecting distributed network-level changes following

neuromodulation, such as those induced by tDCS.[14-19] The DLPFC is the core of the frontoparietal control network (FPCN) which plays a central role in executive function, cognitive flexibility, and goal-directed behavior.[20] It consists of a set of widely distributed but tightly integrated regions, including the DLPFC, inferior parietal lobule (IPL), anterior cingulate cortex (ACC), and parts of the anterior insula and medial frontal cortex.[21] Neuroimaging studies have demonstrated that NIBS effects are not typically confined locally to the targeted region but it modulates the activities in other functionally connected brain regions.[22] For instance, stimulation of the left DLPFC has been associated with alterations in frontoparietal and frontostriatal connectivity, as well as with behavioural improvements in working memory and decision-making.[23, 24] However, the broad current spread inherent to conventional tDCS makes it difficult to disentangle specific pathways or predict off-target effects.

HD-tDCS offers a solution to this problem by enhancing spatial focality and allowing for more accurate targeting of functionally relevant nodes within the FPCN. Computational modelling studies have shown that HD-tDCS montages can constrain the majority of the electric field to a radius of approximately 1-2 cm from the central electrode, significantly improving the anatomical specificity of the induced current.[25, 26] Yet, despite these advances, empirical evidence regarding the effects of HD-tDCS on functional connectivity remains limited. Most studies have either focused on task-based outcomes or examined connectivity changes using relatively coarse analyses.[27, 28 29, 30] This study seeks to address these gaps by using HD-tDCS to stimulate three key nodes of the FPCN-the left DLPFC, right DLPFC, and left IPL and examining pre- and post-stimulation changes in functional connectivity and regional cerebral blood flow (rCBF) using rs-fMRI and pseudo-continuous arterial spin labelling (pCASL). In addition to seed-based connectivity analysis, we employed intrinsic connectivity network (ICN) analysis to characterize global changes across the entire connectome. Participants were randomly assigned to one of four stimulation conditions (right DLPFC, left DLPFC, left IPL, or sham), and connectivity changes were assessed using 4×2 generalized linear model to identify condition-specific effects. By systematically comparing the effects of HD-tDCS across different FPCN nodes, this study

provides novel insights into how focal cortical stimulation can differentially shape large-scale brain networks. These findings have important implications for the use of HD-tDCS in basic neuroscience research and in the development of network-targeted interventions for neuropsychiatric and neurocognitive disorders.

2. Chapter 2: Background

2.1 Brief History and clinical applications of Transcranial Direct Current Stimulation

The concept of using electrical currents to influence brain activity dates to the early 19th century when scientists first explored the idea of brain stimulation.[31] The foundational work in this field began with the discovery of the electrical nature of nerve impulses.[31] In 1803, Giovanni Aldini, an Italian scientist, demonstrated the effects of electrical stimulation on human tissue by applying direct current to the surface of the brain.[31] His experiments, including the application of electricity to the brain of a deceased body, paved the way for later scientific inquiries into the effects of electrical current on nervous system activity.[31] In the late 19th century, the German neurologist Richard Caton's work laid further groundwork for understanding the influence of electrical currents on the brain.[32] Caton discovered that electrical potentials could be recorded from the exposed cerebral cortex of animals, illustrating the electrical properties of the brain and introducing the concept of brain waves. These early experiments were foundational in the development of techniques like electroencephalography (EEG) and, much later, transcranial direct current stimulation (tDCS).[32]

tDCS as a modern neuromodulation technique began to take shape in the late 20th century. The first experimental use of tDCS in humans was reported in the early 2000s by researchers like Nitsche and Paulus. This landmark study involved the application of weak direct currents to the scalp, which led to a shift in cortical excitability and improved motor performance in healthy participants.[7] The simplicity, non-invasiveness, and relatively low cost of tDCS made it a powerful tool for cognitive neuroscience and clinical applications. In these early years, tDCS was primarily used to study motor cortex excitability and its role in motor learning. Subsequent studies demonstrated the potential of tDCS to modulate a wide variety of cognitive functions, such as working memory, attention, and language processing, thus expanding its scope from a purely motor-related tool to a versatile neuromodulation technique.[33] Researchers soon recognized that tDCS could be used to either increase or decrease neural excitability, depending on the polarity of the current. Anodal stimulation (positive electrode) typically increases excitability, while cathodal stimulation (negative electrode) generally

decreases it. These findings laid the groundwork for the clinical applications of tDCS, particularly for conditions that involve impaired brain function.

tDCS has made significant strides in clinical use, particularly in neurorehabilitation and psychiatric disorders. The approval of tDCS in the European Union (EU) for the treatment of depression has been a critical step, reflecting broader acceptance of its therapeutic applications. Although the FDA has not issued full market approval for tDCS as a generalized treatment, it has approved tDCS as an investigational device intended for pain-related indications (e.g., fibromyalgia and migraine). [34] In Canada, Health Canada has similarly approved certain tDCS systems for investigational or therapeutic use.[35] Despite these regulatory nuances, tDCS has gained substantial off-label application in clinical and research contexts targeting a range of neuropsychiatric and neurological disorders.[36]

tDCS has been employed in treating conditions like depression, anxiety, schizophrenia, post-stroke rehabilitation, and even chronic pain.[37] The flexibility of tDCS allows for its adaptation across a wide range of clinical applications. Its non-invasive nature is particularly advantageous for populations who are sensitive to more invasive procedures, such as those suffering from psychiatric disorders or individuals in rehabilitation.

While tDCS is not approved for the treatment of depression by the FDA, it is approved for the use in the EU. This regulatory approval lends further legitimacy to its off-label use for treatment of depression in Canada. Numerous studies have demonstrated that tDCS applied over the DLPFC can have significant therapeutic effects in patients with major depressive disorder MDD. By modulating the excitability of the prefrontal cortex, tDCS can alter mood regulation pathways, providing symptom relief when other treatments fail. In fact, studies have shown that the effects of tDCS can persist even after the stimulation period has ended, suggesting that tDCS induces long-lasting neural changes that benefit patients.[38] Other psychiatric disorders, including bipolar disorder, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD), have also been targeted with tDCS, with varying degrees of success. Beyond psychiatric conditions, tDCS is

used for rehabilitation purposes, particularly following stroke. Motor rehabilitation post-stroke is one of the most well-established uses of tDCS. Applying tDCS to the motor cortex has been shown to enhance motor recovery and plasticity in stroke patients. By modulating cortical excitability, tDCS helps to retrain the brain and promote recovery of motor function.[39] The ease of use, portability, and ability to deliver tDCS in outpatient settings further contribute to its popularity in rehabilitation contexts.

The areas most commonly targeted in tDCS studies are those involved in cognitive processes, motor control, and mood regulation. Early studies primarily focused on the motor cortex, specifically the primary motor cortex (M1), due to its well-established role in motor function and its accessibility for stimulation. However, as research progressed, the clinical and cognitive applications of tDCS expanded to include a variety of brain regions involved in higher-order functions, such as decision-making,[40] working memory,[41] and emotional regulation.[42] One of the most widely studied regions is the dorsolateral prefrontal cortex (DLPFC), which is implicated in executive functions such as working memory, attention, and problem-solving. The DLPFC has become a common target for depression, with many studies showing that tDCS can modulate its activity to improve mood and cognitive function.[43, 44] By stimulating the left DLPFC with anodal tDCS, researchers have observed improvements in symptoms of depression and enhancements in cognitive performance.[38] Other key regions targeted for tDCS include the parietal cortex, which is involved in visuospatial processing and attention, and the occipital cortex, which plays a role in visual processing. The motor cortex, particularly M1, continues to be a prime focus of tDCS applications for motor rehabilitation in stroke patients. Additionally, regions associated with language processing, such as Broca's area and Wernicke's area, have been targeted in studies examining the effects of tDCS on language recovery following stroke or in the treatment of language deficits in patients with aphasia.[45] Additionally, sensory and association cortices—such as the visual cortex—have been stimulated to investigate enhancements in visual attention and perception,[46] while the cerebellum has gained attention in studies targeting motor coordination in conditions like Parkinson's disease and ataxia.[47] While these cortical areas highlight the broad applicability of tDCS across functional domains, the DLPFC has emerged

as the most widely studied and therapeutically relevant target particularly due to its central role in cognitive control, executive function, and emotional regulation.[47, 48] This makes the DLPFC a critical region of interest for interventions addressing mood disorders, cognitive dysfunction, and network-level neuromodulation.

Despite its growing clinical applications, tDCS is not without its limitations. One of the main challenges is its poor spatial resolution. Conventional tDCS uses large sponge electrodes, typically 25–35 cm^2 in size, which leads to diffuse current distribution across cortical regions.[25] This limits the ability to precisely target specific neural networks and may introduce unintended off-target effects. Additionally, individual differences in skull thickness, brain morphology, and cerebrospinal fluid distribution significantly affect the distribution of current, resulting in variable responses across individuals.[49] Another challenge lies in the bidirectional and context-dependent nature of tDCS effects, making it difficult to predict outcomes across different cognitive states or populations. Another limitation is the lack of long-term data on the safety and efficacy of tDCS. While there have been many short-term studies showing positive effects, there is still much to learn about the long-term consequences of repeated tDCS sessions, especially when used as an off-label treatment. Additionally, there are concerns about the optimal dosage of stimulation, which includes parameters such as the duration of stimulation, current intensity, and electrode configuration. The effectiveness of tDCS is also influenced by the specific brain region targeted. While certain areas, such as the DLPFC and motor cortex, have been well-studied, other areas remain underexplored. Furthermore, the mechanisms through which tDCS exerts its effects on neural circuits are still not fully understood. While it is clear that tDCS can modulate cortical excitability, the exact nature of these changes and how they translate to improvements in cognitive function or symptom relief remains an open question.

Finally, while tDCS is widely considered safe when used appropriately, there are concerns about the potential side effects, such as skin irritation, headache, or dizziness. These side effects are generally mild but may limit the acceptability of tDCS for some individuals. Moreover, there is a need for more rigorous safety

protocols and standardized guidelines for tDCS use, particularly in vulnerable populations such as those with neurological or psychiatric conditions.

As researchers sought to overcome some of the limitations of conventional tDCS, high-definition transcranial direct current stimulation (HD-tDCS) was developed.[25] HD-tDCS uses a higher density of electrodes and finer spatial targeting to achieve more focal stimulation, which addresses many of the issues associated with the broad stimulation fields of conventional tDCS. The improved precision of HD-tDCS makes it a promising tool for investigating localized brain areas and understanding the effects of neuromodulation with greater accuracy.

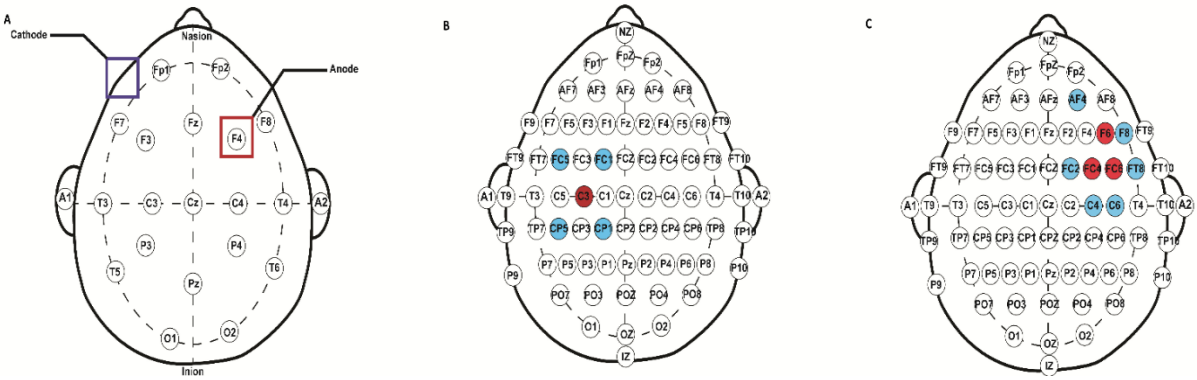

Figure 1. Comparison between different stimulation setups. A). Conventional tDCS setup; B). HD-tDCS setup without HDTargets; C). HD-tDCS setup with HDTargets (Right DLPFC configuration)

2.2 High -Definition tDCS: Mechanisms and Evidence

HD-tDCS is a modern, high-precision neuromodulation technique that builds upon the foundational principles of conventional tDCS. Unlike conventional tDCS, which typically employs two large sponge electrodes, HD-tDCS uses smaller, gel-based electrodes arranged in configurations such as the 4x1 ring montage. This arrangement concentrates current delivery and minimizes the spatial spread of stimulation, allowing for more focal and reproducible modulation of cortical activity.[25, 50] The core principle of HD-tDCS lies in delivering low-intensity electrical current (generally between 1–2 mA) through the scalp to subtly alter neuronal membrane potentials, without eliciting action potentials directly. This change in resting membrane potential modulates neuronal excitability—facilitating or inhibiting spontaneous neuronal firing depending on the polarity of the stimulation (inward vs outward).[7] In conventional tDCS, stimulation is typically framed in terms of anodal vs. cathodal polarity, however HD-tDCS differs in that current flow, it is characterized as inward vs. outward at the cortical target, reflecting its capacity for more precise and focal modulation. The development of tools like HDTargets further enhances this flexibility, allowing to model and optimize current flow directions to target specific brain regions with higher accuracy. A key distinction within HD-tDCS approaches lies in whether modeling tools like HDTargets are used. HD-tDCS without HDTargets typically employs standardized electrode configurations (e.g., 4x1 ring montages) that provide focality over conventional tDCS but do not account for individual anatomical variability. In contrast, HD-tDCS with HDTargets leverages individualized heads models and computational simulations to optimize electrode placement and current direction based on the targeted brain region.

The mechanism by which tDCS modulates neural activity are generally shared across both conventional and HD-tDCS. In both modalities, anodal stimulation typically depolarizes the resting membrane potential, thus bringing neurons closer to the threshold for firing, which is associated with increased excitability. Conversely, cathodal stimulation hyperpolarizes neurons, reducing the likelihood of firing and dampening excitability.[7] Importantly, these effects are not limited to acute changes in membrane potential

but can also induce longer-lasting changes through mechanisms resembling synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD).[4] These effects are believed to be mediated by changes in NMDA receptor activity, calcium signaling pathways, and neurotrophic factors such as brain-derived neurotrophic factor (BDNF). HD-tDCS stands out for its ability to deliver these neuromodulatory effects with a higher spatial precision, allowing more targeted stimulation of specific cortical regions and potentially reducing off-target effects.

A critical advantage of HD-tDCS over conventional tDCS is its increased focality, which allows researchers to modulate discrete brain regions with minimal unintended current spread. Finite element modeling studies have demonstrated that HD-tDCS generates electrical fields that are better confined to the target cortical area, reducing the likelihood of stimulating neighboring regions.[25] This capability is particularly important when targeting functionally specialized areas such as the DLPFC, IPL, or occipital cortex—regions involved in complex cognitive processes, sensorimotor integration, and visual perception. By improving spatial resolution, HD-tDCS enables more accurately test hypotheses about the causal role of specific brain regions in behavior.

The empirical evidence supporting tDCS spans multiple domains, including neurophysiological, behavioral, and imaging-based studies. Electrophysiological research using techniques such as EEG and transcranial magnetic stimulation (TMS) has shown that tDCS can modulate cortical oscillatory dynamics and motor-evoked potentials (MEPs) in a polarity-specific manner.[51, 52] For instance, anodal tDCS over the motor cortex increases MEP amplitude, suggesting enhanced excitability, while cathodal stimulation produces the opposite effect. These findings are consistent across healthy and clinical populations and point to tDCS as a reliable method for influencing neural excitability in a targeted way.

Beyond clinical applications, HD-tDCS has been used as a powerful experimental method in cognitive neuroscience to explore the causal role of specific brain regions in complex behaviours. For instance, studies

using HD-tDCS over the right inferior parietal lobule (IPL) have elucidated its role in attentional reorienting, numerical cognition, and body representation.[51] Similarly, modulation of the medial prefrontal cortex (mPFC) using HD-tDCS has been associated with alterations in social cognition and emotional regulation, suggesting that this method can selectively influence large-scale brain networks associated with higher-order processes.[53] HD-tDCS has also been employed to study brain oscillations by pairing stimulation with EEG recordings, revealing frequency-specific changes in cortical excitability that correspond to behavioural performance.[54] Comparative studies between HD-tDCS and conventional tDCS further underscore the advantages of high-definition approaches. In a direct comparison, HD-tDCS induced more focal electric fields and greater intra-individual reliability in evoked motor responses than standard tDCS.[26] Another study showed that HD-tDCS targeting the DLPFC led to significant improvements in cognitive inhibition compared to sham and conventional stimulation, suggesting that the added focality enhances the functional specificity of the stimulation.[52] Computational analyses also support these findings, showing that HD-tDCS reduces current spread and maximizes the electric field at the target location by up to 50% compared to sponge-based tDCS.[50] This improved focality not only enhances experimental control but also reduces variability in outcomes, a common concern in tDCS studies.

Despite these advantages, several questions remain about the mechanisms and efficacy of HD-tDCS. One major limitation is the incomplete understanding of how focal stimulation affects distributed brain networks. Although HD-tDCS targets a localized cortical site, the brain operates as an interconnected system, and the downstream effects of stimulation may depend on pre-existing network dynamics and functional connectivity. As such, it remains unclear whether observed behavioural changes are due to local modulation or network-wide reconfiguration.[55] Moreover, individual differences in anatomy, neurochemistry, and cognitive state introduce variability in HD-tDCS effects, complicating the interpretation of findings and limiting the generalizability of results. While computational modelling can partially address these issues by predicting current flow based on individual MRI data, real-time monitoring of neural effects remains limited.

Another challenge is the scarcity of large-scale, well-powered clinical trials that evaluate the efficacy of HD-tDCS across diverse patient populations. Most studies to date are limited by small sample sizes, short follow-up durations, and heterogeneity in stimulation protocols. Consequently, although initial findings are promising, robust evidence supporting the superiority of HD-tDCS over conventional tDCS in clinical settings is still emerging. There is also a need for standardized guidelines on electrode placement, stimulation intensity, session frequency, and outcome measures to facilitate replication and comparison across studies. The role of state-dependence and individual variability must also be better understood to optimize the design of personalized stimulation protocols.

Given these unresolved issues, the central research question of whether HD-tDCS can more effectively modulate functional brain connectivity compared to conventional methods, and whether such modulation translates into meaningful cognitive or behavioural outcomes, is both timely and essential. Investigating these questions hold significant value not only for advancing theoretical models of neural plasticity but also for informing the development of precision-based therapeutic strategies in neuropsychiatric care. If HD-tDCS proves capable of consistently influencing connectivity within and across brain networks involved in domains such as executive function, emotional regulation, or motor coordination, it could serve as a transformative tool in non-invasive neurorehabilitation. Furthermore, clarifying the underlying neurophysiological mechanisms may enable synergistic integration with adjunctive treatments like cognitive interventions or pharmacotherapy, thereby enhancing clinical efficacy.

More broadly, this line of inquiry aligns with the evolving paradigm in neuroscience that emphasizes large-scale network interactions over isolated regional activity. HD-tDCS, with its superior spatial precision, adaptability, and safety profile, provides an ideal platform for testing causal links between brain circuits and behaviour. To fully harness its potential, continued empirical exploration is needed, leveraging advances in neuroimaging, electrophysiological recording, and computational modelling. Addressing current

methodological and mechanistic gaps will require a multidisciplinary approach and rigorous experimental design. With such efforts, HD-tDCS may play a central role in the future of personalized, non-invasive brain modulation.

To overcome these limitations, the integration of HD-tDCS with advanced neuroimaging techniques is essential. fMRI provides high spatial resolution and allows for the mapping of stimulation-induced changes in blood oxygenation levels across the entire brain. Among these techniques, rs-fMRI is frequently used in combination with tDCS to capture alterations in intrinsic brain connectivity that occur as a result of stimulation. This multimodal approach allows to assess how targeted stimulation of specific cortical regions influences distributed neural circuits, even in the absence of task engagement.[23] Meanwhile, pseudo-continuous Arterial Spin Labeling (pCASL) offers a non-invasive method to quantify regional cerebral blood flow (rCBF), serving as a proxy for neural activity and metabolic demand. Unlike BOLD fMRI, which is sensitive to relative changes in deoxyhemoglobin, pCASL provides an absolute measure of perfusion, making it highly suitable for assessing physiological effects of brain stimulation in both baseline and task-related states.[56]

Recent studies have begun to explore these combined methodologies. Studies have demonstrated that tDCS-induced changes in motor learning were accompanied by alterations in resting-state connectivity as measured by fMRI.[57] Similarly, when ASL was used, it showed that HD-tDCS applied to the motor cortex increased regional cerebral blood flow in targeted areas.[58] However, few studies have systematically combined HD-tDCS with both fMRI and pCASL, especially in the context of posterior cortical stimulation. The dual use of these imaging techniques enables us to disentangle the effects of HD-tDCS on both functional activation and cerebral perfusion, offering a richer, more multidimensional understanding of brain responses to stimulation.

In this study, these imaging modalities are employed to investigate the effects of HD-tDCS targeted at the left DLPFC, right DLPFC, and left inferior parietal cortex. By examining changes in these regions' functional connectivity (via fMRI) and cerebral blood flow (via pCASL), this study aims to elucidate how focal

neuromodulation influences broader brain networks. The high spatial precision of HD-tDCS, combined with the complementary strengths of fMRI and pCASL, provides an optimal platform to investigate the neural mechanisms of targeted brain stimulation. This multimodal approach not only enhances the scientific validity of the findings but also holds translational relevance for developing more effective, individualized stimulation protocols in clinical populations.

The integration of HD-tDCS with multimodal imaging offers a powerful, comprehensive framework for investigating the causal effects of focal brain stimulation on complex cognitive and neural systems. By advancing our understanding of the mechanisms, effects, and optimal parameters of HD-tDCS, this study contributes meaningfully to the broader field of non-invasive neuromodulation and opens new avenues for both experimental neuroscience and clinical interventions.

2.3 Frontoparietal Control Network

The frontoparietal control network (FPCN), also known as the central executive network, is a large-scale brain system primarily composed of the dorsolateral prefrontal cortex (DLPFC), the anterior prefrontal cortex (aPFC), and regions of the posterior parietal cortex, especially the inferior parietal lobule (IPL) and intraparietal sulcus (IPS). These nodes are bilaterally represented and interconnected through both short-range and long-range white matter tracts, allowing for efficient communication between frontal and parietal cortices. The DLPFC is associated with maintaining and manipulating goal-relevant information, while the IPL and IPS contribute to attentional control and the integration of sensory inputs with motor planning. The aPFC, particularly Brodmann area 10, plays a role in higher-order executive processes such as task switching, metacognition, and strategic planning.[59] Collectively, these regions form a flexible and adaptive network that dynamically coordinates internal cognitive resources in response to external demands.

The FPCN's central function lies in its ability to mediate cognitive control-facilitating the regulation of attention, working memory, response selection, and decision-making. Functional magnetic resonance imaging

(fMRI) studies have consistently shown coactivation of the FPCN during tasks requiring sustained attention, conflict monitoring, and goal-directed behavior.[60] Crucially, the FPCN operates as a "flexible hub" that can reconfigure its connectivity patterns to support varying cognitive tasks, distinguishing it from more static sensory or motor networks.[20] This dynamic capability is made possible by its bidirectional interaction with other large-scale brain systems, including the default mode network (DMN) and salience network (SN), enabling the FPCN to integrate external stimuli with internal representations and behavioral goals.[61]

Neuroimaging data have demonstrated that the FPCN is not uniformly engaged across all cognitive activities; rather, it dynamically recruits or disengages particular nodes depending on task context and demands. This context-sensitive activation pattern allows the FPCN to support a wide range of mental operations, including error monitoring, task switching, working memory updating, and abstract reasoning. Its intrinsic connectivity pattern, as observed during resting-state fMRI, reveals strong functional coherence between its nodes even in the absence of external stimuli, underscoring its role in maintaining an executive scaffold that underpins goal-oriented cognition.[21]

Disruptions in FPCN connectivity are implicated in a wide array of neuropsychiatric and neurological disorders, including major depressive disorder (MDD), schizophrenia, attention-deficit/hyperactivity disorder (ADHD), and Alzheimer's disease. In MDD, hypoactivity and reduced connectivity within the FPCN, especially in the left DLPFC, have been linked to impairments in executive function and emotion regulation.[62] Similarly, in schizophrenia, aberrant FPCN activity has been associated with working memory deficits and cognitive disorganization,[63] while in ADHD, delayed FPCN maturation is thought to underline attentional dysregulation.[64] These findings suggest that the FPCN plays a pivotal role in maintaining cognitive integrity, and its dysfunction may serve as a transdiagnostic marker of cognitive impairment.

Given its centrality to cognitive control, the FPCN has become a major target for neuromodulation using non-invasive brain stimulation techniques such as TMS and tDCS. Repetitive TMS (rTMS) applied to the

left DLPFC has shown clinical efficacy in treating depression and improving executive functioning, presumably by enhancing FPCN connectivity.[65] High-frequency rTMS has been observed to increase cortical excitability and promote neuroplasticity in targeted FPCN nodes.[66] Similarly, anodal tDCS applied to the DLPFC has been shown to enhance working memory, attentional performance, and decision-making by modulating FPCN activity.[67] These changes are supported by electrophysiological and neuroimaging evidence indicating altered synchronization and increased frontoparietal coherence following stimulation.

HD-tDCS represents a more recent advancement that offers improved spatial focality and targeting precision, enabling more selective modulation of FPCN subregions. HD-tDCS studies targeting the left DLPFC or left IPL have demonstrated enhanced executive task performance and increased FPCN connectivity, compared to conventional tDCS.[51, 52] This precision may be particularly beneficial in tailoring interventions for specific cognitive deficits or neuropsychiatric conditions, reducing variability in treatment response and off-target effects.

Beyond cognitive enhancement, modulating the FPCN has shown promise in clinical rehabilitation settings. In stroke patients, targeted stimulation of FPCN nodes has been associated with improved motor planning and functional recovery,[68] while in traumatic brain injury, it may support the restoration of attentional control.[69] Age-related cognitive decline has also been linked to reduced FPCN integrity; stimulation protocols aimed at reinforcing FPCN connectivity in older adults have shown encouraging results in preserving or enhancing executive function and memory.[70]

2.3.1 Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC), situated in the middle frontal gyrus and associated primarily with Brodmann areas 9 and 46, is a crucial node within the prefrontal cortex and plays a central role in executive function.[71] It exhibits extensive connectivity with a wide array of cortical and subcortical structures, including the posterior parietal cortex, motor and premotor cortices, basal ganglia, thalamus,

hippocampus, and limbic regions such as the amygdala and anterior cingulate cortex. [72]This integrative network allows the DLPFC to coordinate sensory, motor, cognitive, and emotional information, supporting its role in adaptive behavior and top-down regulation.

Its afferent inputs from the posterior parietal cortex contribute to functions like visuospatial attention and the dynamic updating of working memory, while its efferent outputs influence motor planning and execution via the premotor and motor cortices.[73] The DLPFC's top-down regulatory role is further exemplified in its modulation of limbic activity, providing a cognitive framework for emotional processing. This functional integration enables individuals to manage complex cognitive tasks, regulate emotions, and maintain goal-directed behavior.[74] Functionally, the DLPFC is fundamental for a variety of executive processes, including abstract reasoning, planning, decision-making, inhibitory control, and especially working memory manipulation.[75] Neuroimaging studies using fMRI consistently demonstrate DLPFC activation during tasks such as the n-back, Stroop, and Wisconsin Card Sorting Test.[76] These tasks require sustained attention, flexible strategy use, and resistance to distraction core functions supported by DLPFC circuitry. The DLPFC works closely with the parietal cortex as part of the frontoparietal network, which orchestrates top-down attentional control and cognitive flexibility, ensuring task-relevant information is prioritized.[21]

DLPFC exhibits functional and structural hemispheric asymmetry. The left DLPFC is predominantly associated with verbal working memory, language processing and cognitive control of emotion.[77, 78] The right DLPFC has a role to play in spatial working memory, attention, inhibitory control and evaluation of risk and uncertainty.[79-81] This lateralization is supported by various neuroimaging studies showing differential activation patterns. For instance, verbal fluency and language tasks preferentially activate the left DLPFC, whereas visuospatial and inhibition response tasks activate the right DLPFC.[82, 83] Clinical studies reflect this asymmetry, hypoactivity in the left DLPFC is commonly reported in major depressive disorders,[84] while hyperactivity or dysregulation is linked to anxiety, impulsivity, and obsessive- compulsive disorders.[85, 86] These findings have

led to lateralized modulation protocols, such as anodal stimulation of the left DLPFC for depression treatment.[65, 87] This hemispheric asymmetry deepens our understanding of DLPFC function and helps in the development of more targeted and effective neurostimulation-based interventions.

In terms of emotional and social cognition, the DLPFC facilitates explicit emotional regulation through strategies like cognitive reappraisal, where reinterpretation of emotional stimuli reduces negative affect.[74] It achieves this by modulating amygdala activity, a process often disrupted in mood disorders.[88] Furthermore, the DLPFC contributes to moral reasoning, empathy, and theory of mind, reflecting its involvement in higher-order social processing. These functions require integration of contextual cues, internal goals, and social expectations, which the DLPFC adeptly manages.[89]

From a developmental perspective, the DLPFC is among the last cortical regions to mature, with developmental trajectories extending into early adulthood.[90] This late maturation aligns with the gradual emergence of complex executive functions during adolescence. Processes such as synaptic pruning and increased myelination enhance neural efficiency and support the specialization of cognitive operations within the DLPFC. However, the same plasticity renders the DLPFC vulnerable to neurodegeneration and psychiatric conditions. Structural declines in cortical thickness and disruptions in connectivity have been observed in aging populations and in conditions like Alzheimer's disease, leading to deficits in executive functioning, memory, and adaptive behavior.[91]

The DLPFC is frequently implicated in psychiatric disorders. Hypoactivity in the left DLPFC is a common feature in major depressive disorder, correlating with poor emotional regulation and impaired decision-making.[92] In schizophrenia, DLPFC dysfunction manifests as disorganized thought, impaired working memory, and reduced cognitive flexibility.[63] Bipolar disorder and ADHD also show altered DLPFC activation and connectivity, affecting impulse control and attentional regulation.[93, 94] Structural imaging often reveals cortical

thinning or volume loss in this region, while functional studies show aberrant activation patterns during executive tasks, reinforcing the link between DLPFC abnormalities and psychopathology.

Experimental methodologies further elucidate the DLPFC's role. Lesion studies demonstrate that damage to the DLPFC impairs reasoning, problem-solving, and temporal organization of behavior.[95] Transcranial magnetic stimulation (TMS) studies provide causal evidence by showing that transient disruption of DLPFC activity induces similar deficits in healthy individuals.[33] Electrophysiological recordings in non-human primates support these findings, with DLPFC neurons displaying task-specific firing patterns and sustained activity during delay periods of working memory tasks.[96] These neural signatures underscore the DLPFC's role in both the maintenance and manipulation of task-relevant information.

Advancements in neuroimaging and computational modeling continue to refine our understanding of the DLPFC. Techniques such as ultra-high field 7T fMRI enable laminar resolution of DLPFC subregions, revealing functional heterogeneity and depth-specific activation.[97] Connectomic analyses are uncovering how the DLPFC integrates with large-scale networks such as the default mode, salience, and frontoparietal networks, highlighting its role as a dynamic hub in cognitive control.[20] Individual differences in DLPFC structure and connectivity are being explored in relation to cognitive resilience, intelligence, and susceptibility to mental illness, informing precision-medicine approaches.[98]

Moreover, interventions targeting the DLPFC such as cognitive training, mindfulness-based therapies, pharmacological treatments, and neurostimulation—are being investigated to enhance executive function and emotional well-being. These approaches seek to harness the plasticity of the DLPFC to improve outcomes in both healthy and clinical populations.[99] Understanding the diverse roles and modulation of the DLPFC thus remains central to both neuroscience research and clinical innovation.

Recent meta-analyses and task-based connectivity studies have begun to delineate the differential activation of subregions within the DLPFC under various cognitive demands. For example, the posterior DLPFC

appears more engaged in context monitoring and response selection, whereas anterior portions are implicated in rule maintenance and abstract reasoning.[100] Studies using graph theoretical approaches indicate that DLPFC nodes exhibit high centrality within task-positive networks, reinforcing its integrative, supervisory role in orchestrating cross-network dynamics.[101] Furthermore, computational models of working memory posit that recurrent excitation within DLPFC microcircuits enables persistent neural firing, a key mechanism for holding information online. Such models are supported by empirical evidence from single-unit recordings in animals and fMRI studies in humans.[102]

Several studies have shown that variability in DLPFC structure and function predicts individual differences in treatment response. For instance, greater baseline activity in the left DLPFC has been associated with better outcomes in cognitive behavioral therapy and antidepressant response, suggesting its role as a prognostic biomarker.[103] Moreover, resting-state functional connectivity between the DLPFC and other prefrontal or limbic regions is being explored to tailor individualized neuromodulatory treatments.[62] Research in populations with traumatic brain injury, autism spectrum disorder, and frontotemporal dementia also implicates the DLPFC in compensatory mechanisms and neural plasticity, opening avenues for rehabilitative strategies.[104]

The DLPFC stands as a cornerstone of cognitive neuroscience, embodying the interface between thought, behavior, and emotion. Its expansive connectivity, functional versatility, and susceptibility to modulation make it both a subject of fundamental interest and a target for therapeutic intervention. Ongoing research continues to unravel its complexity, offering insights into the neural basis of human cognition and the mechanisms underlying mental health and disease.

2.3.2 Inferior Parietal Lobe

The Inferior Parietal Lobe (IPL) is situated on the lateral surface of the cerebral hemisphere, beneath the intraparietal sulcus in the posterior parietal cortex. It includes two major gyri; the supramarginal gyrus

(Broadmann area 40) and the angular gyrus (Broadmann area 39).[15] The IPL is highly interconnected with the frontal, temporal and occipital areas, positioning it as a key hub for integrating multimodal sensory input.

The IPL is crucial for integrative cognitive processes such as attention, working memory and spatial processing.[15] Its contributions are also lateralized, the left IPL is more involved in language, verbal working memory, and mathematical tasks, whereas the right IPL is associated with visuospatial attention and attentional control. Targeting the IPL aims to enhance these integrative functions and leverage its connectivity to optimize the therapeutic effects of tDCS.

The IPL is not only a convergence zone for sensory integration but also serves as a key node in multiple large scale brain networks. It is a core component of the FPCN, a flexible and adaptive network that is responsible for goal directed behavior, cognitive control, and the regulation of activity across other networks like the default mode network and the dorsal attention network.[20, 21] Within the FPCN, the IPL dynamically interacts with the DLPFC to support functions such as task switching, working memory and attentional modulation.

2.4 Transcranial Direct Current Stimulation Effects on Dorsolateral Prefrontal Cortex

Clinical implications of tDCS on the left DLPFC are significant, particularly for psychiatric and neurological disorders that involve dysfunction in executive and emotional regulation. In MDD, hypoactivity in the left DLPFC is commonly observed, which is thought to contribute to the cognitive and emotional deficits characteristic of the disorder. Patients with depression often experience difficulties in attention, decision-making, and emotional regulation, leading to pervasive feelings of sadness, hopelessness, and cognitive impairment.[38] Anodal tDCS, which increases cortical excitability, applied to the left DLPFC has been shown to enhance cognitive function and improve mood in individuals with depression.[105] This non-invasive intervention has been explored as a treatment option for patients who have not responded to traditional pharmacological therapies, offering a promising avenue for intervention.

In schizophrenia, a disorder characterized by cognitive and emotional dysregulation, dysfunction in the DLPFC is a prominent feature. Patients with schizophrenia often exhibit impairments in working memory, attention, and executive functioning, which are believed to be linked to decreased DLPFC activity.[106] Studies have demonstrated that anodal tDCS applied to the left DLPFC can improve cognitive performance and enhance working memory in individuals with schizophrenia.[38] By modulating the DLPFC, tDCS may help to restore some of the cognitive functions that are impaired in schizophrenia, improving overall functioning and quality of life.

Similarly, tDCS has shown promise in treating bipolar disorder, which is marked by extreme mood swings between mania and depression, alongside significant cognitive deficits. Impairments in the DLPFC are thought to contribute to the cognitive dysfunction observed in bipolar disorder, including deficits in working memory, attention, and cognitive flexibility.[38] Anodal tDCS applied to the left DLPFC has been shown to enhance cognitive performance and emotional regulation in individuals with bipolar disorder, potentially improving mood stability and cognitive functioning.[105] By modulating DLPFC activity, tDCS offers a novel non-pharmacological approach to managing both cognitive and emotional symptoms in bipolar disorder.

Beyond these major psychiatric disorders, tDCS targeting the left DLPFC has been explored in other clinical populations. In individuals with Attention-Deficit/Hyperactivity Disorder (ADHD), where the DLPFC plays a crucial role in attention and impulse control, tDCS has been shown to improve attention and working memory.[38] Similarly, in patients with traumatic brain injury (TBI), where the prefrontal cortex, including the DLPFC, is often damaged, tDCS has demonstrated potential in improving cognitive function and emotional regulation.[106] These findings suggest that tDCS may have broad clinical applications, offering a non-invasive intervention for a variety of conditions characterized by DLPFC dysfunction.

The use of tDCS on the left DLPFC, while promising, is not without challenges. One significant issue is the variability in individual responses to tDCS. Factors such as electrode placement, stimulation parameters,

and individual differences in brain anatomy can all influence the effectiveness of the stimulation.[38] For example, optimal electrode placement is crucial for targeting the left DLPFC accurately, as small variations in electrode positioning can significantly affect stimulation outcomes—even in healthy individuals. Studies using MRI-guided modeling have demonstrated that shifts as small as 1–2 cm can lead to considerable differences in the induced electric field distribution, potentially engaging adjacent cortical regions rather than the intended target.[25, 107] This variability is particularly relevant in studies using the 10–10 EEG system for localization, where anatomical differences across individuals can lead to non-uniform targeting. In the context of research involving healthy controls, where subtle neuromodulatory effects are being measured (e.g., changes in intrinsic connectivity or cognitive performance), precise electrode placement is critical to ensure both reliability and reproducibility of stimulation effects. Additionally, the effects of tDCS may be influenced by individual differences in brain structure and function, which can result in inconsistent responses across individuals.[108] Despite these challenges, tDCS remains a promising tool for modulating DLPFC activity, particularly in patients with conditions that involve cognitive and emotional dysregulation.

The long-term effects of tDCS are also not fully understood. While immediate improvements in cognitive and emotional function have been reported following tDCS, there is still limited evidence regarding the long-term impact of repeated tDCS sessions. Some studies have suggested that the benefits of tDCS may be short-lived, with improvements in mood and cognition dissipating after a few days or weeks.[108] More research is needed to determine the optimal frequency and duration of tDCS sessions to achieve sustained therapeutic benefits. Furthermore, the cumulative effects of repeated tDCS over time, especially in clinical populations, require further investigation to ensure the safety and efficacy of long-term use.

Despite these limitations, tDCS continues to be an exciting area of research, particularly in its potential to enhance cognitive and emotional functioning by modulating DLPFC activity. Its non-invasive nature, combined with the growing body of evidence supporting its effectiveness in treating a variety of psychiatric

and neurological disorders, makes it a valuable tool for clinical interventions. As research into the effects of tDCS on the left DLPFC progresses, it is likely that new insights will emerge that could inform the development of more effective treatment protocols and provide a better understanding of the neural mechanisms underlying these effects. In the future, tDCS could become a standard intervention for a variety of cognitive and emotional disorders, offering a safe, non-invasive alternative to pharmacological treatments.

tDCS has emerged as a powerful tool for modulating DLPFC activity, particularly in the left hemisphere, where it plays a central role in executive functions and emotional regulation. The growing body of evidence suggests that tDCS can improve cognitive performance and emotional regulation in individuals with psychiatric and neurological disorders, offering a promising non-invasive intervention. While challenges such as individual variability and the long-term effects of tDCS remain, ongoing research will continue to refine the use of tDCS for modulating the DLPFC, optimizing its therapeutic potential for a variety of clinical populations. As our understanding of the DLPFC and the effects of tDCS expands, the potential for this technology to enhance brain function and improve clinical outcomes will only continue to grow.

2.5 Transcranial Direct Current Stimulation Effects on Inferior Parietal Lobe

tDCS has emerged as a valuable tool to modulate the functional connectivity of the IPL, both for experimental and therapeutic purposes. Studies targeting the IPL have produced encouraging results across a range of domains, although most studies have used conventional tDCS, and more recently, HD-tDCS is being explored for higher targeting precision.

The left IPL, particularly has been a target in studies seeking to improve language, working memory and mathematical cognition. Previous studies have demonstrated that anodal tDCS over the left IPL enhances arithmetic learning performance in healthy adults, suggesting a causal role for this region in mathematical processing.[109] Another study showed that stimulating left IPL improves verbal working memory and modulates event-related potentials associated with working memory.[110] Language related tDCS studies have also

implicated the left IPL in phonological retrieval and semantic integration. Studies have shown that tDCS over the supramarginal gyrus has been found to support phonological access during speech production, and it is often included in montages aimed at facilitating recovery from aphasia following stroke.[111]

On the right hemisphere, tDCS over the IPL has yielded enhancements in visuospatial attention and attentional shifting. For instance, right IPL stimulation facilitated multisensory spatial orienting and improved reaction times in attentional tasks.[112] This suggests a role for the right IPL in bottom-up attention and sensory integration. Additionally, modulation of this region can be useful in rehabilitation of neglect syndrome in right hemisphere stroke patients.[113]

Given the IPL's integrative role in multimodal processing and its function as a dynamic hub within the FCPN, modulating this region with high spatial precision is of particular interest. HD-tDCS offers a methodologically robust approach to isolating the neuromodulatory effects on the IPL. This precision is critical for elucidating the causal contributions of the IPL to cognitive control, attentional allocation, and executive function.

2.6 Investigating HD-tDCS Effects: Rationale for Imaging Modalities and Review of Literature

fMRI is widely regarded as a gold-standard technique for non-invasively measuring brain activity. BOLD-fMRI measures fluctuations in oxygenated blood flow, which are tightly coupled to neural activity. Its high spatial resolution and whole-brain coverage make it exceptionally useful for mapping changes in functional connectivity between brain regions following HD-tDCS. In particular, rs-fMRI has proven valuable in revealing how HD-tDCS influences intrinsic connectivity networks, such as the default mode network, frontoparietal network, and visual networks.[23, 24] Studies have shown that HD-tDCS can increase or decrease connectivity between key regions, depending on the site and polarity of stimulation.

The use of rs-fMRI has enabled researchers to detect both immediate and long-lasting changes in brain network architecture post-stimulation. Studies have shown alterations in motor network connectivity

following HD-tDCS over M1.[114] Similarly, changes in prefrontal-parietal connectivity have been reported in studies targeting cognitive control networks. These connectivity shifts are often associated with behavioral improvements, reinforcing the utility of fMRI as a bridge between neural changes and functional outcomes. Notably, dynamic causal modeling (DCM) and graph theoretical approaches applied to fMRI data have allowed for even more refined analyses of network reorganization, showing increased global efficiency and modularity in response to stimulation.

pCASL, on the other hand, provides a quantitative and direct measurement of cerebral blood flow (CBF), which serves as a surrogate marker of neural activity. Unlike BOLD, which is susceptible to neurovascular coupling variability, ASL techniques offer more stable and reproducible indices of hemodynamic response.[115] This is especially important in clinical and aging populations where vascular reactivity may be compromised. Recent studies have successfully used pCASL to demonstrate both focal and network-wide increases in perfusion following tDCS and HD-tDCS.[58, 116] For instance, increases in CBF in the prefrontal cortex post-stimulation have been linked to enhanced cognitive outcomes in working memory and attention tasks. These findings underscore the importance of perfusion-based markers in tracking the neuromodulatory effects of stimulation.

In HD-tDCS-specific applications, pCASL offers added advantages due to the precision of stimulation. The ability to detect localized changes in perfusion aligns with the improved spatial targeting of HD-tDCS, allowing for validation that the intended cortical regions are indeed modulated. Previous studies have reported region-specific CBF increases using HD-tDCS over the primary motor cortex, with effects persisting beyond the stimulation window.[117] This suggests a longer-term modulation of neurovascular mechanisms, potentially linked to synaptic plasticity. Moreover, pCASL has been used in combination with pharmacological interventions and electrophysiological recordings, providing a multi-dimensional view of how HD-tDCS alters cortical excitability and cerebral perfusion.

Using both fMRI and pCASL in a complementary fashion enables the simultaneous observation of functional and perfusion-related effects of HD-tDCS, bridging the gap between hemodynamic and electrophysiological measures. This multimodal imaging strategy provides robust evidence of neuromodulatory impact and helps disentangle direct effects of stimulation from downstream network-level adaptations. It also addresses the growing recognition that neuromodulation can have complex, distributed effects that are not confined to the stimulated region but propagate through interconnected circuits. For instance, a study combining fMRI and pCASL in patients with depression undergoing prefrontal HD-tDCS revealed parallel increases in CBF and enhanced connectivity within mood regulation networks, demonstrating the translational potential of this approach.

Previous literature using conventional tDCS has already established the utility of fMRI and pCASL in capturing stimulation-induced changes. A study demonstrated modulation of frontoparietal connectivity during a working memory task using anodal tDCS.[118] Similarly, pCASL has shown an increase in regional CBF correlated with behavioral improvements.[116] However, studies specifically examining HD-tDCS with these imaging techniques are still limited but growing. HD-tDCS applied to the DLPFC showed significant modulation in default mode and task-positive networks, highlighting the technique's potential in cognitive enhancement.[119] Other researchers have employed task-based fMRI to track changes in activation during working memory and decision-making tasks, showing that HD-tDCS can enhance task-relevant BOLD signals in a polarity- and region-specific manner.

The combined use of rs-fMRI and pCASL remains underutilized. While some studies have used either modality independently, fewer have leveraged their complementary strengths in a single paradigm. Employing both techniques can offer converging evidence of neuromodulatory effects and increase the sensitivity to detect subtle changes. Additionally, combining these methods allows for validation of BOLD-derived connectivity changes with direct measurements of perfusion, enhancing the interpretability and robustness of

findings. This dual approach can also help distinguish whether observed changes are due to altered neuronal firing rates, neurovascular coupling, or vascular dynamics alone.

Given the superior focality of HD-tDCS and the sensitivity of fMRI and pCASL to both local and network-wide brain dynamics, the integration of these methods represents an optimal strategy to investigate HD-tDCS effects. This approach is particularly relevant when exploring the interactions between specific regions, such as the left inferior parietal lobule and the left occipital cortex, whose connectivity patterns may be intricately altered by targeted stimulation. By leveraging this imaging-based methodology, the current research aims to provide mechanistic insights into how HD-tDCS reshapes brain network architecture, thereby informing its translational application in both clinical and cognitive neuroscience domains.

3. Chapter 3: Rationale

tDCS has shown promise in modulating cortical excitability and supporting therapeutic outcomes in a variety of cognitive and affective disorders.[7] However, conventional tDCS is limited by broad current spread due to large sponge electrodes (12-80 cm^2), leading to non-specific stimulation across wide cortical areas.[25] This reduces the precision of neuromodulation, making it difficult to isolate the effects of stimulation on specific brain networks. HD-tDCS offers an advancement in focal neuromodulation, allowing for current targeting with spatial resolution as fine as 1–2 cm.[26, 52] This enables more anatomically precise stimulation of specific cortical regions, such as those involved in cognitive control and emotional regulation.

This study utilizes HD-tDCS to examine region-specific modulation of the FPCN, a large-scale functional network that includes the DLPFC and IPL, both of which are critical hubs for control, attention, working memory, and emotion regulation.[20, 21] Targeting nodes within the FPCN has shown therapeutic potential across neurological and psychiatric conditions, but the network-level effects of focal HD-tDCS to distinct FPCN hubs remain underexplored.

By targeting the left DLPFC, right DLPFC, and left IPL in a within-group design and assessing changes in intrinsic functional connectivity and rCBF, this study aims to elucidate how focal stimulation of different FPCN nodes can differentially modulate large-scale brain networks. It should be noted that I specifically chose the same analytical framework that was employed in our previous fMRI study where the effect of conventional tDCS was compared between left DLPFC vs. right DLPFC stimulation,[120] so that the results can be directly compared between the HD-tDCS and tDCS. Ultimately, this study seeks to overcome the limitations of conventional tDCS and improve our understanding of network-specific brain modulation by combining HD-tDCS with resting-state fMRI and pCASL providing both methodological refinement and theoretical insights into the functional architecture of the FPCN.

4. Chapter 4: Aims, Objectives and Hypothesis

The overarching objective is to characterize the effects of HD-tDCS applied to frontoparietal cortical nodes and behavioral outcomes in healthy adults. For this, I have carried out a prospective trial where HD-tDCS was used to stimulate key anatomical regions of the FPCN: left DLPFC (n=20), right DLPFC (n=20), and left IPL (n=20), and sham (n=20). My hypothesis was that HD-tDCS would modulate the functional connectivity of the targeted brain regions and affect the respective behavioural performance. To test this hypothesis, I had four specific aims.

Aim 1) To quantify pre- to post-stimulation changes in behavioral performance measured by a battery of cognitive tests that involve FPCN.

Aim 2) To quantify pre- to post-stimulation changes in resting-state functional connectivity within the targeted brain regions.

Aim 3) To quantify pre- to post-stimulation changes in the remote brain regions measured by intrinsic connectivity.

Aim 4) To quantify pre- to post-stimulation changes in cerebral blood flow in the targeted and remote brain regions.

5. Chapter 5: Methods

Eighty participants (male = 33, female = 47) were recruited for this study with the average age of the sample was 32.41 years with a standard deviation of 11.49 years, reflecting a diverse adult population. Participants were recruited from the community at large. This study was approved by the Biomedical Research Ethics Board of the University of Manitoba and all participants provided written informed consent prior to participating. Inclusion criteria: (1). Age > 18-year-old. Exclusion criteria: (1). history or any susceptibility to any neurological or psychiatric disorders (2). abnormal MRI (3). metal implants or cardiac pacemakers; (4) pregnant or breastfeeding women.

After informed consent, cognitive and affective status were assessed using Montreal Cognitive Assessment (MoCA),[121] Automated Neuropsychological Assessment Metrics (ANAM),[122] and Beck-Depression Inventory II (BDI-II).[123] Afterwards participants were randomly assigned to four different treatment groups: HD-tDCS to the left DLPFC; HD-tDCS to the right DLPFC; HD-tDCS to the left IPL; and sham (control) stimulation. Participants undergo brain imaging with a Siemens 3T Magnetom Verio system. This includes structural and functional imaging sessions: T_1-weighted images (8 min), pre-HD-tDCS pCASL (5 min), pre-HD-tDCS resting-state functional MRI (rs-fMRI; 11 min), simultaneous HD-tDCS & rs-fMRI (2 mA, 20 min), post-HD-tDCS rs-fMRI (11 min), post-HD-tDCS pCASL (5 min) and diffusion tensor imaging (DTI; 8 min). Between the pre- and post-HD-tDCS fMRI scans, subjects lay still in the scanner while HD-tDCS was applied. ANAM was repeated after combined fMRI & HD-tDCS sessions.

5.1 Automated Neuropsychological Assessment Metrics

The Automated Neuropsychological Assessment Metrics (ANAM) General Neuropsychological Screening Battery (GNS) with Clinical Toolkit was used to examine participants' overall cognitive performance before and after the HD-tDCS/MRI sessions. ANAM GNS Clinical Toolkit uses a series of computerized tasks to assess cognitive domains such as attention, concentration, reaction time, memory, processing speed, and decision-making.[124] The battery consists of Stroop test, sleepiness scale, symptoms

checklist, mood scale, simple reaction time, code substitution – learning, procedural reaction time, mathematical processing, matching to sample, code substitution – delayed, simple reaction time – repeated, go no go, logical relations, spatial processing, tower puzzle, tapping (right and left), two-choice reaction time, running memory continuous performance test, standard continuous performance test, manikin (variation), pursuit tracking, and switching. ANAM software provides randomized stimuli across tests sessions, creating an almost limitless number of alternative forms and combinations to facilitate repeated measures testing thereby minimizing the practice effects. The software also computes age-corrected performance scores for each test and a composite score (zscore) was calculated.

5.2 Application of HD-tDCS

HD-tDCS was used to deliver direct current to the target via rubber electrodes and HD-tDCS gels. The 9 electrodes (8 channels + 1 ground) positions and current intensity were determined based on computer stimulation using HD-Targets software (Soterix Inc.) that results in maximum focal current on the 3 different target regions with inward field orientation (Figure 2; Table 1).

The targets were identified from a seed-to-voxel functional connectivity analysis using the 39 healthy individuals' baseline rs-fMRI[120] with the left DLPFC as the seed (x= -44, y = 10, z = 30), the coordinate of which was taken from a meta-analysis of Stroop task brain imaging studies.[125] This strategy allowed us to reconstruct our scanner-specific FPCN that may be associated with the Stroop task performance (Figure 3), one of the main cognitive tests that we are investigating.[120] The second target was based on the group-level connectivity analysis for the contralateral region (right DLPFC; x = 42, y = 14, z = 30). The third target was based on the group-level connectivity analysis for ipsilateral posterior region (left inferior parietal lobule; x = -50, y = -36, z = 42). A constant current (not exceeding 2 mA) was delivered for 20 minutes. For sham stimulation, one of the 3 target regions was randomly selected, and the current was applied for 30 seconds ramp-up followed by 30 seconds ramp-down.

Left DLPFC		Right DLPFC		Left IPL	
Electrode	Current (mA)	Electrode	Current (mA)	Electrode	Current (mA)
C3	-0.6412	C4	-0.3548	C3	-0.3375
P3	0.1393	F8	-0.4221	P3	-0.4425
FC1	-0.6326	FC2	-0.2265	P7	-0.0851
FC3	1.2225	AF4	-0.261	CP1	-0.8883
F5	0.3432	FC4	0.4962	CP2	0.0914
FC5	0.2949	F6	0.9606	CP3	1.9086
C5	-0.2119	FC6	0.1538	FC5	-0.0466
AF7	-0.2183	C6	-0.1566	C5	-0.0927
FT7	-0.2959	FT8	-0.1895	TP7	-0.1073

Table 1. Electrodes and current set-up for each HD-tDCS targets

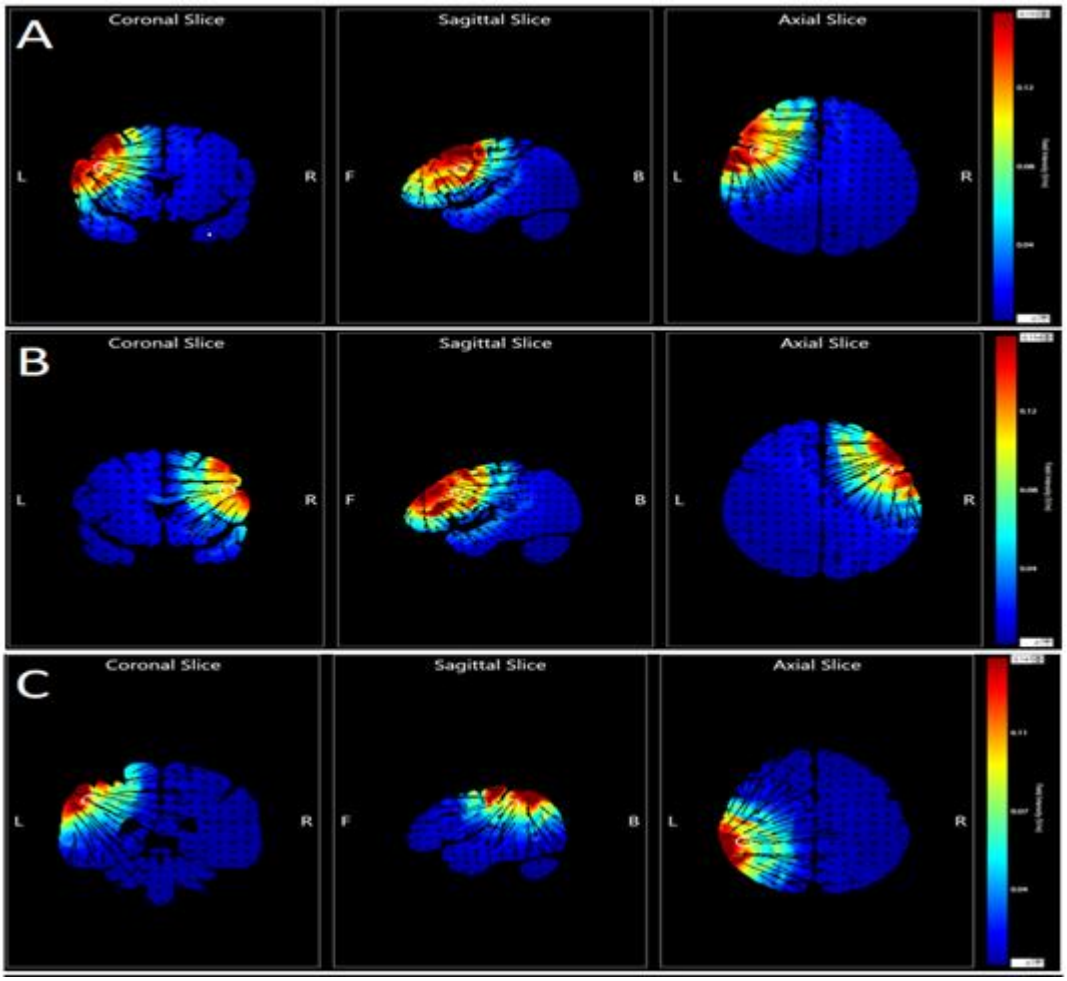

Figure 2. Simulated electrical current in the head model based on magnetic resonance imaging using HDTargets (Soterix, Inc.). **A.** The primary target is the left dorsolateral prefrontal cortex (DLPFC). The target coordinate is taken from a meta-analysis of Stroop task brain imaging studies where it showed most consistent activity (x=-44, y=10, z=30).[125] **B.** The second target is based on the group-level connectivity analysis for the contralateral region (right DLPFC; x = +42, y = +14, z = +30). **C.** The third target is based on the group-level connectivity analysis for ipsilateral posterior region (left inferior parietal lobule; x = -50, y = -36, z = +42).

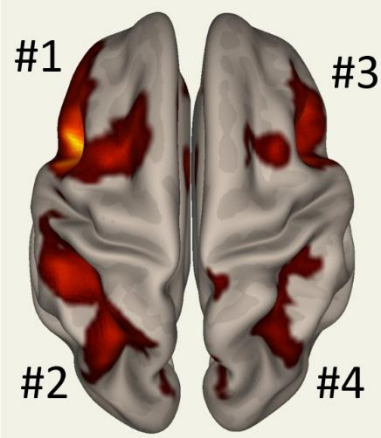

Figure 3. Stimulation Targets**.** The **s**timulation targets were selected to replicate key nodes of the FPCN associated with Stroop task. Seed-based resting-state functional connectivity analysis (n=39) on the left DLPFC (x=-44, y=10, z=30, spherical volume-of-interest with 8mm radius) revealed four distant clusters (p<0.001, peak-level FDR-corrected, k>1,000). The biggest cluster (k = 7,556) was around the left DLPFC (#1). The second biggest cluster (k = 4,076) was on the left parietal-occipital regions (peak coordinate: x = -50, y = -36, z = +42, inferior parietal lobe, #2). The third biggest (k=3,149) was on the right DLPFC (peak coordinate: x = +42, y = +14, z = +30, inferior frontal operculum, #3). The fourth biggest (k=1,394) was on the right parietal-occipital regions (peak coordinate: x = +32, y = -50, z = +42, inferior parietal lobe, #4).

5.3 fMRI acquisition

All participants were scanned with Siemens 3T Magnetom Verio system equipped with 12-channel head coil located at the Kleysen Institute for Advanced Medicine at the University of Manitoba. During scanning, participants were instructed to keep their eyes open and not to fall asleep. The fMRI scanning parameters are as follows: Repetition Time [TR] = 2000 ms; Echo Time [TE] = 28 ms; Flip Angle = 77°; Slice Thickness = 4 mm; Field of View [FOV] = 220 × 220 mm2; voxel size = 3.4 × 3.4 × 4.0 mm. The pCASL acquisition parameters are TR = 4.0 s, TE = 12 ms, FOV = 240 × 240 mm2, matrix = 64 × 64 × 20, slice thickness = 5 mm, inter-slice space = 1 mm, labeling time = 2 s, post label delay time = 1.2 s, bandwidth = 3 kHz/pixel, flip angle = 90°. Forty-five label/control image pairs will be acquired for each

subject. MRI-compatible electrodes and cables were used for HD-tDCS.

The pCASL parameters were as follows: TR/TE = 4000/12, 20 slices, flip angle = 90°, FOV = 240 mm x 240 mm^2, 3.8 mm x 3.8 mm x 5.0 mm resolution, inter-slice space = 1 mm, labelling time = 2.0 s, post label delay time = 1.2 s, bandwidth = 3kHZ/pixel. For each participant, 45 label/control image pairs were acquired.

5.4 Behavioral Data Analysis

Behavioral statistical analysis was conducted using IBM version 27 SPSS software. The primary behavioral outcome variable was Stroop interference score since the HD-tDCS target coordinate was determined from the meta-analysis of brain imaging studies of Stroop task. Repeated measures generalized linear model analysis was performed to assess the interaction effects of stimulation condition and time (4×2; [3 different targets + 1 sham] × before vs. after). A significant interaction effect (group × time) was further analyzed by a post-hoc Bonferroni test. Other behavioral variables computed by ANAM were also analyzed in the same manner.

5.5 fMRI Functional Connectivity Analysis

Standard preprocessing was applied to the rs-fMRI data using the Functional Connectivity toolbox, CONN.[126] The first step of the pipeline is the realignment of the functional images to correct for any head motion artefacts. Next, a slice-timing correction was performed to correct for differences in time for the acquisition of slices in the fMRI acquisition. This was followed by coregistration of the participants functional and structural T1-weighted scans. Segmentation of the anatomical images into cerebral spinal fluid (CSF), white matter and grey matter components and normalization of the functional data into a standard anatomical template in a common space then followed. The resulting image was then smoothed with a full width at height maximum 8 × 8 × 8mm Gaussian kernel. Denoising was applied via linear regression on CSF and white matter masks produced during segmentation. Finally, a band-pass filter of 0.008-0.09Hz was also applied to minimize the influence of physiological, head-motion and other

noise sources.

Three different seed-based connectivity maps with the seeds defined as spherical volumes of interest centred to the target coordinates (left DLPFC, right DLPFC, and left IPL; Figure 3) were produced for each resting-state fMRI session of different stimulation conditions (left DLPFC stimulation, right DLPFC stimulation, left IPL stimulation, and sham stimulation). The 4×2 factorial analysis (stimulation condition and time) was performed, interactions between stimulation location (left DLPFC vs. right DLPFC vs. left IPL vs. sham) and time (before vs. after) were analyzed.

In addition to seed-based connectivity analysis, we conducted voxel-to-voxel IC analysis to obtain a more comprehensive view of functional brain organization. Unlike seed-based connectivity, which rely on a priori defined regions of interest and assess connectivity between predefined nodes and the rest of the brain, IC measures whole-brain connectivity at the voxel level. IC measures the centrality of each voxel by quantifying the strength of its functional connections with all other voxels across the entire brain. For IC analysis, a 4 group (left DLPFC, right DLPFC, left IPL and sham) × 2 time (before and after) general linear model as analyzed to determine any significant interaction effects between the stimulation condition and time. If significant interaction effect was detected, the mean signal intensity (i.e., IC) was extracted from the identified cluster, and 4 × 2 generalized linear model analysis followed by post-hoc Bonferroni test was performed to determine which stimulation effect drove the overall interaction effects. For all analyses, the statistical threshold for a voxel to belong to a cluster was set to $p < .001$ (uncorrected) with a cluster extent threshold of $p < .05$ (false-discovery-rate corrected).

5.6 pCASL Cerebral Blood Flow Analysis

The resting-state pCASL-MRI data was analyzed by ASL Perfusion MRI data processing toolbox (htttps://www.cfn.upenn.edu/~zewang/ASLtbx.php). The ASLtbx batch pipeline performs motion correction, coregistration, smoothing, then computes CBF images. Simple subtraction of label images from control images was performed for each label/control pair within the whole-brain mask. The analysis

parameters were set at default (timeshift=0.5, labeling efficiency = 0.9, labeling time = 1.517s, delay time = 1.2s, and slice time = 35.7s). M0 image, which will be acquired with short TE and long TR, was segmented and the white matter mean values for M0 images were used to calibrate the CBF image scales. The resulting CBF images was spatially normalized and analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm/).

A spherical volume of interest (radius=8mm) was located at each target region (left DLPFC, right DLPFC, and left IPL; Figure 3), and CBF values were extracted. 4×2 repeated measures general linear model analysis was performed to determine any interaction effects of stimulation condition and time. An explorative voxel-based 4×2 factorial analysis was performed to examine the other remote effects of different HD-tDCS stimulation sites.

6. Chapter 6: Results

6.1 Demographic information of participants

Demographic data from all participants are summarized in Table 2. No significant differences in age ($F(3, 76) = 0.318$, $p = .813$), sex ($F(3, 80) = 5.11$, $p = .164$), BDI ($F(3, 76) = .655$, $p = .582$) or MoCA ($F(3, 76) = 1.102$, $p = .354$) scores were found across the groups. All participants were above the cut off for cognitive decline (≥ 26). All participants completed both the pre- and post-stimulation assessments and were included in the final analysis. No differences in age, MoCA score or BDI score were found between males and females in each group ($p = .818$).

	Left DLPFC	Right DLPFC	Left IPL	Sham	p-value
Total Participants	20	20	20	20	
Age	32.45 ± 8.87	33.70 ± 13.48	33.15 ± 14.58	30.35 ± 8.31	0.813
MoCA	28.30 ± 2.03	28.40 ± 1.76	27.50 ± 1.70	27.60 ± 2.37	0.354
BDI-II	4.95 ± 6.76	5.45 ± 4.26	7.00 ± 6.80	7.60 ± 9.04	0.582

Table 2. Participant Demographics by Stimulation Condition.

6.2 Behavioral Effects of HD-tDCS

The primary behavioral outcome was interference score. No significant differences in interference score were noted across groups at baseline (F(1, 3)) = .276, p = .834). No significant differences were noted in the different tests which were acquired from ANAM battery (p > 0.3, Table 3).

Test	Group	Pre (Mean ± SD)	Post (Mean ± SD)	F-value	p-value
Interscore	Left DLPFC	17.28 ± 11.24	17.67 ± 10.47	0.276	0.834
	Right DLPFC	14.84 ± 8.69	16.32 ± 8.69		
	Left IPL	13.63 ± 8.43	14.89 ± 9.18		
	Sham	18.05 ± 8.00	20.68 ± 7.87		
Code Substitution Learning	Left DLPFC	52.89 ± 15.27	64.61 ± 16.76	0.931	0.431
	Right DLPFC	51.00 ± 9.87	64.42 ± 11.89		
	Left IPL	50.00 ± 12.06	59.68 ± 18.32		
	Sham	55.63 ± 9.35	70.69 ± 11.74		
Procedural Reaction Time	Left DLPFC	103.18 ± 17.52	100.94 ± 20.00	0.497	0.685
	Right DLPFC	99.84 ± 10.03	103.26 ± 11.88		
	Left IPL	93.53 ± 14.31	93.58 ± 19.19		
	Sham	106.19 ± 17.96	105.88 ± 11.01		
Math Processing	Left DLPFC	26.12 ± 17.50	27.71 ± 7.43	0.336	0.799
	Right DLPFC	24.21 ± 6.37	28.16 ± 6.38		
	Left IPL	22.05 ± 6.17	24.21 ± 7.67		
	Sham	21.25 ± 5.56	24.81 ± 6.73		
Matching to Sample	Left DLPFC	45.06 ± 12.09	40.65 ± 11.59	0.380	0.768
	Right DLPFC	37.89 ± 9.84	35.84 ± 10.37		
	Left IPL	38.32 ± 14.29	32.95 ± 14.77		
	Sham	44.06 ± 13.55	40.31 ± 6.01		

Test	Group	Pre (Mean ± SD)	Post (Mean ± SD)	F-value	p-value
Code Substitution Delayed	Left DLPFC	49.10 ± 17.87	64.90 ± 17.53	0.551	0.650
	Right DLPFC	54.42 ± 14.25	65.75 ± 13.63		
	Left IPL	44.89 ± 21.00	58.44 ± 18.14		
	Sham	44.80 ± 16.50	58.90 ± 18.60		
Simple Reaction Time - R	Left DLPFC	208.12 ± 37.07	214.47 ± 33.50	1.037	0.382
	Right DLPFC	194.21 ± 47.90	188.84 ± 56.48		
	Left IPL	208.63 ± 29.42	197.16 ± 44.96		
	Sham	214.56 ± 25.54	215.88 ± 22.12		
Running Memory	Left DLPFC	75.53 ± 32.64	81.06 ± 36.19	1.037	0.383
	Right DLPFC	90.29 ± 19.48	104.50 ± 18.12		
	Left IPL	83.29 ± 23.25	93.00 ± 25.43		
	Sham	92.38 ± 28.05	105.00 ± 15.22		
Simple Reaction Time	Left DLPFC	234.17 ± 45.77	186.94 ± 55.60		
	Right DLPFC	220.11 ± 28.56	185.95 ± 49.80		
	Left IPL	226.05 ± 35.15	176.63 ± 57.63		
	Sham	226.31 ± 27.57	200.56 ± 47.17		

Table 3. Summarization of different cognitive tests.

6.3 Functional Connectivity Analysis

6.3.1 Seed-Based Connectivity Analysis

Seed-to-voxel analyses were performed using the left DLPFC, right DLPFC, and left IPL as seed regions. These analyses aimed to detect changes in resting-state connectivity patterns from pre- to post-stimulation across the four experimental groups (left DLPFC, right DLPFC, left IPL, and sham). Seed-based connectivity analysis did not reveal any statistically significant differences between pre- and post-stimulation sessions in any of the stimulation groups.

6.3.2 Intrinsic Connectivity Analysis

In contrast to the seed-based analysis, intrinsic connectivity analysis revealed significant interaction effects between time (pre vs. post) and stimulation condition (left DLPFC, right DLPFC, left IPL, and sham). The significant cluster was located in the cerebellar vermis ($p < .05$, cluster-level FWE corrected, k = 104, peak MNI coordinates x = +00 y = -54 z = -34; Figure 4).

Post-hoc comparisons indicated that this increase was specific to the right DLPFC group ($p < .001$) and was not observed in the sham group or other stimulation conditions ($p > .2$). It also indicated that there was a decrease specific to the left IPL group ($p = .012$)

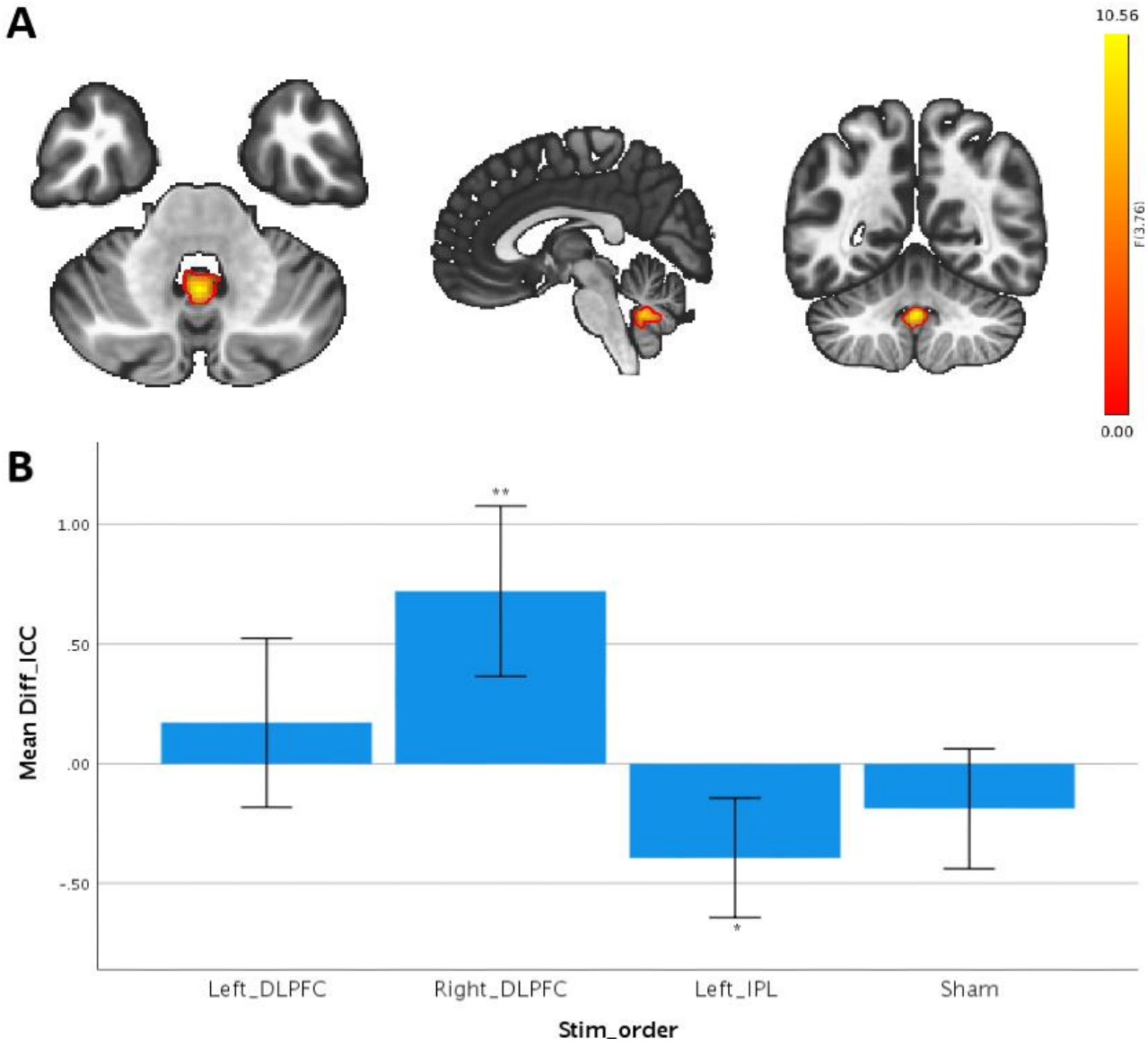

Figure 4. Changes in IC following HD-tDCS. A). Interaction effect showing significant changes in intrinsic connectivity with cluster-level FWE correction (***p*** < .001, *k* = 104). The highlighted cluster (peak MNI coordinates: x = + 00, y = - 54, z = -34) corresponds to the cerebellar vermis. B). Mean delta IC values were extracted from the identified cluster for post-hoc analysis. IC was increased for the right DLPFC group (**p < .001) and decreased for left IPL group (*p = .012)

6.4 pCASL Cerebral Blood Flow Analysis

No significant changes in CBF were found in the whole-brain voxel-based analysis or in any of the ROIs as well as the clusters identified from the voxel-to-voxel intrinsic connectivity analyses.

7. Chapter 7: Discussion

This study examined both behavioral and neurophysiological (by neuroimaging) effects of HD-tDCS targeting three different brain regions associated with FPCN, i.e., left DLPFC, right DLPFC, and left IPL, which was compared to sham stimulation. The key finding was a significant interaction effect in the cerebellar vermis, mainly driven by the increased and decreased IC following the right DLPFC and the left IPL stimulation, respectively. The lack of significant connectivity changes in the sham condition underscores the specificity of the effects, supporting the effectiveness of our sham control and confirms that observed changes were not attributable to scanner drift, time effects, or participant expectancy. This result indicates that HD-tDCS targeting the right DLPFC or the left IPL selectively modulates functional connectivity with specific downstream regions, particularly within the cerebellum, and may reflect targeted engagement of fronto-parieto-cerebellar circuits.

The enhanced coupling between the right DLPFC and cerebellar vermis aligns with prior anatomical and neuroimaging research demonstrating reciprocal pathways between the prefrontal cortex and cerebellum via cortico-ponto-cerebellar and cerebello-thalamo-cortical loops. These pathways support the role of the cerebellum in higher-order cognitive functions including working memory, executive control, and emotional regulation, in addition to its established role in motor coordination.[131] The cerebellar vermis, in particular, has been implicated in the modulation of affective and autonomic processes, and its increased connectivity with the DLPFC may represent a mechanism through which cognitive-emotional integration is enhanced following stimulation. Interestingly, the right DLPFC stimulation nor the left IPL stimulation produced no significant changes in behavioral performance on the cognitive tasks. This dissociation between neural modulation and behavioral output aligns with growing evidence suggesting that neuromodulatory interventions can alter large-brain networks in the absence of immediate behavioral effects.[127, 128]

The left IPL stimulation decreased IC in the cerebellar vermis, which was the opposite to the right DLPFC stimulation. While previous studies using inhibitory continuous theta burst stimulation over the left IPL

has demonstrated state-dependent reductions in connectivity between the IPL and cerebellar regions particularly during high demand cognitive tasks,[129] there remains a lack of comparable data using HD-tDCS. Our findings provide novel evidence that HD-tDCS, when precisely delivered to IPL, can disrupt cortico-cerebellar network coupling, specifically between IPL and cerebellum.[130] Given the IPL's role in the FPCN and its strong anatomical and functional links with the cerebellum,[21] especially the vermis, the present findings highlight the potential of HD-tDCS to modulate deeper subcortical-cortical pathways.

Unlike our previous study with a conventional tDCS[26, 52], we did not observe any significant changes in the targeted brain areas (cf. We have previously demonstrated that the right DLPFC stimulation increased the IC in the right DLPFC[120]). One potential explanation is that inter-individual variability in the EEG 10–10 system, which was utilized to place stimulation electrodes guided by HDTargets software, may have led to variability in the exact region stimulated across participants. It should be noted that the conventional tDCS uses a large sponge electrode (e.g., 4×6cm) and a fairly large region is stimulated thus there is bound to be an overlapping brain region affected by tDCS even if there is a mismatch across individuals. The lack of significant effects in the ROI-based functional connectivity nor the rCBF analysis in the present study using HD-tDCS also supports the variability of the actual site of stimulation. Nevertheless, increased intrinsic connectivity in the cerebellar vermis was consistently observed following stimulation of the right DLPFC. This finding potentially suggests that a large area in the right DLPFC maintains indirect but functionally meaningful, converging connections with the cerebellar vermis via cortico-ponto-cerebellar pathways.[21, 23, 132] Interestingly, stimulation to the left DLPFC nor left IPL produced significant changes in the intrinsic connectivity. While our explorative analysis revealed some subtle modulations adjacent to the target areas, the absence of robust findings in these conditions may relate to several factors. First, hemispheric asymmetries in neural responsiveness to stimulation have been documented in prior studies. For instance, right prefrontal regions have been more strongly associated with attentional and inhibitory functions and may therefore be more sensitive to stimulation in healthy adults.[133] Second, the left DLPFC is more commonly involved in language and verbal

working memory, and the absence of behavioral tasks targeting these domains may have limited our ability to detect stimulation effects on these networks.[51] Indeed, we have previously identified a similar asymmetric effects of DLPFC stimulation (i.e., only the right DLPFC stimulation had a significant effect on IC, but not the left DLPFC stimulation) using the same imaging protocols while the stimulation was performed using a conventional tDCS.[120]

Our previous study has demonstrated that tDCS led to significant alterations in IC, while seed-based connectivity analyses did not yield any notable effects.[120] This study emphasized that seed-based approaches may be limited by their dependence on predefined regions of interest, potentially missing broader or more diffuse changes in network connectivity. In contrast, IC analysis does not depend on pre-defined ROI therefore is more sensitive to distributed patterns of neural modulation.[120] The convergence between our previous[120] and current findings reinforces the utility of voxel-wise metrics in capturing the widespread, network-level effects of non-invasive brain stimulation techniques.[134, 135]

Unexpectedly, behavioural outcomes also showed no significant effects. This is in contrast to our previous study where the right DLPFC stimulation resulted in increased interference score after the conventional tDCS,[120] although others have found small or absent effects after a single–session stimulation.[46, 136] It is possible that the cognitive task employed was not sensitive enough to detect subtle neuromodulatory effects or that participants were already performing at near-ceiling levels. Together, the absence of behavioural effects underscores the variability in tDCS responsiveness and highlights the need for future studies to investigate dose-response relationships, individual differences, and alternative outcome measures.

The observed enhancement in DLPFC-cerebellar connectivity may have significant implications for the development of cognitive and clinical interventions. Aberrant connectivity within fronto-cerebellar circuits has been implicated in a variety of neuropsychiatric and neurodevelopmental conditions, including depression, schizophrenia, autism spectrum disorder, and attention-deficit/hyperactivity disorder.[137] Given the role of the

DLPFC in executive functioning and cognitive regulation, and the cerebellum's involvement in fine-tuning cognitive output, noninvasive modulation of these regions may offer a mechanism for therapeutic intervention. Future research should explore the behavioral correlations of increased fronto-cerebellar connectivity and evaluate whether repeated HD-tDCS sessions yield lasting improvements in cognitive performance and clinical symptoms.

7.1 Limitations and Future Directions

While HD-tDCS is designed to improve the spatial precision of stimulation compared to conventional tDCS, it is important to acknowledge that the actual physiological targeting remains an area of active investigation. Traditional tDCS typically employs large sponge electrodes (12-80 cm^2), resulting in widespread current diffusion and stimulation of broad cortical areas. In contrast, HD-tDCS utilizes smaller electrodes arranged in ring configurations (often 4×1 montage) that can theoretically constrain current to a more focal cortical target, with modelling studies suggesting focal effects within a radius of approximately 1–2 cm from the central electrode. The anatomical precision can be further enhanced by electrical current simulation using a head model such as HDTargets software and utilizing more montage (e.g., 8×1).

The ability of focal stimulation is a strength of HD-tDCS, but the spatial resolution of fMRI (~2–3 mm^3) in most standard acquisitions) may not be sufficient to capture subtle, localized changes induced by HD-tDCS. This raises the possibility that the stimulation-related changes in the present study may have occurred in highly localized regions but were undetectable or averaged out at the level of voxel clusters required for group-level analysis. Development of hardware (e.g., MRI with stronger magnet) and software can enhance the spatial resolution of fMRI. Employing more rigorous analytic pipeline that addresses motion artifacts, physiological noise, or state-dependent factors such as fatigue or arousal may improve the sensitivity of detecting subtly influenced connectivity measures. Inclusion of physiological recordings (e.g., heart rate, respiration) and state questionnaires would improve interpretability in future studies. Another important technical limitation is the mismatch between head model MRI and the subject brain anatomy. The use of the EEG 10–10 system to

determine electrode placement introduces inter-subject variability. While this system allows for standardized positioning, it does not account for individual cortical folding patterns or skull conductivity differences, potentially leading to variability in the actual cortical regions stimulated. As a result, the assumption in our SPM analysis that the same anatomical target was stimulated across all participants may be overly simplistic. Using subject-specific seed regions could enhance anatomical specificity and yield more consistent outcomes.

Finally, the limited sample composition hinders the generalizability of our findings. Although our sample size (N = 80) provided sufficient power to detect significant interaction effects in IC changes, all participants were healthy young adults, which may limit the transferability of our findings to older populations or clinical cohorts. Future research should examine the effects of HD-tDCS in individuals with cognitive or affective disorders, where baseline dysconnectivity may interact with stimulation effects in clinically meaningful ways.

Future directions should prioritize multimodal integration of fMRI, behavioral outcomes, and computational modeling to build a more mechanistic understanding of how HD-tDCS alters brain networks and supports cognitive change. Adaptive stimulation protocols, which adjust current intensity or target location based on real-time neuroimaging or behavioral feedback, represent a promising frontier. Furthermore, expanding to transdiagnostic populations and evaluating combined interventions (e.g., HD-tDCS paired with cognitive training or psychotherapy) may help optimize the clinical utility of this technique. There is also growing interest in understanding individual predictors of responsiveness to stimulation, including baseline connectivity, genetic factors, and cortical excitability profiles, which may ultimately support the development of personalized neuromodulation protocols.

8. Chapter 8: Conclusion

In conclusion, this study demonstrates that HD-tDCS targeted to the right DLPFC produces significant and selective increases in intrinsic connectivity in the cerebellar vermis. These effects appear to be both regionally and network-specific and were not observed with left DLPFC, IPL, or sham stimulation. Our findings provide new evidence that HD-tDCS can modulate long-range brain networks in a controlled and reproducible manner, supporting its utility for basic neuroscience research and its promise for future clinical interventions. Further research is needed to explore the behavioral and clinical consequences of these network changes and to refine HD-tDCS protocols for maximum efficacy and individual relevance.

References

(1) Filmer, H. L.; Mattingley, J. B.; Dux, P. E. Improved multitasking following prefrontal tDCS. *Cortex* **2013**, *49* (10), 2845-2852. DOI: 10.1016/j.cortex.2013.08.015.

(2) Wolkenstein, L.; Plewnia, C. Amelioration of Cognitive Control in Depression by Transcranial Direct Current Stimulation. *Biological psychiatry (1969)* **2013**, *73* (7), 646-651. DOI: 10.1016/j.biopsych.2012.10.010.

(3) Chen, J.; Wang, Z.; Chen, Q.; Fu, Y.; Zheng, K. Transcranial Direct Current Stimulation Enhances Cognitive Function in Patients with Mild Cognitive Impairment and Early/Mid Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Brain sciences* **2022**, *12* (5), 562. DOI: 10.3390/brainsci12050562.

(4) Stagg, C. J.; Antal, A.; Nitsche, M. A. Physiology of Transcranial Direct Current Stimulation. *The journal of ECT* **2018**, *34* (3), 144-152. DOI: 10.1097/YCT.0000000000000510.

(5) Nitsche, M. A. M. D.; Cohen, L. G. M. D.; Wassermann, E. M. M. D.; Priori, A. M. D. P.; Lang, N. M. D.; Antal, A. P.; Paulus, W. M. D.; Hummel, F. M. D.; Boggio, P. S. P.; Fregni, F. M. D. P.; et al. Transcranial direct current stimulation: State of the art 2008. *Brain stimulation* **2008**, *1* (3), 206-223. DOI: 10.1016/j.brs.2008.06.004.

(6) Lefaucheur, J.-P.; Antal, A.; Ayache, S. S.; Benninger, D. H.; Brunelin, J.; Cogiamanian, F.; Cotelli, M.; De Ridder, D.; Ferrucci, R.; Langguth, B.; et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical neurophysiology* **2017**, *128* (1), 56-92. DOI: 10.1016/j.clinph.2016.10.087.

(7) Nitsche, M. A.; Paulus, W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology* **2000**, *527* (3), 633-639. DOI: 10.1111/j.1469-7793.2000.t01-1-00633.x.

(8) Cammisuli, D. M.; Cignoni, F.; Ceravolo, R.; Bonuccelli, U.; Castelnuovo, G. Transcranial Direct Current Stimulation (tDCS) as a Useful Rehabilitation Strategy to Improve Cognition in Patients With Alzheimer's Disease and Parkinson's Disease: An Updated Systematic Review of Randomized Controlled Trials. *Frontiers in neurology* **2022**, *12*, 798191-798191. DOI: 10.3389/fneur.2021.798191.

(9) Brunoni, A. R.; Ferrucci, R.; Fregni, F.; Boggio, P. S.; Priori, A. Transcranial direct current stimulation for the treatment of major depressive disorder: A summary of preclinical, clinical and translational findings. *Progress in neuro-psychopharmacology & biological psychiatry* **2012**, *39* (1), 9-16. DOI: 10.1016/j.pnpbp.2012.05.016.

(10) Bai, S.; Dokos, S.; Ho, K.-A.; Loo, C. A computational modelling study of transcranial direct current stimulation montages used in depression. *NeuroImage (Orlando, Fla.)* **2014**, *87*, 332-344. DOI: 10.1016/j.neuroimage.2013.11.015.

(11) Hecht, D. Depression and the hyperactive right-hemisphere. *Neuroscience research* **2010**, *68* (2), 77-87. DOI: 10.1016/j.neures.2010.06.013.

(12) Borckardt, J. J.; Bikson, M.; Frohman, H.; Reeves, S. T.; Datta, A.; Bansal, V.; Madan, A.; Barth, K.; George, M. S. A Pilot Study of the Tolerability and Effects of High-Definition Transcranial Direct Current Stimulation (HD-tDCS) on Pain Perception. *The journal of pain* **2012**, *13* (2), 112-120. DOI: 10.1016/j.jpain.2011.07.001.

(13) Logothetis, N. K.; Pauls, J.; Augath, M.; Trinath, T.; Oeltermann, A. Neurophysiological investigation of the basis of the fMRI signal. *Nature (London)* **2001**, *412* (6843), 150-157. DOI: 10.1038/35084005.

(14) Boggio, P. S.; Sultani, N.; Fecteau, S.; Merabet, L.; Mecca, T.; Pascual-Leone, A.; Basaglia, A.; Fregni, F. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. *Drug and alcohol dependence* **2008**, *92* (1), 55-60. DOI: 10.1016/j.drugalcdep.2007.06.011.

(15) Seghier, M. L. The Angular Gyrus: Multiple Functions and Multiple Subdivisions. *The Neuroscientist (Baltimore, Md.)* **2013**, *19* (1), 43-61. DOI: 10.1177/1073858412440596.

(16) Culham, J. C.; Kanwisher, N. G. Neuroimaging of cognitive functions in human parietal cortex. *Current Opinion in Neurobiology* **2001**, *11* (2), 157-163. DOI: 10.1016/S0959-4388(00)00191-4.
(17) Silvanto, J.; Muggleton, N.; Walsh, V. State-dependency in brain stimulation studies of perception and cognition. *Trends in cognitive sciences* **2008**, *12* (12), 447-454. DOI: 10.1016/j.tics.2008.09.004.
(18) Fox, M. D.; Buckner, R. L.; White, M. P.; Greicius, M. D.; Pascual-Leone, A. Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate. *Biological psychiatry (1969)* **2012**, *72* (7), 595-603. DOI: 10.1016/j.biopsych.2012.04.028.
(19) Li, S.-J.; Biswal, B.; Li, Z.; Risinger, R.; Rainey, C.; Cho, J.-K.; Salmeron, B. J.; Stein, E. A. Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI. *Magnetic resonance in medicine* **2000**, *43* (1), 45-51. DOI: 10.1002/(SICI)1522-2594(200001)43:1<45::AID-MRM6>3.0.CO;2-0.
(20) Cole, M. W.; Reynolds, J. R.; Power, J. D.; Repovs, G.; Anticevic, A.; Braver, T. S. Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature neuroscience* **2013**, *16* (9), 1348-1355. DOI: 10.1038/nn.3470.
(21) Vincent, J. L.; Kahn, I.; Snyder, A. Z.; Raichle, M. E.; Buckner, R. L. Evidence for a Frontoparietal Control System Revealed by Intrinsic Functional Connectivity. *Journal of neurophysiology* **2008**, *100* (6), 3328-3342. DOI: 10.1152/jn.90355.2008.
(22) Ko, J. H.; Tang, C. C.; Eidelberg, D. Brain stimulation and functional imaging with fMRI and PET. *Handb Clin Neurol* **2013**, *116*, 77-95. DOI: 10.1016/b978-0-444-53497-2.00008-5 From NLM.
(23) Keeser, D.; Meindl, T.; Bor, J.; Palm, U.; Pogarell, O.; Mulert, C.; Brunelin, J.; Möller, H.-J.; Reiser, M.; Padberg, F. Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI. *The Journal of neuroscience* **2011**, *31* (43), 15284-15293. DOI: 10.1523/JNEUROSCI.0542-11.2011.
(24) Meinzer, M.; Antonenko, D.; Lindenberg, R.; Hetzer, S.; Ulm, L.; Avirame, K.; Flaisch, T.; Flöel, A. Electrical Brain Stimulation Improves Cognitive Performance by Modulating Functional Connectivity and Task-Specific Activation. *The Journal of neuroscience* **2012**, *32* (5), 1859-1866. DOI: 10.1523/JNEUROSCI.4812-11.2012.
(25) Datta, A. M. S.; Bansal, V. B. S.; Diaz, J. B. S.; Patel, J. M. S.; Reato, D. M. S.; Bikson, M. P. Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain stimulation* **2009**, *2* (4), 201-207.e201. DOI: 10.1016/j.brs.2009.03.005.
(26) Edwards, D.; Cortes, M.; Datta, A.; Minhas, P.; Wassermann, E. M.; Bikson, M. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: A basis for high-definition tDCS. *NeuroImage (Orlando, Fla.)* **2013**, *74*, 266-275. DOI: 10.1016/j.neuroimage.2013.01.042.
(27) Dedoncker, J.; Brunoni, A. R.; Baeken, C.; Vanderhasselt, M.-A. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain stimulation* **2016**, *9* (4), 501-517. DOI: 10.1016/j.brs.2016.04.006.
(28) Sehm, B.; Kipping, J.; Schäfer, A.; Villringer, A.; Ragert, P. A Comparison between Uni- and Bilateral tDCS Effects on Functional Connectivity of the Human Motor Cortex. *Frontiers in human neuroscience* **2013**, *7*, 183-183. DOI: 10.3389/fnhum.2013.00183.
(29) Miranda, P. C.; Mekonnen, A.; Salvador, R.; Ruffini, G. The electric field in the cortex during transcranial current stimulation. *NeuroImage (Orlando, Fla.)* **2013**, *70*, 48-58. DOI: 10.1016/j.neuroimage.2012.12.034.
(30) Van Overwalle, F.; Manto, M.; Leggio, M.; Delgado-García, J. M. The sequencing process generated by the cerebellum crucially contributes to social interactions. *Medical hypotheses* **2019**, *128*, 33-42. DOI: 10.1016/j.mehy.2019.05.014.
(31) Parent, A. Giovanni Aldini: From Animal Electricity to Human Brain Stimulation. *Canadian journal of neurological sciences* **2004**, *31* (4), 576-584. DOI: 10.1017/S0317167100003851.

(32) Ormerod, W. Richard Caton (1842–1926): pioneer electrophysiologist and cardiologist. *Journal of medical biography* **2006**, *14* (1), 30-35. DOI: 10.1258/j.jmb.2006.04-22.
(33) Fregni, F.; Boggio, P. S.; Nitsche, M.; Bermpohl, F.; Antal, A.; Feredoes, E.; Marcolin, M. A.; Rigonatti, S. P.; Silva, M. T. A.; Paulus, W.; et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental brain research* **2005**, *166* (1), 23-30. DOI: 10.1007/s00221-005-2334-6.
(34) Marom, B.; Ana, G.-Á.; Abhishek, D.; Bernadette, G.; Morten Goertz, J.; Sungjin, K.; Jinuk, K.; Adam, K.; Kiwon, L.; Timothy, M.; et al. Limited output transcranial electrical stimulation 2023 (LOTES-2023): Updates on engineering principles, regulatory statutes, and industry standards for wellness, over-the-counter, or prescription devices with low risk Limited output transcranial electrical stimulation 2023 (LOTES-2023): Updates on engineering principles, regulatory statutes, and industry standards for wellness, over-the-counter, or prescription devices with low risk. *Brain stimulation* **2023**, *16* (3), 840-853.
(35) Soterix Medical Launches PainX tDCS Treatment in Canada with Health Canada Approval. *Health & Medicine Week* **2016**, 4506.
(36) Kennedy, S. H.; Lam, R. W.; McIntyre, R. S.; Tourjman, S. V.; Bhat, V.; Blier, P.; Hasnain, M.; Jollant, F.; Levitt, A. J.; MacQueen, G. M.; et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Canadian journal of psychiatry* **2016**, *61* (9), 540-560. DOI: 10.1177/0706743716659417.
(37) Wen, Y.-R.; Shi, J.; Hu, Z.-Y.; Lin, Y.-Y.; Lin, Y.-T.; Jiang, X.; Wang, R.; Wang, X.-Q.; Wang, Y.-L. Is transcranial direct current stimulation beneficial for treating pain, depression, and anxiety symptoms in patients with chronic pain? A systematic review and meta-analysis. *Frontiers in molecular neuroscience* **2022**, *15*, 1056966. DOI: 10.3389/fnmol.2022.1056966.
(38) Brunoni, A. R.; Valiengo, L.; Baccaro, A.; Zanão, T. A.; de Oliveira, J. F.; Goulart, A.; Boggio, P. S.; Lotufo, P. A.; Benseñor, I. M.; Fregni, F. The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study: Results From a Factorial, Randomized, Controlled Trial. *JAMA psychiatry (Chicago, Ill.)* **2013**, *70* (4), 383-391. DOI: 10.1001/2013.jamapsychiatry.32.
(39) Hummel, F.; Celnik, P.; Giraux, P.; Floel, A.; Wu, W.-H.; Gerloff, C.; Cohen, L. G. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain (London, England : 1878)* **2005**, *128* (3), 490-499. DOI: 10.1093/brain/awh369.
(40) Philiastides, Marios G.; Auksztulewicz, R.; Heekeren, Hauke R.; Blankenburg, F. Causal Role of Dorsolateral Prefrontal Cortex in Human Perceptual Decision Making. *Current biology* **2011**, *21* (11), 980-983. DOI: 10.1016/j.cub.2011.04.034.
(41) Talsma, L. J.; Kroese, H. A.; Slagter, H. A. Boosting Cognition: Effects of Multiple-Session Transcranial Direct Current Stimulation on Working Memory. *Journal of cognitive neuroscience* **2017**, *29* (4), 755-768. DOI: 10.1162/jocn_a_01077.
(42) Shahani, B.; Russell, W. R. Motor neurone disease. An abnormality of nerve metabolism. *Journal of neurology, neurosurgery and psychiatry* **1969**, *32* (1), 1-5. DOI: 10.1136/jnnp.32.1.1.
(43) Stengel, C.; Sanches, C.; Toba, M. N.; Valero-Cabré, A. Things you wanted to know (but might have been afraid to ask) about how and why to explore and modulate brain plasticity with non-invasive neurostimulation technologies. *Revue neurologique* **2022**, *178* (8), 826-844. DOI: 10.1016/j.neurol.2021.12.014.
(44) Koenigs, M.; Grafman, J. The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural brain research* **2009**, *201* (2), 239-243. DOI: 10.1016/j.bbr.2009.03.004.
(45) Cotelli, M.; Manenti, R.; Brambilla, M.; Petesi, M.; Rosini, S.; Ferrari, C.; Zanetti, O.; Miniussi, C. Anodal tDCS during face-name associations memory training in Alzheimer's patients. *Frontiers in aging neuroscience* **2014**, *6*, 38-38. DOI: 10.3389/fnagi.2014.00038.

(46) Tremblay, S.; Lepage, J.-F.; Latulipe-Loiselle, A.; Fregni, F.; Pascual-Leone, A.; Théoret, H. The Uncertain Outcome of Prefrontal tDCS. *Brain stimulation* **2014**, *7* (6), 773-783. DOI: 10.1016/j.brs.2014.10.003.
(47) Fregni, F.; Boggio, P. S.; Nitsche, M. A.; Marcolin, M. A.; Rigonatti, S. P.; Pascual-Leone, A. Treatment of major depression with transcranial direct current stimulation. *Bipolar disorders* **2006**, *8* (2), 203-204. DOI: 10.1111/j.1399-5618.2006.00291.x.
(48) Brunoni, A. R.; Vanderhasselt, M.-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and cognition* **2014**, *86*, 1-9. DOI: 10.1016/j.bandc.2014.01.008.
(49) Li, L. M.; Uehara, K.; Hanakawa, T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in cellular neuroscience* **2015**, *9*, 181-181. DOI: 10.3389/fncel.2015.00181.
(50) Dmochowski, J. P.; Datta, A.; Huang, Y.; Richardson, J. D.; Bikson, M.; Fridriksson, J.; Parra, L. C. Targeted transcranial direct current stimulation for rehabilitation after stroke. *NeuroImage (Orlando, Fla.)* **2013**, *75*, 12-19. DOI: 10.1016/j.neuroimage.2013.02.049.
(51) Kuo, H.-I.; Bikson, M.; Datta, A.; Minhas, P.; Paulus, W.; Kuo, M.-F.; Nitsche, M. A. Comparing Cortical Plasticity Induced by Conventional and High-Definition 4 × 1 Ring tDCS: A Neurophysiological Study. *Brain stimulation* **2013**, *6* (4), 644-648. DOI: 10.1016/j.brs.2012.09.010.
(52) Villamar, M. F.; Volz, M. S.; Bikson, M.; Datta, A.; DaSilva, A. F.; Fregni, F. Technique and Considerations in the Use of 4x1 Ring High-definition Transcranial Direct Current Stimulation (HD-tDCS). *Journal of visualized experiments* **2013**, (77), e50309-e50309. DOI: 10.3791/50309.
(53) Aparício, L. V. M.; Guarienti, F.; Razza, L. B.; Carvalho, A. F.; Fregni, F.; Brunoni, A. R. A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials. *Brain stimulation* **2016**, *9* (5), 671-681. DOI: 10.1016/j.brs.2016.05.004.
(54) Gbadeyan, O.; Steinhauser, M.; McMahon, K.; Meinzer, M. Safety, Tolerability, Blinding Efficacy and Behavioural Effects of a Novel MRI-Compatible, High-Definition tDCS Set-Up. *Brain stimulation* **2016**, *9* (4), 545-552. DOI: 10.1016/j.brs.2016.03.018.
(55) Pascual-Leone, A.; Shafi, M. Brain Stimulation Techniques and Network Studies of Brain Function. Vol. 1; 2012; pp 100-123.
(56) Vidorreta, M.; Wang, Z.; Rodríguez, I.; Pastor, M. A.; Detre, J. A.; Fernández-Seara, M. A. Comparison of 2D and 3D single-shot ASL perfusion fMRI sequences. *NeuroImage (Orlando, Fla.)* **2013**, *66*, 662-671. DOI: 10.1016/j.neuroimage.2012.10.087.
(57) Stagg, C. J.; Bachtiar, V.; Amadi, U.; Gudberg, C. A.; Ilie, A. S.; Sampaio-Baptista, C.; O'Shea, J.; Woolrich, M.; Smith, S. M.; Filippini, N.; et al. Local GABA concentration is related to network-level resting functional connectivity. *eLife* **2014**, *3*, e01465-e01465. DOI: 10.7554/eLife.01465.
(58) Zheng, X.; Alsop, D. C.; Schlaug, G. Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. *NeuroImage (Orlando, Fla.)* **2011**, *58* (1), 26-33. DOI: 10.1016/j.neuroimage.2011.06.018.
(59) Badre, D.; D'Esposito, M. Is the rostro-caudal axis of the frontal lobe hierarchical? *Nature reviews. Neuroscience* **2009**, *10* (9), 659-669. DOI: 10.1038/nrn2667.
(60) Dosenbach, N. U. F.; Fair, D. A.; Cohen, A. L.; Schlaggar, B. L.; Petersen, S. E. A dual-networks architecture of top-down control. *Trends in cognitive sciences* **2008**, *12* (3), 99-105. DOI: 10.1016/j.tics.2008.01.001.
(61) Menon, V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in cognitive sciences* **2011**, *15* (10), 483-506. DOI: 10.1016/j.tics.2011.08.003.
(62) Liston, C.; Chen, A. C.; Zebley, B. D.; Drysdale, A. T.; Gordon, R.; Leuchter, B.; Voss, H. U.; Casey, B. J.; Etkin, A.; Dubin, M. J. Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression. *Biological psychiatry (1969)* **2014**, *76* (7), 517-526. DOI: 10.1016/j.biopsych.2014.01.023.

(63) Minzenberg, M. J.; Laird, A. R.; Thelen, S.; Carter, C. S.; Glahn, D. C. Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia. *Archives of general psychiatry* **2009**, *66* (8), 811-822. DOI: 10.1001/archgenpsychiatry.2009.91.
(64) Cortese, S.; Kelly, C.; Chabernaud, C.; Proal, E.; Di Martino, A.; Milham, M. P.; Castellanos, F. X. Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies. *The American journal of psychiatry* **2012**, *169* (10), 1038-1055. DOI: 10.1176/appi.ajp.2012.11101521.
(65) George, M. S.; Wassermann, E. M.; Williams, W. A.; Callahan, A.; Ketter, T. A.; Basser, P.; Hallett, M.; Post, R. M. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* **1995**, *6* (14), 1853-1856. DOI: 10.1097/00001756-199510020-00008.
(66) Luber, B.; Lisanby, S. H. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *NeuroImage (Orlando, Fla.)* **2014**, *85* (3), 961-970. DOI: 10.1016/j.neuroimage.2013.06.007.
(67) Kuo, M.-F.; Paulus, W.; Nitsche, M. A. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *NeuroImage (Orlando, Fla.)* **2014**, *85*, 948-960. DOI: 10.1016/j.neuroimage.2013.05.117.
(68) Bolognini, N.; Rossetti, A.; Casati, C.; Mancini, F.; Vallar, G. Neuromodulation of multisensory perception: A tDCS study of the sound-induced flash illusion. *Neuropsychologia* **2011**, *49* (2), 231-237. DOI: 10.1016/j.neuropsychologia.2010.11.015.
(69) Leung, A.; Metzger-Smith, V.; He, Y.; Cordero, J.; Ehlert, B.; Song, D.; Lin, L.; Shahrokh, G.; Tsai, A.; Vaninetti, M.; et al. Left Dorsolateral Prefrontal Cortex rTMS in Alleviating MTBI Related Headaches and Depressive Symptoms. *Neuromodulation (Malden, Mass.)* **2018**, *21* (4), 390-401. DOI: 10.1111/ner.12615.
(70) Berryhill, M. E.; Jones, K. T. tDCS selectively improves working memory in older adults with more education. *Neuroscience letters* **2012**, *521* (2), 148-151. DOI: 10.1016/j.neulet.2012.05.074.
(71) Petrides, M.; Pandya, D. N. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *The European journal of neuroscience* **1999**, *11* (3), 1011-1036. DOI: 10.1046/j.1460-9568.1999.00518.x.
(72) Miller, E. K.; Cohen, J. D. An Integrative Theory of Prefrontal Cortex Function. *Annual review of neuroscience* **2001**, *24* (1), 167-202. DOI: 10.1146/annurev.neuro.24.1.167.
(73) Barbey, A. K.; Koenigs, M.; Grafman, J. Dorsolateral prefrontal contributions to human working memory. *Cortex* **2013**, *49* (5), 1195-1205. DOI: 10.1016/j.cortex.2012.05.022.
(74) Ochsner, K. N.; Gross, J. J. The cognitive control of emotion. *Trends in cognitive sciences* **2005**, *9* (5), 242-249. DOI: 10.1016/j.tics.2005.03.010.
(75) D'Esposito, M.; Detre, J. A.; Alsop, D. C.; Shin, R. K.; Atlas, S.; Grossman, M. The neural basis of the central executive system of working memory. *Nature (London)* **1995**, *378* (6554), 279-281. DOI: 10.1038/378279a0.
(76) MacDonald, A. W.; Cohen, J. D.; Stenger, V. A.; Carter, C. S. Dissociating the Role of the Dorsolateral Prefrontal and Anterior Cingulate Cortex in Cognitive Control. *Science (American Association for the Advancement of Science)* **2000**, *288* (5472), 1835-1838. DOI: 10.1126/science.288.5472.1835.
(77) Braver, T. S.; Cohen, J. D.; Nystrom, L. E.; Jonides, J.; Smith, E. E.; Noll, D. C. A Parametric Study of Prefrontal Cortex Involvement in Human Working Memory. *NeuroImage (Orlando, Fla.)* **1997**, *5* (1), 49-62. DOI: 10.1006/nimg.1996.0247.
(78) Ochsner, K. N.; Bunge, S. A.; Gross, J. J.; Gabrieli, J. D. E. Rethinking Feelings: An fMRI Study of the Cognitive Regulation of Emotion. *Journal of cognitive neuroscience* **2002**, *14* (8), 1215-1229. DOI: 10.1162/089892902760807212.
(79) Garavan, H.; Ross, T. J.; Kaufman, J.; Stein, E. A. A midline dissociation between error-processing and response-conflict monitoring. *NeuroImage (Orlando, Fla.)* **2003**, *20* (2), 1132-1139. DOI: 10.1016/S1053-8119(03)00334-3.
(80) Aron, A. R.; Robbins, T. W.; Poldrack, R. A. Inhibition and the right inferior frontal cortex. *Trends in cognitive sciences* **2004**, *8* (4), 170-177. DOI: 10.1016/j.tics.2004.02.010.

(81) Goel, V.; Dolan, R. J. Explaining modulation of reasoning by belief. *Cognition* **2003**, *87* (1), B11-B22. DOI: 10.1016/S0010-0277(02)00185-3.
(82) Wagner, A. D.; Maril, A.; Bjork, R. A.; Schacter, D. L. Prefrontal Contributions to Executive Control: fMRI Evidence for Functional Distinctions within Lateral Prefrontal Cortex. *NeuroImage (Orlando, Fla.)* **2001**, *14* (6), 1337-1347. DOI: 10.1006/nimg.2001.0936.
(83) Cabeza, R.; Nyberg, L. Imaging Cognition II: An Empirical Review of 275 PET and fMRI Studies. *Journal of cognitive neuroscience* **2000**, *12* (1), 1-47. DOI: 10.1162/08989290051137585.
(84) Grimm, S.; Boesiger, P.; Beck, J.; Schuepbach, D.; Bermpohl, F.; Walter, M.; Ernst, J.; Hell, D.; Boeker, H.; Northoff, G. Altered Negative BOLD Responses in the Default-Mode Network during Emotion Processing in Depressed Subjects. *Neuropsychopharmacology (New York, N.Y.)* **2009**, *34* (4), 932-943. DOI: 10.1038/npp.2008.81.
(85) Nitschke, J. B.; Heller, W.; Palmieri, P. A.; Miller, G. A. Contrasting patterns of brain activity in anxious apprehension and anxious arousal. *Psychophysiology* **1999**, *36* (5), 628-637. DOI: 10.1111/1469-8986.3650628.
(86) Fitzgerald, P. B.; Laird, A. R.; Maller, J.; Daskalakis, Z. J. A meta-analytic study of changes in brain activation in depression. *Human brain mapping* **2008**, *29* (6), 683-695. DOI: 10.1002/hbm.20426.
(87) Lefaucheur, J.-P.; Aleman, A.; Baeken, C.; Benninger, D. H.; Brunelin, J.; Di Lazzaro, V.; Filipović, S. R.; Grefkes, C.; Hasan, A.; Hummel, F. C.; et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical neurophysiology* **2020**, *131* (2), 474-528. DOI: 10.1016/j.clinph.2019.11.002.
(88) Johnstone, T.; van Reekum, C. M.; Urry, H. L.; Kalin, N. H.; Davidson, R. J. Failure to Regulate: Counterproductive Recruitment of Top-Down Prefrontal-Subcortical Circuitry in Major Depression. *The Journal of neuroscience* **2007**, *27* (33), 8877-8884. DOI: 10.1523/JNEUROSCI.2063-07.2007.
(89) Shamay-Tsoory, S. G.; Aharon-Peretz, J.; Perry, D. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain (London, England : 1878)* **2009**, *132* (3), 617-627. DOI: 10.1093/brain/awn279.
(90) Gogtay, N.; Giedd, J. N.; Lusk, L.; Hayashi, K. M.; Greenstein, D.; Vaituzis, A. C.; Nugent, T. F.; Herman, D. H.; Clasen, L. S.; Toga, A. W.; et al. Dynamic Mapping of Human Cortical Development during Childhood through Early Adulthood. *Proceedings of the National Academy of Sciences - PNAS* **2004**, *101* (21), 8174-8179. DOI: 10.1073/pnas.0402680101.
(91) Fjell, A. M.; Walhovd, K. B. Sleep Patterns and Human Brain Health. *The Neuroscientist (Baltimore, Md.)* **2025**, 10738584241309850. DOI: 10.1177/10738584241309850.
(92) Mayberg, H. S.; Silva, J. A.; Brannan, S. K.; Tekell, J. L.; Mahurin, R. K.; McGinnis, S.; Jerabek, P. A. The Functional Neuroanatomy of the Placebo Effect. *The American journal of psychiatry* **2002**, *159* (5), 728-737. DOI: 10.1176/appi.ajp.159.5.728.
(93) Rubia, K.; Smith, A. B.; Taylor, E.; Brammer, M. Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. *Human brain mapping* **2007**, *28* (11), 1163-1177. DOI: 10.1002/hbm.20347.
(94) Phillips, M. L.; Travis, M. J.; Fagiolini, A.; Kupfer, D. J. Medication Effects in Neuroimaging Studies of Bipolar Disorder. *The American journal of psychiatry* **2008**, *165* (3), 313-320. DOI: 10.1176/appi.ajp.2007.07071066.
(95) Passingham, R. E. The frontal lobes D. T. Stuss and D. F. Benson. Raven press, New York (1986). 303 pp. US $65.50. *Neuroscience* **1987**, *21* (2), 663-663. DOI: 10.1016/0306-4522(87)90155-2.
(96) Funahashi, S.; Bruce, C. J.; Goldman-Rakic, P. S. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of neurophysiology* **1989**, *61* (2), 331-349. DOI: 10.1152/jn.1989.61.2.331.
(97) Huber, L.; Handwerker, D. A.; Jangraw, D. C.; Chen, G.; Hall, A.; Stüber, C.; Gonzalez-Castillo, J.; Ivanov, D.; Marrett, S.; Guidi, M.; et al. High-Resolution CBV-fMRI Allows Mapping of Laminar

Activity and Connectivity of Cortical Input and Output in Human M1. *Neuron (Cambridge, Mass.)* **2017**, *96* (6), 1253-1263.e1257. DOI: 10.1016/j.neuron.2017.11.005.
(98) Basten, U.; Hilger, K.; Fiebach, C. J. Where smart brains are different: A quantitative meta-analysis of functional and structural brain imaging studies on intelligence. *Intelligence (Norwood)* **2015**, *51*, 10-27. DOI: 10.1016/j.intell.2015.04.009.
(99) Klingberg, T. Training and plasticity of working memory. *Trends in cognitive sciences* **2010**, *14* (7), 317-324. DOI: 10.1016/j.tics.2010.05.002.
(100) Nee, D. E.; Wager, T. D.; Jonides, J. Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cognitive, affective, & behavioral neuroscience* **2007**, *7* (1), 1-17. DOI: 10.3758/CABN.7.1.1.
(101) Power, Jonathan D.; Cohen, Alexander L.; Nelson, Steven M.; Wig, Gagan S.; Barnes, Kelly A.; Church, Jessica A.; Vogel, Alecia C.; Laumann, Timothy O.; Miezin, Fran M.; Schlaggar, Bradley L.; et al. Functional Network Organization of the Human Brain. *Neuron (Cambridge, Mass.)* **2011**, *72* (4), 665-678. DOI: 10.1016/j.neuron.2011.09.006.
(102) Compte, A.; Brunel, N.; Goldman-Rakic, P. S.; Wang, X.-J. Synaptic Mechanisms and Network Dynamics Underlying Spatial Working Memory in a Cortical Network Model. *Cerebral cortex (New York, N.Y. 1991)* **2000**, *10* (9), 910-923. DOI: 10.1093/cercor/10.9.910.
(103) Siegle, G. J.; Thompson, W.; Carter, C. S.; Steinhauer, S. R.; Thase, M. E. Increased Amygdala and Decreased Dorsolateral Prefrontal BOLD Responses in Unipolar Depression: Related and Independent Features. *Biological psychiatry (1969)* **2007**, *61* (2), 198-209. DOI: 10.1016/j.biopsych.2006.05.048.
(104) Sharp, D. J.; Scott, G.; Leech, R. Network dysfunction after traumatic brain injury. *Nature reviews. Neurology* **2014**, *10* (3), 156-166. DOI: 10.1038/nrneurol.2014.15.
(105) Fregni, F.; Boggio, P. S.; Nitsche, M. A.; Rigonatti, S. P.; Pascual-Leone, A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. *Depression and anxiety* **2006**, *23* (8), 482-484. DOI: 10.1002/da.20201.
(106) Smith, E. E.; Jonides, J.; Marshuetz, C.; Koeppe, R. A. Components of Verbal Working Memory: Evidence from Neuroimaging. *Proceedings of the National Academy of Sciences - PNAS* **1998**, *95* (3), 876-882. DOI: 10.1073/pnas.95.3.876.
(107) Woods, A. J.; Antal, A.; Bikson, M.; Boggio, P. S.; Brunoni, A. R.; Celnik, P.; Cohen, L. G.; Fregni, F.; Herrmann, C. S.; Kappenman, E. S.; et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical neurophysiology* **2016**, *127* (2), 1031-1048. DOI: 10.1016/j.clinph.2015.11.012.
(108) Fregni, F.; Pascual-Leone, A. Technology Insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. *Nature clinical practice. Neurology* **2007**, *3* (7), 383-393. DOI: 10.1038/ncpneuro0530.
(109) Cappelletti, M.; Lee, H. L.; Freeman, E. D.; Price, C. J. The Role of Right and Left Parietal Lobes in the Conceptual Processing of Numbers. *Journal of cognitive neuroscience* **2010**, *22* (2), 331-346. DOI: 10.1162/jocn.2009.21246.
(110) Heimrath, K.; Sandmann, P.; Becke, A.; Müller, N. G.; Zaehle, T. Behavioral and Electrophysiological Effects of Transcranial Direct Current Stimulation of the Parietal Cortex in a Visuo-Spatial Working Memory Task. *Frontiers in psychiatry* **2012**, *3*, 56-56. DOI: 10.3389/fpsyt.2012.00056.
(111) Turkeltaub, P. E.; Benson, J.; Hamilton, R. H.; Datta, A.; Bikson, M.; Coslett, H. B. Left lateralizing transcranial direct current stimulation improves reading efficiency. *Brain stimulation* **2012**, *5* (3), 201-207. DOI: 10.1016/j.brs.2011.04.002.
(112) Bolognini, N.; Olgiati, E.; Rossetti, A.; Maravita, A. Enhancing multisensory spatial orienting by brain polarization of the parietal cortex. *The European journal of neuroscience* **2010**, *31* (10), 1800-1806. DOI: 10.1111/j.1460-9568.2010.07211.x.

(113) Dae-Hyouk, B.; Soon-Young, B. Effect of combination of transcranial direct current stimulation and feedback training on visuospatial neglect in patients with subacute stroke : a pilot randomized controlled trial. *Journal of Physical Therapy Science* **2015**, *27* (9), 2759-2761.
(114) Rosso, C.; Valabregue, R.; Arbizu, C.; Ferrieux, S.; Vargas, P.; Humbert, F.; Attal, Y.; Messé, A.; Zavanone, C.; Meunier, S.; et al. Connectivity between Right Inferior Frontal Gyrus and Supplementary Motor Area Predicts After-Effects of Right Frontal Cathodal tDCS on Picture Naming Speed. *Brain stimulation* **2014**, *7* (1), 122-129. DOI: 10.1016/j.brs.2013.08.007.
(115) Detre, J. A.; Rao, H.; Wang, D. J. J.; Chen, Y. F.; Wang, Z. Applications of arterial spin labeled MRI in the brain. *Journal of magnetic resonance imaging* **2012**, *35* (5), 1026-1037. DOI: 10.1002/jmri.23581.
(116) Stagg, C. J.; Lin, R. L.; Mezue, M.; Segerdahl, A.; Kong, Y.; Xie, J.; Tracey, I. Widespread Modulation of Cerebral Perfusion Induced during and after Transcranial Direct Current Stimulation Applied to the Left Dorsolateral Prefrontal Cortex. *The Journal of neuroscience* **2013**, *33* (28), 11425-11431. DOI: 10.1523/JNEUROSCI.3887-12.2013.
(117) Jamil, A.; Batsikadze, G.; Kuo, H. I.; Meesen, R. L. J.; Dechent, P.; Paulus, W.; Nitsche, M. A. Current intensity- and polarity-specific online and aftereffects of transcranial direct current stimulation: An fMRI study. *Human brain mapping* **2020**, *41* (6), 1644-1666. DOI: 10.1002/hbm.24901.
(118) Peña-Gómez, C.; Sala-Lonch, R.; Junqué, C.; Clemente, I. C.; Vidal, D.; Bargalló, N.; Falcón, C.; Valls-Solé, J.; Pascual-Leone, Á.; Bartrés-Faz, D. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. *Brain stimulation* **2012**, *5* (3), 252-263. DOI: 10.1016/j.brs.2011.08.006.
(119) Meinzer, M.; Lindenberg, R.; Antonenko, D.; Flaisch, T.; Floel, A. Anodal Transcranial Direct Current Stimulation Temporarily Reverses Age-Associated Cognitive Decline and Functional Brain Activity Changes. *The Journal of neuroscience* **2013**, *33* (30), 12470-12478. DOI: 10.1523/JNEUROSCI.5743-12.2013.
(120) Carther-Krone, T.; McAllister, Z. A.; Choi, E. H.; Ryner, L.; Ko, J. H. Asymmetric Modulation of Brain Connectivity by Anodal Transcranial Direct Current Stimulation in Healthy Individuals: A Single-Blind, Randomized Sham-Controlled Trial. *Human brain mapping* **2025**, *46* (7), e70218-n/a. DOI: 10.1002/hbm.70218.
(121) Badre, D.; Wagner, A. D. Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* **2007**, *45* (13), 2883-2901. DOI: 10.1016/j.neuropsychologia.2007.06.015.
(122) Ibarra, S. Automated Neuropsychological Assessment Metrics. Springer International Publishing, pp 444-447.
(123) Brown, K. W.; Ryan, R. M. The Benefits of Being Present: Mindfulness and Its Role in Psychological Well-Being. *Journal of personality and social psychology* **2003**, *84* (4), 822-848. DOI: 10.1037/0022-3514.84.4.822.
(124) Jones, W. P.; Loe, S. A.; Krach, S. K.; Rager, R. Y.; Jones, H. M. Automated Neuropsychological Assessment Metrics (Anam) and Woodcock-Johnson III Tests of Cognitive Ability: A Concurrent Validity Study. *Clinical neuropsychologist* **2008**, *22* (2), 305-320. DOI: 10.1080/13854040701281483.
(125) Cieslik, E. C.; Mueller, V. I.; Eickhoff, C. R.; Langner, R.; Eickhoff, S. B. Three key regions for supervisory attentional control: Evidence from neuroimaging meta-analyses. *Neuroscience and biobehavioral reviews* **2015**, *48*, 22-34. DOI: 10.1016/j.neubiorev.2014.11.003.
(126) Whitfield-Gabrieli, S.; Nieto-Castanon, A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect* **2012**, *2* (3), 125-141. DOI: 10.1089/brain.2012.0073 From NLM.
(127) Li, L. M.; Violante, I. R.; Leech, R.; Ross, E.; Hampshire, A.; Opitz, A.; Rothwell, J. C.; Carmichael, D. W.; Sharp, D. J. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Human brain mapping* **2019**, *40* (3), 904-915. DOI: 10.1002/hbm.24420.
(128) Horvath, J. C.; Forte, J. D.; Carter, O. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in

healthy human subjects: A systematic review. *Neuropsychologia* **2015**, *66*, 213-236. DOI: 10.1016/j.neuropsychologia.2014.11.021.
(129) Pascual-Leone, A.; Walsh, V.; Rothwell, J. Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity. In *Curr Opin Neurobiol*, Elsevier Ltd: England, 2000; Vol. 10, pp 232-237.
(130) Schmahmann, J. D. The cerebellum and cognition. *Neuroscience letters* **2019**, *688*, 62-75. DOI: 10.1016/j.neulet.2018.07.005.
(131) Stoodley, C. J.; Schmahmann, J. D. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. *NeuroImage (Orlando, Fla.)* **2009**, *44* (2), 489-501. DOI: 10.1016/j.neuroimage.2008.08.039.
(132) Kelly, R. M.; Strick, P. L. Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a Nonhuman Primate. *The Journal of neuroscience* **2003**, *23* (23), 8432-8444. DOI: 10.1523/JNEUROSCI.23-23-08432.2003.
(133) Dambacher, F.; Schuhmann, T.; Lobbestael, J.; Arntz, A.; Brugman, S.; Sack, A. T. No Effects of Bilateral tDCS over Inferior Frontal Gyrus on Response Inhibition and Aggression. *PloS one* **2015**, *10* (7), e0132170-e0132170. DOI: 10.1371/journal.pone.0132170.
(134) Beckmann, C. F.; DeLuca, M.; Devlin, J. T.; Smith, S. M. Investigations into resting-state connectivity using independent component analysis. *Philosophical transactions of the Royal Society of London. Series B. Biological sciences* **2005**, *360* (1457), 1001-1013. DOI: 10.1098/rstb.2005.1634.
(135) Smith, S. M.; Fox, P. T.; Miller, K. L.; Glahn, D. C.; Fox, P. M.; Mackay, C. E.; Filippini, N.; Watkins, K. E.; Toro, R.; Laird, A. R.; et al. Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences - PNAS* **2009**, *106* (31), 13040-13045. DOI: 10.1073/pnas.0905267106.
(136) Horvath, J. C.; Forte, J. D.; Carter, O. Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain stimulation* **2015**, *8* (3), 535-550. DOI: 10.1016/j.brs.2015.01.400.
(137) Ha, M.; Park, S. H.; Park, I.; Kim, T.; Lee, J.; Kim, M.; Kwon, J. S. Aberrant cortico-thalamo-cerebellar network interactions and their association with impaired cognitive functioning in patients with schizophrenia. *Schizophrenia (Heidelberg, Germany)* **2023**, *9* (1), 50-50. DOI: 10.1038/s41537-023-00375-8.