

Investigation of Non-Invasive Brain Stimulation for Dementia:
Coordinate Systems, Sham Coils, and Cognitive Outcomes

By

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Abstract

Dementia in general and Alzheimer's disease (AD) in particular are among the most pressing health challenges associated with aging, with limited treatment options available. Non-invasive brain stimulation (NIBS), including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), and cognitive training (CT) has emerged as promising technologies to modulate neural networks and potentially stabilize cognitive decline. This thesis investigates NIBS techniques as potential interventions for dementia and AD and addresses methodological challenges in their application and evaluation.

First, a technical investigation into TMS coil positioning demonstrates that, even with neuronavigation, targeting accuracy can vary significantly in some participants; highlighting important considerations for reproducibility, interpretation of TMS studies, and clinical applications.

Second, the magnetic fields produced by a sham TMS coil were examined. This work demonstrated that sham coils can induce unintended electric fields in the brain, albeit off target, raising important considerations for study design and interpretation of TMS results.

Third, in a randomized, crossover, double-blind, sham-controlled clinical trial we investigated the effects of 40 Hz transcranial alternating current stimulation (tACS) combined with CT. Results demonstrated improvements in both cognitive performance and neuropsychiatric symptoms, supporting the therapeutic potential of gamma-tACS.

Finally, results from a longitudinal analysis evaluated the cognitive trajectories of participants with dementia who underwent multiple rounds of 4-week non-invasive interventions, including tES, TMS, and/or CT. The results revealed a slower rate of cognitive

decline compared to the expected trajectory in untreated AD, while longer no-treatment intervals were associated with greater post-treatment decline.

Together, these studies provide new evidence supporting the feasibility and potential efficacy of NIBS in dementia, while addressing key methodological and technical challenges. The findings contribute to the development of safer, more targeted, and more effective interventions to mitigate cognitive decline in dementia.

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Dedication

To my husband, my parents, my sister, and all my grandparents,
for the lifelong support and encouragement.

Contributions of Authors

This thesis is a “sandwich thesis” consisting of four individual manuscripts completed in collaboration with others. At the time of writing (November 2025), the manuscripts had the following status:

- M. A. Uehara, N. Jacobson, and Z. Moussavi, “How accurate are coordinate systems being used for transcranial magnetic stimulation?,” *Frontiers in Human Neuroscience*, vol. 18, Jan. 2024. <https://doi.org/10.3389/fnhum.2024.1342410> – [peer-reviewed journal; Chapter 2]
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- M. A. Uehara, S. Kalia, M. G. Campuzano, M. Jafari-Jozani, B. Lithgow and Z. Moussavi, “Cognitive and neuropsychiatric effects of 40 Hz tACS simultaneously with cognitive exercises for dementia: a randomized, crossover, double-blind, sham-controlled study,” *Medicina*, vol. 61, no. 4, p. 757, Apr. 2025. <https://doi.org/10.3390/medicina61040757> – [peer-reviewed journal; Chapter 4]
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Mrs. Maria Anabel Uehara was the main contributor and first author of all the manuscripts presented in this thesis. Mrs. Maria Anabel Uehara’s contribution to this work includes developing the research questions, designing the studies, writing or assisting with the

ethics documents, performing treatments, gathering data, conducting the analysis, writing the manuscripts, submitting the manuscripts and responding to reviewer's comments. Dr. Zahra Moussavi contributed to the conception, design, ethics documents, funding, and editing all the manuscripts. Dr. Sumeet Kalia contributed by providing statistical analysis feedback and editing the manuscripts presented in Chapter 4 and 5. Mrs. Mari Garcia Campuzano contributed to recruiting participants, collecting data, and editing the manuscripts presented in Chapter 4 and 5. Dr. Brian Lithgow contributed by editing the manuscripts presented in Chapter 3 and 4. Dr. Mohammad Jafari-Jozani contributed by providing statistical analysis feedback and editing the manuscript presented in Chapter 4. Dr. Natasha Jacobson contributed by editing the manuscript presented in Chapter 2. Dr. Elham Salimi contributed by running the COMSOL model and editing the manuscript presented in Chapter 3. Dr. Grant Rutherford contributed by editing the manuscript presented in Chapter 3.

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List of Abbreviations

AC	Anterior Commissure
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
APB	Abductor Pollicis Brevis Muscle
<i>B</i>	Magnetic Flux Density (vector variable)
CT	Cognitive Training
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
EEG	Electroencephalography
EMG	Electromyography
EVestG	Electrovestibulography
FDI	First Dorsal Interosseus Muscle
FEM	Finite Element Modeling
fMRI	Functional Magnetic Resonance Imaging
GUI	Graphical User Interface
LTD	Long-Term Depression
LTP	Long-Term Potentiation
M1	Primary Motor Cortex
MADRS	Montgomery-Åsberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSO	Maximum Stimulator Output
NIBS	Non-Invasive Brain Stimulation
NPI-Q	Neuropsychiatric Inventory Questionnaire
PC	Posterior Commissure
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
tES	Transcranial Electrical Stimulation
TMS	Transcranial Magnetic Stimulation
tRNS	Transcranial Random Noise Stimulation
WMS	Wechsler Memory Scale

Chapter 1: Introduction

1.1 Motivation

Dementia is a general term for a significant decline in cognitive function and daily functioning; it has several types including Alzheimer's disease (AD) and cerebral vascular disease being the most common. Globally, more than 55 million individuals live with dementia. In Canada alone, an estimated 771,939 people were living with dementia as of January 1, 2025 [1], [2]. Dementia not only imposes an economic burden, costing trillions of dollars annually worldwide, but it also puts an emotional and physical strain on patients, families, and caregivers. However, current pharmacological treatments provide only modest symptomatic relief and are associated with adverse effects [3]. With no known cure and an increasing ageing population, there is an urgent need to explore alternative or adjunctive interventions that may slow or stabilise cognitive decline.

Non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), and cognitive training (CT) have emerged as promising approaches to modulate neural circuits, promote plasticity and potentially influence disease progression [4]. Recent studies suggest that NIBS can target mechanisms impaired in dementia, such as disrupted neural activity, network connectivity, and oscillatory activity [5]. However, existing research is limited by the methodology, small sample sizes, and a lack of long-term data. This thesis is motivated by two main goals: (1) to refine and evaluate the methodological rigour of NIBS delivery (targeting accuracy and sham as a placebo) and (2) to investigate NIBS's therapeutic potential in dementia.

1.2 Dementia and Alzheimer's Disease

Dementia is a progressive neurodegenerative syndrome characterized by a decline in memory, reasoning, and other cognitive functions that interferes with activities of daily living [1]. It encompasses multiple disorders including Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. The clinical presentation of dementia depends on the underlying pathology and the brain regions affected, but memory impairment is often an early symptom. As the disease progresses, individuals experience deficits in executive functioning, visuospatial orientation, and language abilities, eventually leading to dependency for basic activities of daily living [6]. Neuropsychiatric symptoms such as depression, anxiety, agitation, apathy, aggression, and psychosis are also common [7].

Pathologically, AD is characterized by extracellular beta-amyloid plaques, intracellular tau neurofibrillary tangles, synaptic dysfunction, neuronal loss, oxidative stress, microglial activation, and a progressive decline in neural network integrity [8]. Structural neuroimaging studies show atrophy in the entorhinal cortex and hippocampus and, as AD progresses, atrophy spreads to the medial temporal lobe. Furthermore, functional imaging reveals hypometabolism or hypoperfusion in the temporoparietal, posterior cingulate, and precuneus regions [8], [9]. Importantly, the dorsolateral prefrontal cortex (DLPFC), is a hub for executive function and working memory. It also exhibits both structural and functional changes, including reduced connectivity with frontoparietal and hippocampal circuits [10], [11]. Current research on using electroencephalography (EEG) shows alterations in neuronal oscillatory activity, including reduced gamma-band power in the frontal region [12]. These changes may reflect impaired synchronization across cortical circuits. These network-level abnormalities provide a theoretical

basis for targeting regions like the DLPFC with brain stimulation to restore oscillatory activity and improve cognitive function.

Currently available pharmacological treatments, such as cholinesterase inhibitors and N-methyl-D-aspartic acid receptor antagonists memantine [13], [14], offer only modest symptomatic relief and do not alter disease progression. Recently approved monoclonal antibodies targeting amyloid, such as lecanemab, aim to reduce beta-amyloid burden but have shown limited cognitive efficacy and carry safety concerns, including brain swelling and bleeding [15]. With no known cure and a rapidly ageing population, there is an urgent need for alternative or adjunctive interventions that may slow or stabilise cognitive decline. Non-pharmacological treatments, including NIBS and CT, are promising approaches.

1.3 Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a NIBS technology that uses pulsed magnetic fields over a targeted region of the brain. Using Michael Faraday's principle of electromagnetic induction, TMS depolarizes the neurons of the cerebral cortex synchronously when delivered at a sufficient intensity [16], [17]. More specifically, a TMS coil generates a time-varying electromagnetic field of approximately 1 to 3 T by a fast discharge, within 1 ms through a fast discharge of current [18]. The magnetic field induces an electric current in cortical tissue, resulting in localized neuronal depolarization.

The geometry of the TMS coil determines both the focality and depth of the induced electric field (Figure 1-1). One of the most widely used coil configuration is the figure-eight coil because it generates a more focused magnetic field at the intersection of the two loops [19], [20]. The penetration depth of the magnetic field for these coils is approximately 1.5 to 2 cm deep from the scalp with a stimulation focus area of approximately 2 to 4 cm² [18], [19]. The strength

of the magnetic field decreases exponentially with distance from the coil surface [21], allowing surface neurons to be strongly activated while deeper regions experience weaker modulation. Although the stimulation is considered focal, targeting a specific cortical region, secondary effects may occur in connected brain networks through transsynaptic propagation. For example, stimulation of the dorsolateral prefrontal cortex may modulate activity in the anterior cingulate cortex, a relationship supported by functional connectivity findings [22].

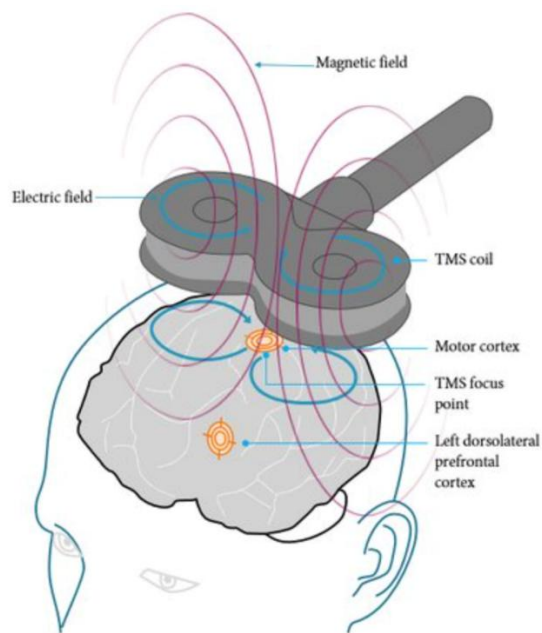


Figure 1-1. A figure-eight TMS coil positioned over the scalp, generating a magnetic field that induces an electric field in the underlying cortex, resulting in a focal stimulation point [23].

Since its introduction in 1985, TMS has evolved from a neurophysiological tool to a clinically approved therapeutic modality [24]. Repetitive TMS (rTMS) involves delivering trains of pulses at specific frequencies to induce lasting changes in cortical excitability. Health Canada has approved rTMS for the treatment of major depressive disorder [25], obsessive-compulsive disorder [26], and smoking cessation [27]. Beyond psychiatry, TMS is actively being explored in neurological conditions such as stroke rehabilitation, chronic pain, Parkinson's disease, and AD.

In the context of dementia, rTMS offers an appealing therapeutic approach due to its ability to modulate cortical excitability, restore disrupted oscillatory activity, and strengthen connectivity in regions affected by neurodegeneration.

Building on these therapeutic applications, our research group has contributed to this field through a large multi-site clinical trial investigating rTMS for cognitive decline in AD [28]. In this study, 156 participants with mild to moderate AD were enrolled across three sites and randomized into two active treatment groups (2 weeks or 4 weeks of rTMS) and one sham group [29]. Stimulation targeted the bilateral DLPFC using neuronavigation with Talairach coordinates ($x = \pm 50$, $y = 30$, $z = 36$) [30]. Results showed significant cognitive improvement across all groups immediately post-intervention and up to two months after, but no difference between active and sham groups was seen at post-intervention and up to six-month follow-up [29]. This unexpected finding raised critical methodological questions on: (1) the precision of targeting protocols, and (2) the validity of sham coils, which may induce weak electric fields capable of neuromodulation. These issues directly motivated Chapters 2 and 3 of this thesis, which systematically evaluate targeting accuracy and sham coil validity.

1.3.1 Mechanisms of TMS

TMS modulates brain activity through electromagnetic induction, with the primary biophysical mechanism being the induction of action potentials through depolarization of myelinated axons, particularly at axonal terminations and bends [31]. However, the downstream neurophysiological, neurochemical, and vascular effects of TMS are complex and depend on stimulation parameters, cortical state, and network organization.

When a TMS pulse is delivered, it induces an electric field that preferentially activates pyramidal neurons aligned tangentially to the cortical surface [32]. Single-pulse TMS generates

transient excitatory postsynaptic potentials measurable as motor-evoked potentials when targeting the motor cortex. In contrast, rTMS can induce long-lasting changes in cortical excitability through mechanisms analogous to long-term potentiation (LTP) and long-term depression (LTD). LTP refers to a sustained increase in synaptic strength following repeated stimulation, which enhances the efficiency of signal transmission between neurons [33]. Conversely, LTD is a long-lasting reduction in synaptic strength, weakening neuronal communication. Both processes are key mechanisms of synaptic plasticity underlying learning and memory [33].

High-frequency rTMS has been shown to induce LTP with calcium concentration increase in postsynaptic neuron and low-frequency rTMS has been shown to have LTD effects [34], [35]. LTP and LTD is dependent not only on frequency of rTMS, but also intensity and duration [36]. For example, one study showed that doubling the duration of rTMS pulses changed the effects from facilitating to inhibiting neuronal activity [37]. Another study showed that increasing the pulse intensity changed the effect from inhibitory effects to facilitating neuronal activity [38].

Beyond local synaptic changes, rTMS influences large-scale neural networks and oscillatory synchrony, which are critical to cognitive functioning and disrupted in dementia. Studies have shown that high-frequency rTMS not only increases cortical excitability but also functional connectivity and network efficiency between distant brain regions [39]. Importantly, stimulation effects spread from the site of coil placement into connected networks, meaning that inducing effects in one region can yield widespread changes in a network [40].

The DLPFC, a frequent rTMS target in both depression and dementia, serves as a critical area of the executive control network and maintains strong functional connectivity with the

hippocampus, posterior cingulate cortex, and default mode network (DMN) [41]. The DMN is a brain network of interconnected brain regions typically active during internally directed cognitive processes such as self-reflection, mind wandering, and recalling personal experiences [42]. Stimulating the DLPFC, therefore, offers a means of modulating distributed neural systems involved in attention and working memory. In AD, the disruption of brain networks, particularly the DMN, and dysregulation in gamma-band oscillations are biomarkers of disease progression [43]. By entraining neural oscillations in higher frequency bands, such as gamma-band, and improving inter-regional synchrony, high-frequency rTMS may thereby help to restore network integrity, increase information transfer efficiency, and support cognitive performance [41], [44].

Thus, rTMS affects the brain across multiple levels, from modulating single neurons to reorganizing networks. These multi-scale effects show its potential as a therapeutic tool for neurodegenerative diseases.

1.4 Cognitive Training (CT)

Cognitive training (CT) refers to practice on specific exercises designed to improve specific cognitive function such as memory, attention, or executive processing. It assumes that repeated engagement in cognitively demanding tasks can strengthen underlying neural circuits and enhance performance within the trained tasks; thus, leading to neuroplasticity. Through repeated activation, CT has been shown to produce functional and structural changes in the brain and recruit compensatory networks across cortical regions, thus helping with maintaining cognitive function especially in neurodegenerative disease [45].

CT can be delivered using paper-based or computerized tasks, either individually or in group settings. Recent advances in digital health have popularized computerized CT, enabling standardized delivery and adaptive task difficulty. One meta-analysis showed that individualized

training tends to yield larger cognitive gains than group-based interventions [46]. However, while CT reliably enhances performance on trained tasks, transfer effects to untrained domains or to everyday functioning have been inconsistent across studies [47], [48], [49].

Clinical studies suggest that CT can provide modest but measurable improvements in global cognition and in specific domains such as attention, executive function, and processing speed among individuals with MCI or early-to-moderate dementia [50]. The degree of improvement appears to depend on both training intensity and supervision: supervised (or “tutored”) CT has been shown to produce greater and more generalized cognitive benefits than unsupervised approaches, likely due to enhanced engagement, motivation, and timely feedback from facilitators [51], [52], [53].

Despite these encouraging findings, the long-term efficacy of CT in dementia remains uncertain. Furthermore, CT alone may not sufficiently stimulate neuroplastic mechanisms required for long-lasting improvement of cognitive abilities or stability of neurodegenerative diseases. These limitations suggests that CT may need to be combined with other interventions, such as NIBS, to amplify neuroplastic changes and prolong cognitive benefits.

1.5 Transcranial Electrical Stimulation (tES)

Transcranial electrical stimulation (tES) refers to a family of NIBS methods that deliver weak electrical currents (typically 1–2 mA) through scalp electrodes to modulate neuronal excitability and oscillatory activity. Unlike TMS, which induces suprathreshold electric fields that directly trigger action potentials, tES operates subthreshold, altering the likelihood of neuronal firing by shifting the resting membrane potential or entraining ongoing neural rhythms [54], [55]. Over the past two decades, tES has gained increasing attention as a safe, portable, and

low-cost neuromodulation technique with therapeutic potential across neurological and psychiatric disorders.

The three main modalities of tES are transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). These approaches share the same delivery method but differ in waveform and underlying mechanisms. This thesis will focus on tDCS and tACS as these were the modalities used in the studies presented. Although tRNS has shown promise in modulating cortical excitability, it was excluded from this work due to tolerability issues encountered during pilot testing. A constant unidirectional current delivered through tDCS alters the resting membrane potential in a polarity-dependent manner: anodal stimulation increases excitability, while cathodal stimulation decreases it [55]. In contrast, tACS delivers sinusoidal currents at specific frequencies to interact with endogenous brain rhythms, allowing frequency-specific entrainment of neural oscillations [54].

Given that dementia involves widespread network disconnection and disrupted neural synchronization, tES has been proposed as a strategy to enhance communication within residual networks. Clinical studies using anodal tDCS over the DLPFC or temporal regions have reported modest yet consistent improvements in attention, working memory, and global cognition in MCI and AD [56], [57], [58]. Similarly, tACS studies have demonstrated that stimulating at gamma frequency, most commonly 40 Hz, can entrain neural oscillations and improve cognitive and behavioral outcomes [59], [60].

The effect of tES depend strongly on stimulation parameters including current intensity, frequency, electrode montage, and number of sessions, and on the underlying brain state during application. Typical dementia protocols involve 20–30 minute sessions administered across

several weeks, often targeting the DLPFC or temporoparietal areas [61]. However, considerable variability in methodology and individual anatomy contributes to inconsistent effects, motivating ongoing efforts to develop personalized tES protocols.

1.5.1 Mechanisms of tDCS and tACS

tES influences neural activity through small shifts (approximately 0.5 mV to 1 mV) in the transmembrane potential that alter neuronal excitability without directly eliciting action potentials [18]. These effects depend on the orientation of neurons relative to the electric field, the morphology of the cortex, and ongoing network activity [62].

Under anodal tDCS, depolarization of pyramidal neurons increases the probability of firing, while cathodal stimulation tends to hyperpolarize neurons and suppress activity. In gyri and sulci, the polarity of the local field varies with curvature, explaining inter-individual variability [62]. The prolonged effects of tDCS may be due to LTP and LTD caused by elevations in the calcium concentration for postsynaptic neurons leading to increased synaptic strength [63], [64]. LTP with increased calcium concentration in the post-synaptic neuron has been found under the cathode for tDCS [65]. However, these changes are also affected by the intensity [66], and duration of stimulation [67]. At the vascular level, cerebral blood flow of anodal tDCS was found to significantly increase during and after stimulation whereas cathodal tDCS initiated a small increase during stimulation and a decrease after the stimulation [68]. However, the response to tDCS appears to have high inter-individual variability and is also dependent on the stimulation location [69].

Rather than changing excitability in a fixed direction, tACS dynamically synchronizes or entrains neuronal populations to the applied frequency oscillations [54], [70]. The degree of

entrainment depends on phase alignment between the external current and intrinsic oscillations when aligned, network activity can be amplified, improving coherence across regions [71], [72].

Neural oscillations organize information flow in the brain and the ones focused in this thesis involve theta-band (4 Hz to 8 Hz) supports working memory and gamma-band (30 Hz to 80 Hz) underlies perception, learning, and memory binding [73]. By delivering oscillatory currents, tACS enables selective enhancement of specific frequency bands and restoration of disrupted synchronization. In AD, reduced gamma activity correlate with cognitive decline [74].

Preclinical work shows that 40 Hz stimulation can reduce beta-amyloid and phosphorylated tau deposition, likely via microglial activation and improved glymphatic clearance [75], [76], [77], [78]. Human trials have reported enhanced EEG gamma power, improved memory, and reduced neuropsychiatric symptoms following gamma-tACS [59], [79]. Recent findings also demonstrate that 5 Hz theta-tACS applied over the left dorsolateral prefrontal cortex can enhance theta-band EEG power and improve response speed during high-load working memory tasks, suggesting its potential for modulating task-relevant neural oscillations [80]. Application of both theta and gamma frequencies for left prefrontal cortex has been studied to enhance the spatial working memory theta-gamma coupling [81].

While tDCS primarily modulates cortical excitability through polarity-dependent shifts and plasticity mechanisms, tACS targets network dynamics by entraining oscillatory activity. This distinction underpins the rationale for using tACS in this thesis to restore disrupted gamma-band synchrony and improve cognitive function in dementia.

1.5.2 tES Paired with CT

The brain's ongoing activity at the time of application determines the physiological effects of stimulation, given the state-dependent nature of tES. When stimulation is delivered

while relevant neural circuits are actively engaged, the induced electric fields can reinforce or amplify functional pathways that are already recruited for a task [61]. This principle provides a strong rationale for combining tES with CT to ensure that the stimulation targets functionally active networks rather than resting or unrelated regions. Therefore, pairing tES with CT aims to leverage synergistic plasticity, the combination of externally induced modulation and behaviorally driven neural activation. Some studies have demonstrated that this approach can yield larger, longer-lasting, beyond trained-task improvements than either intervention alone [52], [53], [82], [83]. For example, anodal tDCS and CT has been shown to enhance working memory and executive function in both healthy adults and individuals with MCI or AD [84], [85], [86]. However, some studies failed to prove the added benefit of tDCS with CT compared to only CT [87], [88], [89].

In dementia research, pairing gamma-frequency tACS with CT is of particular interest as gamma oscillations are disrupted early in AD. Applying 40 Hz tACS can entrain gamma activity across cortical networks, while CT simultaneously activates these same circuits through task performance. Early studies combining tACS with CT in dementia populations have reported cognitive benefits especially for tACS [52], [53]. This integrative approach aligns with the growing shift toward multimodal interventions that combine behavioral, cognitive, and neuromodulatory strategies to target multiple levels of brain function simultaneously.

Our research team conducted a pilot study combining 40 Hz tACS with structured CT in dementia [53]. Twenty-eight participants with various degrees of dementia completed a 4-week treatment block (5 days/week, two 30-minute sessions/day) of tutored CT using the MindTriggers app [90]. The tACS group received simultaneous CT with 40 Hz stimulation via electrodes placed over the left DLPFC and contralateral supraorbital area, while the control

group completed CT without stimulation. Both groups improved significantly post-intervention, but the tACS group demonstrated superior retention and continued improvement at 1-month follow-up [53]. These findings informed Chapter 4, which builds on this work using a randomized, sham-controlled, double-blind crossover design with a larger sample and robust methodology.

1.6 Goal and Objectives

The overarching goal of this thesis is to investigate the methodological and efficacy of NIBS for dementia, with the aim of developing safer, more effective, and more targeted approaches to slow down cognitive decline.

The specific objectives of this thesis were to:

1. Investigate the precision of stimulation delivery when using neuronavigation systems, by comparing the actual stimulation site with mean Talairach coordinates. By identifying methodological limitations and sources of targeting error, this study contributes to improving reproducibility, reliability, and interpretability of TMS research and treatment protocols (Chapter 2).
2. Quantify the magnitude and spatial distribution of the magnetic fields and induced electric fields from a widely used sham TMS coil. These findings provide insight into the effectiveness of sham conditions, highlight potential sources of unintended neural stimulation, and inform the interpretation of placebo response considerations in clinical trials (Chapter 3).
3. Evaluate the therapeutic potential of 40 Hz tACS paired with CT, through a randomized, crossover, double-blind, sham-controlled trial in individuals with dementia. This objective examined whether simultaneous stimulation and CT could

- enhance cognitive performance and reduce neuropsychiatric symptoms, providing evidence for gamma-frequency entrainment as a therapeutic tool (Chapter 4).
4. Assess the long-term effects of repeated non-invasive interventions on cognitive trajectories in dementia. This objective examines whether multiple courses of TMS, tES, and/or CT can slow cognitive decline compared to the expected trajectory in untreated AD (Chapter 5).

1.7 Report Organization

This report is composed of six chapters. Chapter 1 introduces the key concepts, background information, and research objectives. Chapters 2 through 5 consist of individual manuscripts, including three published papers in peer-reviewed journals and one manuscript to be submitted for publication. Chapters 2 and 3 focus on methodological aspects of TMS, examining stimulation accuracy and sham coil validity. Chapter 4 investigates the combined effects of 40 Hz tACS and CT, and Chapter 5 presents a longitudinal study assessing the cognitive trajectories following repeated non-invasive interventions, including rTMS, tES with CT, and CT alone. Finally, Chapter 6 summarizes the key findings presented in the previous chapters and a discussion of recommendations for future work.

Chapter 2: How accurate are coordinate systems being used for Transcranial Magnetic Stimulation?

This chapter examines the accuracy of neuronavigation systems used in TMS, specifically those that rely on the Talairach coordinate system. The objective of this work was to evaluate whether a mean Talairach coordinate for the hand area of the primary motor cortex corresponds to the true stimulation site capable of eliciting a motor response. The motivation for this work stemmed from a large multi-site rTMS study on AD that used Talairach coordinates, with the goal of determining whether neuronavigation is necessary and how its accuracy may explain variability in treatment outcomes. This work has been published in a peer-reviewed journal as cited below:

M. A. Uehara, N. Jacobson, and Z. Moussavi, “How accurate are coordinate systems being used for transcranial magnetic stimulation?,” *Front Hum Neurosci*, vol. 18, p. 1342410, Jan. 2024, doi: 10.3389/fnhum.2024.1342410.

2.1 Abstract

When applying transcranial magnetic stimulation (TMS) to the brain, it is desired to be as precise as possible to reach a target area in the brain. For that, neuronavigational system using individuals' MRI scans were developed to guide TMS pulses delivery. All neuronavigational systems need coordinates of the target area to guide the TMS coil. Talairach coordinate system, which uses the Talairach-Tournoux atlas is the most common system used with TMS pulses. In this study we investigated how an average Talairach coordinate from 50 healthy individuals is close to the actual location of the hand area of the primary motor cortex to investigate if that elicit a motor response in the hand; thus, investigating the fitness and accuracy of the Talairach

coordinate system. We performed this experiment on six individuals (ages 61-82). When applying TMS single pulses to hand area with the given Talairach coordinate system adjusted with the MRI of each participant, three participants had involuntary twitch and three participants had no consistent physical response, as corroborated by electromyography of the abductor pollicis brevis and first dorsal interosseous muscles at the resting motor threshold intensity. Subsequently, by trial-and-error, the hand area was successfully stimulated on those three non-responder participants. The largest deviation from the Talairach coordinates was found to be 19.5 mm, measured on the surface of the cranium, between the true hand area and the mean Talairach coordinate. This finding implies that using generalized coordinates might be misleading when choosing the optimal location for brain stimulation.

2.2 Introduction

Coordinate systems for neuronavigation have become a frequently used method for localizing transcranial magnetic stimulation (TMS) pulses for a desired target area of the brain. All neuronavigational systems need the coordinates of the target area to be able to guide the TMS coil. Talairach coordinate system, derived from the atlas of a post-mortem human brain dissection, is the most common system used in neuronavigation along with TMS pulses. However, the accuracy of the selected coordinates is unknown as it relies on humans having homogenous functional neuroanatomy. Therefore, this paper aims to test if a mean Talairach coordinate for the hand area primary motor cortex (M1) can elicit an involuntary hand twitch and test its accuracy compared to the traditional trial-and-error method.

2.2.1 Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method that uses pulsed magnetic fields over a targeted brain region. The selected stimulation site depends on the treatment protocol or to examine a specific neurological function of the brain. A common stimulation area for depression and Alzheimer's disease treatment is the dorsolateral prefrontal cortex (DLPFC) due to its association with cognitive control and the limbic system [29], [91], [92].

Repetitive TMS pulses have been used as a means of treatment for many different neurological or mental disorders such as Alzheimer's disease [29], persistent post-concussion syndrome [93], major depression [91], and obsessive-compulsive disorder [94]. In those treatment studies, the target area of the brain is localized by either physical measurement based on 10-20 electroencephalography (EEG) system [95] or using a neuronavigation system. While neuronavigation systems such as Brainsight [96] promise precision within a few millimetres of the target area, the system's accuracy is limited by the accuracy of the used reference coordinate system. In this study, coordinate system accuracy and target area localization accuracy were investigated. The motor cortex is one of the only stimulation sites that enable the evaluation of whether TMS pulses induce neuron excitation. Thus, localization accuracy for the hand area was investigated by comparing trial-and-error and neuronavigation with Talairach coordinate system.

2.2.2 Resting Motor Threshold (RMT)

The resting motor threshold (RMT) is the minimum intensity of the TMS machine that is needed to evoke an involuntary motor response in an individual. RMT is determined using single TMS pulses applied over the hand area of the M1 when the hand is at rest. The two methods of determining RMT response from the TMS pulses are: (1) physical response, and (2)

electromyography (EMG) signal analysis; though, it is always recommended to also use visual response in addition to EMG analysis. Visual inspection of physical response requires the administrator of TMS to observe the hand for an involuntary twitch following every pulse. Using this method, the definition of RMT is the minimum stimulus intensity required to evoke a visible motor response of the hand at rest for more than 50% of pulses [97]. The second method uses EMG data from the first dorsal interosseous (FDI) muscle or abductor pollicis brevis (APB). RMT is defined by this method as the minimum intensity required to evoke a peak-to-peak motor evoked potential of 50 μ V in 5 out of 10 trials [98]. Assuming that the neurons excitability is the same across the neocortex, RMT is used as an individual's minimum magnetic field intensity to apply TMS to anywhere over the cortex. Although some researchers have questioned such homogeneity in the neuronal threshold of excitation in different parts of the brain [99], it is common practice to apply TMS pulses at 80-120% of the RMT for treatment or other neuroscience investigation [100], [101], [102].

2.2.3 Stimulation Site Localization

Trial-and-error is the most used technique to determine RMT. The TMS coil is placed over the estimated motor cortex area to observe an involuntary hand twitch to confirm target acquisition. Despite its preferential use, trial-and-error is only successful if practiced by experienced researchers. These researchers must define the starting point of localizing the M1 and subsequently manoeuvre the coil's position and angle while the coil centre is tangential and in contact with the participant's scalp. RMT tests apply single TMS pulses over the left or right M1. The location that produces the largest response in the relevant hand is defined as the "hotspot". However, this technique is restricted to the motor cortex, as other brain areas do not have a behavioural or signature output to confirm stimulation site accuracy.

Another strategic method to localize brain stimulation sites is imaging-based navigation [magnetic resonance imaging (MRI), functional MRI, or EEG]. This technique selects a desired brain structure on a person's MRI to determine the location to stimulate [103]. Consequently, MRI-based and fMRI-based navigations are limited to the accuracy of the used coordinates and the degree of researchers' expertise in brain anatomy, respectively. For example, precentral motor hand area localization relies on familiarity with the cerebral gyrus shape. Research has shown that the M1 hand area can be identified in an individual's MRI as the "hand knob", an omega or epsilon shape along the motor cortex [104]. Imaging-based navigation utilizes neuronavigation for precise navigation of the TMS coil over the skull to target specific brain regions. However, one should note that the accuracy of a neuronavigation system is proportional to the accuracy of the given coordinates of the desired target area to the software [105]. Therefore, the question would be how accurate the coordinate of the target area is.

The International 10-20 EEG system estimates the targeted cerebral region by measuring the scalp, creating a grid, and using references such as the inion, nasion, and preauricular points [106]. Similar to this EEG measurement estimation, the "5 cm rule" developed by George et al. [107], was created to target the DLPFC by measuring 5 cm anterior to the M1 hand area. This was developed in consultation with the Talairach atlas to quickly target a commonly used treatment site. Furthermore, the Beam-F3, is another method to easily target DLPFC for TMS treatment administration which follows the International 10-20 system with less measurements [108]. This method has been shown to be more precise and reliable than the 5 cm rule [109]; however, a recent study pointed out the assumptions used by the Beam-F3 method which produces an error due to head shape [110].

For all brain localization methods, there is a trade-off between accuracy and cost (in time and money) except for the trial-and-error method. However, trial-and-error has limited application due to its requirement for direct measurable response.

2.2.4 Coordinate Systems

Coordinate systems for the human brain are used to document the location of the brain independent of the size and shape of an individual brain. MRIs are transformed into a specific standard sized template brain for a common coordinate space. Transformation of an individual's MRI to a template brain is through the alignment of the anterior commissure (AC) and the posterior commissure (PC), which indicates the x-, y-, and z-axis. The individual's brain is scaled to match the template brain by scaling the distance between the AC and PC and all brain quadrants' size [103]. The most widely used spaces are the Talairach-Tournoux atlas, generated from a single dissected brain and the Montreal Neurological Institute (MNI) template, created from averaging multiple MRIs. This study will focus on testing the Talairach coordinates.

Previous research compared four TMS coil positioning strategies by analysing the cognitive effects [111]. The four positioning strategies are fMRI-guided TMS neuronavigation, MRI-guided TMS neuronavigation, group functional Talairach coordinates, and 10-20 EEG position P4. They concluded that Talairach coordinates had reduced effect sizes compared to fMRI-guided and MRI-guided neuronavigation approaches due to the consideration of interindividual variance, thereby improving TMS coil targeting [111].

Another study compared Talairach coordinates with the 5 cm rule to target the DLPFC [112]. The study determined the mean distance of the motor cortex to the suggested Talairach coordinate was 91.81 mm [112]. Therefore, the Talairach coordinate is significantly farther away from the motor cortex than 5 cm, depicting the inaccuracy of using simple EEG measurement

method. It is important to note that the Talairach-Tournoux system was considered to provide accurate positioning to DLPFC location.

We investigated whether the mean Talairach coordinate can stimulate the FDI or APB of the M1 of individuals using TMS. The mean Talairach coordinates derived from 50 right-handed healthy individuals is reported by Mylius et al. [113], as [-35.45, -26.12, 67.00].

As for testing the MNI coordinates, it was difficult to find an MNI coordinate to test. The majority of studies report the coordinate deeper in the cortex from fMRI studies that do not represent the TMS pulse localization coordinates that are used in TMS studies. Other studies have reported Talairach coordinates that were converted to MNI coordinates which in theory are the same location and would not be a different test as that for Talairach coordinate. Nevertheless, we determined the true hand area for each participant using trial-and-error method and reported both Talairach and MNI coordinates from the Brainsight TMS neuronavigation system.

2.3 Method

We collected data from five older adults from a TMS study for Alzheimer's disease [53], and one healthy individual (62 years old). The participant demographics can be found in Table 2-1. T1-weighted MRIs from all participants were uploaded to the Rogue Research Brainsight TMS neuronavigation system. The MRI configuration on Brainsight, as shown in Figure 2-1, includes linear transformation, anatomical landmark registration, and Talairach coordinate setup. Linear transformation of the MRI to standardized space was performed by indication of AC and PC and ensuring the boundaries of the brain are properly identified for scaling. Anatomical landmarks including nasion (bridge of the nose), tip of the nose, right and left preauricular points were indicated on the automatic skin reconstruction. The final setup of the MRI was to register the mean Talairach coordinate of hand area M1 derived from 50 right-handed healthy individuals

[-35.45, -26.12, 67.00] to each participant's MRI [113]. This study was approved by the University of Manitoba Biomedical Research Ethics Board as a sub-study under HS19998 (B2016:077). All participants signed an informed consent form prior to their participation.

Table 2-1. Participant demographics

Characteristic	Mean (Standard Deviation)
Age	72 (9.3)
Sex (Male/Female)	(4/2)
Resting Motor Threshold Values	52 (5.8)
Handedness (Right/Left)	(6/0)

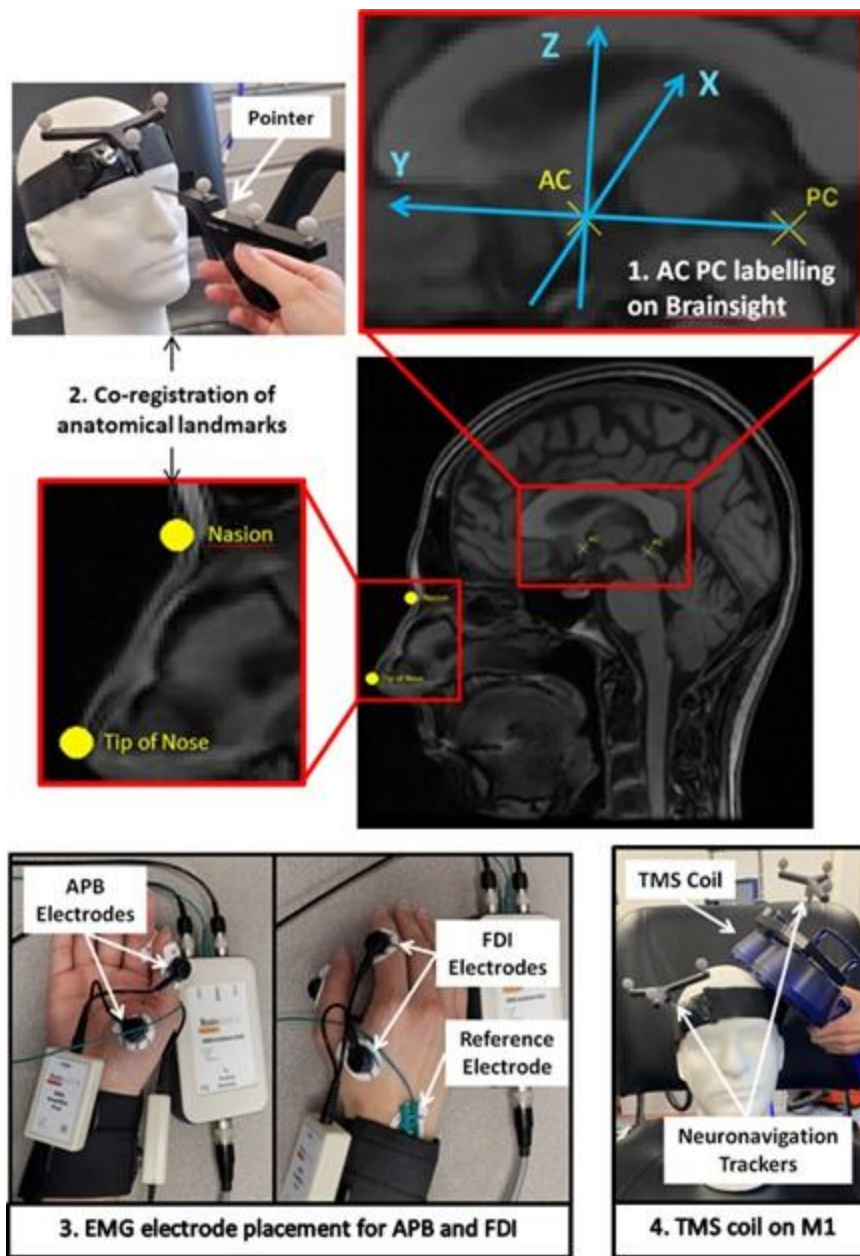


Figure 2-1. Schematic of the study protocol depicting the Brainsight software setup of participants' MRI, EMG electrode placement on APB and FDI muscles, and demonstration of Magstim TMS coil placement on the motor cortex.

For each participant, the mean Talairach coordinate was tested first, and then by trial-and-error, the true “hotspot” was determined. To begin the session, a headband with neuronavigation tracker was placed on the participant. Co-registration of the participants to their MRI was

performed with a pointer indicating the physical location of the anatomical landmarks. EMG electrodes were placed on the FDI and APB muscle, the two most used muscles for RMT measurements [114], to corroborate the findings from visual response when performing RMT measurement. Brainsight2 EMG pods were used to collect the EMG data using Kendall disposable surface EMG/ECG/EKG electrodes (24 mm, Ag/AgCl). Through a trigger cable between Magstim TMS and Brainsight computer system, the EMG signals were displayed on Brainsight software for a period of time around each TMS pulse. The Rapid2 Magstim Stimulator on single TMS pulse setting with the figure-eight AirFilm Coil was used to determine RMT. Subsequently, the participant received single TMS pulses 5 to 10 seconds apart targeted to the pre-registered coordinates by Brainsight's visual feedback on the coil position. Secondly, the trial-and-error method was used to determine the true "hotspot" for the M1 performed by an experienced TMS user. The intensity is reduced to the minimum intensity required to produce an involuntary visible response verified with FDI and APB EMG signals. The Brainsight system records the location of every pulse. Therefore, for the trial-and-error methods the coordinates for the M1 of the thumb in both MNI and Talairach coordinate systems were determined for the participant.

2.4 Results

Using the mean Talairach coordinate [-35.45, -26.12, 67.00] to stimulate the right hand, no consistent physical response was observed in 50% of the participants at their RMT intensity. For one participant, no response was detected in the electromyography data from both FDI and APB muscles at 10% higher than the known RMT. For two participants, 50% of the pulses had an observable response at 10% higher than the known RMT. The remaining three participants, the Talairach coordinate provided the hotspot for the hand area.

The accurate Talairach and MNI coordinates shown in Table 2-2 were determined using the trial-and-error method for the three participants with no consistent response at the mean Talairach coordinate. The scalp distance between the “hotspot” for RMT and the mean Talairach coordinate, [-35.45, -26.12, 67.00] [113], are shown in Table 2-2 with the maximum being displayed in Figure 2-2. The mean scalp distance between the hotspot and the mean Talairach coordinate for our sample is 6.1 mm (SD = 8.1).

Table 2-2. Hotspot coordinates for participants with no consistent response at the mean Talairach coordinate

Participant	Talairach Coordinates	MNI Coordinates	Scalp Distance ^a
1	[-47.01, -8.07, 69.70]	[-48.54, -1.70, 74.36]	19.5 mm
2	[-39.85, -15.77, 65.99]	[-40.90, -10.11, 70.85]	12.3 mm
3	[-39.88, -21.64, 75.06]	[-40.85, -15.54, 81.41]	5 mm

^aDistance between participant’s hotspot and mean Talairach coordinate [-35.45, -26.12, 67.00].

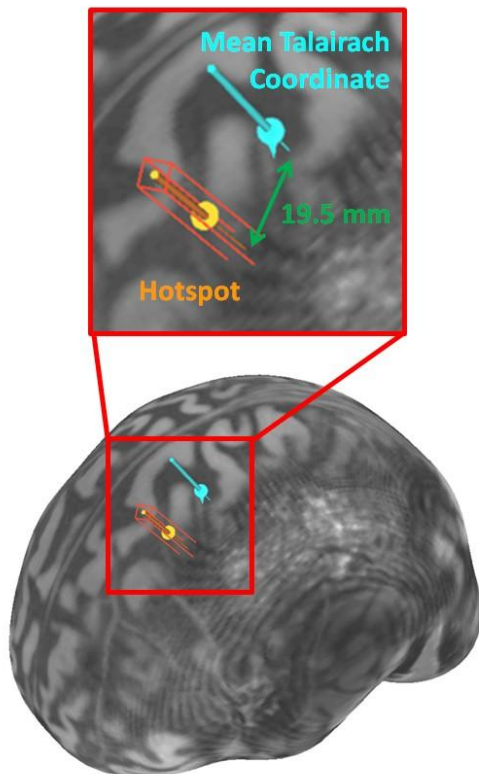


Figure 2-2. Brain surface visualization rendered from Participant 1's MRI with the hotspot and the mean Talairach coordinate.

2.5 Discussion

In this study, the M1 was the selected stimulation site to measure a direct response from TMS to assess localization accuracy. Findings indicated that the mean Talairach coordinate could target the hand area of the M1 for 50% of the participants as evidenced by insufficient EMG signals on two muscles, and a lack of physical response. From trial-and-error, the largest deviation of the “hotspot” was 19.5 mm from the mean Talairach coordinates.

Three key factors to explain the result of this study are (1) the high interindividual variability in the brain functional localization, (2) the sample size used to determine the average coordinate, and (3) the sample size of this study. Using normalized MRIs to a standard template does not guarantee that functional locations of the brain are normalized, but only that the size of the brain is normalized. Therefore, the high interindividual variability that exists in the brain structure must be considered [115]. Secondly, only 50 people were used to determine the mean Talairach coordinate. Thus, it is possible that a larger sample size could improve coordinate accuracy, though the concern of heterogeneous brain structures persists. Our limited sample size of 6 participants does not provide enough data to determine whether generalized coordinates should be used on majority of people.

Dorsolateral prefrontal cortex is the most common site for TMS treatment of many neurological disorders including depression, Alzheimer's disease, obsessive compulsive disorder, and more. There are contradictory results seen in literature whether the left, right, or both DLPFC are effective treatment locations. One concern in the prefrontal cortex is the variability in sulcal morphology, making it difficult to select an accurate anatomical location for

all participants [103], [115]. Furthermore, it has been shown that the “hand knob” shape within the M1 presents high interindividual variability [116]. Therefore, using the localization method based on functional anatomical knowledge may not be reliable.

Another consideration for TMS localization is the error margin that stimulates the targeted region. The action potentials that occur due to the TMS pulse affect the neurons at the cortex of the targeted region and the surrounding neurons. One research paper has suggested knowledge gaps in critical stimulation site accuracy for effective treatment [91]. Furthermore, weaker magnetic fields have been shown to affect treatment outcomes [117], [118] which may contribute to the error margin for localization.

Numerous studies have used MNI or Talairach coordinates to determine the stimulation site [112], [119], [120], [121]. A common practice for TMS studies is to use coordinates from previous studies based on Brodmann’s area or the mean MNI or Talairach coordinates from functional studies as the treatment site. The coordinates in standard space do not consider all the variability between people in the functional locations. This can affect treatment effectiveness and may shed light on inconsistencies in literature.

A few papers discussed the necessity of fMRI to accurately determine the stimulation site [111], [122]. It is suggested that the inaccurate stimulation site from methods such as mean coordinates, EEG measurements, or the 5 cm rule may be the reason for inconsistent results from TMS studies. However, fMRI is a very costly solution that is not accessible to all, and different methods should be further studied to improve accuracy.

In conclusion, using mean Talairach coordinates for TMS might not stimulate the targeted neurons for a particular treatment. This study determined that the mean Talairach coordinate [-35.45, -26.12, 67.00] for the left M1 hand area had a maximum error of 19.5 mm

from the true hand area for 6 participants. The coordinate system was created to compare brain sites between people and localize findings of anatomical or functional studies. Researchers commonly use these coordinates to target specific sites, but their study design needs to consider localization accuracy. Furthermore, fMRI studies may provide improved location accuracy with the drawback of the cost in both time and money. Future research may determine improved and accurate targeting systems. Alternatively, establishing an appropriate error margin of localization accuracy may allow researchers to use MNI or Talairach coordinates to estimate the stimulation site for a specific region such as the DLPFC. This study emphasized the importance of understanding the coordinate system for brain imaging and its dependency on homogeneity of human brains.

Chapter 3: Estimation of Induced Electric Field from a Sham Transcranial Magnetic Stimulation Coil

This chapter investigates whether a sham TMS coil generates measurable induced electric fields that could inadvertently stimulate cortical tissue. The objective of this work was to estimate the magnitude and distribution of the electric field from a commonly used sham coil at different stimulator intensities. The motivation for this study stemmed from results of a large repetitive TMS clinical trial in AD, which showed similar efficacy between real and sham conditions. This raised the question of whether sham coils may still deliver neural stimulation, thereby confounding trial outcomes. By characterizing the electric fields generated by the sham coil, this study provides critical insight into the validity of sham conditions, with implications for both experimental design and interpretation of clinical trial findings. This work will be submitted to *Bioelectromagnetics*. The authors are Maria Anabel Uehara, Elham Salimi, Grant Rutherford, Brian Lithgow, and Zahra Moussavi.

3.1 Abstract

Objective: Investigate the magnetic and electric fields of the real and sham Magstim™ 70 mm figure-of-eight Air Film coils to determine the induced cortical stimulation.

Methods: We measured the magnetic field of the real and sham coils using a Hall effect sensor. Peak magnetic fields were recorded to compare the distribution and magnitude of the magnetic fields produced under the coils. COMSOL Multiphysics was used to simulate the induced electric fields by adjusting the coil current to match measured values. A geometric brain model was used to estimate the induced electric field at cortical depth.

Results: The sham coil produced 24% of the magnetic field strength of the real coil, with its peak fields occurring near the centers of its individual circular windings rather than directly beneath the coil center. At the cortical depth corresponding to the average scalp-to-cortex distance, the sham coil generates a peak electric field that is 19% of the real coil's field strength.

Conclusion: The sham coil still generates electric fields that could be capable of modulating surface neural activity.

Significance: These findings highlight the need for improved sham coil designs to ensure closer to placebo responses.

3.2 Introduction

To evaluate the efficacy of a technology as a treatment tool for any condition, its effect must be compared against those of a placebo. Thus, many researchers have investigated the efficacy of repetitive transcranial magnetic stimulation (rTMS) using a real coil as a therapeutic tool for several neurological and psychiatric disorders while controlling for placebo effects using a sham coil. These sham coils are typically made by the same manufacturer to resemble the real coil in appearance and to produce similar auditory and sensory effects, while ideally generating no significant magnetic field with the potential to modulate neural activity. However, there are some challenges in the design of a sham coil to stimulate only the scalp without significant stimulation to the brain. The placebo and sensory effects of sham TMS have must be carefully considered as discussed in [123]. That study demonstrated that sham TMS can elicit specific behavioral effects even without direct neural stimulation, emphasizing that sham TMS is not always an inert control. These findings underscore the need for cautious interpretation of sham TMS effects in both basic and clinical research.

It is not well-known that the stimulation provided by nearly all sham coils still generate magnetic fields that stimulate more than the scalp, capable of inducing weak currents in the brain. While these induced currents may not directly excite neurons, they could have neuromodulatory effects similar to those of transcranial alternating current stimulation (tACS), which has been shown to alter sub-scalp neural threshold and activity even with weak current stimulation such as 1.5 mA [124].

A previous study compared the real and sham coils of the MagVenture MagPro X100 Stimulator, measuring the magnetic field over a 19 cm by 19 cm grid with a 1 cm resolution [117]. They used a dipole approximation model and found that the real TMS coil produced a magnetic field approximately 20 times stronger than the sham coil, while the induced electric field of the real coil was about 15 times stronger than that of the sham coil. The sham coil's additional magnetic shielding broadened its field distribution and reduced its overall strength [117]. To estimate the electric fields, they used a finite element model (FEM) of an individual's head derived from MRI data, with 5 different tissue types. The simulations revealed that the electric fields from sham coils could reach to 5 V/m, based on the provided figures, a level sufficient to modulate cortical excitability [117]. In contrast, the electric field from the real TMS coil remained below 100 V/m. The study also compared the electric fields produced by real and sham TMS coils with those induced by transcranial direct current stimulation (tDCS) at 1 mA. They found that tDCS produced electric fields below 0.3 V/m—substantially lower than those generated by the sham TMS coil. Since tDCS at this intensity has been shown to modulate brain activity [125], the authors concluded that assuming sham TMS functions purely as a placebo may be misleading. If sham coils produce stronger fields than tDCS, they may also induce neural modulation, potentially leading to an underestimation of the true effects of real TMS [117].

Another study measured the electric field distributions induced by both real and sham configurations of the Magstim 70 mm Air Film Coil and the MagVenture Cool-B65 A/P coil using a hemispherical measurement grid approximating the cortical surface [126]. Although the measurements were conducted in air, thus neglecting the effects of electrostatic fields generated by interfacial charge accumulation, the results revealed distinct difference between the Magstim and MagVenture sham coils. They found that the Magstim sham coil induced a peak electric field of 34 V/m, corresponding to 25.3% of the real coil's peak electric field, while the MagVenture sham coil produced only 14 V/m, corresponding to 7.7% of the real coil's field strength. Interestingly, although both sham coils produced weaker electric fields compared to their real coils, their spatial field distributions differed considerably. The Magstim sham coil induced virtually no electric field directly under the coil center. However, the peak fields were 3–7 cm from the center of the coil. In contrast, the MagVenture sham coil retained a figure-of-eight field distribution similar the real coil, with reduced focality. These findings highlight that different sham coil designs can produce distinct patterns and strengths of electric fields in the brain, reinforcing the need for careful interpretation of sham-controlled TMS studies, particularly when assuming that sham stimulation is used as a placebo control [126].

Given these findings, it is not surprising that some rTMS studies have failed to find significant differences between real and sham treatments. For example, studies on depression [118], [127], [128] and Alzheimer's disease [124] have reported no significant therapeutic advantage of real TMS over sham TMS. Possible explanations for these results include the attention participants received from health care professionals during a study [118], placebo effect, sensory side effects [123], and the effects from subthreshold rTMS [129]. On the other hand, the study in [124] that has been the largest study on Alzheimer's disease treatment by

rTMS to date with 156 participants with Alzheimer's disease randomly assigned to real and sham rTMS treatment groups, speculated the effect of sham coil could be similar to that of tACS as both real and sham stimulation improved the condition significantly at post-treatment. The authors used this argument to explain why they did not find any significant difference between the treatment outcomes of the two groups on average not only immediately post-treatment but also up to 6-month post-treatment (both groups improved post-treatment) [124].

rTMS devices utilize the electromagnetic induction theory to stimulate the brain non-invasively using pulsed magnetic fields. The rapidly changing magnetic field is generated by passing brief, high current pulses, typically lasting 150 to 400 μ s, through the coil. TMS protocols can involve single pulses, paired pulses, or trains of repetitive stimulation at varying frequencies, often delivering hundreds to thousands of pulses in a session [130].

A widely used coil design is the figure-of-eight consisting of two circular coils beside one another forming a figure eight. The direction and amplitude of the current in these loops determines the magnetic field distribution and intensity. In a real TMS coil, currents travel in opposite directions in each circular loop, creating a strong magnetic field directly beneath the coil centre, as shown in Figure 3-1. However, based on previous literature [131], [132], we speculate that sham coils use a different winding configuration, with currents traveling in the same direction within both loops. This design reduces the maximum magnetic field strength and alters its spatial distribution. Specifically, instead of a single peak located directly beneath the center of the coil—as seen in the real coil—the sham coil produces two distinct peaks located beneath the centers of each individual circular loop. As a result, the magnetic field distribution in the sham coil is more laterally spread, with reduced intensity at the midpoint between the loops. That is why the manufacturers call the sham coil an “off-target” sham coil [133].

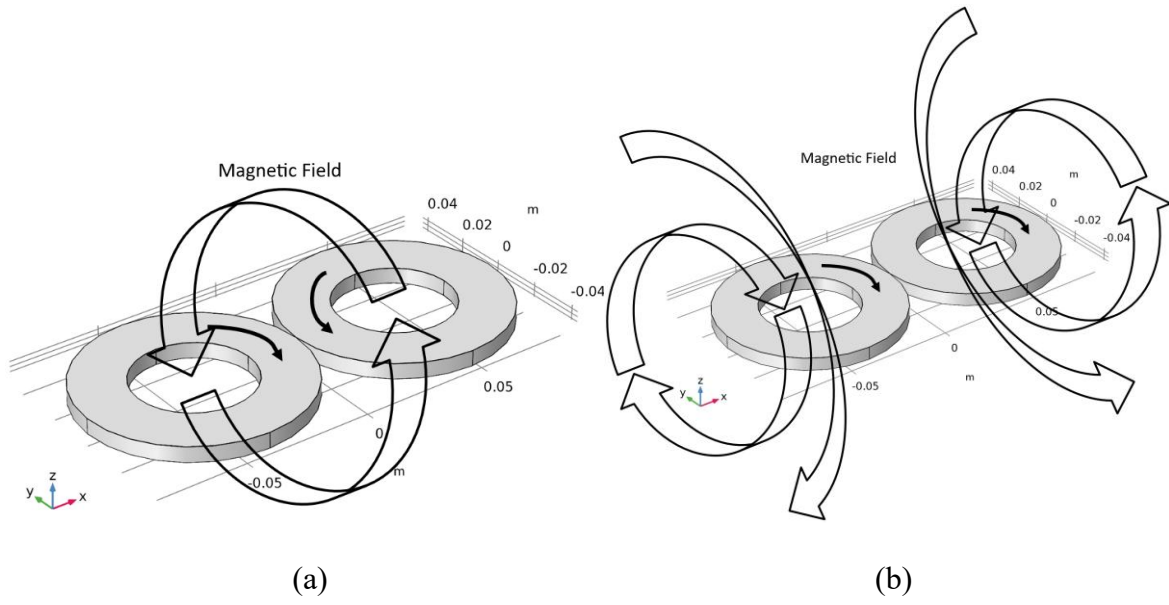


Figure 3-1. Figure-of-eight (a) real and (b) sham TMS coil current direction and magnetic field.

MagstimTM holds a patent for their Double 70 mm Air Film sham and real TMS coils which states that the windings for the sham coil are in the same direction, cancelling a significant part of the magnetic fields [134], [135]. Therefore, near the coil centre, the magnetic field is markedly reduced, but the surrounding area has significant magnetic fields, capable of reaching the scalp [131], [132]. Moreover, the peak energy stored in the capacitors prior to discharge for the sham coil is the same as the real coil and therefore, the sham coil provides a certain amount of undesirable stimulation [134].

While previous work has compared real and sham coils from several manufacturers, detailed characterization of the Magstim 70 mm Air Film sham coil remains limited despite its extensive use in both research and clinical trials, including large Alzheimer's disease studies. In this paper, we provide detailed analysis of the spatial electric field distribution produced by this sham coil, demonstrating how its winding configuration leads to off-centre peaks rather than a focal center-aligned field. By contextualizing these findings within the large rTMS efficacy

study as a treatment of Alzheimer's disease [124] with similar significantly positive results for both real and sham groups, we highlight why this sham coil cannot be assumed to be inert. This work therefore clarifies how induced fields from the Magstim sham coil may contribute to cortical modulation and influence interpretation of sham-controlled rTMS efficacy results.

3.3 Methods

Two TMS coils were tested in this study: the MagstimTM Double 70 mm Air Film real coil (P/N: 3910-00; Magstim Co., United Kingdom) and the MagstimTM Double 70 mm Air Film sham coil (P/N: 3950-00). These coils visually appear identical (Figure 3-2(a)). Both coils were connected to the MagstimTM Rapid² (P/N: 3004-00) stimulator (Figure 3-2(c)), which generates biphasic pulsed magnetic fields, as used in [124].

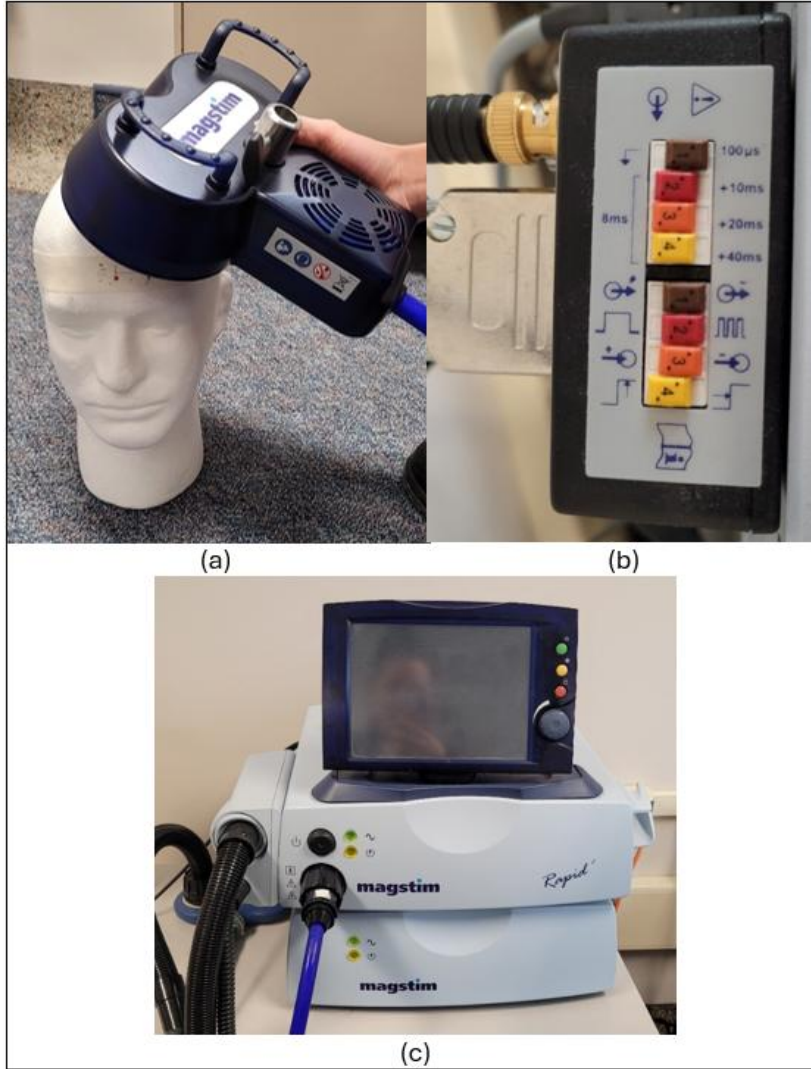


Figure 3-2. (a) MagstimTM Double 70 mm Air Film Coil Real and Sham with identical appearance and only differentiation being the identification number on the cable, (b) Trigger on the MagstimTM Rapid2 stimulator, and (c) MagstimTM Rapid2 stimulator.

3.3.1 Magnetic Flux Density Measurements

Magnetic flux density, B was measured using a three-axis hall effect sensor (3D HALL sensor – SENM3Dx, SENIS AG, Switzerland) (Figure 3-3(c)), capable of simultaneously acquiring all three axis components of magnetic flux density, B_x , B_y , and B_z [136]. This sensor was selected for its broad frequency bandwidth (up to 300 kHz), measurement range (30 mT to 4

T), measurement resolution ($1 \mu\text{T}$), and built-in calibration features. The sensor's on-chip correction for sensitivity, offset, noise, and temperature drift ensured accurate readings, with real-time warnings displayed via the graphical user interface (GUI) when temperature fluctuations could affect accuracy. The sensor was connected to a Raspberry Pi, which managed gain adjustments via the GUI. The system's direct analog data access was essential to accurately measure the short-duration magnetic pulses.

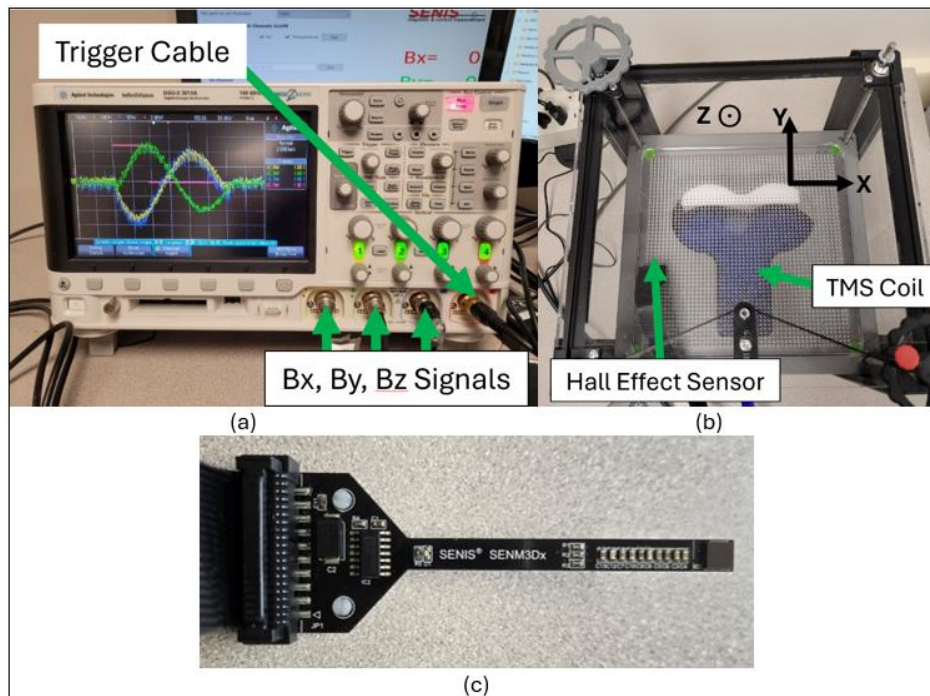


Figure 3-3. Magnetic field measurement devices and setup. (a) Oscilloscope used to gather the analog data (triggered by the TMS stimulator and connected to the Hall effect sensor, (b) Platform used to hold the TMS coil with the patient side coil facing up and the Hall effect sensor on top of a parallel plastic flat surface at a specific distance from the coil, and (c) SENIS 3DHALL sensor.

Measurements were acquired using a 4-channel oscilloscope with 4 GHz sampling rate (InfiniiVision DSO-X 3014A, Agilent Technologies, United States of America), as shown in Figure 3-3(a), which captured the analog outputs from all three sensor axes. The oscilloscope

was triggered using a BNC-to-BNC cable connected to the Magstim™ Rapid² stimulator's trigger output, interfaced via the Magstim Stimulator Interface Module, as depicted in Figure 3-2(b). A single measurement file was recorded per pulse, as the oscilloscope was configured to stop capturing once the pulse occurred. The signals from all three axes were saved as CSV files for post-processing.

Prior to data collection, the sensor's operation was validated using two methods: i) measuring the axial magnetic flux density inside a solenoid with known geometry and current and verifying the results against theoretical values, ii) measuring the amplitude and phase of the magnetic flux density at certain points under the TMS coils and verify the results against expectations based on coil design and current direction, in line with prior literature [126], [131], [133].

To systematically measure the spatial distribution of magnetic flux density using the Hall effect sensor, a 23 cm × 27 cm rectangular grid with 0.5 cm resolution was used. The Hall effect sensor was mounted on a plastic platform with a precisely spaced hole grid, ensuring consistent placement via two sensor-aligned guide pins. This setup enabled a total of 2,585 measurement points across the grid, capturing the B_x , B_y , and B_z field components beneath each coil. The grid structure and TMS coil support system were 3D-printed, as seen in Figure 3-3(b), allowing for precise sensor and coil positioning so that the measurement grid aligned with the coil placement in both position and angle. In comparison to our method, another research group modeled 25 commercial TMS coils, including figure-of-eight coils, using an automated measurement setup over a 28 cm by 28 cm area at a 24 cm distance from the coil, with 6–8 mm resolution in the x and y directions (parallel to the coil surface) and 10 mm resolution in the z direction (perpendicular to the coil surface, representing depth of penetration) [137]. Similarly, another

study measured the magnetic field of a Magstim 70 mm Double Air Film Coil using Hall-effect sensors over a 35 cm by 23 cm area with 5.29 mm resolution [138].

The 0.5 cm resolution was selected based on preliminary tests using a 2 cm grid spacing, which was found to be insufficient for capturing the field variation across the coil. The 0.5 cm spacing was chosen as the smallest manageable resolution for manual data collection, given that budget constraints prevented the use of an automated measurement system.

Measurements were taken at 2 cm and 3 cm distance from the coil surface, with B_x and B_y components recorded parallel to the coil surface and B_z measured perpendicular to the coil surface, as shown in Figure 3-3(b). The Magstim™ Rapid2 stimulator was set to single-pulse mode at 50% intensity. The Magstim™ Rapid2 stimulator was set to single-pulse mode at 50% intensity. This intensity level was chosen because higher output, particularly at 100%, resulted in significant signal distortion, likely due to electromagnetic interference affecting the recording device and insufficient shielding on the sensor cables. Using 50% maximum stimulator output (MSO) provided a clean and reliable signal without compromising the ability to characterize the magnetic field. Since the relationship between stimulator output and magnetic field strength is approximately linear, selecting a mid-range intensity allowed for accurate measurement and meaningful comparison of field distributions. To ensure accurate timing and synchronization with the oscilloscope, the stimulator was configured to output a negative trigger signal, set to generate a single output pulse for each stimulation pulse, with edge triggering enabled.

All magnetic flux density data were recorded as CSV files from the oscilloscope and processed using MATLAB. First, a 4th-order Butterworth low-pass filter (cutoff frequency: 80 kHz) was applied to remove high-frequency noise from the raw signals. The filtered signals were then analyzed using peak-finding functions to identify the maximum and minimum values,

which were used to calculate the amplitude and phase of the magnetic flux density for each axis (B_x , B_y , and B_z). Finally, the oscilloscope's raw voltage output was converted to magnetic flux density in Tesla (T) using sensor-specific conversion factors provided in the SENIS datasheet [136].

The processed data were then used to generate 2D heat maps of the magnetic flux density for both the real and sham coils at distances of 2 cm and 3 cm from the coil surfaces.

3.3.2 Simulation of TMS Coils

The TMS coil simulations were conducted using COMSOL Multiphysics, Magnetic and Electric Fields module, modeling both the real and sham coils, as illustrated in Figure 3-1. The real and sham coils were modeled identically, except for the applied current intensity and direction, which was adjusted to match experimental measurements. The coil parameters provided in Table 3-1. The parameters were obtained from the manufacturer and reported in previous research [139]. Additionally, similar parameter values were reported in a literature that used computed tomography scans to obtain the dimensions of the coils [138].

Table 3-1. Parameters of the real and sham TMS coils used for COMSOL simulation.

Parameter	Value
Material	Copper
Number of turns	11
Insulation thickness	0.1 mm
Coil height	6 mm
Inner radius	2.265 cm
Outer radius	4.3 cm

To determine the optimal current that would scale the simulation to match the measured magnetic flux density, we used a threshold-based averaging approach. Specifically, we first

calculated the magnitude of the magnetic flux density vector from the measured and simulated B_x , B_y , and B_z components. We then extracted all values above the 75th percentile of the distribution for each dataset. The average of these higher-intensity values was computed and used to represent the dominant magnetic field region. The ratio of the measured to simulated averages yielded a scaling factor to determine the optimal currents for the simulation to match the measurements. Our approach contrasts with methods used in another study [140], where only the single peak value was used to scale the simulation. We chose to avoid over-reliance on a single peak value, which may be affected by local artifacts or alignment inaccuracies and instead use a more stable estimate of the stimulation strength based on a broader region of interest. After applying the optimal scaling factor, an average percent error was computed using the absolute difference between the modulus of the measured data and modulus of the simulated data, normalized to the modulus of the measured values.

Once the numerical model was adjusted to closely match the measured magnetic flux density, it was used to calculate the induced electric field in a homogeneous spherical volume, representing a geometric model of the cortex, with a radius of 6.9 cm and a conductivity of 0.33 S/m [137]. The sphere was centrally positioned under the coil with its vortex 1.6 cm away from the coil surface. The average coil-to-cortex distance (1.6 cm) was derived from [141]. The head radius was assumed to be 8.5 cm, as used in prior research [142], [143], [144] resulting in the cortex radius of $r = 8.5 - 1.6 = 6.9$ cm. To reduce numerical artifacts and eliminate surface discontinuities in the simulated electric field, the field was extracted approximately 3 mm below the initially defined cortical surface, at a depth corresponding to a radius of 6.55 cm [140]. In this model, the effect of scalp and skull conductivities on the induced electric field is negligible [140], therefore, they are not included in order to reduce computational complexity.

The induced electric field was calculated using the frequency-domain equation:

$$\mathbf{E} = -j\omega\mathbf{A} - \nabla V, \quad (1)$$

where $\omega=2\pi f$ with f being the fundamental frequency, $\mathbf{A}$ is the magnetic vector potential and V is the electric potential. The fundamental frequency of the pulsed magnetic flux density sinusoid was extracted from Hall effect sensor measurements and validated using references [133], [137]. Finally, electric field distributions were visualized, and the peak electric fields of the real and sham coils were compared in terms of magnitude and spatial distribution on the spherical surface.

3.4 Results

3.4.1 Measured and Simulated Magnetic Flux Density

Figure 3-4 depicts a typical measurement of $\mathbf{B}_x$, $\mathbf{B}_y$, and $\mathbf{B}_z$ generated by a single pulse of the real coil recorded from the Hall effect sensor using the 4-channel oscilloscope. The measured pulse width is 340 μs , corresponding to the fundamental frequency of 2.9 kHz which was used in the numerical model to compute the induced electric field based on equation (1). The measured pulse width in agreement with previous reports in literature [133], [137]. The magnitude of $\mathbf{B}_x$, $\mathbf{B}_y$, and $\mathbf{B}_z$ at set locations under the real and sham coils were extracted from the recorded oscilloscope data.

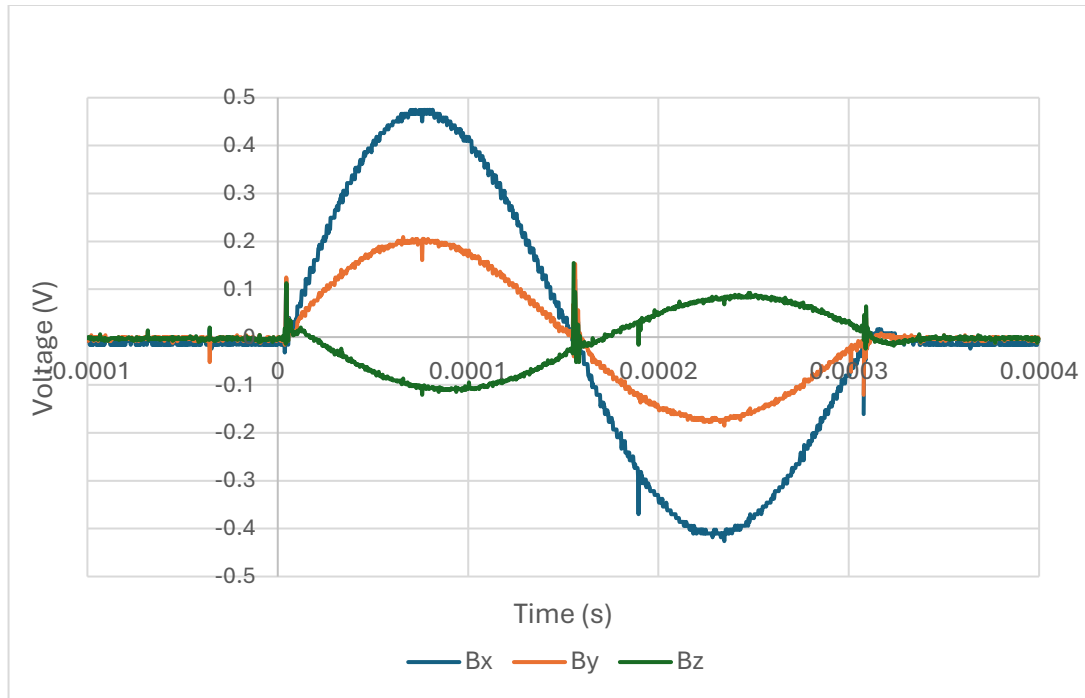


Figure 3-4. Example of the raw data collected from the hall effect sensor using a four-channel oscilloscope. The plots correspond to B_x , B_y , and B_z components of the magnetic flux density at ($x = 1$ cm, $y = -4.5$ cm, $z = 3$ cm) of the real TMS coil, where each signal was later converted from volts to Tesla using the sensor's calibration parameters.

The magnitude of the measured magnetic flux density components ($|B_x|$, $|B_y|$, and $|B_z|$) over a 23 cm x 27 cm plane at distances 2 cm and 3 cm below the surface of the real coil are shown in Figure 3-5(a) and (c), respectively. The measured results for the sham coil are shown in Figure 3-6(a) and (c). The magnitude of the total magnetic flux density, $|B|$, at a distance 2 cm below the coil surface for real and sham coils are shown in Figure 3-7(a) and (b), respectively. At 50% stimulator intensity, the real coil's peak flux density reached 153.68 mT at 2 cm, whereas the sham coil produced peak value of 36.31 mT. The sham coil's field strength was approximately 24% of that of the real coil. The total field distribution of the real coil followed the expected spatial pattern, with peak intensity occurring beneath the coil center and declining

radially outward. In contrast, the sham coil's peak intensity occurred off-centre, aligning more with the centers of each individual circular winding rather than beneath the midpoint of the entire coil structure. These observations support the assumption that the current flows in the same direction in both windings of the sham coil, in contrast to the real coil, where the current flows in opposite directions.

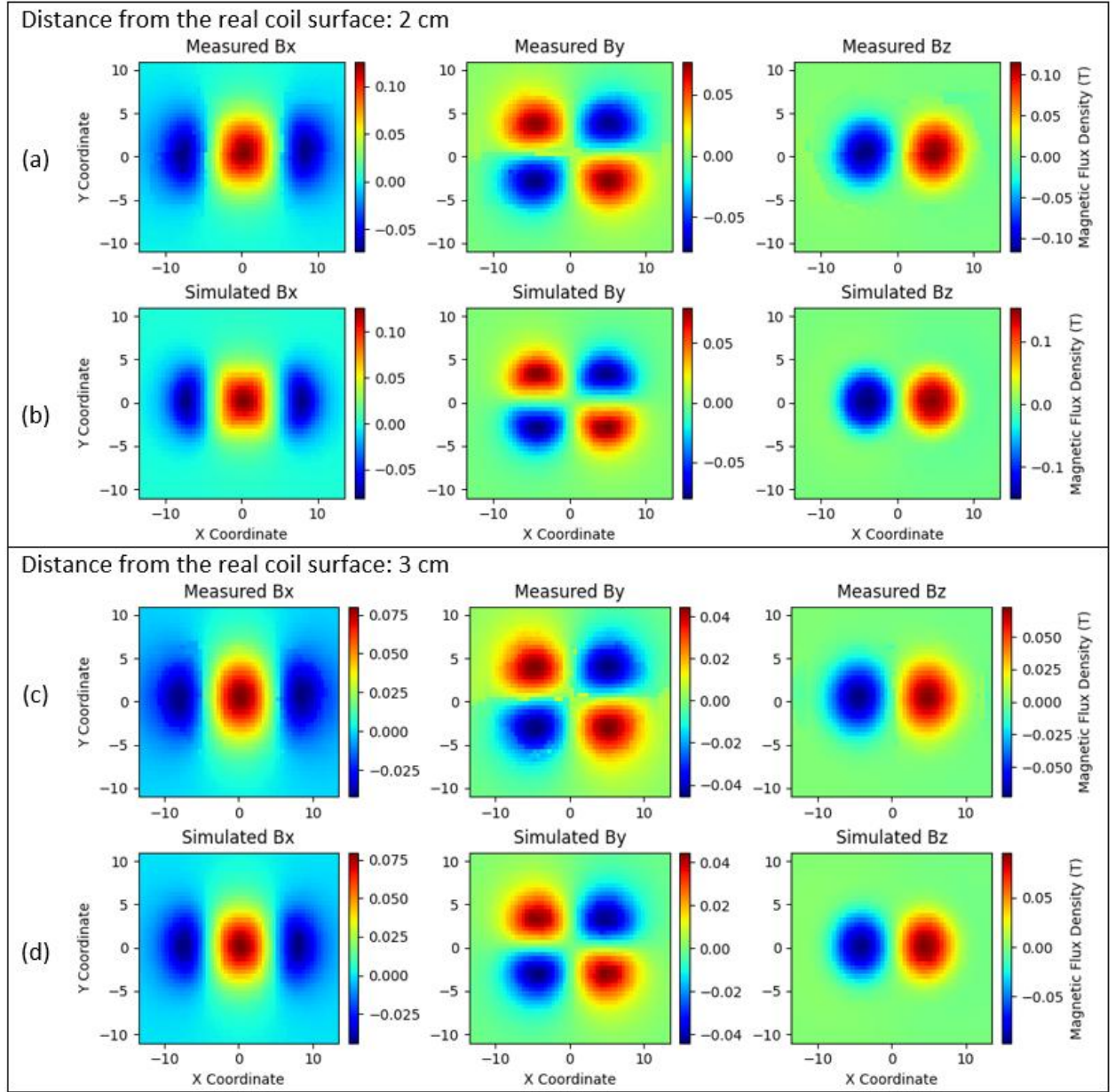


Figure 3-5. Magnetic flux density distribution for real TMS coil: (a) Magnitudes of the measured magnetic flux density components using the Hall effect sensor at 2 cm from the coil surface; (b) Magnitudes of the simulated magnetic flux density components at 2 cm from the coil surface; (c) Magnitudes of the measured magnetic flux density components using the Hall effect sensor at 3 cm from the coil surface; (d) Magnitudes of the simulated magnetic flux density components at 3 cm from the coil surface.

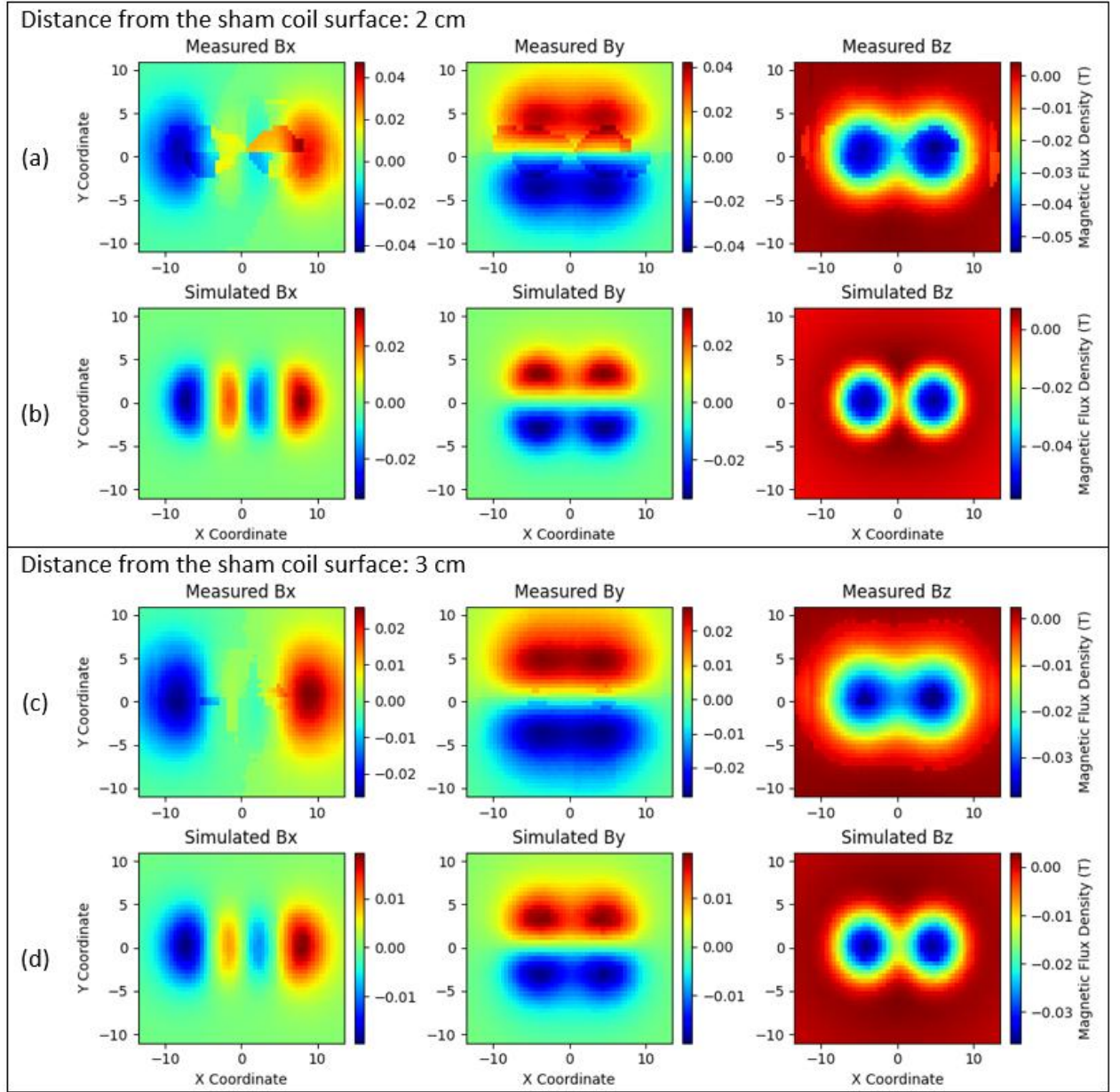


Figure 3-6. Magnetic flux density distribution for sham TMS coil: (a) Magnitudes of the measured magnetic flux density components using the Hall effect sensor at 2 cm from the coil surface; (b) Magnitudes of the simulated magnetic flux density components at 2 cm from the coil surface; (c) Magnitudes of the measured magnetic flux density components using the Hall effect sensor at 3 cm from the coil surface; (d) Magnitudes of the simulated magnetic flux density at 3 cm from the coil surface.

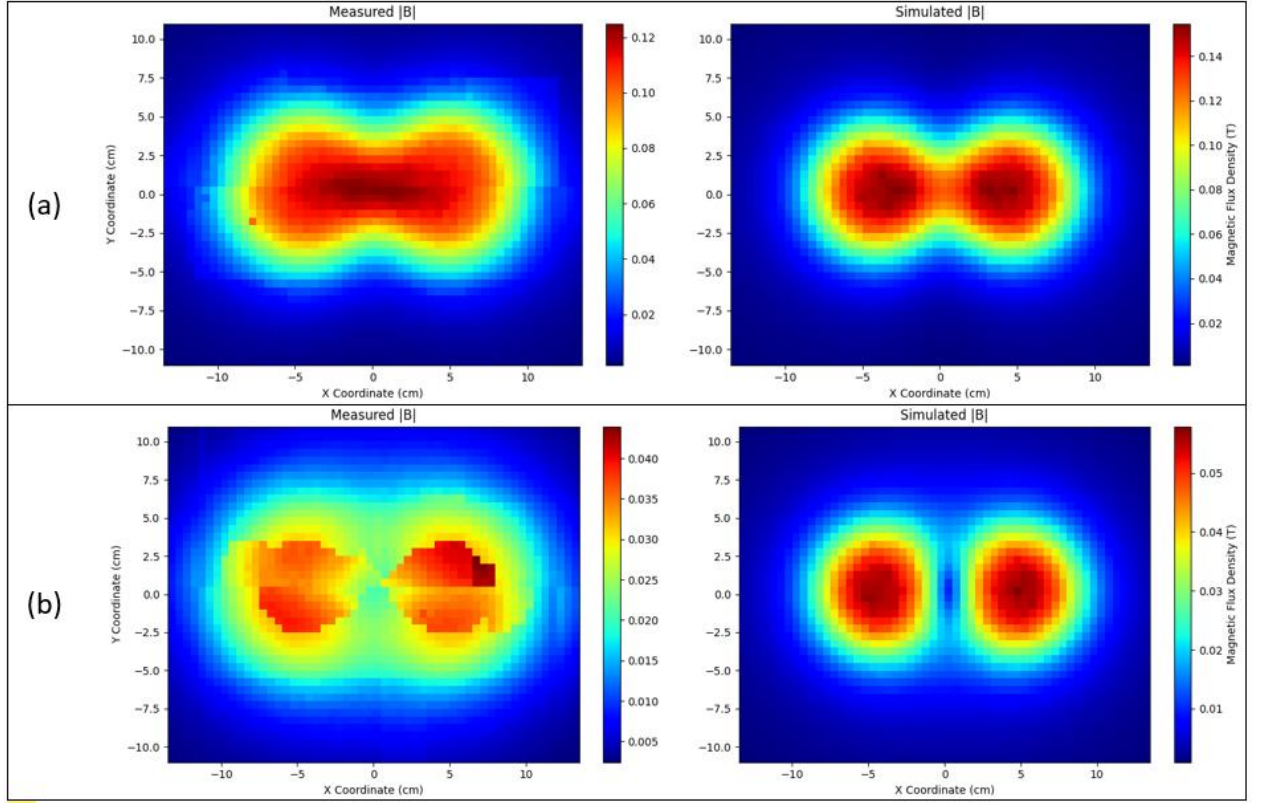


Figure 3-7. Measured and simulated magnitude of total magnetic flux density, $|B|$, 2 cm below the coil surface: (a) Real TMS coil; (b) Sham TMS coil.

The magnitudes of the simulated B_x , B_y , and B_z components for a current of 10 A flowing in opposite directions in the two windings (representing the real coil) at distances of 2 cm and 3 cm below the coil surface are shown in Figure 3-5 (b) and (d), respectively. The results for a current of 10 A flowing in the same directions in the two windings (representing the sham coil) are shown in Figure 3-6 (b) and (d). The simulated magnetic flux density distributions for both the real and sham coils closely matched the measured values. The simulated currents were optimized to **1404 A** and **566 A** for the real and sham numerical models, respectively, to match the amplitudes of the simulated and measured magnetic flux densities, with a residual error of 27.97% for the real coil and 41.69% for the sham coil. The significantly smaller scaling factor

for the sham coil's simulated current suggests the presence of another mechanism to reduce the effective magnetic field. The relationship between the intensity of stimulation, determined by the percentage of MSO on the stimulator, and the magnetic flux density can be seen in Figure 3-8. As expected, a linear relationship is observed between percentage MSO and magnetic flux density generated by the Magstim stimulator.

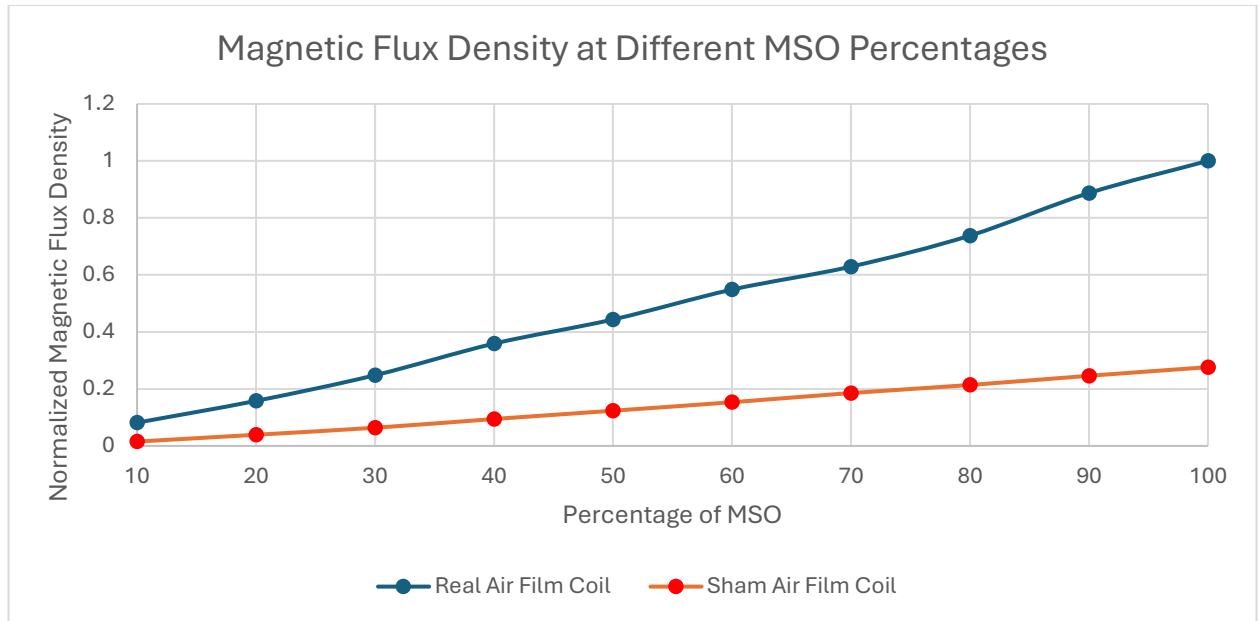


Figure 3-8. Magnetic flux density of the real and sham coils at different percentages of the maximum stimulator output (MSO).

3.4.2 Computed Induced Electric Field

Figure 3-9(a) and (b) show the amplitude of the induced electric field on the surface of the spherical model of the cortex for the real and sham coils, respectively. The electric field distribution over the cortical surface differs between the real and sham coils. The peak induced electric field for the real coil is 36.51 V/m located directly beneath the coil center, whereas for the sham coil, the maximum E-field is 6.87 V/m and occurs 2 cm to 3 cm lateral to the coil center. At the approximate cortical depth, the sham coil generates a peak electric field that is

19% of the real coil's field strength. On the geometric cortical surface, the real coil's peak electric field is six times greater than that of the sham coil, highlighting the significant attenuation and redistribution of the electric field in the sham condition.

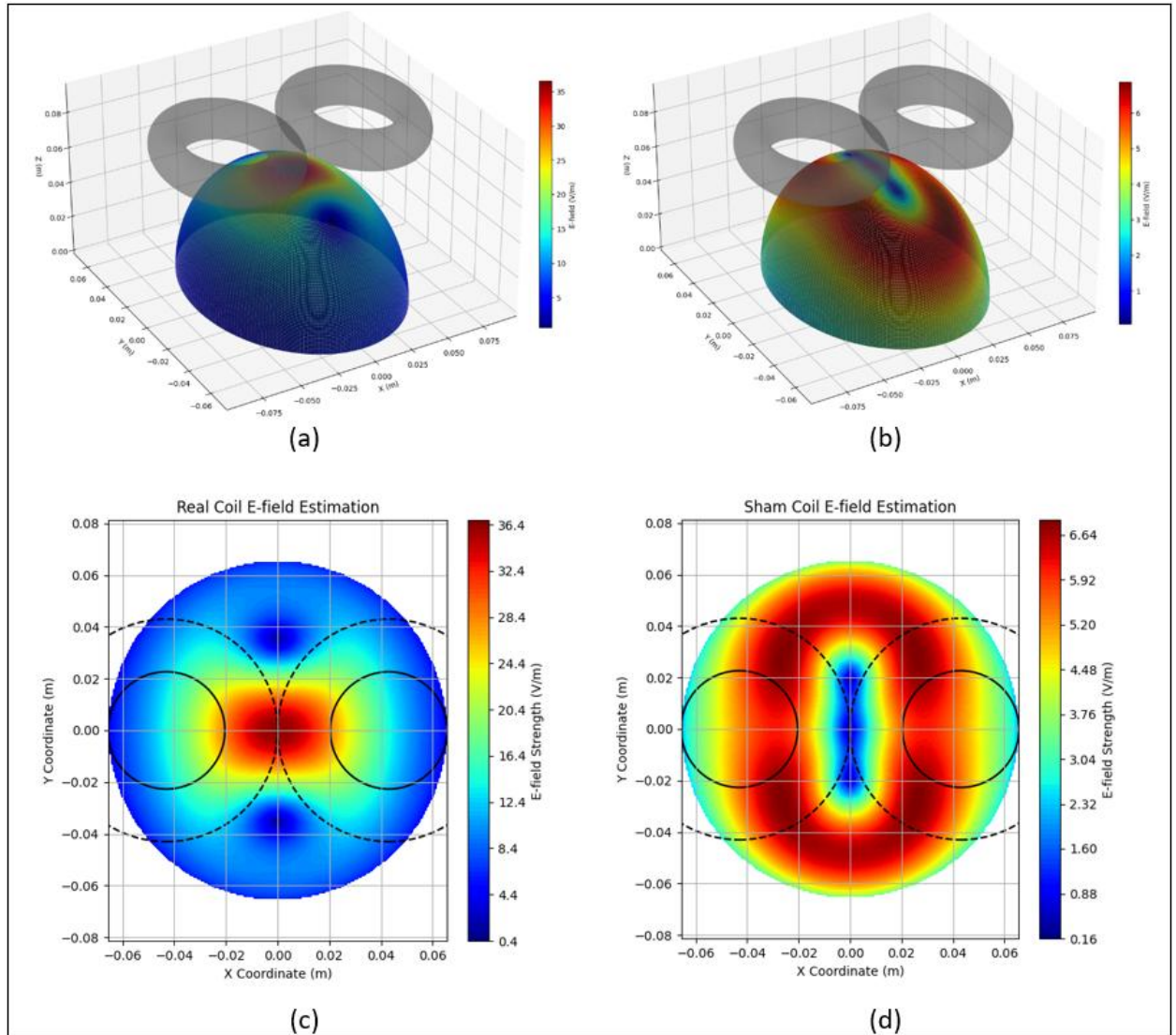


Figure 3-9. Simulated electric field distribution on a geometric brain surface: (a) 3D view with the real TMS coil; (b) 3D view with the sham TMS coil; (c) Top view with the real TMS coil; (d) Top view with the sham TMS coil. Note: color scales differ between real and sham TMS coil plots to illustrate each coil's electric field distribution.

3.5 Discussion

The results of the study support the fact that the currents' directions within the figure-of-eight real coil are in the opposite direction and in the sham coil they are in the same direction, supported by a study on TMS coil design [131]. Congruent with other studies [117], [126], our results show that the MagstimTM sham TMS coil generates significant magnetic flux density, reaching up to 24% of the real TMS coil. The highest induced electric field from the sham TMS coil was found to be 19% of the real coil's field strength, with the peaks located at approximately 2 to 3 cm from the coil's center.

Comparing these findings with other studies is challenging as most papers do not report absolute peak magnetic or electric field values [137], [138], [142]. Instead, they typically present relative ratios and spatial distributions of the fields. For example, one study on such a comparison analyzed the real and sham coil from MagVenture, reported the induced electric field using an MRI head model of a subject was less than 100 V/m for real coil, while it was less than 5 V/m for the sham coil [117]. However, the stimulator intensity was not specified, and the values were extracted from a figure rather than provided numerically. The fact that the real coil's electric field was more than double what we simulated suggests that the study likely modeled stimulation closer to 100% MSO. Additionally, the MagVenture sham coil has a different design, with a field distribution that more closely matches the real coil but at a much lower intensity. We only found one study that reported peak electric field values for the Magstim coils: 133 V/m for the real coil and 34 V/m for the sham counterpart at 100% MSO, corresponding to 25.3% of the real coil's field [126]. However, it is uncommon to use 100% MSO for TMS in practice as such high intensities are often very uncomfortable and can cause pain and other side effects.

This study was motivated by findings from a large clinical trial of rTMS for Alzheimer's disease where the real and sham groups showed similar treatment efficacy; both groups exhibited significant improvement post-treatment [124]. Our results indicate that both real and sham coils induce electric fields in the cortex, though the sham coil stimulates a different region at a lower intensity with a slightly more dispersed distribution. The sham coil functions as a real coil, but it stimulates "off the target" [133]. Given the fact that the exact location of the stimulation is also not exact and precise [145], it is not surprising that why sham coil can also be effective for some patients.

In our study, we chose conductivity value of 0.33 S/m which has been previously used in other studies [101], [137], [139]. Our approach provides generalizable results rather than findings specific to a single MRI-based head model like seen in [138]. Additionally, we selected the average scalp-to-cortex distance for Alzheimer's disease patients based on a previous study [141], as the large clinical trial that prompted this investigation focused on individuals with Alzheimer's disease.

A strength of our study is that it is based on both coil geometries and manufacturer data from [139], which were confirmed by a previous study that used computed tomography imaging to analyze coil structure [138]. Additionally, we incorporated direct magnetic field measurements, whereas some studies rely solely on magnetic field modeling [117], [137].

It has been suggested that the significant electric field induced by the sham coil produces low-field effects that influence neuromodulation [146]. The peak cortical electric field we estimated for the Magstim sham coil (6.87 V/m) falls within the range known to influence neuronal activity. For comparison, tACS studies have shown that even weaker oscillating fields of approximately 0.1–0.5 mV/mm can modulate spike timing, alter subthreshold membrane

potentials, and entrain ongoing brain rhythms [147], [148], [149]. Although the mechanisms differ (pulsed magnetic stimulation vs. continuous sinusoidal fields), both sham rTMS and tACS deliver rhythmic stimulation capable of interacting with endogenous neural oscillations, raising the possibility that sham rTMS may produce measurable physiological effects at the cortical surface.

To the best of our knowledge, there are no studies that have compared tACS with sham rTMS in terms of the induced electric fields or effectiveness for treatments. However, one study has shown that the induced electric fields from sham TMS was approximately 15 times stronger than 1 mA tDCS induced electric fields [117]. This comparison is important because tDCS, even at such low intensities, has consistently been shown to alter cortical excitability, affecting synaptic plasticity, and inducing measurable behavioral and neurochemical changes [150], [151], [152]. Therefore, if lower electric fields from tDCS can cause such changes, sham TMS which induces larger electric fields could also have an effect in the brain. For example, tDCS has been associated with neurobiological effects, such as reducing gamma-aminobutyric acid cortical concentrations, activation of glial cells, and increase of intracellular calcium ion concentrations, caused by such low electric fields [153], [154].

The main challenge for designing sham coils is to provide the same sensory, visual, and auditory experience as the real TMS treatment without providing any stimulation to the brain. However, it is difficult to reduce the field sufficiently to prevent stimulation completely [135]. The residual brain stimulation is a limitation of sham TMS that is a trade-off for providing the sensory experience as real TMS [123]. Nevertheless, the sham Air Film coil has a different scalp sensation due to sudden sharp sensations in the surrounding area and not directly under the coil where the real coil produces the sensations. This is because of the difference in the magnetic

field distribution. Furthermore, the auditory clicking sound is slightly softer for the sham Air Film coil compared to the real coil. Visually, real and sham Air Film coils look identical and provide similar experience. A previous method that has been used in our lab before sham coils were commercially sold was to place a wooden block between the participant scalp and the coil. The biggest downfall of this method is that visually it is obviously different to the participant. On the other hand, the magnetic field of the coil when using a wooden block as the “sham” was approximately 25% than that of the Air Film coil but at the cost of a significantly damped scalp sensations, and softer clicking sounds.

Researchers have attempted multiple versions of sham TMS or having a control condition including stimulating another part of the brain or tilting the coil perpendicular to the scalp surface [123], [155]. Others have looked at changing the coil design [131], [132], [156], or using electrical stimulation for a sham coil [157]. Many of the current sham coils available reduce the induced electric field approximately 75-90% depending on the coil [117]. Designing a sham coil that can be an excellent placebo and could be used in a crossover design study is extremely challenging. After knowing exactly the sound, scalp sensation and how the coil looks, it is easy to compare and distinguish sham from real coils and almost no studies have examined the full gamete of placebo effects or the success of blinding participants from the stimulation condition [123].

3.5.1 Limitations

This study has several limitations that should be considered when interpreting the results. First, we were unable to use a detailed head model with appropriate tissue properties. While a head model would provide more precise estimations of the induced electric fields, these values would still vary across individuals due to differences in anatomy and tissue conductivity. Prior

work comparing spherical and MRI-derived models has shown that while overall spatial patterns are preserved, absolute field magnitudes can differ, particularly in regions with strong curvature or conductivity boundaries. Applying our approach to a subject-specific realistic head model would be feasible but substantially more computationally demanding and outside the scope of this work. Therefore, our estimates should be interpreted as approximate field magnitudes rather than individualized predictions.

Second, our findings are constrained by the accuracy and precision of the measurement setup. Minor coil-to-sensor misalignment and environmental electromagnetic noise likely contributed to the residual errors observed during the scaling procedure (approximately 28% for the real coil and 42% for the sham coil). These errors reflect the inherent challenges of measuring rapidly changing magnetic fields and may affect the quantitative precision of the estimated electric fields. To minimize these effects, we 3D-printed a structure to hold the TMS coils in a fixed position and ensure precise sensor placement with proper alignment. Even with careful measurements, small measurement errors could influence the reported field strengths.

Lastly, all reported magnetic and electric field values were obtained at 50 % of the MSO. Although we confirmed the linearity of the magnetic field with MSO percentage, the absolute values may differ at higher or lower stimulation intensities. As a result, induced electric field values at intensities other than 50% MSO should be interpreted with caution.

3.5.2 Conclusion

In conclusion, our findings demonstrate that based on the magnetic and electric field distribution, the sham TMS coil induces electric fields in the surrounding area of the targeted stimulation site which arguably provides some subthreshold stimulation. This weak but measurable electric field may influence neuronal activity, which must be considered when

interpreting the results of TMS studies. However, the challenge of designing a sham TMS coil that replicates all the sensations associated to real TMS without stimulating the brain remains an ongoing issue. Developing improved sham TMS methods that minimize unintended neural modulation while mimicking the sensory experience of real TMS is crucial for ensuring more accurate placebo-controlled rTMS studies. These findings suggest that previous studies using sham TMS as a control may need to be re-evaluated, as unintentional brain stimulation could have confounded treatment outcomes.

Chapter 4: Cognitive and Neuropsychiatric Effects of 40 Hz tACS Simultaneously with Cognitive Exercises for Dementia: A Randomized, Crossover, Double-Blind, Sham-Controlled Study

This chapter investigates the cognitive and neuropsychiatric effects of tACS at 40 Hz when paired with simultaneous CT in individuals living with dementia. The motivation for this work stemmed from the limitations of TMS, which, while effective, delivers suprathreshold stimulation that can be uncomfortable or potentially harmful. In contrast, tACS offers a below-threshold alternative capable of modulating neural oscillations associated with cognitive function. Building on the pilot study presented in Section 1.5.3, this randomized, double-blind, sham-controlled crossover trial was designed to rigorously assess both short- and long-term effects of gamma-frequency tACS combined with structured cognitive training. The findings contribute to the growing evidence supporting non-invasive neuromodulation as a scalable and tolerable intervention for dementia. This work has been published in a peer-reviewed journal as cited below:

M. A. Uehara, S. Kalia, M. G. Campuzano, M. Jafari-Jozani, B. Lithgow, and Z. Moussavi, “Cognitive and Neuropsychiatric Effects of 40 Hz tACS Simultaneously with Cognitive Exercises for Dementia: A Randomized, Crossover, Double-Blind, Sham-Controlled Study,” *Medicina*, vol. 61, no. 4, Apr. 2025, doi: 10.3390/medicina61040757.

4.1 Abstract

Background and Objectives: Transcranial alternating current stimulation (tACS) at 40 Hz has shown potential to enhance cognitive function. However, research on its combination with cognitive exercises, particularly its long-term effects in a dementia population, remains limited.

This study investigated the effects of 40 Hz tACS paired with simultaneous cognitive exercises on cognition, neuropsychiatric symptoms, and the depression status of individuals with dementia in a sham-controlled, double-blind crossover design. *Materials and Methods:* A total of 42 participants with dementia were randomized into two groups: (1) the R1S2 group received 40 Hz real tACS with cognitive exercises, followed by a ≥ 8 -week washout period, and then sham tACS with cognitive exercises; (2) the S1R2 group received the reversed sequence. tACS was applied at 1.5 mA peak-to-peak with electrodes over the left dorsolateral prefrontal cortex and contralateral supraorbital area. Participants received two 30 min stimulation sessions per day, 5 days per week, for 4 consecutive weeks, paired with cognitive exercises using the MindTriggers app. The primary outcome was the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and the secondary outcomes included the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Neuropsychiatric Inventory Questionnaire (NPI-Q). All outcome measures were assessed before and after each treatment block. *Results:* Real tACS paired with cognitive exercises significantly improved ADAS-Cog scores post-treatment compared to pre-treatment (p -value = 0.019), whereas sham tACS did not. Furthermore, real tACS produced significant long-term improvements approximately 2–3 months post-treatment in ADAS-Cog scores compared to sham (p -value = 0.048). Both real (p -value = 0.003) and sham (p -value = 0.015) tACS significantly reduced NPI-Q scores post-treatment. MADRS scores significantly improved (p -value = 0.007) post-treatment for real tACS but not sham. *Conclusions:* The 40 Hz tACS paired with cognitive exercises improves cognition, neuropsychiatric symptoms, and depression post-treatment in dementia, with sustained cognitive effects. The findings highlight its potential as a non-invasive therapeutic intervention for dementia.

4.2 Introduction

Dementia affects over 55 million individuals globally, and its prevalence is expected to increase further with aging populations [158]. Neurodegenerative dementia including Alzheimer's disease (AD) as its most common type, is a progressive condition characterized by memory loss, difficulties with problem-solving, language deficits, and challenges in performing daily activities [1]. Despite significant advancements in research, there remains no cure for dementia, highlighting an urgent need for innovative therapeutic approaches such as non-invasive brain stimulation and cognitive training to mitigate cognitive decline, improve quality of life, slow the progress of the condition and avoid institutionalization. In recent years, non-invasive brain stimulation techniques, such as transcranial alternating current stimulation (tACS) and cognitive training have been investigated for its potential therapeutic effects in slowing down the progression of dementia and improving cognitive function. This paper presents the results of gamma-tACS (at 40 Hz) paired with simultaneous cognitive exercises as a treatment for individuals with dementia (the majority (62%) with AD) in a double-blind, sham-controlled crossover design study.

tACS has gained attention for its ability to modulate brain activity and target specific neural oscillations associated with cognition [159]. It is a non-invasive, relatively inexpensive and safe brain stimulation technology that is easy to administer; it applies low-amplitude oscillating electrical currents through scalp electrodes to entrain neural oscillatory activity in targeted frequency bands [160]. Neural oscillations play a critical role in regulating cognitive processes, and specific frequency bands have been linked to distinct cognitive domains. Specifically, the gamma band (~30-100 Hz) is associated with higher cognitive functions such as learning, episodic and working memory, and attention [161]. Given that dementia is

characterized by disruptions in neural oscillations critical for memory and attention, tACS offers a targeted therapeutic approach to restore these oscillatory patterns and address associated cognitive impairments.

Our research team previously conducted two pilot studies to investigate the cognitive effects of daily tutored cognitive exercises without or with simultaneous gamma-tACS (40 Hz) with cognitive exercises. The first was a study of cognitive exercise for 8 weeks, 3 days/week on 24 healthy older adults placed in either cognitive training ($n = 13$) group or control ($n = 11$) group [51]. The results showed significant improvement in Wechsler Memory Scale (WMS) scores from baseline to post-treatment in the cognitive training group compared to the control group. The second was a treatment study on 28 individuals with AD in two groups receiving tutored cognitive exercises with tACS ($n=19$) and without ($n = 9$) tACS for 4 weeks, 5 days/week [52], [53]. Gamma (40 Hz) tACS was administered at 1.5 mA peak-to-peak for 30-min over the left dorsolateral prefrontal cortex (DLPFC), with the reference electrode placed over the contralateral supraorbital area. Treatments were delivered in two 30-min sessions daily, 5 days per week, for 4 weeks. Results showed that both groups revealed statistically significant improvement in WMS scores from baseline to post-treatment; however, only the tACS with cognitive training group showed a marginally significant trend towards sustained improvement at the 1-month follow-up. While these findings suggest potential cognitive benefits of pairing 40 Hz tACS with cognitive exercises, the study [52], [53] lacked a control group with sham tACS.

Beyond our research group, several studies have explored the efficacy of applying multiple sessions of tACS in populations with dementia and MCI as a potential treatment. One sham-controlled study applied 40 Hz tACS at 2 mA over the bilateral temporal lobes to individuals with AD ($n = 23$ tACS, $n = 27$ sham) for 20-min per session, 5 sessions per week,

over 6 weeks [162]. The tACS group showed significant improvements in both Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores immediately following the intervention. However, while MMSE improvements remained significant at the 12-week follow-up, ADAS-Cog scores regressed to baseline, highlighting potential short-term cognitive benefits of tACS that may require ongoing treatment for sustained effects [162]. Conversely, another study found sustained benefits for a home-based tACS intervention lasting up to 2-3 months [163]. In that single-arm study ($n = 8$, AD), participants received 40 Hz tACS over the left angular gyrus for 20-min per session, 5-7 times per week, for 14 weeks. Memory performance, as measured by the Memory Index Score, improved after the treatment period with sustained benefits observed even during the hiatus phase. However, statistical analyses were not reported, limiting the ability to draw definitive conclusions about the reliability of these effects [163]. A separate study explored different tACS montages, applying 40 Hz stimulation over unilateral temporo-frontal or bitemporal lobes in a small cohort of AD participants ($n = 15$) [78]. Participants received 1-hour sessions 5 days per week for either 2 or 4 weeks. Arterial spin labeling magnetic resonance imaging revealed a significant increase in blood perfusion in the bilateral temporal lobes following tACS treatment [78]. Moreover, these perfusion changes correlated positively with improvements in episodic memory and gamma-band spectral power, further supporting the potential of tACS to modulate both neurophysiological and cognitive outcomes in AD [78]. Together, these studies provide growing evidence that 40 Hz tACS can enhance cognitive performance in individuals with MCI and AD. However, methodological variations, including differences in stimulation duration, cortical targets, and study designs, highlight the need for further investigation. While these

studies demonstrate cognitive improvements following gamma-tACS, the underlying neural mechanisms remain an area of active research.

The exact mechanism of tACS is still not entirely understood [164]. However, through different approaches including in vivo and in vitro animal studies, the main mechanisms for tACS are modulation of the neuronal membrane potential, the entrainment of neural oscillations and spike-timing dependent plasticity [165], [166]. At the cellular level, tACS alters the transmembrane potential of neurons by synchronizing with the stimulation, with even small changes capable of affecting the firing rate of active neurons [166]. By delivering oscillating electrical currents, tACS can synchronize brain activity at specific frequencies, such as the gamma band, which is associated with higher cognitive functions like memory processing and attention [161]. This synchronization facilitates communication between brain regions, potentially improving memory consolidation and cognitive performance [167]. Additionally, gamma-tACS may exert therapeutic effects through several mechanisms, such as reducing phosphorylated tau deposition [77], enhancing synaptic plasticity and cognitive function [160], increasing blood oxygenation to specific brain regions when applying at 40 Hz [78], [168] and improving intracortical connectivity [59]. These findings suggest that tACS may provide multifaceted benefits by targeting both neuronal and pathological processes underlying dementia.

As another non-invasive therapeutic technologies, cognitive training programs designed to build cognitive reserve to maintain cognitive function by engaging neural networks through structured exercises [51], [169], [170]. Previous research indicates that multiple, regimented brain exercises sessions significantly enhance cognitive function in healthy older adults [51], [171], [172]. One long-term study demonstrated that consistent cognitive training not only improves cognitive performance but also reduces dementia risk over a 10-year follow-up period

compared to an untreated control group [173]. Additionally, two studies reported that computer-based cognitive training programs effectively improve impaired cognitive functions in early AD [174], [175]. However, these benefits were mostly observed in the trained tasks, with limited transfer to untrained tasks, potentially due to unsupervised training [172], [173], [175], [176], [177]. Studies suggest that structured interventions, where a treatment administrator guides participants through cognitive exercises daily, show broader improvements in daily life beyond the practiced exercises [51], [52], [53], [178], [179]. This approach ensures personalized feedback and sustained participant engagement, optimizing the benefits of cognitive training.

There were several shortcomings in previous studies, including having small sample size ($n < 30$), or the lack of a sham-controlled condition to account for placebo effects, and the absence of randomization in group assignments. This study aimed to address these limitations by implementing a sham-controlled, double-blind crossover design to control for placebo effects and minimize inter-subject variability by allowing participants to be their own controls. The goal was to investigate the immediate and longer-term cognitive effects of pairing 40 Hz tACS and cognitive exercises in individuals with dementia.

4.3 Materials and Methods

4.3.1 Study Design and Participants

This was a sham-controlled, double-blind crossover design clinical trial to investigate the effects of tACS paired with cognitive exercises conducted at Riverview Health Center. The crossover design was selected to control between-subject variability and maximize statistical power given the limited pool of eligible participants for recruitment; thus, allowing each individual to serve as their own control [180]. The study protocol published in [181] details the full methodological framework, including the sample size calculation, which estimated that 60

participants would be enrolled in either R1S2 or S1R2 group. Participants were randomly assigned to one of two groups, R1S2 or S1R2; the stratification parameters were age (above or below 70 years), sex (male or female), and cognitive level measured by Montreal Cognitive Assessment (MoCA) (above or below 18 MoCA score) to ensure balanced key demographic characteristics. Randomization was conducted using the PROC PLAN procedure from SAS to generate the groups [182]. The team member who made the database also wrote the code to generate the randomization.

Each group received two 4-week blocks of treatment; R1S2 group received real tACS in period 1 and sham in period 2, while the S1R2 group received sham first and real second. Both real and sham tACS treatments were paired with cognitive exercises using MindTriggers app [90]. The two treatment blocks were separated by at least 8 weeks. Figure 4-1 shows the crossover design schematically.

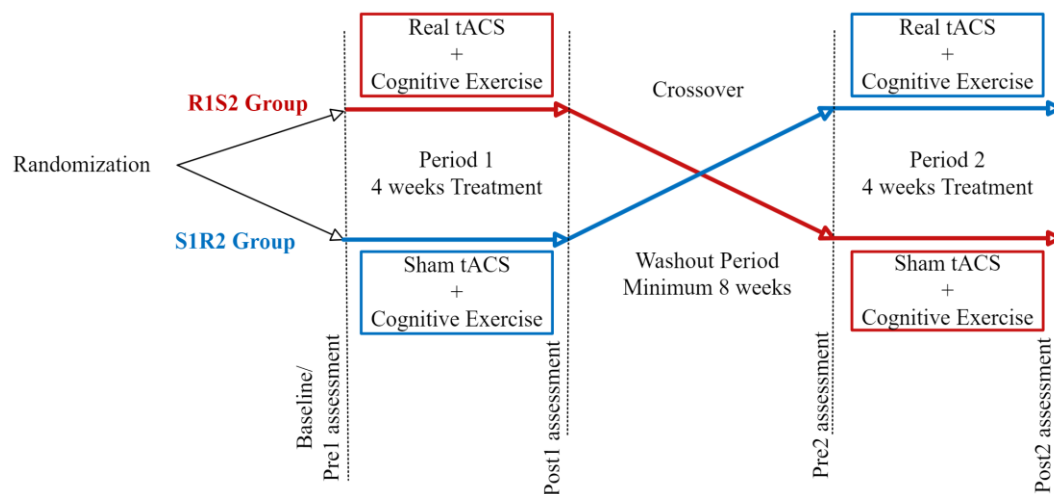


Figure 4-1. Schematic representation of the crossover study design.

The eligibility criteria for enrolling individuals into this study were:

- Age between 50 and 95 years

- MoCA score between 5 and 25
- Being on a stable dose of dementia-related medication or no medication 3 months prior to the study
- Ability to read, write and speak English or Spanish fluently

Exclusion criteria included were:

- Diagnosis of Parkinson's disease, Parkinsonian dementia, Huntington's disease, significant aphasia, intellectual disability, severe depression or anxiety, bipolar disorder, schizophrenia, or other major mood disorder
- History of epileptic seizures or epilepsy
- Impaired vision or hearing severe enough to impair performance in cognitive tests
- Current substance abuse disorder
- Currently participating in another therapeutic study for dementia
- Plans to change their dementia-related medication during the study's period

Participants were monitored closely to ensure the adherence of participants to the protocol.

Potential participants were recruited from previous studies or referrals from family physicians, geriatricians, neurologists and psychiatrists, who also provided the participants' diagnostic reports. Individuals were interviewed to determine if they met the inclusion and exclusion criteria including the MoCA [183]. All participants, along with a family member or legal guardian, were asked to sign an informed consent form (approved by the Biomedical Research Ethics Board of the University of Manitoba) prior to enrollment. Before the baseline assessment, participants were assessed for their ability to tolerate tACS. If the participant was unable to tolerate tACS, they were offered the option to only play cognitive exercises, which

their performance data are not included in the study analysis presented in this paper. Lastly, each participant was assigned an anonymized code for data recording to ensure confidentiality.

Enrollment into the study and assignment of the group was completed by the study coordinator (M.G.C.) by using the computerized randomization code.

4.3.2 Intervention

The treatment protocol for both real and sham tACS was 4 consecutive weeks, 5 days per week (excluding weekends), two 30-min stimulation paired with cognitive training sessions per day with a 30-min break in between, all in-person. The tACS was administered using the Soterix Medical Stimulator tES (New York, USA) machine with the following parameters:

- Waveform: Bipolar Sinusoid
- Frequency: 40 Hz
- Current Intensity: 0.75 mA amplitude (1.5 mA peak-to-peak)

Sham tACS using the Soterix device administers an initial increasing ramp up of current intensity for 30 seconds and ramp down to 0 mA for another 30 seconds and remains at 0 mA until the last minute of stimulation where the current again ramps up and ramps down within 1 minute.

Sponge electrodes soaked in saline were placed over the dorsolateral prefrontal cortex (F3 on the 10-20 electroencephalogram system) and contralateral supraorbital area. The treatment administrators were trained to ensure the electrodes had good contact with the scalp by checking the readings on the Soterix machine. They were also asked to record any side effects or adverse effects such as discomfort, sensitivity, burning, fatigue, headaches, dizziness, disorientation, itching/tingling, pain, and any other mentioned sensations they observed, or the participant mentioned throughout the session.

Participants were instructed and helped by the treatment administrators to perform cognitive exercises using the MindTriggers app while receiving the real or sham tACS [90] on an iPad. The cognitive exercises that every participant played at every treatment session included spatial cognition, associative memory, visual memory, image-word association, categorization, and memorize and rewrite sentences.

4.3.3 Assessments and Outcome Measures

Participants were assessed 3-7 days before the first treatment of each treatment block and 3-7 days after the last treatment of each treatment block by an assessor who was blinded to the treatment type (real or sham). The primary outcome measure was the changes in ADAS-Cog scores, a widely recognized tool for assessing cognitive function in individuals with AD or dementia. The ADAS-Cog consists of 11 tasks that evaluate multiple cognitive domains including memory, language, orientation, and praxis, making it a comprehensive measure for monitoring therapeutic and intervention outcomes [184]. The ADAS-Cog score ranges from 0 to 70, with lower scores indicating better cognitive performance and higher scores reflecting greater cognitive impairment.

The secondary outcome measures were the changes in Neuropsychiatric Inventory Questionnaire (NPI-Q) [185] and the Montgomery-Åsberg Depression Rating Scale (MADRS) [186]. The NPI-Q assesses the severity of neuropsychiatric symptoms over the past month using 12 questions. Symptom severity is rated on a scale from 1 (mild) to 3 (severe), with a total severity score ranging from 0 to 36. The version used in this study does not include caregiver burden. MADRS assesses depression severity across 10 items, each item rates on a scale from 0 to 6. Thus, the total score ranges from 0 (no depression) to 60 (severe depression).

4.3.4 Statistical Analysis

The baseline characteristics with continuous data (age, MoCA, MADRS, ADAS-Cog, and NPI-Q) were tested for any significant difference between R1S2 and S1R2 groups using independent t-test or their non-parametric equivalent if the assumptions of normality and homogeneity of variance were not satisfied. Categorical characteristics (sex, handedness, and education) were tested using chi-square test for any significant difference between R1S2 and S1R2.

To appropriately analyze the crossover design, we followed the statistical framework outlined in [187](pp. 7- 29) and [188](pp. 194-199) for all outcome measures (ADAS-Cog, NPI-Q, and MADRS). A mixed-effects model was implemented to evaluate the carry-over effect, period effect, and treatment effect, with participants included as the random effect. Following the mixed model analysis in [187], [188], for participant $i (= 1, 2, \dots, n_g)$ assigned to group $g (= R1S2, S1R2)$, where n_g is the total number of participants in group g , let $Y_{igp}^{(a)}$ denote the patient response at period $p (= 1, 2)$. We assume the following model:

$$Y_{igp} = y_{igp}^{(a=2)} - y_{igp}^{(a=1)} \quad (1)$$

$$Y_{igp} = \mu + \pi_p + \tau_{d[g,p]} + \gamma_{d[g,p-1]} + s_{ig} + \varepsilon_{igp} \quad (2)$$

where $y_{igp}^{(a)}$ denotes the measured outcome at either pre-treatment ($a = 1$) or post-treatment ($a = 2$) with larger values indicating an improved score; μ denotes the intercept; π_p denotes the effect associated with period; $\tau_{d[g,p]}$ denotes the effect associated with the treatment applied in period p of group g , $d[g, p]$ is either real or sham treatment; $\gamma_{d[g,p-1]}$ denotes carry-over effect where it is assumed that $\gamma_{d[g,0]} = 0$; s_{ig} denotes the random effect associated with participant i in group g ; and $\varepsilon_{igp}^{(a)}$ denotes the random errors with mean 0 and variance σ_e^2 . To

account for potential violations of model assumptions, such as heteroscedasticity or autocorrelation, the robust sandwich estimator is used. This method provides consistent estimates of the covariance matrix for parameter estimates even when the parametric model fails to hold. The model is implemented in SAS 9.4 M8 using the proc mixed procedure with the empirical option and Kenward-Roger degrees of freedom method. We did not perform separate preliminary tests for period and carry-over effects as explained in [188](pp. 39-44) that such tests lead to biased estimates of the direct treatment difference and increase the probability of Type I errors.

The hypotheses of this study were as follows:

1. Real tACS paired with cognitive exercises improves ADAS-Cog, NPI-Q, and MADRS scores in individuals with dementia more than sham stimulation $[\tau_{d[g,p]} \neq 0]$.
2. Both real tACS and sham tACS treatments, when combined with cognitive exercises, lead to improvements in ADAS-Cog, NPI-Q, and MADRS scores in individuals with dementia after a 4-week treatment period.
3. Real tACS will produce sustained improvements in ADAS-Cog, NPI-Q, and MADRS scores after the first treatment period compared to sham tACS. This will be observed by comparing the scores at the post-treatment assessment of the first period to the pre-treatment assessment of the second period.

To test the second hypothesis that both real and sham treatments would result in significant improvements in all outcome measures post-treatment compared to pre-treatment scores, we conducted one-sided paired t-tests separately for each treatment type. The significance

threshold was adjusted to $\alpha = 0.025$ following Bonferroni correction to account for multiple comparisons. To ensure there is no influence from carryover effect, only period 1 data was used.

Similar to our previous clinical trial [124], we used both ADAS-Cog and NPI-Q to classify the response rate of participants into four categories: “Marked”, “Moderate”, “No-Change” and “Declining.” The criteria for classification are as follows (Note that the AND is a logical and):

- Marked Response: A ≥ 3 -point improvement in the ADAS-Cog score from pre- to post-treatment block.
- Moderate Response: An improvement in the ADAS-Cog score between 1 and 3 points AND an improvement or no change in the NPI-Q score.
- No-Change Response: A change in the ADAS-Cog score between -1 and 1 points, OR an ADAS-Cog score improvement between 1 and 3 points AND a decline in the NPI-Q score.
- Declining Response: A decline of more than 1 point in the ADAS-Cog score.

The response rates were categorized into responders (combined "Marked" and "Moderate" responses) and non-responders (combined "No-Change" and "Declining" responses) due to limited samples. To assess treatment effects, we performed McNemar’s test, a statistical test for paired categorical data, comparing response rates between the real tACS and sham conditions within subjects. Additionally, we reported descriptive statistics, including the percentages of each response type within each treatment group and period.

To evaluate the third hypothesis regarding long-term effects of tACS compared to sham, independent sample t-tests were used to compare changes in the outcome measures during the washout period. For this analysis, we calculated the change during the washout period by

subtracting the post1 from the pre2 values, which served as the follow-up assessment. The one-sided independent sample t-tests were then conducted to compare the calculated changes between the real tACS and sham tACS groups.

4.4 Results

The study was conducted from 20 December 2021 to 31 July 2024, as originally planned, and concluded upon completion of the study period. A total of 55 participants with dementia were enrolled in the study. However, ten participants were lost to attrition, including seven who formally withdrew for various reasons, while three did not provide any reason. Of the seven withdrawn subjects, six had been assigned to R1S2 and one to S1R2 groups, resulting in five with usable data up to post1 or pre2. Table 4-1 lists the reasons for participants' withdrawal and time of withdrawal. Furthermore, four participants had protocol breaches, which were excluded from the analysis; two participants were assigned to the R1S2 group, and two were in the S1R2 group. There were four participants whose data were excluded because (1) they live out of town and were not blinded; were (2) performing the treatment remotely, hence no tACS; and were (3) not compliant with the cognitive exercises. A flowchart of the enrolled participants and the participants excluded from the analysis is shown in Figure 4-2. The demographics for the 42 participants who were included in the analysis is shown in Table 4-2, including *p*-values comparing the baseline characteristics between R1S2 and S1R2. As shown, there were no significant differences between the two groups in terms of age, MoCA, MADRS, ADAS-Cog, NPI-Q, and sex, although education is marginally significant between R1S2 and S1R2. Importantly, no serious adverse effects were reported during this study. As for the washout period, while the majority followed the protocol of 8 weeks, some, due to unforeseen reasons,

e.g., illness, emergencies, etc., had a longer washout period. The average washout duration for the R1S2 and S1R2 groups were 11.3 and 10.7, respectively.

Table 4-1. Reasons for participant withdrawal in the clinical trial.

Participant	Group	Withdrawal Reason	Time of Withdrawal
P008	R1S2	Personal issues	After 4 treatment days in the first period
P012	R1S2	Difficulty attending the treatments due to health decline	After pre2 assessment
P016	R1S2	Moving to a long-term care facility	After 14 treatment days in the second period
P021	R1S2	Difficulty attending the treatments due to health decline	After post1 assessment
P037	S1R2	Participant and their caregiver perceived the study as too long	After post1 assessment
P039	R1S2	Did not want to participant and continued health decline	After post 1 assessment
P046	R1S2	Hesitant to start treatment	After 9 treatment days in the first period

Note: Pre2 assessment is the assessment before the second period. Post1 assessment is the post-treatment assessment of the first period.

Table 4-2. Descriptive statistics summarizing the demographic characteristics of study participants stratified by group.

Participant Characteristic	R1S2 Group (<i>n</i> = 21)	S1R2 Group (<i>n</i> = 21)	<i>p</i> -value
Age (years)	72.9 ± 8.6	76.3 ± 9.3	0.227
MoCA	16 ± 5.8	16 ± 5.1	0.955
MADRS	4.3 ± 4.3	5.7 ± 8.0	0.969
ADAS-Cog	22.2 ± 8.9	21.4 ± 9.7	0.783
NPI-Q	7.7 ± 4.5 (<i>n</i> = 17)	5.5 ± 4.4 (<i>n</i> = 21)	0.141
Sex			
Female	10 (47.6 %)	6 (28.6 %)	0.341
Male	11 (52.4 %)	15 (71.4 %)	
Handedness			
Right	18 (85.7 %)	20 (95.2 %)	
Left	3 (14.3 %)	0	
Ambidextrous	0	1(4.8 %)	
Education			
High school or below	9 (42.9 %)	10 (47.6 %)	0.133
Above a high school diploma	12 (57.1 %)	11 (52.4 %)	

Note: The *p*-values correspond to the appropriate independent t-test, Mann Whitney U test, or Chi-squared test to compare R1S2 and S1R2 group baseline characteristics. Continuous variables are presented as *mean* ± *SD* and categorical variables as *n* (%).

Abbreviations: Montreal Cognitive Assessment (MoCA), Montgomery–Åsberg Depression Rating Scale (MADRS), Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Neuropsychiatric Inventory-Questionnaire (NPI-Q)

4.4.1 ADAS-Cog Results

The mixed-effects model analysis revealed no significant period effect (*p*-value = 0.633), carry-over effect (*p*-value = 0.414), or treatment effect (*p*-value = 0.934) observed on ADAS-Cog score differences (Table 4-3 and Table 4-4). Residual diagnostics confirmed model assumptions. The Anderson–Darling test showed no significant deviation from normality ($A^2 = 0.267$, *p*-value > 0.250). Levene’s test indicated homogeneity of variances across periods ($F = 0.09$, *p*-value = 0.765). Residuals plotted against the order of data collection showed no

discernible pattern, suggesting independence and no autocorrelation. Figure 4-3 (a) illustrates group means of ADAS-Cog scores for all four assessments, stratified by group.

Table 4-3. Solution for fixed effects in the mixed-effects model analysis for ADAS-Cog score differences.

Effect	Estimate	Standard Error	DF	t Value	Pr > t
Intercept	-0.4635	0.8841	35	-0.52	0.6034
Carry-over (no)	-1.8178	2.2005	35	-0.83	0.4144
Period (1)	0.6519	1.3514	35	0.48	0.6326
Treatment (Real)	-0.1181	1.4140	35	-0.08	0.9339

Table 4-4. Type 3 tests of fixed effects in the mixed-effects model analysis for ADAS-Cog score differences.

Effect	Num DF	Den DF	F Value	Pr > F
Period	1	35	0.23	0.6326
Treatment	1	35	0.01	0.9339
Carry-over	1	35	0.68	0.4144

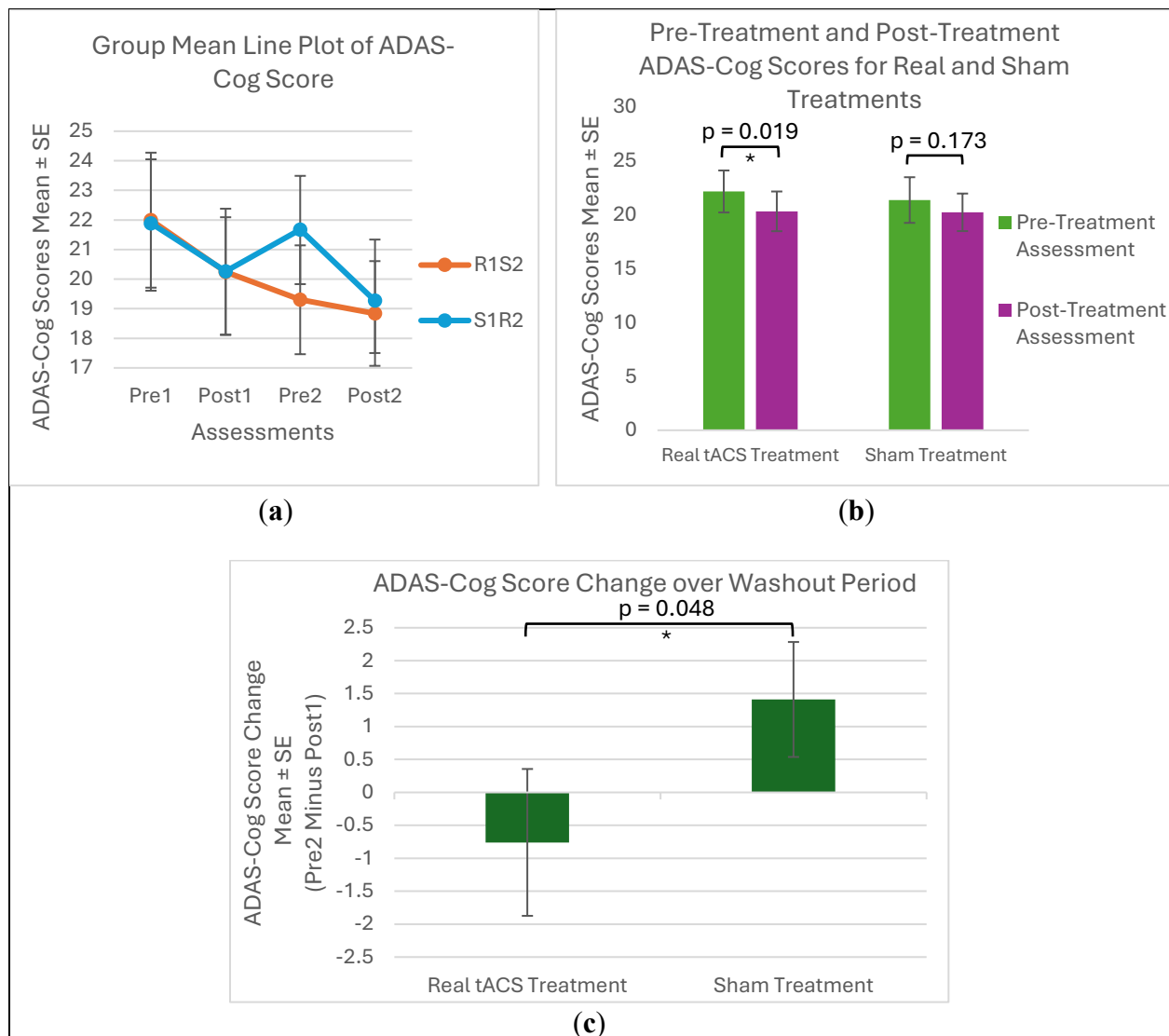


Figure 4-3. (a) Mean ADAS-Cog scores for each assessment, stratified by group; (b) ADAS-Cog score changes from pre-treatment to post-treatment in period 1; (c) ADAS-Cog score changes during the washout period. Lower scores indicate improvement. * $p < 0.05$.

Two paired samples t -tests were conducted to compare the ADAS-Cog scores before and after each treatment (real and sham) using data from period 1. To correct for multiple comparisons, a Bonferroni correction was applied, setting the adjusted significance threshold at $\alpha = 0.025$. For the paired t -test for real tACS treatment, the assumption of normality was tested using the Shapiro–Wilk test on the difference in ADAS-Cog scores (p -value = 0.749). Outliers

were assessed using Z-scores, and no outliers were detected. As shown in Figure 4-3 (b), there was a significant difference in the scores before treatment ($M = 22.17$, $SD = 8.93$) and after real tACS treatment ($M = 20.32$, $SD = 8.45$) ($t(20) = 2.2183$, $p\text{-value} = 0.019$). However, a paired samples t -test conducted to compare the ADAS-Cog scores before and after the sham tACS treatment showed no significant difference in the scores before ($M = 21.37$, $SD = 9.71$) and after treatment ($M = 20.23$, $SD = 7.99$) ($t(20) = 0.9638$, $p\text{-value} = 0.173$) (Figure 4-3 (b)). Similarly, the Shapiro-Wilk test indicated normality ($p\text{-value} = 0.883$), and no outliers were detected using Z-scores. These results suggest that the real treatment had a significant effect on the ADAS-Cog scores post-treatment whereas sham treatment did not.

To analyze the long-term effects of tACS, an independent-sample t -test was used to compare changes in ADAS-cog scores during the washout period (from post1 to pre2) between the real and sham tACS groups. The pre2 assessment served as the follow-up reference point, allowing for a direct comparison of score changes. Prior to conducting the t -test, the Shapiro-Wilk test confirmed the normality of the data ($p\text{-value} = 0.983$ for the real treatment group and $p\text{-value} = 0.522$ for the sham treatment group), and Levene's test verified the homogeneity of variances ($p\text{-value} = 0.610$). The results indicated a significant difference between the real tACS treatment ($M = -0.76$, $SD = 4.32$, $n = 19$) and sham tACS treatment ($M = 1.41$, $SD = 3.60$, $n = 20$) ($t(37) = -1.709$, $p\text{-value} = 0.048$) (Figure 4-3 (c)), over the washout period. This suggests that real tACS had a significant effect on the improvement of ADAS-Cog scores during the washout period, while sham tACS did not produce a comparable change. These findings highlight the potential long-term benefits of real tACS in cognitive function beyond the immediate treatment phase.

4.4.2 NPI-Q Results

There were 4 participants from the R1S2 group who were missing NPI-Q scores due to either being unable to reach their caregivers or the assessor forgetting to administer the assessment.

The mixed-effects model analysis of the NPI-Q score differences revealed no significant treatment effects (p -value = 0.387) observed in the data (Table 4-5 and Table 4-6). However, there was a significant period effect (p -value = 0.003) and a marginally significant carryover effects (p -value = 0.066) or observed in the data. Residual diagnostics confirmed the homogeneity of variance and independence, and no autocorrelation was detected. The Anderson-Darling test showed significant deviation from normality ($A^2 = 1.080$, p -value = 0.008); however, given the use of the robust sandwich estimator, the model remains valid despite this violation. Levene's test indicated homogeneity of variances across periods ($F = 3.09$, p -value = 0.084). Residuals plotted against the order of data collection showed no discernible pattern, suggesting independence and no autocorrelation. Figure 4-4 (a) illustrates group means of NPI-Q scores for all four assessments, stratified by group.

Table 4-5. Solution for fixed effects of the mixed-effects model analysis for NPI-Q score differences.

Effect	Estimate	Standard Error	DF	t Value	Pr > t
Intercept	-1.3077	0.5031	31	-2.60	0.0142*
Carry-over (no)	2.8981	1.5208	31	1.91	0.0660
Period (1)	-3.9904	1.2539	31	-3.18	0.0033**
Treatment (Real)	-1.2154	1.3850	31	-0.88	0.3869

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4-6. Type 3 tests of fixed effects in the mixed-effects model analysis for NPI-Q score differences.

Effect	Num DF	Den DF	F Value	Pr > F
Period	1	35	10.13	0.0033**
Treatment	1	35	0.77	0.3869
Carry-over	1	35	3.63	0.0660

Note: ** $p < 0.01$.

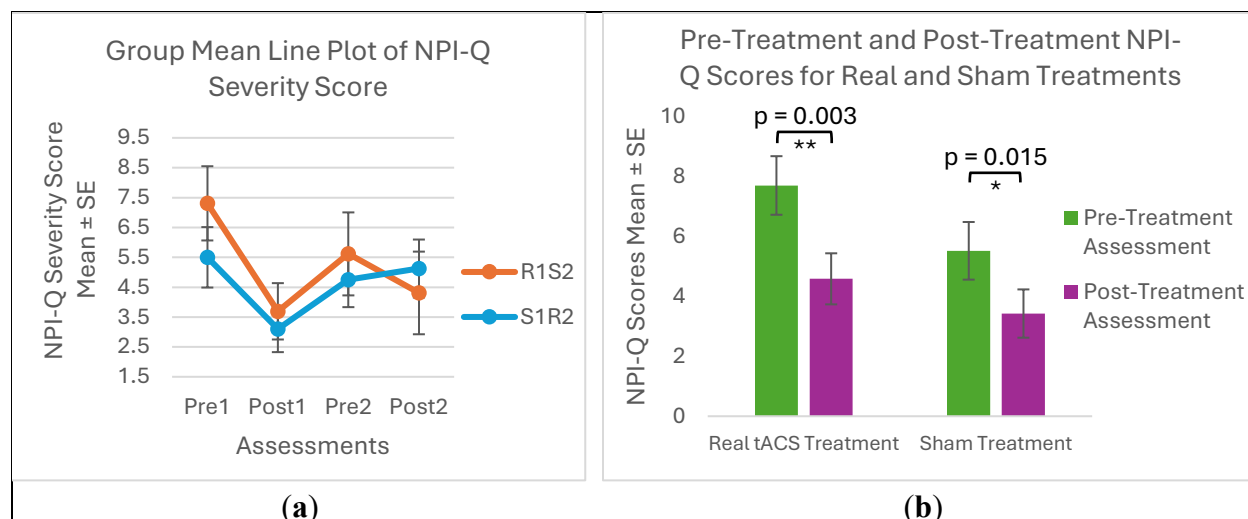


Figure 4-4. (a) Mean NPI-Q presence scores for each assessment, stratified by group; (b) NPI-Q score changes from pre-treatment to post-treatment in period 1. Lower scores indicate improvement. * $p < 0.05$, ** $p < 0.01$.

Two paired samples t-tests were used to compare the NPI-Q scores before and after each treatment (real and sham). As shown in Figure 4-4 (b), there was a significant difference in the scores before treatment ($M = 7.71$, $SD = 4.48$) and after real tACS treatment ($M = 4.59$, $SD = 3.91$) ($t(16) = 3.096$, $p\text{-value} = 0.003$). The Shapiro-Wilk test indicated normality for real ($p\text{-value} = 0.084$) and sham ($p\text{-value} = 0.101$) and no outliers were detected using Z-scores. The paired samples t-test conducted to compare the NPI-Q scores before and after the sham tACS treatment showed a significant difference in the scores pre1 ($M = 5.52$, $SD = 4.41$) and post1 ($M = 3.43$, $SD = 3.70$) ($t(20) = 2.3294$, $p\text{-value} = 0.015$). These results suggest that both real and sham treatments had a significant effect on the neuropsychiatric symptom scores post-treatment compared to pre-treatment, with real tACS showing a greater effect.

A two-sample *t*-test was then used to compare changes in NPI-Q scores during the washout period, between the real tACS and sham tACS groups. Prior to conducting the *t*-test, the Shapiro–Wilk test confirmed the normality of the data (*p*-value = 0.842 for the real treatment group and *p*-value = 0.413 for the sham treatment group), and Levene’s test verified the homogeneity of variances (*p*-value = 0.946). The results indicated no significant difference between the real tACS treatment (M = 1.6, SD = 3.62, *n* = 15) and sham tACS treatment (M = 1.65, SD = 3.59, *n* = 20) (*t*(33) = −0.0406, *p*-value = 0.484). This suggests that there were no significant long-term effects of real tACS compared to sham tACS on neuropsychiatric symptoms during the washout period.

4.4.3 Response Rate

Table 4-7 presents the frequency of each response (Marked, Moderate, No-Change, and Declining) for both real and sham tACS treatment groups, separated by treatment periods (Period 1 and Period 2). To further evaluate the significance of changes in response rates, McNemar's test was conducted to compare the proportion of responders (combined Marked and Moderate) between real and sham tACS treatments. From the contingency table, adding Marked and Moderate Responses for the real treatment shows that 57.7% of participants responded positively to real tACS and adding Marked and Moderate Responses for sham treatment shows that 39.4% responded to sham tACS. The test revealed no statistically significant difference in response rates between real and sham tACS conditions ($\chi^2(1) = 1.56$, *p*-value = 0.211), indicating that response rates were comparable across conditions.

Table 4-7. Frequency of the different response types in each treatment and each period.

Group	Period	Treatment	Marked Response	Moderate Response	No-Change Response	Declining Response
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R1S2	1	Real	5 (15.2 %)	2 (6.1 %)	3 (9.1 %)	3 (9.1 %)
	2	Sham	4 (12.1 %)	0	5 (15.2 %)	4 (12.1 %)
S1R2	1	Sham	7 (21.2 %)	2 (6.1 %)	6 (18.2 %)	5 (15.2 %)
	2	Real	9 (27.3 %)	3 (9.1 %)	4 (12.1 %)	4 (12.1 %)

Note: The values are written as n (%) where the percentage is calculated out of the total number of participants.

4.4.4 MADRS Results

The mixed-effects model analysis comparing real and sham tACS on MADRS scores revealed no significant carryover effects (p -value = 0.644), period effects (p -value = 0.734), or treatment effect (p -value = 0.422) (Table 4-8 and Table 4-9). Residual diagnostics confirmed model assumptions. The Anderson-Darling test showed no significant deviation from normality ($A^2 = 0.47$, p -value = 0.244). Levene's test indicated the homogeneity of variances across periods ($F = 0.15$, p -value = 0.700). Residuals plotted against the order of data collection showed no discernible pattern, suggesting independence and no autocorrelation. Figure 4-5 (a) illustrates group means of MADRS scores for all four assessments, stratified by group.

Table 4-8. Solution for fixed effects in the mixed-effects model analysis for MADRS score differences.

Effect	Estimate	Standard Error	DF	t Value	Pr > t
Intercept	-0.4118	0.9524	35	-0.43	0.6681
Carry-over (no)	-1.0206	2.1898	35	-0.47	0.6441
Period (1)	0.3324	0.9693	35	0.34	0.7337
Treatment (Real)	-1.0176	1.2536	35	-0.81	0.4224

Table 4-9. Type 3 tests of fixed effects in the mixed-effects model analysis for MADRS score differences.

Effect	Num DF	Den DF	F Value	Pr > F
Period	1	35	0.12	0.7337
Treatment	1	35	0.66	0.4224

Carry-over	1	35	0.22	0.6441
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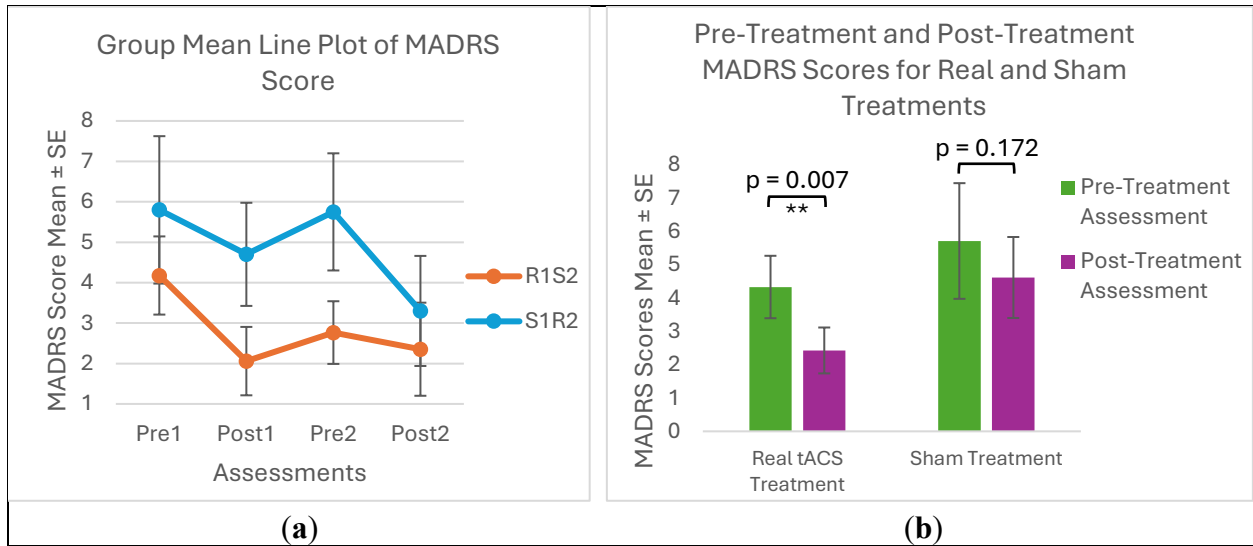


Figure 4-5. (a) Mean MADRS scores for each assessment, stratified by group; (b) MADRS score changes from pre-treatment to post-treatment in period 1. Lower scores indicate improvement. ** $p < 0.01$.

Wilcoxon signed-rank tests were used due to the Shapiro-Wilk test results (p -value < 0.03 for real and sham) to compare the MADRS scores before and after each treatment (real and sham). As shown in Figure 4-5 (b), there was a significant difference in the scores before ($M = 4.33$, $SD = 4.29$) and after real tACS treatment ($M = 2.43$, $SD = 3.16$); $V = 81$, p -value = 0.007. However, sham tACS treatment showed no difference in the scores before ($M = 5.71$, $SD = 7.96$) and after treatment ($M = 4.62$, $SD = 5.57$); $V = 51.5$, p -value = 0.172. These results suggest that real tACS treatment significantly improved depression scores post-treatment, whereas sham treatment did not show a significant effect.

A two-sample t -test was used to compare changes in MADRS scores during the washout period between the real tACS and sham tACS groups. The Shapiro-Wilk test confirmed the normality of the data (p -value = 0.918 for the real treatment group and p -value = 0.111 for the sham treatment group), and Levene's test verified the homogeneity of variances (p -value =

0.660). The results indicated a significant difference between the real tACS treatment ($M = 1.16$, $SD = 3.44$, $n = 19$) and sham tACS treatment ($M = 1.05$, $SD = 4.08$, $n = 20$) ($t(37) = -0.089$, p -value = 0.535). This suggests that there were no significant long-term effects of real tACS compared to sham tACS on depression during the washout period.

4.5 Discussion

In this study, we demonstrated that tACS paired with cognitive exercises significantly improves cognitive function with sustained effects lasting up to approximately 2-3 months compared to sham tACS with cognitive exercises (p -value = 0.048). The results align with findings from our previous pilot studies [51], [52], [53], which reported significant cognitive improvements with tACS paired with cognitive exercise compared to baseline. However, while the pilot study [53] showed a non-significant trend toward sustained cognitive effects of real tACS group lasting up to 1-month after treatment, this study demonstrated statistically significant long-term effects lasting on average up to 2-3 months post-treatment. These differences could all be due to small sample numbers in our pilot studies compared to this study.

Our findings are mostly consistent with previous research on tACS in dementia. One study applying 40 Hz tACS over the left angular gyrus for 14 weeks showed a trend toward improvement at the end of the treatment period and toward sustained benefits lasting 2-3 months measured by Memory Index Score [163]. Another study applying 40 Hz tACS over bitemporal lobes for 6 weeks found significant post-treatment improvements in the tACS group whereas sham group did not [162]. However, long-term effects differed, as ADAS-Cog scores in that study returned to baseline by the 12-week follow-up, while MMSE scores showed sustained improvement. Unlike these earlier studies, our results provide stronger evidence for the additive

effects of tACS paired with structured cognitive training showing sustained improvements 2-3 months post-treatment in ADAS-Cog scores.

The selection of the left DLPFC for stimulation was based on its central role in the default mode network, which is crucial for cognition, particularly memory consolidation and retrieval commonly impaired in dementia [189]. While there are many regions affected by dementia including the hippocampus and temporal lobe [190], there is evidence that the DLPFC is also significantly impacted. Structural and functional imaging studies have reported DLPFC involvement in AD [191], [192], and preclinical work [193] supports this by showing how the prefrontal cortex layer 3 pyramidal cells displayed the lowest number of terminals. Given this, targeting the DLPFC with 40 Hz tACS may be particularly effective in modulating oscillatory dynamics relevant to cognitive dysfunction in dementia. Previous studies have demonstrated cognitive benefits when 40 Hz tACS is applied to the DLPFC [160], [168]. Additionally, a sham-controlled study comparing 40 Hz tACS and tDCS over the DLPFC in individuals with MCI found that tACS led to significant improvements in the Stroop-color test compared to tDCS, suggesting distinct cognitive benefits [194]. These findings reinforce the rationale for targeting the DLPFC in dementia research.

Both tACS and cognitive exercises have been shown to individually benefit cognitive function in individuals with dementia. However, their combination appears to amplify these effects. To date, our research team is the only one to have explored gamma-tACS paired with cognitive exercises [52], [53]. Other studies have paired cognitive training with either theta-tACS or tDCS. For example, one study applying theta-tACS everyday for 1 week in individuals with MCI found significant improvement not only in the trained task but also in sustained attention, inhibitory control and attentional orienting transferring benefits to untrained tasks

[195]. However, they did not find improvement in working memory capacity and that improvements were mostly seen in tasks related to the trained task. Another study applying theta-tACS, sham, or tDCS in healthy older adults for 10 sessions, twice weekly, found significant improvements in composite cognitive scores across all groups immediately post-intervention, with tDCS producing greater improvements in those with lower baseline MoCA scores [196]. The present study adds to this body of research by demonstrating the potential for gamma-tACS and cognitive exercise to produce lasting cognitive benefits.

A key in our study is that the daily cognitive exercises were not used as an evaluation tool, but rather as a means to cognitively challenge participants. Each session was guided by a trained treatment administrator, ensuring engagement and adherence to the exercises. Cognitive exercises assisted by a treatment administrator to instruct and help participants produced superior outcomes compared to unsupervised training, consistent with findings from [53], [173]. This suggests that structured interventions with professional guidance enhance engagement and task-specific learning. It can be seen clearly from Figure 4-3(a) that the ADAS-Cog scores improved after 4 weeks of treatment that both real tACS and sham tACS improved from the cognitive exercises. However, the combination of tACS and cognitive training likely amplified these effects by concurrently modulating neural oscillations and activating task-relevant networks. When delivered during cognitive engagement, 40 Hz tACS may help entrain gamma oscillations in regions involved in the task, promoting more synchronized neural firing. This synchronization can enhance network efficiency and may support neuroplastic changes in circuits activated by the cognitive exercises. Multiple, high-frequency sessions further reinforced these benefits, contributing to sustained cognitive improvements lasting up to approximately 2-3 months post-treatment as seen in Figure 4-3(a) by the continued decline of ADAS-Cog scores from post1 to

pre2 for R1S2 group compared to S1R2 group whose ADAS-Cog scores returned to their baseline score. As previously mentioned in the introduction, previous studies have suggested that one of the effects of 40 Hz tACS is improving blood perfusion in the targeted area [78]. It is possible that repeated daily stimulation influenced blood flow dynamics, which may have contributed to the sustained cognitive improvements observed in the real tACS group compared to sham. The analysis on NPI-Q assessment, which measures neuropsychiatric symptoms, found a significant period effect and marginally significant carry-over effect. This may be attributed to the nature of the assessment, as it relies on caregivers' reports rather than participant self-assessments, with an assessor completing the final scoring. Caregivers' responses may be influenced by factors such as emotional state, memory, expectations, or prior exposure to treatment [197]. The period effect suggests that caregivers may have formed assumptions about treatment efficacy based on their experiences in the first period. Analysis of the first-period data, due to the period effect, indicated a significant improvement in NPI-Q post-treatment compared to baseline for real and sham groups. However, there was no significant difference in the long-term effects of either treatment on neuropsychiatric symptoms.

The response rates to treatment, based on ADAS-Cog and NPI-Q, were 57.7% for real tACS and 39.4% for sham treatment. This response rate is lower than in our previous clinical trial on repetitive transcranial magnetic stimulation treatments for AD [124]; however, in this study, we categorized "Responders" and "Non-responders" more strictly. Notably, one non-responder we suspect has posterior cortical atrophy (PCA), a condition that a participant of a previous study was also not responsive to any brain stimulation. Another non-responder exhibited significant anxiety, which may have influenced cognitive performance.

Depression is often a confounding variable for cognitive improvement. It is important to note that among our participants, six had mild depression and two had moderate depression at baseline, as measured by MADRS. Depression is common in people living with dementia [198], and addressing mood disturbances is critical for improving overall quality of life in this population. In the analysis of MADRS scores, we found a significant improvement in depression scores post-treatment compared to pre-treatment in the real tACS but not in the sham. However, neither treatment group had long-lasting effects on depression scores. These results suggest that the relationship between cognitive and depression scores may not be as strongly correlated as initially assumed. While cognitive scores improved post-treatment and continued to improve during the washout period for the real tACS group, MADRS scores did not follow the same pattern. The improvement in MADRS scores post-treatment may have been influenced by both tACS and the social interaction in the lab. However, the increase in MADRS score during washout period (i.e. increased depression) may be due to the loss of social interaction or the possibility that tACS does not have long-lasting effects on depression. Contrary to our results, a meta-analysis on 40 Hz tACS found no significant improvement in depression scores post-treatment but they stated that there were participants who reported improvements, suggesting that a larger sample size may find significant effects [199].

4.5.1 Limitations

This study has several limitations that should be acknowledged. First, the relatively small sample size ($n = 42$), which is commonly seen in studies involving participants with dementia and brain stimulation, limits the generalizability of the findings. Recruitment challenges for this population, combined with the demanding protocol, made it difficult to recruit a larger sample. While our initial target was 60 participants, this number was not met by the study's conclusion.

Future studies with larger samples are necessary to validate these results and may provide information on whether mild dementia participants improve more compared to moderate dementia participants. Second, the study experienced a notable withdrawal rate of 18.2%, which may introduce selection bias and impact the reliability of the outcomes. Future research should explore ways to improve retention through enhanced participant support and reduced protocol burden. The third limitation is the variability in the washout period, which ranged from 8 weeks to 7 months. Initially, we aimed to maintain a fixed washout period, and most participants adhered to the 8-week schedule. However, numerous factors, including health issues, transportation difficulties due to the weather, and travel plans, hindered strict adherence to the study schedule, leading to variations in the washout period. This inconsistency impacted the analysis of long-term effects and limited our ability to accurately assess potential carry-over effects in the crossover design. Implementing a fixed or a washout period with less variability in future crossover trials may improve the interpretability of long-term outcomes. However, this approach may present a trade-off, as it could impact participant retention, particularly since individuals in this age group often travel for extended periods. Fourth, our participants had various dementia diagnoses including mixed dementia, AD, posterior cortical atrophy, vascular dementia, and frontotemporal dementia. Although the majority of participants had AD or mixed AD (62%), due to the variability in underlying pathology, progression rates, and responses to treatment, these different diagnoses may have introduced heterogeneity into the results, making it difficult to generalize the findings. Our decision to include a broader range of dementia diagnoses was driven by the need to recruit enough participants to approach the original sample size calculation. While this approach aimed to enhance the statistical power of the study, it introduced variability in the dementia types, which complicates the interpretation of the results.

Recruiting enough participants to stratify them based on their specific dementia diagnosis and ensuring an adequate sample size are very challenging. However, future research should consider addressing these challenges to better understand the differential effects of the intervention.

Conducting subgroup analyses may help determine whether certain types of dementia respond better to the intervention compared to others. Fifth, the potential practice effect with ADAS-Cog must be considered, as repeated exposure to the same cognitive tests could lead to improved scores unrelated to the intervention itself [200]. Our attempt to control for practice effect was to use alternate versions of ADAS-Cog that use different word lists. Nevertheless, the remaining tests are the same across the assessments. Additionally, the influence of participants' mood on the day of their assessment will influence their test result. However, it is very difficult to control for a participant's mood and find a way to mitigate this effect, but having a large sample size can help overcome this confounding variable. Addressing these limitations in future research will be crucial to refining the study design and enhancing the reliability of the findings.

4.6 Conclusions

This study provides compelling evidence that 4 consecutive weeks of gamma-frequency transcranial alternating current stimulation (tACS) paired with cognitive exercises can significantly improve cognition, neuropsychiatric symptoms, and depression in individuals with dementia. With this crossover, sham-controlled, double-blind design, we demonstrated that real tACS not only improves cognitive performance post-treatment but also produces sustained benefits compared to sham stimulation. The findings from this study highlight the significance of combining tACS and cognitive exercise as a promising non-invasive treatment for dementia and related cognitive disorders.

Chapter 5: ADAS-Cog Trajectories Differ from Expected Decline in Dementia Following Repeated Non-Invasive Interventions Over 3 Years

This chapter investigates the long-term cognitive trajectories of individuals living with dementia who received repeated non-invasive interventions, including tES, TMS, and/or CT. The motivation for this study came from recognizing the extensive longitudinal dataset accumulated over seven years through multiple clinical trials. This dataset provides an unprecedented opportunity to examine whether repeated non-pharmacological interventions could alter the typical trajectory of cognitive decline in dementia and AD. By analyzing data from participants who underwent multiple treatment blocks, this study aimed to assess the feasibility and potential impact of sustained non-invasive interventions on cognitive outcomes over time. This work has been published in a peer-reviewed journal as cited below:

M. A. Uehara, S. Kalia, M. G. Campuzano, and Z. Moussavi, “ADAS-Cog Trajectories Differ from Expected Decline in Dementia Following Repeated Non-Invasive Interventions over 3 Years,” *Medicina*, vol. 61, no. 11, Nov. 2025, doi: 10.3390/medicina61111994.

5.1 Abstract

Background and Objectives: Non-pharmaceutical interventions such as cognitive training, transcranial electrical stimulation (tES), and repetitive transcranial magnetic stimulation (rTMS) have shown promise in improving cognitive outcomes in Alzheimer’s disease (AD) and dementia. However, the long-term effects of repeated non-invasive interventions remain unknown. This study investigated whether repeated non-invasive interventions administered over a span of 1 to 3 years were associated with slower cognitive decline compared to typical AD

progression, and whether longer no-treatment intervals between treatments predicted greater post-treatment decline.

Materials and Methods: Seventy-three participants living with dementia or AD received 2 to 9 blocks of non-invasive treatments (including tES, rTMS, cognitive training). Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) scores were collected longitudinally up to 3 years (36 months), across multiple intervention and assessment sessions. A mixed-effects model was used to estimate the rate of cognitive decline, adjusting for baseline age, sex, and baseline cognition (MoCA) with participants being the random effect. The observed rate of change was compared to a meta-analysis estimate of AD progression. Additionally, a linear mixed-effects model using robust sandwich estimation of standard errors was employed to assess whether the no-treatment interval was associated with changes in ADAS-Cog scores.

Results: Participants showed a significantly slower rate of cognitive decline than expected from the AD reference rate ($p < 0.001$), with many demonstrating stabilized ADAS-Cog scores during their respective treatment periods, ranging from 1 to 3 years. Medication analyses revealed no significant effect of AD medications, antidepressants, antihypertensives, or cholesterol-lowering agents on cognitive outcomes. Furthermore, longer no-treatment intervals were significantly associated with greater post-treatment decline ($p < 0.001$).

Conclusions: Repeated non-invasive treatments seem to slow the rate of cognitive decline in individuals living with dementia when administered over a prolonged period. This study provides evidence supporting the feasibility and effects of personalized long-term non-invasive treatment strategies for dementia.

5.2 Introduction

Over the last two decades, there have been thousands of studies analyzing the immediate and short-term effects of non-invasive interventions including cognitive training (CT) either alone or paired with electrical or magnetic stimulation in individuals with dementia and particularly with Alzheimer's disease (AD). However, to our knowledge, no study to date has investigated the long-term effects of repeated blocks of non-invasive interventions, especially when administered over a period longer than one year, on sustained cognitive improvement in individuals living with dementia or AD.

Non-invasive brain stimulation (NIBS) interventions, including repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES) both aim to stimulate the brain without surgery. They use different mechanisms: rTMS uses pulsed magnetic fields whereas tES uses electric fields, but with commonality in that they try to modulate neuronal networks by either directly influencing neuron firing or by influencing excitability and plasticity [4].

There is growing evidence supporting the short-term and mid-term effects of non-invasive brain stimulation (NIBS) interventions, including repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES), in people living with AD/dementia. The two main types of tES are transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS). A recent meta-analysis reported that anodal tDCS significantly improved global cognition in individuals with AD, compared to sham, as measured by the Mini-Mental State Examination (MMSE); they also demonstrating good tolerability, with only mild adverse effects and no difference in dropout rates between real and sham groups [201]. Protocols across the included studies ranged from single sessions to

interventions lasting up to six months. Another meta-analysis similarly found that tDCS improved MMSE scores; in addition, they reported sustained effects lasting up to eight weeks [202]. Their analysis further indicated that stimulation sessions longer than 20 minutes and targeting the temporal cortex were more effective in enhancing global cognition than shorter sessions or left dorsolateral prefrontal cortex (DLPFC) stimulation [202]. In contrast, a separate meta-analysis found that both left DLPFC and temporal lobe stimulation enhanced memory performance, and that repeated tDCS sessions exerted cumulative positive effects on overall cognitive function, as assessed by multiple instruments including the Montreal Cognitive Assessment (MoCA), MMSE, and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) [203].

While tDCS has been studied for many years, emerging evidence suggests that tACS may have similar or more potential to enhance cognitive function in individuals with AD. One systematic review found that gamma- and theta-tACS protocols were associated with improvements in memory, executive function, and global cognition, particularly in older adults with cognitive impairment [204]. However, the review also highlighted substantial methodological heterogeneity across studies—including differences in stimulation frequency, electrode montage, current intensity, session number, and cognitive outcome measures—which limits direct comparisons and generalizability. Another literature review focusing specifically on gamma-frequency tACS (typically 40 Hz) in mild cognitive impairment (MCI) and AD populations reported promising effects on memory and attention, with some studies suggesting that repeated sessions, many studies following 20 sessions over 4 weeks, may yield cumulative benefits [160]. These findings highlight the emerging potential of tACS for cognitive

enhancement in AD, warranting further investigation into optimal stimulation parameters and long-term efficacy.

In addition to the literature on tES, one meta-analysis found that using high-frequency rTMS (≥ 10 Hz) targeting the DLPFC for people living with AD had significant improvement in cognitive outcomes such as ADAS-Cog and MMSE scores, immediately post-intervention compared to baseline [205]. This same meta-analysis found that significant results were from studies that had one block of treatment (including 20 or 30 successive treatment sessions) with excitatory stimulation (frequency ≥ 10 Hz) treatment sessions compared to those with a block of less than 10 sessions or those with inhibitory stimulation (rTMS frequency < 2 Hz). Furthermore, their analysis found that the observed improvements lasted about 1.5 months, with significantly better ADAS-Cog scores at the shorter follow-up durations compared to 3 months [205]. Another meta-analysis similarly reported significant improvement in global cognition, MMSE and MoCA, applying real rTMS treatment in AD and MCI populations at immediately post-treatment as well as at long-term (≥ 6 weeks) compared to those receiving sham stimulation [206]. The same meta-analysis study reviewed tDCS studies and found that tDCS improved memory and executive function but not global cognition [206].

While tES or rTMS alone has been shown to have short-term benefits, combining tES or rTMS with CT has been explored as a strategy for greater cognitive benefit [50], [207], [208]. A systematic review found that pairing rTMS or tDCS with CT significantly improved global cognition in people living with AD and MCI [207]. Subgroup analyses revealed that rTMS combined with CT was particularly effective, and participants with AD showed greater improvement compared to MCI. Additionally, tDCS combined with CT significantly improved language function but not global cognition or other cognitive domains. Follow-up assessment

data ranged from 2 weeks to 6 months and indicated sustained benefits for global cognition and attention/working memory in individuals with AD receiving rTMS with CT but not tDCS with CT [207]. However, this result should be interpreted with caution, as the tDCS studies included only 3 to 24 sessions over 1 to 8 weeks, whereas the rTMS studies typically involved 20 to 30 sessions delivered over 4 weeks to 3 months. These findings suggest that combining rTMS or tDCS with CT may enhance cognitive outcomes more than either intervention alone, especially in AD population [207]. Evidence for stand-alone CT is, however, more muted. A review covering 11 studies in mild-to-moderate AD or vascular dementia found limited cognitive gains overall by CT interventions lasting between 5 to 24 weeks; though one high-quality trial of individualized cognitive rehabilitation did show promising improvements after 8 weeks of treatment in specific functional and memory tasks [50].

Several recent studies have begun to explore the effects of longer-term non-invasive interventions in individuals living with AD, highlighting the potential benefits of sustained treatment over extended periods. For example, our research team has previously run a randomized crossover sham-controlled clinical trial on the efficacy of 40 Hz tACS paired with CT on dementia [208]. This crossover design had two 4-week treatment blocks (either real tACS or sham) separated by a minimum of 8 weeks. We found that the group who received real tACS first had sustained cognitive improvement during the washout period of on average 11 weeks compared to the group that received sham first [208]. Furthermore, the overall trend for all participants was that they improved by the end of the study compared to their baseline score. One study conducted 20Hz-rTMS over the precuneus over 52 weeks in people living with mild-to-moderate AD and found that the real rTMS experienced significantly lower cognitive decline, using Clinical Dementia Rating Sum of Boxes and ADAS-Cog, preserved daily functioning, and

reduced behavioral symptoms compared to sham [209]. This intervention involved 2 weeks of treatments 5 days per week and then one treatment a week for 50 weeks [209]. Similarly, another study conducted the largest multisite randomized controlled rTMS clinical trial following participants for up to 6 months post-treatment [28]. Both active and sham groups showed sustained cognitive improvement up to 2 months post-treatment [28]. The intervention involved 2 or 4 weeks of daily rTMS over bilateral DLPFC, with follow-up assessments extending to 28 weeks post-baseline [28]. Another randomized controlled trial evaluated the effects of repeated cycles of CT over one year in participants living with AD receiving cholinesterase inhibitors. The experimental group underwent five 4-week blocks of CT (20 sessions per block, 2 h/day, 5 days/week) with a 4-week break between treatment blocks [210]. Compared to controls who received non-specific cognitive activities, the experimental group showed significant improvement in MMSE, Milan Overall Dementia Assessment, and multiple neuropsychological tests compared to controls receiving non-specific cognitive activities [210]. Even with these findings from one-year interventions, the literature still lacks investigations of long-term, repeated, multi-modal non-invasive interventions, especially those beyond one year and including multiple treatment blocks.

It has been hypothesized that repeated or maintenance stimulation over extended periods may sustain and strengthen neuroplastic changes induced by the treatment. Studies have suggested that repeated NIBS can lead to lasting changes caused by synaptic long-term potentiation (LTP), cortical excitability, and changes in functional and structural connectivity of networks [4], [211]. In dementia, repeated stimulation and cognitive engagement may help maintain neural circuits and slowing decline. Previous studies have proposed that maintenance or booster stimulation sessions could prolong the treatment effects [209], [212], [213]. This

supports the rationale for investigating the long-term effects of repeated non-invasive interventions over time.

Our team has been investigating the efficacy of various non-invasive interventions as a treatment for individuals living with AD/dementia repeatedly over the past 7 years; thus, we have cognitive assessment data of the same patients over the years. In this study, we aimed to analyze longitudinal data from participants who received at least two rounds of non-invasive treatment, including tACS, tDCS, rTMS with or without CT and only CT intervention over a span of 3 years. As individuals with neurodegenerative dementia are expected to decline over time, we hypothesize there would be a significantly slower rate of decline for those receiving repeated NIBS and/or CT compared to untreated patients. We also explored whether dementia-related medication would have any effect on the rate of decline, and also whether longer treatment gaps would be associated with greater post-treatment cognitive decline. To our knowledge, this is the first study of its kind to integrate longitudinal cognitive data, no-treatment interval analysis, and the impact of medication in evaluating the long-term effects of repeated non-invasive interventions. Determining whether repeated non-invasive interventions can slow cognitive decline is critical, as it would demonstrate their potential as a long-term treatment strategy to help maintain independence, reduce caregiver burden, delay institutionalization, lower healthcare costs, and improve quality of life for individuals living with dementia.

5.3 Methods

5.3.1 Participants

Participants were enrolled in a series of non-invasive interventions involving tES [52], [53], [208], rTMS [28], and/or CT. This analysis included 73 participants with dementia who received between 2 and 9 treatment blocks; each block was 20 sessions over 4 weeks with the

exception of one block of treatment that was 10 sessions over two-weeks of rTMS treatment ($n = 7$) and one block of treatment that was 24 sessions over 8 weeks tACS paired with CT treatment ($n = 2$). Participants were recruited through posters posted throughout the community and physicians' referrals, and all clinical trials were conducted at Riverview Health Centre in Winnipeg, Canada. Figure 5-1 shows a flowchart of the above-mentioned studies and inclusion of the participants. Table 5-1 summarizes participant flow for each source study, including total enrollment, number who completed the study, number who withdrew, and number whose data were included in this analysis. For the first three studies [28], [52], [53], [208], all participants included in this analysis completed the study, and there were no withdrawals. For the first study [52], [53], withdrawals occurred either due to the COVID-19 pandemic or participants choosing not to continue after completing a treatment block. For the second study [28], reasons for withdrawal are detailed in [214] with a full analysis of attrition. For the third study [208], withdrawal reasons are summarized in Table 5-1 of the original publication. For the fourth study [215], it is ongoing and thus, most participants have not yet completed the study which involves multiple treatment blocks with washout periods in between. The analysis for this study used the data available up to 3 September 2025. All clinical trials received ethics approval from the University of Manitoba Biomedical Research Ethics Board and were registered on ClinicalTrials.gov site online. Informed consent was obtained from all participants prior to their enrollment in each of the original studies included in this analysis.

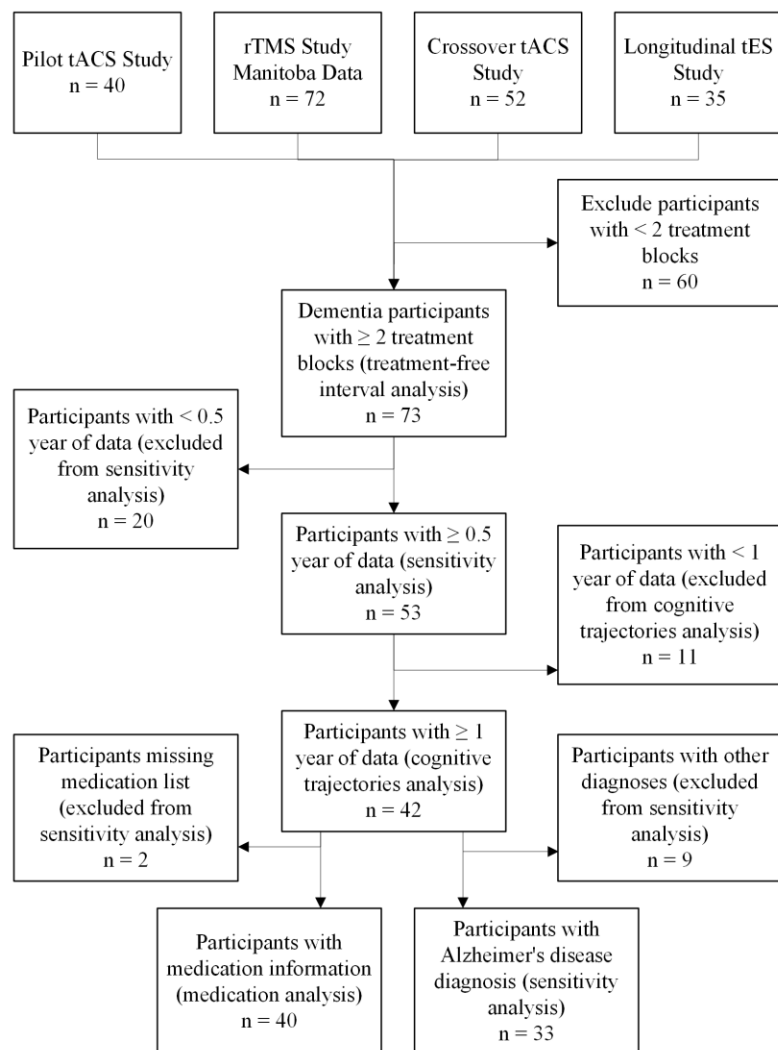


Figure 5-1. Flowchart of participants who received at least two treatment blocks and analysis inclusion.

Table 5-1. Summary of participant enrollment, completion, withdrawal, and inclusion in analysis for each study.

Study	Total Enrolled	Completed	Withdrawn	Used in Analysis
[18,19] <i>n</i> = 40		<i>n</i> = 31	<i>n</i> = 9	<i>n</i> = 26
[13] <i>n</i> = 72		<i>n</i> = 61	<i>n</i> = 11	<i>n</i> = 33
[11] <i>n</i> = 52		<i>n</i> = 42	<i>n</i> = 10	<i>n</i> = 42
[21] <i>n</i> = 35		<i>n</i> = 8	<i>n</i> = 6	<i>n</i> = 28

5.3.2 Study Design

The studies from which we adopted data varied in design and intervention structure. In the pilot study, participants were assigned to either CT alone for 4 weeks or CT paired with tACS delivered for 4 or 8 weeks [52], [53]. A randomized controlled trial compared two active rTMS protocols (2 or 4 weeks) against sham stimulation [28]. Another study used a crossover design in which participants completed both real and sham tACS combined with CT, separated by an average washout period of 11 weeks [208]. The ongoing longitudinal study enrolls participants in a single-arm protocol where each participant receives multiple tES modalities in randomized order, with washout period of 2–5 months between blocks [215]. Table 5-2 includes summarized information about the different interventions.

Table 5-2. Summary of included clinical trials contributing data to the current longitudinal analysis.

Study	Study Design	Assessments	Treatment Schedule	Stimulation Parameters
[18,19]	3 groups, no randomization, no blinding: 1. CT only (4 weeks) 2. tACS + CT (4 weeks) 3. tACS + CT (8 weeks)	Baseline, post-treatment, 1-month follow-up: • WMS • MADRS	5 days/week, 4 weeks OR 3 days/week, 8 weeks	Two 30 min sessions/day with a 30-min break in between, 40 Hz tACS, 0.75 mA, left DLPFC
[13,22]	3 groups, stratified randomization, double-blind: 1. Active rTMS (2 weeks) 2. Active rTMS (4 weeks) 3. Sham rTMS (4 weeks)	Baseline (week 0), week 3, 5, 12, 20 and 28: • ADAS-Cog	5 days/week for 2 or 4 weeks	20 Hz, 1.5 s trains with 10 s intertrain interval, 25 trains bilaterally, 90–100% resting motor threshold, left and right DLPFC
[11]	Crossover, stratified randomization, double-blind:	Baseline, post-treatment: • ADAS-Cog	Two 30 min sessions/day, 5 days/week for 4 weeks, with average	Two 30 min sessions/day with a 30-min break in between, 40 Hz tACS, 0.75 mA, left DLPFC

1.	tACS + CT (4 weeks), washout (2–7 months), sham + CT (4 weeks)	• WMS (missing data) • MADRS	washout period of 11 weeks	
	2. sham + CT (4 weeks), washout (2–7 months), tACS + CT (4 weeks)			
[21]	Single-arm, simple randomization, double-blind, longitudinal, each participant receives all tES protocols + CT in randomized order for 4 weeks with a 2–5-month washout period	Baseline, post-treatment, 1-month follow-up: • ADAS-Cog • WMS (missing data) • MADRS	Two 30 min sessions/day, 5 days/week for 4 weeks, with washout period between treatment blocks of 2–5 months	Two 30 min sessions/day with a 30 min break in between, left DLPFC • Personalized gamma-tACS (0.75 mA) • Personalized theta-tACS (1 mA) • tDCS (1 mA) - Sham tACS

Abbreviations: ADAS-Cog = Alzheimer’s Disease Assessment Scale—Cognitive Subscale, CT = cognitive training, DLPFC = dorsolateral prefrontal cortex, MADRS = Montgomery–Åsberg Depression Rating Scale, rTMS = repetitive transcranial magnetic stimulation, tACS = transcranial alternating current stimulation, tDCS = transcranial direct current stimulation, tES = transcranial electrical stimulation, WMS = Weschler Memory Scale.

5.3.3 Treatment Protocols

Despite differences in design, the interventions shared several commonalities. First, the stimulation target across all brain stimulation protocols was the DLPFC. For tACS and tDCS protocols, the reference electrode was placed over the right supraorbital area. Second, CT was consistently delivered using the MindTriggers app with support from a treatment administrator. Third, assessments were conducted before and after each treatment block, with some protocols also including 1-month follow-up assessments; the rTMS study [28] had four follow-up assessments up to 6 months post-treatment.

As can be seen in Table 5-2, treatment blocks consisted of one of the following protocols: gamma tACS combined with CT, theta tACS with CT, tDCS with CT, real rTMS, sham rTMS, sham tES with CT, or CT alone. Each treatment block consisted of 20 sessions administered on weekdays over 4 weeks, with the exception of 2 participants who completed the 8 weeks (3 days/week, 24 total sessions) of tACS + CT and 7 participants who completed 2 weeks (5 days/week, 10 total sessions) of rTMS. Participants received the same protocol per treatment block and treatments generally lasted between 20 min and 1.5 hours, often involving two 30-min treatments separated by a break. Detailed methodologies for each intervention can be found in [29], [53], [215], [216].

5.3.4 Inclusion and Exclusion Criteria

Inclusion criteria across studies typically required a physician-confirmed diagnosis of dementia. However, the rTMS study specifically required a diagnosis of AD. Additional common criteria included the ability to read and write in English or Spanish to complete assessments, and a MoCA score below 26. Participants were excluded if they had a history of epileptic seizures or epilepsy (for brain stimulation protocols), uncorrected visual or hearing impairment that interfered with cognitive testing, substance use disorder, participating in another therapeutic study for dementia, change in dementia-related medication during the treatment block, or a major mood disorder diagnosis.

For the current analysis, participants were eligible if they had completed at least two non-invasive interventions as part of the original studies. To ensure sufficient longitudinal data, only individuals with cognitive assessments (ADAS-Cog or Wechsler Memory Scale) spanning 1 to 3 years were included in the main analysis. These data could originate from a single study or

multiple studies among the four studies' datasets. Participants with less than 6 months of data were excluded from the dataset.

5.3.5 Outcome Measures

The primary outcome was the ADAS- Cog [184] or completed Wechsler Memory Scale (WMS) [217] in some of the studies. For ADAS-Cog, Scores range from 0 to 70, with higher scores indicating greater cognitive impairment. The ADAS-Cog includes tasks assessing memory, language, praxis, and orientation. In the pilot tACS study [52], [53], WMS was administered in place of ADAS-Cog as can be seen in Table 5-2. Therefore, the data from that pilot study required conversion using a predictive model to enable longitudinal integration with the studies using ADAS-Cog.

The assessments were administered at variable intervals: at baseline, post-treatment, and (for most studies) at follow-up. To standardize timepoints across participants, we created a six-month grid (0, 6, 12, 18, 24, and 30 months) and assigned the closest available assessment to each timepoint, allowing a maximum deviation of one month. Some participants ($n = 7$) had long periods (up to 6 months) between treatment blocks with no assessments; thus, we linearly interpolated the ADAS-Cog score with the assessments around the timepoint of interest. The average deviation from exact 6-month spacing was less than one month.

5.3.6 Estimating ADAS-Cog from WMS Data

To be able to compare data from all these studies, some studies used only WMS as the outcome measure while the majority of them used ADAS-Cog or both ADAS-Cog and WMS. Thus, we had to convert one scale to another in order to compare the cognitive status of participants over time. To estimate ADAS-Cog scores from WMS subcomponents, a multiple linear regression model was fitted using all available paired longitudinal assessments ($n = 378$)

from 57 participants who had completed both WMS and ADAS-Cog within the same week. Twenty WMS subcomponents were included as predictors, including Logical Memory, Visual Reproduction, Verbal Paired Associates, Immediate and Delayed Memory Indices, and composite memory scores. While the ADAS-Cog distribution exhibited mild positive skewness and heteroscedasticity, model residuals were approximately symmetric, and prediction performance was stable. To account for potential non-constant variance, robust (heteroscedasticity-consistent) standard errors were used. Model performance was evaluated using the root mean square error, mean absolute error, and intraclass correlation coefficient. The final model was applied to 111 assessments with only WMS from 26 participants to estimate ADAS-Cog scores. The decision to estimate ADAS-Cog from WMS was based on the fact that both assess cognitive function, particularly memory, with several overlapping components. The decision to estimate ADAS-Cog from WMS is supported by prior studies demonstrating strong correlations between the two measures [218] and high test–retest reliability of WMS-IV in dementia populations [219].

5.3.7 Cognitive Trajectories Analysis

To assess whether repeated non-invasive treatments were associated with a slower rate of cognitive decline over time, we used a linear mixed effects model with ADAS-Cog as the outcome and time (in months) as a fixed effect. The model included fixed effects for baseline age, sex, and baseline MoCA score as covariates. A random intercept was specified for each participant to account for within-subject correlation due to repeated measures. The model was estimated using the lme4 (version 1.1-37) and lmerTest (version 3.1-3) packages in R version 4.3.2 [220].

The primary analysis included participants who received at least two treatment blocks and had at least 1 year of data ($n = 42$) with various durations: 19 participants had data up to 1 year, 5 up to 1.5 years, 5 up to 2 years, 6 up to 2.5 years, and 7 up to 3 years. Model assumptions were evaluated via visual inspection of residuals, and multicollinearity was assessed using variance inflation factors, all of which were below a threshold of 5.

To compare the observed rate of ADAS-Cog change in our studies with the average rate of progression reported in a meta-analysis of 140 clinical trials, which estimated a mean decline of 5.82 points per year (0.485 points/month) in placebo-treated participants [221], we conducted a one sample t-test. The statistic was calculated as the difference between the estimated slope and the reference value, divided by the standard error of the estimated slope. Because the one-sample t-test assumes independent and identically distributed observations, we used robust sandwich estimator of standard errors to account for potential correlation among repeated measures. Robust standard errors were estimated using the sandwich package (version 3.1-1) in R [222].

Two sensitivity analyses were conducted to assess the robustness of the primary findings. Firstly, we repeated the model using all available data, including participants with only 6 months of assessments ($n = 53$). The second analysis repeated the model using all available data with restricted samples to participants diagnosed with AD.

5.3.8 Medication Analysis

To examine whether concurrent medications influenced cognitive trajectories, we conducted exploratory analyses by medication category. Medication lists were recorded at baseline of each treatment block, and participants did not change medication or dosage during the treatment and follow-up assessments. It was also confirmed that participants did not have medication changes between different treatment blocks. Approximately half of the total sample

was included in these medication analyses, and this subgroup was drawn from the primary analysis dataset. Participants were grouped dichotomously for each medication category:

- AD medications: cholinesterase inhibitors (donepezil, galantamine, rivastigmine) or memantine
- Antidepressants: selective serotonin reuptake inhibitors (SSRIs) (paroxetine, citalopram, escitalopram, fluoxetine, sertraline) or other types (bupropion, trazodone)
- Hypertension medications: valsartan, telmisartan, ramipril, enalapril, candesartan, irbesartan, perindopril, fosinopril, hydrochlorothiazide, nifedipine, amlodipine, bisoprolol, atenolol, metoprolol
- Cholesterol medications: atorvastatin, rosuvastatin, simvastatin, ezetimibe

For each medication category, we fit a linear mixed-effects model with ADAS-Cog as the outcome. Fixed effects included time (in months), medication status, and their interaction, along with baseline age, sex, and MoCA score as covariates. The interaction term tested whether the rate of cognitive change differed by medication group. Random intercepts were specified for each participant to account for repeated measures.

5.3.9 No-Treatment Interval Analysis

To investigate the effect of no-treatment intervals on changes in cognitive function, we employed a robust linear mixed-effects model using the `rlmer` function from the R package `robustlmm` (version 3.3-3) [220]. The dependent variable was the change in ADAS-Cog score, and the primary predictor was the duration of the no-treatment interval (days). Participant-level random intercepts accounted for repeated measures. Robust sandwich estimation was applied to address deviations from normality and heteroscedasticity [223]. This analysis included all 73

participants, contributing 266 observations. No-treatment intervals ranged from 3 weeks to 5.5 years. These intervals include intervals between treatment blocks within a study, gaps between separate studies, or the time from the last treatment to a follow-up assessment.

5.4 Results

Participant demographics for the ADAS-Cog trajectories analysis ($n = 42$) are shown in Table 5-3, including a breakdown of clinical diagnoses. Participants received between 2 and 9 blocks of non-invasive treatment and were followed for up to 3 years. The number of participants contributing data up to each timepoint was: 19 at 1 year, 5 at 1.5 years, 5 at 2 years, 6 at 2.5 years, and 7 at 3 years.

Table 5-3. Participant demographic and clinical characteristics at baseline by analysis (cognitive trajectories and no-treatment interval).

CharacteristicCategories		Cognitive Trajectories Analysis		No-Treatment Interval Analysis	
		Count (<i>n</i>)	Percent (%)	Count (<i>n</i>)	Percent (%)
Sex	Female	17	40.5	26	35.6
	Male	25	59.5	47	64.4
Education	Primary education	8	19	12	16.4
	Secondary education	10	23.8	18	24.7
	Some post-secondary education	3	7.1	6	8.2
	College Diploma	2	4.8	3	4.1
	Bachelor's degree	11	26.2	20	27.4
	Master's degree	5	11.9	8	11.0
	Doctorate degree	3	7.1	6	8.2
Handedness	Right	38	90.5	67	91.8
	Left	3	7.1	5	6.8
	Ambidextrous	1	2.4	1	1.4
Diagnosis	Alzheimer's disease	32	78	46	67.7
	Dementia	7	14.7	12	16.4
	Vascular Dementia	2	4.9	7	9.6
	Mild Cognitive Impairment	1	2.4	5	6.8
	Posterior Cortical Atrophy	0	0	1	1.4
	Lewy Body Dementia	0	0	1	1.4

	Frontotemporal Dementia	0	0	1	1.4
Medication	Alzheimer's Disease	23	57.5		
	Antidepressants	7	17.5		
	Hypertension	17	55		
	Cholesterol	18	45		
		Mean	SD	Mean	SD
Age (years)		72.1	8.9	73.6	8.6
MoCA		17.1	5.1	17.1	5.3
MADRS		6.1	8.1	5.3	6.6
ADAS-Cog		20.7	8.6	21.7	9.2

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognitive

Subscale, MADRS = Montgomery–Åsberg Depression Rating Scale, MoCA = Montreal Cognitive Assessment

5.4.1 Estimating ADAS-Cog from WMS Data

To compare across studies that used WMS and ADAS-Cog, we developed a method to estimate ADAS-Cog scores for assessments where only the WMS was available. A multiple linear regression model was fitted using all available paired longitudinal data (378 assessments from 57 participants). The model achieved good predictive performance with a root mean square error of 4.92 and a mean absolute error of 3.60. Agreement between observed and predicted ADAS-Cog values was high, as indicated by an intraclass correlation coefficient of 0.86 (95% CI: 0.83 to 0.88, $p < 0.001$). Model residuals showed mild deviation from normality (Shapiro–Wilk $p < 0.001$) and heteroscedasticity (Breusch–Pagan $p < 0.001$); thus, robust standard errors were used. The estimated coefficients and corresponding robust p values are shown in Table 5-4.

Table 5-4. Multiple linear regression coefficients for predicting ADAS-Cog from WMS components.

Variable	Coefficient (β)	Robust SE	t Value	p Value
Intercept	55.032	10.212	5.389	1.29×10^{-7}
Brief Cognitive Status Exam Total Raw Score	−0.222	0.033	−6.716	7.38×10^{-11}

Logical Memory I	-0.659	0.155	-4.251	2.72×10^{-5}
Logical Memory II	0.251	0.145	1.733	0.084
Verbal Paired Associates I	-0.682	0.190	-3.599	3.65×10^{-4}
Verbal Paired Associates II	0.692	0.491	1.410	0.159
Visual Reproduction I	-0.152	0.144	-1.053	0.293
Visual Reproduction II	0.461	0.176	2.616	0.009
Symbol Span	-0.081	0.062	-1.312	0.190
Logical Memory II Recognition	0.116	0.089	1.308	0.192
Verbal Paired Associates II Recognition	-0.174	0.063	-2.750	0.006
Verbal Paired Associates II Recall	0.079	0.096	0.820	0.413
Visual Reproduction II Recognition	0.010	0.233	0.042	0.967
Auditory Memory Sum of Scaled Scores	-0.562	0.677	-0.831	0.407
Auditory Memory Index	-0.766	0.341	-2.245	0.025
Visual Memory Sum of Scaled Scores	-1.760	0.794	-2.217	0.027
Visual Memory Index	-0.283	0.142	-2.001	0.046
Immediate Memory Sum of Scaled Scores	2.920	0.866	3.372	8.28×10^{-4}
Immediate Memory Index	0.040	0.042	0.950	0.343
Delayed Memory Sum of Scaled Scores	0.614	0.386	1.591	0.112

5.4.2 Cognitive Trajectories Analysis

A linear mixed effects model was used to assess longitudinal changes in ADAS-Cog scores among participants who received at least two blocks of non-invasive treatment and completed at least three assessments ($n = 42$). The model included fixed effects for time (in months), baseline age, sex, and baseline MoCA score, with a random intercept for participant. Time was modeled as a continuous linear variable. There was a significant effect of time in months ($\beta = 0.23$, $p < 0.001$), indicating that ADAS-Cog scores increased gradually over the assessed period but at a slower rate than typically expected. Higher baseline MoCA scores were significantly associated with lower ADAS-Cog scores ($\beta = -1.48$, $p < 0.001$). Age ($\beta = 0.06$, $p = 0.56$) and sex ($\beta = -1.05$, $p = 0.54$) were not significant predictors. The random intercept standard deviation was 4.50, and the residual standard deviation was 5.66. The model explained 53% of the variance in ADAS-Cog scores attributable to fixed effects and 71% when including

between-subject variability. The full fixed-effect results can be found in Table 5-5. Model diagnostics confirmed that residuals were normally distributed with no major deviations or heteroscedasticity. Variance inflation factors for all predictors were below 2, indicating no multicollinearity.

Table 5-5. Fixed effects from the linear mixed-effects model estimating longitudinal changes in ADAS-Cog scores ($n = 42$). Estimates are adjusted for baseline age, sex, and MoCA score. A random intercept was included for each participant.

	Estimate	SE	df	t Value	p Value
Intercept	41.249	7.254	38.085	5.686	1.52×10^{-6}
Time (months)	0.227	0.045	163.040	5.089	9.82×10^{-7}
Baseline Age (years)	0.056	0.095	39.322	0.591	0.558
Sex (male)	-1.050	1.689	38.126	-0.622	0.538
Baseline MoCA Score	-1.478	0.165	38.406	-8.966	5.89×10^{-11}

To contextualize the observed slope, we conducted a one-sample t-test comparing the rate of ADAS-Cog change in this cohort to the average AD progression rate reported in a meta-analysis of 140 clinical trials (0.485 points/month) [221]. Robust standard errors were used to account for potential violations of independence assumption inherent to repeated measures data. The observed slope (0.23 ± 0.07 , 95% CI: 0.09 to 0.37) was significantly lower than the expected rate ($t = -3.59$, $df = 163.04$, $p < 0.001$), suggesting that participants in this study experienced slower-than-expected cognitive decline. Figure 5-2 shows the observed ADAS-Cog trajectory alongside the expected decline in untreated AD. Figure 5-3 shows a similar plot with observed ADAS-Cog scores stratified by maximum assessment duration.

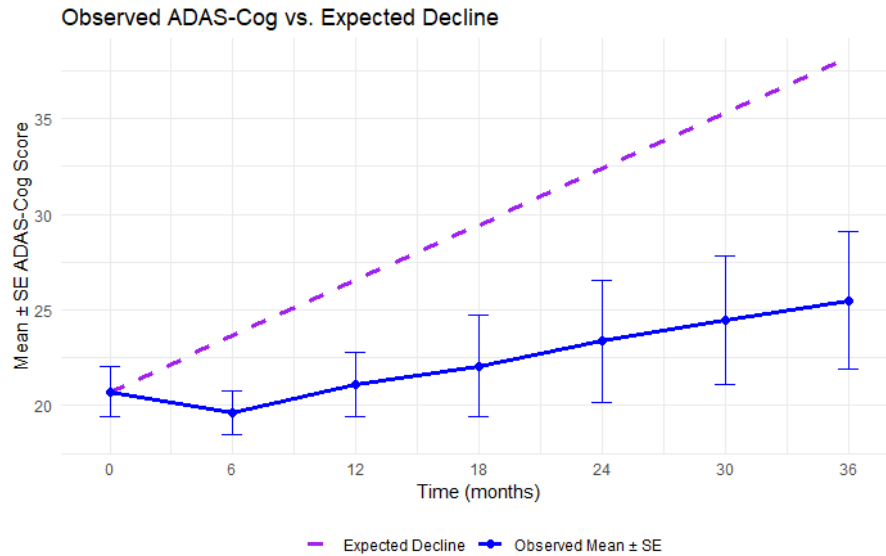


Figure 5-2. Overall trajectory of the observed ADAS-Cog scores for participants who received multiple treatment blocks compared to the expected decline in AD.

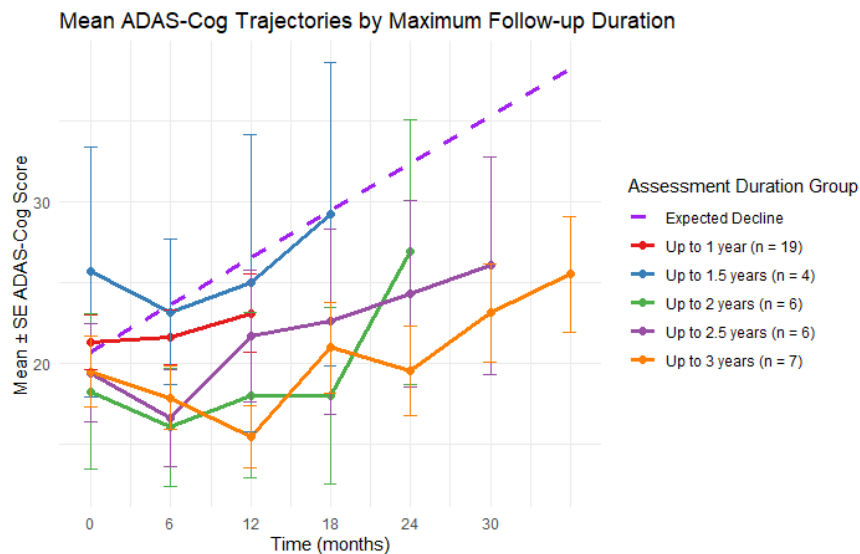


Figure 5-3. Observed ADAS-Cog trajectories stratified by the maximum duration of available assessment data, rounded down to 6-month intervals, ranging from 1 year to 3 years. Assessments were associated with repeated treatment blocks, with participants receiving between 2 and 9 treatment blocks during these periods.

As a sensitivity analysis, we repeated the model using all participants who received at least two treatment blocks, with at least 6 months of data ($n = 53$). Results were consistent with the primary analysis: both the effect of time in months ($\beta = 0.19, p < 0.001$), and the MoCA score ($\beta = -1.61, p < 0.001$) remained a strong predictor, supporting the robustness of the findings. The full fixed-effect results can be found in Table 5-6. We also conducted a second sensitivity analysis restricted to participants diagnosed with AD ($n = 36$). The effect of time remained significant ($\beta = 0.20, p < 0.001$), and MoCA score continued to be a strong negative predictor of ADAS-Cog performance ($\beta = -1.45, p < 0.001$), further supporting the consistency of the observed trajectories across subgroups. The full-fixed effect results can be found in Table 5-7.

Table 5-6. Fixed effects from the sensitivity analysis using the linear mixed-effects model with all available participants ($n = 53$), including those with only six months of follow-up.

	Estimate	SE	df	t Value	p Value
Intercept	44.349	7.052	45.125	6.289	1.15×10^{-7}
Time (months)	0.191	0.037	199.660	5.126	6.97×10^{-7}
Baseline Age (years)	0.053	0.092	46.063	0.571	0.571
Sex (male)	-0.031	1.656	44.257	-0.019	0.985
Baseline MoCA Score	-1.610	0.150	47.695	-10.723	2.66×10^{-14}

Table 5-7. Fixed effects from the sensitivity analysis using the linear mixed-effects model restricted to participants with clinical diagnosis of AD ($n = 36$).

	Estimate	SE	df	t Value	p Value
Intercept	43.970	8.227	31.607	5.345	7.55×10^{-6}
Time (months)	0.200	0.043	156.744	4.595	8.84×10^{-6}
Baseline Age (years)	0.040	0.110	32.643	0.360	0.721
Sex (male)	-2.306	1.918	30.601	-1.203	0.238
Baseline MoCA Score	-1.447	0.186	32.472	-7.761	6.80×10^{-9}

5.4.3 Medication Analysis

The exploratory analysis on whether medication modified cognitive trajectories across all models showed that baseline MoCA scores and time (in months) remained strong predictors of ADAS-Cog. However, none of the medication categories significantly influenced baseline ADAS-Cog or the rate of cognitive change. For AD medications, neither the main effect ($p = 0.12$) nor the interaction with time ($p = 0.30$) reached significance. Similarly for antidepressants (main effect: $p = 0.11$; interaction: $p = 0.78$), hypertension medications (main effect: $p = 0.35$; interaction: $p = 0.40$), and cholesterol medication (main effect: $p = 0.83$; interaction: $p = 0.23$) showed no significant associations with ADAS-Cog scores. These findings suggest that within this sample, use of common AD, psychiatric, or cardiovascular medications did not alter the trajectory of cognitive change during repeated non-invasive interventions. All model full fixed-effect results can be found in Table 5-8 to Table 5-11.

Table 5-8. Fixed effects from linear mixed-effects model examining the effect of AD medications (cholinesterase inhibitors or memantine) on ADAS-Cog trajectories.

	Estimate	SE	df	t Value	p Value
Intercept	35.191	7.416	36.133	4.745	3.24×10^{-5}
Time (months)	0.181	0.066	155.117	2.754	6.58×10^{-3}
AD Med. (yes)	3.075	1.963	63.229	1.566	0.122
Baseline Age (years)	0.111	0.093	36.665	1.189	0.242
Sex (male)	-0.266	1.692	35.729	-0.157	0.876
Baseline MoCA Score	-1.480	0.159	35.823	-9.335	3.96×10^{-11}
Time: AD Med. (yes)	0.094	0.091	158.269	1.034	0.303

Table 5-9. Fixed effects from linear mixed-effects model examining the effect of antidepressant medications (SSRIs or other antidepressants) on ADAS-Cog trajectories.

	Estimate	SE	df	t Value	p Value
Intercept	40.238	7.186	35.326	5.599	2.53×10^{-6}
Time (months)	0.230	0.051	158.638	4.527	1.17×10^{-5}

Antidepressant (yes)	4.152	2.541	64.352	1.6234	0.107
Baseline Age (years)	0.064	0.094	36.514	0.681	0.500
Sex (male)	-1.211	1.700	35.024	-0.712	0.481
Baseline MoCA Score	-1.480	0.164	35.894	-9.052	8.53×10^{-11}
Time: Antidepressant (yes)	-0.032	0.115	154.353	-0.277	0.782

Table 5-10. Fixed effects from linear mixed-effects model examining the effect of hypertension medications on ADAS-Cog trajectories.

	Estimate	SE	df	t Value	p Value
Intercept	42.345	7.369	35.935	5.746	1.53×10^{-6}
Time (months)	0.272	0.068	155.957	4.022	8.97×10^{-5}
Hypertension Med. (yes)	-1.875	1.998	63.188	-0.939	0.351
Baseline Age (years)	0.048	0.096	37.342	0.503	0.618
Sex (male)	-1.553	1.747	35.363	-0.889	0.380
Baseline MoCA Score	-1.441	0.167	36.349	-8.612	2.65×10^{-10}
Time: Hypertension Med. (yes)	-0.078	0.091	155.828	-0.849	0.397

Table 5-11. Fixed effects from linear mixed-effects model examining the effect of cholesterol medications on ADAS-Cog trajectories.

	Estimate	SE	df	t Value	p Value
Intercept	40.599	7.531	35.015	5.391	4.90×10^{-6}
Time (months)	0.274	0.061	157.476	4.518	1.22×10^{-5}
Cholesterol Med. (yes)	0.442	2.064	60.516	0.214	0.831
Baseline Age (years)	0.066	0.101	36.036	0.657	0.515
Sex (male)	-1.361	1.777	35.74	-0.766	0.449
Baseline MoCA Score	-1.473	0.170	35.457	-8.643	2.99×10^{-10}
Time: Cholesterol Med. (yes)	-0.111	0.092	156.304	-1.212	0.227

5.4.4 No-Treatment Interval Analysis

Participant demographics for the no-treatment interval analysis ($n = 73$) are shown in Table 5-2, including a breakdown of clinical diagnoses. The robust mixed model revealed a statistically significant positive relationship between no-treatment interval and cognitive decline, with an estimated increase in ADAS-Cog change of 0.0108 points per additional no-treatment day (95% CI not reported here; SE = 0.002; $t = 6.892$, $p < 0.001$). This suggests that longer intervals without treatment are associated with cognitive decline (Figure 5-4). The estimated

intercept, representing the predicted cognitive change immediately after treatment, was positive but not statistically significant (Estimate = 0.556, SE = 0.404, $t = 1.375$). Between-subject variability in baseline cognitive change was minimal after accounting for no-treatment days, as indicated by negligible random intercept variance. Robustness weights showed that a minority of residuals were down weighted, confirming the presence of some outliers that were controlled in the analysis.

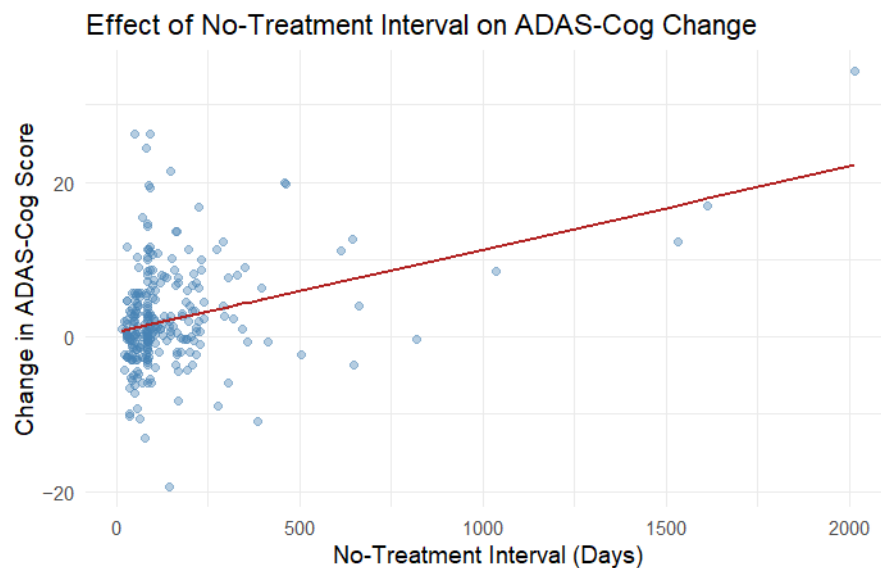


Figure 5-4. Association between no-treatment interval and change in ADAS-Cog score. Each point represents an observation from an individual participant. The solid red line indicates the fitted relationship from the robust mixed-effects model, showing an overall positive association between longer no-treatment intervals and greater cognitive decline.

5.5 Discussion

This study investigated the long-term ADAS-Cog trajectory of participants with dementia or AD who received multiple rounds of non-invasive treatments, including tACS, tDCS, rTMS, and CT, over a period of 1 to 3 years. By tracking ADAS-Cog scores at multiple timepoints, we estimated the rate of decline over time and compared it to the expected trajectory of untreated

AD. A meta-analysis on AD of over 140 clinical trials reports an average decline of 5.82 ADAS-Cog points per year (approximately 0.485 points per month) in placebo-treated participants, which serves as our reference rate of decline [221]. Our participants had a mean age of 72.1 years and baseline ADAS-Cog of 20.7, compared to 73.5 years and 24.5 ADAS-Cog score in the meta-analysis. These differences were modest, particularly for age, supporting the validity of this comparison, but it is important to note the slightly milder baseline impairment in our sample. The results showed that the rate of cognitive decline, as measured by the ADAS-Cog, was significantly slower than the average decline in AD [221]. In fact, for many participants, cognitive scores remained stable over time, diverging meaningfully from the expected trajectory of disease progression.

This study adds to the growing research largely focused on short-term outcomes. The meta-analyses of high-frequency rTMS (>5 Hz) over the DLPFC have shown improvements in ADAS-Cog, MMSE, and MoCA, but the longest follow-up in these studies was only three months, with most follow-ups under 6 months [205], [206]. Similarly, combining tDCS with CT has been shown to produce short-term gains in working memory, attention, or language function, and stand-alone CT programs has shown modest benefits [50] with diminishing effects within months. Even the long-term studies, such as 52-week rTMS over the precuneus [209] or 12-month CT programs [210], [224], have not explored repeated treatment blocks or follow-up beyond a year.

Most importantly, the observed slowing of cognitive decline may have a higher significance beyond the test scores. Because transportation was confirmed with each participant for every treatment block, we know that none of our participants were institutionalized during the assessments of this study. These outcomes, though they are difficult to record in a

standardized method, indicate the potential of repeated, long-term non-invasive interventions not only to slow measurable cognitive decline but also to preserve autonomy and reduce caregiver burden. These functional implications align with the benefits in daily functioning reported in the year-long rTMS and multimodal CT trials [210], [224] and strengthen the argument for sustained, maintenance-oriented intervention strategies in AD.

The secondary analysis revealed a significant association between longer no-treatment intervals and increased cognitive decline, with ADAS-Cog scores worsening by approximately 0.01 per additional day without intervention. This finding emphasizes the importance of consistent and repeated treatment periods in maintaining cognitive function. While most studies focus on the efficacy of the intervention and its sustained effects [50], [205], [206], [207], or a prolonged treatment protocol such as weekly treatments for a year [209], [210], [224], our results suggest that a balance between the cognitive decline during a no-treatment interval and accommodating personal schedule requires further research. Prior studies found that discontinuation of medication such as cholinesterase inhibitors in AD can lead to cognitive decline [225], [226]. Many participants' caregivers expressed a preference for treatment blocks spaced out over time to accommodate personal schedules, including travel, seasonal accessibility, and lifestyle flexibility. These preferences highlight the need for adaptable treatment models that balance clinical efficacy with real-world feasibility. Our findings support the possibility of delivering interventions in periodic blocks, provided that washout durations are carefully managed to minimize cognitive regression. Future studies should explore optimal scheduling strategies, including the maximum tolerable washout length, to guide maintenance protocols that preserve cognitive stability while respecting individual needs.

Analyses of medication use revealed that AD medications, antidepressants, hypertension medications, and cholesterol medications had no significant effect on the rate of cognitive decline. All participants were required to be on stable doses of medication prior to and throughout the study period, and we verified that no changes in medications occurred between different studies for those who were part of multiple studies. Thus, the expected rate of cognitive decline in our study population was unlikely to be attributable to pharmacological treatment. However, subgroup sizes were limited, particularly for anti-depressants, so these results should be interpreted with caution. Although our study found no significant effects of medications on cognitive trajectory, previous research suggests that certain medication classes such as SSRIs, cholinesterase inhibitors, and N-methyl-D-aspartate receptor antagonists may modulate the effects of tDCS [227], [228], [229], [230]. However, evidence for similar interactions with rTMS and tACS remains limited.

There are several strengths in this study. First, to the best of our knowledge, this is the longest longitudinal assessment period in a population receiving non-invasive interventions for dementia, with some participants followed for over 3 years. Second, the use of linear mixed models with participant-level random intercepts allowed us to estimate the average rate of cognitive change over time while accounting for individual variability. Third, by comparing the observed rate of change to the average decline rate derived from a meta-analysis of 140 placebo-controlled AD clinical trials, we were able to compare our results to the expected decline rate. This comparison enhances the clinical relevance of our findings and provides a clearer interpretation than relying solely on within-group change scores. Finally, the sensitivity analyses, including models that use all available data and those restricted to participants diagnosed with AD, yielded consistent results, further supporting the robustness of our findings.

There are several limitations including no untreated or placebo control group within our dataset. While the comparison to an external benchmark offers a meaningful reference, a more rigorous approach would involve a randomized control condition to ensure baseline characteristics, such as population characteristics, severity, and assessment protocols, are comparable across groups. Second, participants received different types of non-invasive treatments from different studies, complicating the interpretation of which treatments were the most effective or if receiving more than one type of treatment is better. While this heterogeneity reflects real-world clinical practice, where treatment is often tailored to individual needs and disease progression, it also introduced variability in study design and follow-up schedules. Although combining the datasets was justified by the shared outcome measure (ADAS-Cog) and using standardized timepoints, this heterogeneity complicates interpretation and limits generalizability. Third, conversion of WMS scores to ADAS-Cog introduces potential measurement error, and assuming linear change over time may oversimplify the trajectory of cognitive decline. Fourth, the sample size at longer follow-up intervals was limited which may introduce bias or reduce power to detect small effects. Additionally, the modest sample sizes within multiple subgroup analyses may further limit statistical power. Fifth, because inclusion required at least one year of follow-up and participants who continued receiving multiple treatments were retained, introducing selection bias, limiting generalizability to more advanced individuals or higher dropout risk. Finally, in a small number of cases (7 out of 231 data entries), we linearly interpolated around the regularly scheduled timepoint to retain longitudinal continuity. However, cognitive decline in dementia is rarely linear, and this approach may artificially smooth or underestimate decline.

5.6 Conclusions

Overall, our findings suggest that repeated, personalized, non-invasive interventions may help sustain cognitive function and slow the decline of the disease in individuals with dementia over time. These results question the current understanding that such treatments only produce immediate or short-term effects and provide initial evidence that prolonged use may offer sustained benefit. A periodic “booster” treatment of NIBS and/or CT may preserve cognition over many years. Future research should systematically evaluate optimal treatment schedules, combinations of modalities, and patient characteristics that predict long-term responsiveness. By reframing intervention strategies in AD to include ongoing, low-burden, non-pharmacological maintenance, it may be possible to meaningfully extend independence and quality of life for people living with dementia.

Chapter 6: Conclusions

6.1 Summary of Findings

In this thesis, the overarching goal was to investigate NIBS as a dementia treatment with the aim to improve stimulation precision, understand the validity of sham coil, and evaluate the efficacy of NIBS for cognitive and neuropsychiatric outcomes.

The motivation for the first two studies (Chapters 2 and 3) arose from the findings of a large clinical trial that examined the effects of rTMS in AD showing similar efficacy between real and sham stimulation groups. This raised two methodological questions:

1. Are average coordinates for stimulation targeting sufficiently accurate?
2. Do sham coils provide a truly placebo condition?

The first study (Chapter 2) investigated the accuracy of neuronavigation systems that use standardized coordinates to localize stimulation targets. The study revealed that mean Talairach coordinates for the hand area of the primary motor cortex often deviate substantially from the true stimulation site capable of eliciting a motor response, with deviations up to 19.5 mm. These findings demonstrate that generalized coordinates may not accurately represent functional neuroanatomy and relying on generalized coordinate systems may be misleading when trying to find the optimal location for TMS.

The second study (Chapter 3) investigated whether a widely used sham TMS coil produces induced electric fields capable of stimulating the cortex. Magnetic field measurements were used to create accurate simulations of both real and sham coils. Using computational modeling, the study demonstrated that the sham coil produced a more widespread distribution of high-intensity electric fields than expected, suggesting that “sham” stimulation may have unintended physiological effects. This finding is critical for interpreting placebo effects in

clinical trials, as the similarity in efficacy between real and sham stimulation observed in the large rTMS clinical trial may have partially resulted from unintended stimulation induced by the sham coil.

After addressing these methodological considerations, the thesis transitioned to exploring the therapeutic potential of tES in dementia. The third study (Chapter 4) evaluated the cognitive and neuropsychiatric effects of 40 Hz tACS administered simultaneously with CT in individuals living with dementia, using a randomized, double-blind, sham-controlled, crossover design. The results showed that 40 Hz tACS paired with CT significantly improved ADAS-Cog scores and reduced neuropsychiatric symptoms post-treatment, whereas sham stimulation did not produce similar improvements. Moreover, participants who received real tACS in the first treatment block exhibited a significantly smaller decline during the washout period compared to those who received sham first, reflecting a relative stabilization of cognitive scores following real stimulation. These findings support the hypothesis that 40 Hz tACS can enhance cognitive function when paired with CT post-treatment with sustained benefits compared to sham paired with CT.

The final study (Chapter 5) merged the investigations of magnetic and electrical stimulation by examining the long-term effects of repeated non-invasive interventions, including TMS, tES and/or CT, administered over a span of up to three years in individuals living with dementia. Using longitudinal ADAS-Cog assessments, the study employed mixed-effects modeling to compare observed cognitive trajectories against the expected rate of decline in untreated AD populations. Results revealed a significantly slower rate of cognitive decline among participants receiving repeated interventions, with many demonstrating stable or improved ADAS-Cog scores over time. Furthermore, longer no-treatment intervals between

blocks were associated with greater post-treatment decline, underscoring the importance of consistent and sustained intervention. Medication analyses showed no significant impact of AD, depression, hypertension, or cholesterol medication on cognitive outcomes, suggesting that the observed benefits were attributable to the non-pharmacological treatments. These findings provide compelling evidence for the feasibility and efficacy of long-term, personalized, non-invasive intervention strategies in mitigating cognitive deterioration in dementia, and highlight the potential of maintenance-oriented protocols to preserve autonomy and reduce caregiver burden.

Collectively, the findings from this thesis provide both methodological and efficacy insights into the application of NIBS for dementia. The methodological studies demonstrate the need for precise localization and accurate sham designs to ensure optimal study design and interpretability. The interventional studies demonstrated the cognitive and neuropsychiatric benefits of NIBS following both 4 weeks of treatment and repeated interventions over time. Together, these results contribute to the growing body of evidence supporting NIBS as a promising treatment for dementia.

6.2 Recommendations for Future Work

The studies presented in this thesis highlight both the therapeutic potential and methodological challenges of NIBS for dementia. While these findings advance understanding, they also reveal limitations such as small sample sizes, reliance on generalized rather than individualized targeting coordinates, simplified head models for electric field estimation, standardized instead of personalized stimulation protocols, and challenges related to long-term accessibility and scalability. Building on these findings, several directions for future work are proposed to advance the precision, safety, and efficacy of stimulation-based interventions.

6.2.1 Neuronavigation Accuracy

The findings from Chapter 2 emphasized the limitations of using generalized Talairach coordinates for localizing stimulation targets. The next step would be a comparative study examining the effectiveness of different localization strategies. Specifically, three parallel groups could be compared: one receiving stimulation guided by generalized coordinates, another using scalp-based measurements (commonly used in clinical settings), and a third using individualized fMRI-derived coordinates. Such a study would help determine whether the additional cost and complexity of fMRI-derived coordinates yield measurable improvements in treatment precision, consistency, and outcomes compared to scalp-based measurements or generalized coordinates.

6.2.2 TMS Coil

Chapter 3 demonstrated that sham TMS coils can induce measurable electric fields, questioning their validity as true placebo conditions. Future work should extend this investigation by testing other coil models and their corresponding sham counterparts to establish a broader understanding of the magnitude of unintended neural activation across commercially available systems. Additionally, simulating the induced electric fields on participant MRI scans from the Weston rTMS study would provide valuable insight into how anatomical variability influences both real and sham stimulation effects and connect these anatomical differences to treatment response. These findings could inform sham coil designs that better replicate the sensations from TMS without inducing cortical activation, thus improving the validity of future TMS trials.

6.2.3 Transcranial Electrical Stimulation Studies

The tES studies in this thesis demonstrated promising effects of gamma-tACS paired with CT, as well as potential long-term benefits from repeated non-invasive interventions. Future research should investigate whether personalized tACS frequencies, determined by individual EEG spectral peaks, results in greater cognitive and neuropsychiatric improvements compared to standardized 40 Hz protocol. This comparison is critical to determine if individualized entrainment provides superior benefits and represents a more effective approach.

In addition, home-based tES delivery should be explored as a scalable solution for long-term intervention. Older adults often face accessibility challenges due to mobility or weather-imposed limitations, when attending daily sessions at a research facility. Implementing home-based tES could enhance recruitment, retention, and adherence to treatment schedules. A feasibility study should evaluate safety, usability, adherence, and caregiver-assisted administration in participants' homes, as well as compare cognitive outcomes to those achieved with in-lab protocols.

Furthermore, a longitudinal, sham-controlled, crossover, single-arm study comparing different tES modalities (tDCS, theta-tACS, and gamma-tACS) paired with CT would help identify whether response patterns are patient-specific or modality-dependent. Such work would not only advance understanding of frequency-specific effects on cognition and brain function but also inform optimal treatment personalization strategies. Importantly, this longitudinal framework could help establish the long-term effects of repeated interventions of tES paired with CT with a standardized protocol for a large sample size.

Future studies should combine NIBS with neuroimaging and electrophysiological techniques such as EEG, fNIRS, electrovestibulography (EVestG), MRI, and positron emission

tomography. These multimodal approaches serve two critical purposes. First, they can identify predictive biomarkers of responsiveness, enabling personalized treatment by determining which individuals are most likely to benefit from specific stimulation parameters. For example, MRI provides high-resolution structural information that can guide individualized targeting of stimulation sites. EEG complements this by directly measuring neuronal oscillatory activity and connectivity, to assess whether stimulation entrains targeted frequency bands or restores disrupted networks. Furthermore, fNIRS offers real-time measures of cortical hemodynamics (oxygenated and deoxygenated hemoglobin), providing insight into how NIBS modulates neurovascular coupling and regional activation patterns during cognitive tasks. EVestG, a novel electrophysiological tool, can distinguish participants with cerebrovascular symptomology, a common comorbidity in dementia, and assess whether these vascular features influence responsiveness to stimulation. Moreover, EVestG-derived biomarkers may predict treatment outcomes, supporting stratification of participants in future trials.

Second, neuroimaging and electrophysiology can explain the underlying mechanisms for cognitive and neuropsychiatric improvements. For instance, future research could study whether stimulation enhances functional connectivity, shifts oscillatory power across frequency bands, or alters activity within networks affected by dementia, such as the default mode or frontoparietal networks. At the molecular level, positron emission tomography imaging of beta-amyloid or tau could reveal whether repeated stimulation influences disease pathology. Together, these insights would advance neuromodulation and inform strategies to optimize stimulation protocols for individuals with dementia.

In summary, this thesis advances both the methodological foundations and the efficacy of NIBS for dementia. The first two studies showed that stimulation targeting and sham coil design

can influence study validity and the interpretation of clinical outcomes, highlighting the importance of precision and careful protocol development. Building on this, the interventional studies provide evidence that tACS, particularly at 40 Hz paired with structured cognitive training, can improve cognitive and neuropsychiatric outcomes, with effects that continue beyond the immediate treatment period. The long-term longitudinal results further suggest that repeated, individualized neuromodulation may help slow cognitive decline over months to years, supporting the potential value of maintenance-based, non-pharmacological approaches in dementia care. Overall, the work in this thesis contributes methodological, mechanistic, and clinical insights and supports the continued development of safe, targeted, and scalable NIBS interventions for individuals living with dementia.

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Appendix A – Participant Information and Consent Form

A.1 Pilot tACS Study

Title of Study: “Brain Fitness App for aging with a healthy brain and detecting cognitive declines”

Protocol number: “Ver 9, May. 2021”

Principal Investigator: Dr. Zahra Moussavi, Electrical & Computer Engineering, University of Manitoba, Winnipeg, Phone: [REDACTED], Email: Zahra.Moussavi@umanitoba.ca

Sponsor: “AGE-WELL NCE Inc”

The Brain Exercises of this study was initially developed by a funding from AGE-WELL NCE. The cost of this current study is supported by a private donor.

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of the study

For this project, we have developed a new series of brain exercises, called Brain Fitness App, for memory and cognitive improvement. Through this clinical trial, we are investigating whether the developed exercises do improve the memory and cognition as intended, and if they do, what their main effect is. The results of this study will help a better understanding of human brain development and cognitive learning.

A total of 90 participants over 20 years of age with mild Alzheimer’s or cognitive impairment will participate in this study.

Study Procedures

The Brain Fitness app consists of a series of memory and spatial orientation brain exercises with several difficulty levels. Assessments consist of evaluation for cognitive function, memory and depression. After volunteers provide consent by signing this form, he or she will be assessed by completing the Montreal Cognitive Assessment (MoCA). The results of this test will determine a volunteer’s eligibility for enrollment.

Study Procedures:

Each participant will receive two sessions of brain exercises (each about 30-45 min) with a dedicated tutor (qualified trainee). There will be about 30-min break between the two sessions. During each session, we will stop sooner than 45 minutes if the participant feels mentally fatigue. The brain exercises sessions will occur in our laboratory. If we are unable to run the assessment in-person due to pandemic, we will have it Online by video conferencing, which in that case you will receive the detailed instructions to set up your iPad for screen sharing and video conferencing.

Also, assessments will be scheduled before the exercise program, after the exercise program and a follow-up assessment one month after the post-intervention assessment.

There are two different scheduling options:

- Option 1: 5 days per week, twice a day for 4 consecutive weeks. (Approximate commitment time: Intervention time = 45 minutes x 2 times per day x 5 days per week x 4 weeks = 30 hours and Assessment time = 2 hours x 3 assessments = 6 hours)
- Option 2: 3 days per week, twice a day for 8 consecutive weeks (Approximate commitment time: Intervention time = 45 minutes x 2 times per day x 3 days per week x 8 weeks = 36 hours and Assessment time = 2 hours x 3 assessments = 6 hours)

The location for these trainings will be Riverview Health Center, Administration Building. Once you arrive for the session, please check for the exact room with the research assistant in room PE-449.

Additionally, if participants are attending the sessions in our laboratory, they can receive an optional electrical stimulation called transcranial alternating current stimulation (tACS). This applies an alternating current to a person's brain by two electrodes placed on the scalp. The participants, who choose this option, will receive simultaneous stimulation during the brain exercise tutored sessions. Studies have shown that simultaneous application of the electrical stimulation and cognitive exercises further enhances the cognitive function by boosting the working memory improvement. Thus, this may lead to further improvements from any potential positive effects of the brain exercises. This option is not available for participant receiving the brain exercises sessions online.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff first.

If you find the treatment program beneficial, we can offer it every 4 months up to 5 years as long as our budget allows.

Assessments

We will run several assessments that include a questionnaire for assessing depression level (as a confounding variable), a series of memory assessment and a test for spatial

orientation that involves playing a virtual reality type of game. The assessments will occur in our laboratory. If we are unable to run the assessment in-person due to pandemic, we will have it online, by video conferencing; in that case you will receive detailed instructions by email.

Risks and Discomforts

There is no risk in completing any of the brain exercises games. Among the assessments, only in the spatial virtual reality experiment, about 10% of population may feel motion sickness; in that case, we will stop the experiment and will not proceed with that test. In addition, some may feel uncomfortable with some of the questions in Montgomery-Asberg Depression Rating Scale (MADRS) questionnaire, which in that case, we will not persist.

In case the MADRS questionnaire uncovers severe depression, we recommend contacting the following services: 1. Mobile Crisis Services (204-940-1781), 2. Manitoba Suicide Prevention (1-877-435-7170), and 3. Mental Health Crisis Line (204-786-8686). We also recommend consultation with your family doctor. If you grant us permission to contact your family physician, we will contact him/her.

If any Group B participant decides to receive simultaneous tACS during the brain exercise tutored sessions, there are some potential mild risks. These include mild pain, mild headaches or fatigue. Also, the electrodes may cause tingling, itching, burning sensation, or skin redness. There is however a serious risk of seizure from tACS in people with history of epilepsy or in people who have an increased risk of getting seizures. If you have a history of seizure, you should not receive tACS. You will be asked some questions regarding your or your family's medical history, if you have certain conditions. Please respond completely and accurately to these questions for your safety.

If participating during COVID-19 pandemic, be aware that you have to wear mask for the entire time while you are visiting our labs. We do follow a strict guideline (attached) for operation during the pandemic; we also recommend to do all the assessments that require a longer time to be done remotely and online unless it is not possible. Nevertheless, there might be an increased risk of being infected by COVID-19.

In addition to the above-mentioned risks, please read the important information about COVID-19 and its risks for research participation in the attached Appendix.

Benefits

There may or may not be direct benefit to you from participating in this study. We hope the information learned from this study will benefit other people with memory and cognitive declines related to dementia and age-related cognitive disorders, such as Alzheimer's disease in the future. The regular brain exercises may improve the cognitive state of the

participants. However, we cannot guarantee or promise that you will receive any individual benefits from this project.

Costs

All the procedures, which will be performed as part of this study, are provided at no cost to you. You will receive no payment or reimbursement for any expenses related to taking part in this study.

Confidentiality

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. In case of Online assessment, the video conference assessment will be recorded and the recording will be kept for a period of 2 months on our secure server following the assessment date for analyzing the scores and verification; afterward, it will be deleted permanently. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

Any data recorded during the brain exercises and assessments will be de-identified with a participant's assigned code. The master file linking the names and codes will be saved in a secure and physically separate server of the principal investigator's department. The assessment data with the brain exercise data with the assigned code will be saved onto the principal investigator's online server.

The University of Manitoba Biomedical Research Ethics Board may review records related to the study for quality assurance purposes.

All paper records will be kept in a locked secure cabinet in a locked room and secure online database respectively. Only those authorized persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. The file containing information revealing any personal information such as your name, address or telephone number will be saved on the secure server of the PI's home department.

Voluntary Participation/ Withdrawal Policy

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate or to withdraw from the study will not affect your care at this center. If the study staff feel that it is in your best interest to withdraw you from the study, they will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Results of the Study

You are welcome to ask for your own performance in the assessments after the end of the study (2 months period). You may also ask about the results of the study once we finish analysis and publish it (approximately a year after the study). For this information, you may contact the principal investigator of the study, Dr. Zahra Moussavi (Zahra.Moussavi@umanitoba.ca).

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the principal investigator: Dr. Zahra Moussavi at [REDACTED]

For questions about your rights as a research participant, you may contact The University of Manitoba, Biomedical Research Ethics Board Office at [REDACTED].

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Zahra Moussavi and/or her study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my records that relate to this study by The University of Manitoba Biomedical Research Ethics Board for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I agree to being contacted in relation to this study: **Yes** ☐ **No** ☐

I agree to my family physician being notified of my participation in this study: **Yes** ☐ **No** ☐

I agree to receive transcranial alternating current stimulation during the brain exercise tutor sessions:

Yes ☐ No ☐ N/A ☐

Participant signature _____

Date _____

(day/month/year)

Participant printed name: _____

Date of Birth: _____

Contact Number: _____ Email: _____

In cases where a legal representative gives consent on behalf of participant:

Legal representative's signature _____

Date _____

(day/month/year)

Legal representative's printed name: _____

Relationship to Participant: _____

The study coordinator Part

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Coordinator's Signature: _____

Date _____

Coordinator's Printed Name: _____

(day/month/year)

Role in the study: _____

Relationship to study team members _____ [eg. supervisor, teacher/professor or family member.]

Assigned Code: _____

A.2 Crossover 40 Hz tACS Study

Title of Study: "Investigating the Effect of Cognitive Training Simultaneous with Real and Sham Transcranial Alternating Current Stimulation on the Executive Brain Functions in Dementia Population"

Protocol Version: "Version 3, Feb. 2022"

Principal Investigator: "Dr. Zahra Moussavi, Biomedical Engineering, University of Manitoba,
[REDACTED]"

Co-Investigator: "*Prof. Brian Lithgow, Biomedical Engineering, University of Manitoba*"

Co-Investigator: "*Dr. Mohammad Jafari-Jozani, Dept of Statistics, University of Manitoba,*"

Funder: MITACS

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

You are being asked to participate in a research study on investigating efficacy of a new treatment for dementia. You may discuss your decision about participating in this clinical trial with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand.

The study investigator and institution are receiving funds from the funder, **MITACS, Canada** for the cost of the project to conduct this study.

Purpose of Study

This research is being conducted to study whether tACS (Transcranial Alternating Current Stimulation) paired with cognitive exercises could be potentially used as a treatment for dementia and its subtypes including mild cognitive impairment, Alzheimer's, Lewy Body, and Fronto-temporal dementia. tACS is a technique that stimulates the brain by a very small electrical current through two electrodes placed over the head.

Screening Visit

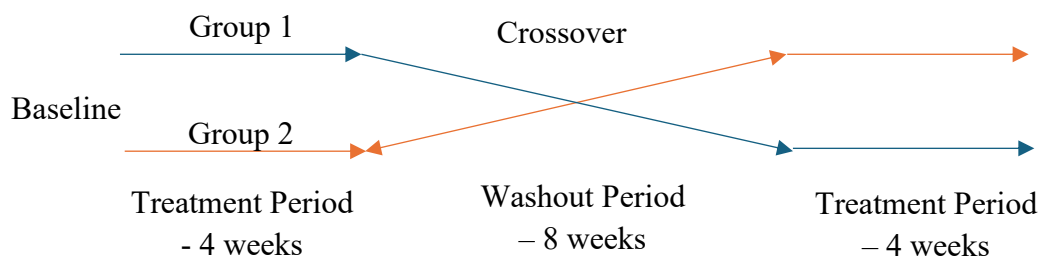
To participate in the study, you need to be between 50 to 95 years and diagnosed with mild or moderate stage dementia by your family doctor. You are required to ask your family doctor to fax us your full diagnostic report. Afterwards, we will check your eligibility to confirm your continuation in the study. Individuals diagnosed with Parkinson's, Parkinsonian dementia, Huntington disease, speech significant aphasia and intellectual disability, major depression/anxiety, bipolar disorder, schizophrenia or any other major mood disorder, or those with a history of epileptic seizure will be excluded. Your cognitive functioning will be screened

by a questionnaire called “Montreal Cognitive Assessment (MoCA)”; those with a score between 5 to 24 out of 30 are eligible to be enrolled in this study. The screening visit is normally in-person in our lab, while in some circumstances (e.g. for out-of-town volunteers) we can also run it by video conferencing using Zoom or TEAMS. A screening session may take up to one hour.

Study Design

Our study design is a double-blind cross-over design. It means that you will start receiving either real or sham (not real stimulation but looks like real) tACS stimulation plus cognitive exercises for 4 weeks every day except the weekends; then, wait for 8 weeks of no treatment sessions and then another 4 weeks of either sham or real tACS therapy and cognitive exercises. If you are assigned to receive real tACS first, on the second period you will receive sham one and vice versa. The diagram below shows the study design graphically. Neither you nor assessors know which group you are assigned to; that is why it is called double-blind. Your group assignment can be revealed to you by the PI of the study after the 16 weeks period of the study upon receiving your request. The purpose of sham treatment is to have a control group data that the plausible improvement as a result of tACS can be compared to. With our cross-over study design, every participant receives both real and sham treatments at one of the two period of the treatment.

In case you cannot tolerate tACS stimulation (some people cannot focus on cognitive exercises while receiving tACS), you will be assigned to a third group in which you will receive only cognitive exercises for 4 weeks, every day (except the weekends) with the help of a tutor.



tACS Study Procedures

tACS applies a very small electric current thorough two electrodes placed over the head. One of the study research assistants will need to measure your head size to identify the exact location of the electrodes.

At each day of treatment, you will receive tACS (either sham or real) while working on some cognitive games on an iPad with the help of a tutor. There will be two sessions per day; each is about 30 minutes with 30 minutes break in between.

Assessments

Your cognitive functioning will be assessed at baseline and also at the end of the treatment period, with additional assessments at every 4 or 8 weeks up to 4 months after the baseline. These assessments involve some questionnaires, games, and tests of memory and other thinking abilities. Some of your responses will be recorded and transcribed in order to analyze your speech patterns. A family member or friend will also be asked to complete questionnaires about symptoms or difficulties you may be having. The purpose of the tests and questionnaires is to measure any improvement that may occur with tACS plus cognitive exercises treatment.

The assessments of out-of-town participants could be performed online using either Zoom and TEAMS, whichever is more convenient.

The results of your assessments (individually) will be provided to you upon your request by the principal investigator of the study (Dr. Zahra Moussavi). Also, the results of the study in general will be disseminated to public once we reach our target number of participants.

You will also be asked to volunteer for EVestG assessment; that has a separate consent form, in which its plausible minimal risks are explained in detail.

Time Commitment

There are two different time commitments: one is for daily treatment sessions and one is for the assessment sessions.

Treatment Sessions Time Commitment: The study has two periods of 4-weeks daily treatment (except weekends); each 4-weeks intervention include 20 daily sessions of 1.5 hours/day but given the preparation time allow 2 hours/day.

Assessment Sessions Time Commitment: We run assessments 4 times (on 4 days over 16 weeks); each assessment session can take up to 4 hours. If you also participate in EVestG assessment study, it will take another 2 hours; it could be arranged on the same day or in a different day depending on your preference and our study staff availability.

Benefits

It is possible that you may experience better memory after a period of treatment, however it is not known if individuals will experience an improvement in memory. Other possible benefits include contributing to a better understanding of brain activity. We cannot guarantee or promise that you will receive any benefits from this project.

Costs

All clinic and professional fees, diagnostic, laboratory tests are provided at no cost to you. There will be no cost for the study treatment that you will receive. Please let us know if you need reimbursement for any transportation and/or accommodation costs as we might be able to help from a donation budget.

Risks and Discomforts

The tACS procedure used in this study is considered to be of minimal risk. These include mild pain, mild headaches or fatigue. Also, the electrodes may cause tingling, itching, burning

sensation, or skin redness. There is however a serious risk of seizure from tACS in people with history of epilepsy or in people who have an increased risk of getting seizures. If you have a history of seizure, you should not receive tACS. You will be asked some questions regarding your or your family's medical history, if you have certain conditions. Please respond completely and accurately to these questions for your safety. Also, if you have any medical head implant, your doctor will need to provide a written document stating tACS can be safely applied for your continuation in the study.

There are no physical risks of performing the computer tasks and assessments. You may find some of the tasks dull or tiring.

As for assessments that use technologies, there is a minimal risk of feeling dizzy while running the virtual reality task, which in that case, we will stop the experiment. Another assessment is to attach a headband that has light electrodes; it is called functional near infra-red spectroscopy (fNIRS) to measure the blood flow to your brain. There is no risk in using fNIRS; you may only feel a bit pressure over your forehead due to the head band.

While running a questionnaire to assess participants' depression level, if one expresses suicidal thoughts, we will encourage the participant to call his/her family doctor as well as calling the following help lines:

1. Mobile Crisis Services (204-940-1781),
2. Manitoba Suicide Prevention (1-877-435-7170),
3. Mental Health Crisis Line (204-786-8686)."

In addition to the above-mentioned risks, please read the important information about COVID-19 and its risks for research participation in the attached Appendix.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however, your name and other identifying information will not be used or revealed. Any document containing your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Anonymized audio speech recordings will be kept for a period of 5 years following the conclusion of the study. In case of Online assessment, the video conference recording will be kept for a period of 2 months on our secure server following the assessment date for analyzing the scores and verification; then, it will be deleted entirely. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

Increasingly, the scientific community, the granting agencies and medical scientific journals require that data be stored and made available for secondary review and analyses. Data sharing will of course be anonymized in terms of confidential information. Your demographic information (e.g., age, sex, etc.) along with your performance data anonymously (without your name, contact information or any identifying information) may be sent outside of the University of Manitoba or Riverview Health Centre to other

researchers, academic institutions, health care facilities, or organizations for further analysis, testing or as part of the research study. Information gathered in this research study may be published or presented in public forums, however your name and other identifying personal information will not be revealed. Any document containing your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. **Anonymized audio speech recording will be kept for 5 years following the conclusion of the study. In the case of online assessments, the video conference recording will kept for a period of 2 months on our secure server following the assessment date of analyzing the scores and verification and then will be deleted entirely.** However, despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave the Riverview Health Centre. In case of any publication of results of this study, information will be provided in such a way that you cannot be identified.

With your permission, your Family Physician (GP) may be notified if we find any concern and need consult.

This study is registered on a publicly available Registry Databank. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://ClinicalTrials.gov>. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Also, if your study doctor feels that it is in your best interest to withdraw you from this study, your study doctor will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

As we also run some parallel studies to this one, you may be asked if you would be willing to participate in an additional study to investigate the efficacy of treatment, which you may or may not accept.

Results of the Project

All participants have the option of receiving a lay summary of their own assessments after the 16 weeks period of the study. If you wish to be informed of your results, please inform the research staff at the time of your participation or you may contact the principle investigator of this study, Dr. Zahra Moussavi by email (Zahra.Moussavi@umanitoba.ca).

Questions

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact Dr. Zahra Moussavi [REDACTED]. For questions about your rights as a research participant, you may contact the University of Manitoba Biomedical Research Ethics Board at [REDACTED].

Statement of Consent

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. The University of Manitoba may look at your research records to see that the research is being done in a safe and proper way.

This research has been approved by the University of Manitoba Biomedical Research Ethics Board. If you have any concerns or complaints about this project you may contact any of the above-named persons or the University of Manitoba Bannatyne Campus at [REDACTED] 204-789-3389. A copy of this consent form has been given to you to keep for your records and reference.

I agree to being contacted in relation to this study. Yes ☐ No ☐

I agree to my family physician being notified of my participation in this study. Yes ☐ No ☐

Participant signature _____ **Date** _____

Participant printed name: _____ **(day/month/year)**

Date of Birth: _____

Contact Number: _____ **Email:**

In cases where a legal representative gives consent on behalf of participant:

Legal representative's signature _____ **Date**

Legal representative's printed name: _____
(day/month/year)

Relationship to Participant: _____

The study coordinator Part

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Coordinator's Signature: _____

Date

Coordinator's Printed Name: _____

(day/month/year)

Role in the study: _____

Relationship to study team members _____ *[eg. supervisor, teacher/professor or family member.]*

Assigned Code: _____

A.3 Maintenance tES Study

Title of Study: "Investigating the Effect of Cognitive Training Simultaneous with Real and Sham Transcranial Alternating Current Stimulation on the Executive Brain Functions in Dementia Population"

Title of Sub-Study: "Longitudinal Study to Investigate Different Treatment Protocols of Transcranial Electrical Stimulation for Individuals with Dementia"

Protocol Version: "Version 4, May 14, 2024"

Principal Investigator: "Dr. Zahra Moussavi, Biomedical Engineering, University of Manitoba, [REDACTED]"

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

You are being asked to participate in a research study on investigating efficacy of a new treatment for dementia. You may discuss your decision about participating in this clinical trial with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand.

Purpose of maintenance Sub-Study

This research is being conducted to investigate which frequency of the stimulation is best for you. We will use tACS (Transcranial Alternating Current Stimulation) at different frequencies or tDCS (Transcranial Direct Current Stimulation) paired with cognitive exercises. You also have the option to have background music of your choice during the treatment sessions as the auditory stimulation has also shown potential as a treatment for dementia. tACS and tDC are techniques that stimulates the brain by a very small electrical current through two electrodes placed over the head.

Screening Visit

To participate in the study, we will check your eligibility to confirm your continuation in the study. The screening visit is normally in-person in our lab, while in some circumstances (e.g. for out-of-town volunteers) we can also run it by video conferencing using Zoom or TEAMS. A screening session may take up to one hour.

Study Design

Our study design is a longitudinal, double-blind, sham-controlled design. It means that you will receive 5 different tACS/tDCS treatment protocols randomly ordered with cognitive exercises with optional background music of your choice. Each treatment session block includes every day (except weekends) treatment in two sessions of 30 minutes each for 4 weeks consecutively. Between the different treatments, there is 12 weeks of no treatment sessions (washout period). The table below shows the study timeline with the treatment protocols being one of the following: tACS at 40 Hz, personalized theta tACS, personalized gamma tACS, tDCS, and sham stimulation. With our longitudinal study design, every participant receives all 5 treatments, and after that we will continue with the frequency (type) of stimulation that has the highest efficacy for each participant. Sham stimulation is being used to measure the placebo effect. Sham stimulation is a very small amount of electrical stimulation only lasts for a couple of seconds and would have no effect on the brain's activity; thus, we can compare its effect that is considered placebo with the effect of the real stimulation.

In case you cannot tolerate tACS/tDCS stimulation (some people cannot focus on cognitive exercises while receiving tACS), you will be assigned to a different protocol in which you will receive only cognitive exercises for 4 weeks, every day (except the weekends) with the help of a tutor.

Month 1	Months 2-4	Month 5	Months 6-8	Month 9	Months 10-12	Month 13
4 Weeks of Treatment Using Protocol 1	12 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 2	12 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 3	12 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 4

tACS and tDC Study Procedures

tACS and tDC apply a very small electric current thorough two electrodes placed over the head. One of the study research assistants will need to measure your head size to identify the exact location of the electrodes.

At each day of treatment, you will receive tACS or tDCS while working on some cognitive games on an iPad or computer with the help of a tutor. There will be two sessions per day; each is about 30 minutes with 30 minutes break in between. During the sessions, you may listen to music of your choice if you like.

Assessments

Your cognitive functioning will be assessed at baseline and also at the end of the treatment period. These assessments involve some questionnaires, games, and tests of memory and other thinking abilities. Some of your responses will be recorded and transcribed in order to analyze your speech patterns. A family member or friend will also be asked to complete questionnaires about symptoms or difficulties you may be having. The purpose of the tests and questionnaires is to measure any improvement that may occur with tACS plus cognitive exercises treatment. We will also measure the treatment effects on balance, blood oxygenation changes, and the effects on the frequency bands from electroencephalography measurements.

The assessments of out-of-town participants could be performed online using either Zoom or TEAMS, whichever is more convenient.

The results of your assessments (individually) will be provided to you upon your request by the principal investigator of the study (Dr. Zahra Moussavi). Also, the results of the study in general will be disseminated to public once we reach our target number of participants.

Time Commitment

There are two different time commitments: one is for daily treatment sessions and one is for the assessment sessions.

Treatment Sessions Time Commitment: The study has six periods of 4-weeks daily treatment (except weekends); each 4-weeks intervention include 20 daily sessions of 1.5 hours/day but given the preparation time allow 2 hours/day.

Assessment Sessions Time Commitment: Each block of treatment (repeated every 4 months) has 3 assessments: pre- and post-treatment and one month after the end of treatment (follow-up). The in-person assessments all together can take up to 4 hours.

Benefits

It is possible that you may experience better memory after a period of treatment, however it is not known if individuals will experience an improvement in memory. Other possible benefits include contributing to a better understanding of brain activity. We cannot guarantee or promise that you will receive any benefits from this project.

Costs

There will be no cost for the study treatment that you will receive.

Risks and Discomforts

The tACS and tDC procedure used in this study is considered to be of minimal risk. These include mild pain, mild headaches or fatigue. Also, the electrodes may cause tingling, itching, burning sensation, or skin redness. There is however a serious risk of seizure from

tACS in people with history of epilepsy or in people who have an increased risk of getting seizures. If you have a history of seizure, you should not receive tACS. You will be asked some questions regarding your or your family's medical history, if you have certain conditions. Please respond completely and accurately to these questions for your safety. Also, if you have any medical head implant, your doctor will need to provide a written document stating tACS can be safely applied for your continuation in the study.

There are no physical risks of performing the computer tasks and assessments. You may find some of the tasks dull or tiring.

As for assessments that use technologies, there is a minimal risk of feeling dizzy while running the virtual reality task, which in that case, we will stop the experiment. Another assessment is to attach a headband that has light electrodes; it is called functional near infra-red spectroscopy (fNIRS) to measure the blood flow to your brain. There is no risk in using fNIRS; you may only feel a bit pressure over your forehead due to the head band.

While running a questionnaire to assess participants' depression level, if one expresses suicidal thoughts, we will encourage the participant to call his/her family doctor as well as calling the following help lines:

1. Mobile Crisis Services (204-940-1781),
2. Manitoba Suicide Prevention (1-877-435-7170),
3. Mental Health Crisis Line (204-786-8686)."

In addition to the above-mentioned risks, please read the important information about COVID-19 and its risks for research participation in the attached Appendix.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however, your name and other identifying information will not be used or revealed. Any document containing your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Anonymized audio speech recordings will be kept for a period of 5 years following the conclusion of the study. In case of Online assessment, the video conference recording will be kept for a period of 2 months on our secure server following the assessment date for analyzing the scores and verification; then, it will be deleted entirely. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

Increasingly, the scientific community, the granting agencies and medical scientific journals require that data be stored and made available for secondary review and analyses. Data sharing will of course be anonymized in terms of confidential information. Your demographic information (e.g., age, sex, etc.) along with

your performance data anonymously (without your name, contact information or any identifying information) may be sent outside of the University of Manitoba or Riverview Health Centre to other researchers, academic institutions, health care facilities, or organizations for further analysis, testing or as part of the research study. Information gathered in this research study may be published or presented in public forums, however your name and other identifying personal information will not be revealed. Any document containing your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba.

Anonymized audio speech recording will be kept for 5 years following the conclusion of the study. In the case of online assessments, the video conference recording will kept for a period of 2 months on our secure server following the assessment date of analyzing the scores and verification and then will be deleted entirely. However, despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave the Riverview Health Centre. In case of any publication of results of this study, information will be provided in such a way that you cannot be identified.

With your permission, your Family Physician (GP) may be notified if we find any concern and need consult.

This study is registered on a publically available Registry Databank. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://ClinicalTrials.gov>. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Also, if your study doctor feels that it is in your best interest to withdraw you from this study, your study doctor will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

As we also run some parallel studies to this one, you may be asked if you would be willing to participate in an additional study to investigate the efficacy of treatment, which you may or may not accept.

Results of the Project

All participants have the option of receiving a lay summary of their own assessments after the 16 weeks period of the study. If you wish to be informed of your results, please inform the research staff at the time of your participation or you may contact the principle investigator of this study, Dr. Zahra Moussavi by email (Zahra.Moussavi@umanitoba.ca).

Questions

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact Dr. Zahra Moussavi ([REDACTED]). For questions about your rights as a research participant, you may contact the University of Manitoba Biomedical Research Ethics Board at [REDACTED].

Statement of Consent

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. The University of Manitoba may look at your research records to see that the research is being done in a safe and proper way.

This research has been approved by the University of Manitoba Biomedical Research Ethics Board. If you have any concerns or complaints about this project you may contact any of the above-named persons or the University of Manitoba Bannatyne Campus at [REDACTED] 204-789-3389. A copy of this consent form has been given to you to keep for your records and reference.

I agree to being contacted in relation to this study. **Yes** ☐ **No** ☐

I agree to my family physician being notified of my participation in this study. **Yes** ☐ **No** ☐

Participant signature _____ **Date** _____

Participant printed name: _____ **(day/month/year)**

Date of Birth: _____

Contact Number: _____ **Email:** _____

In cases where a legal representative gives consent on behalf of participant:

Legal representative's signature _____

Date

Legal representative's printed name: _____
(day/month/year)

Relationship to Participant: _____

The study coordinator Part

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Coordinator's Signature: _____

Date

Coordinator's Printed Name: _____

(day/month/year)

Role in the study: _____

Relationship to study team members _____ [eg. supervisor,
teacher/professor or family member.]

Assigned Code: _____

A.4 Longitudinal tES Study

Title of Study: "Investigating the Effect of Different Frequencies of Transcranial Electrical Stimulations Paired with Cognitive Training on the Executive Brain Functions in Dementia Population"

Protocol Version: "Version 6, June 5, 2025"

Principle Investigator: "Maria Anabel Uehara, Biomedical Engineering, University of Manitoba"

Supervisor: "Dr. Zahra Moussavi, Biomedical Engineering, University of Manitoba,

██████████"

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

You are being asked to participate in a research study on investigating efficacy of a new treatment for dementia. You may discuss your decision about participating in this clinical trial with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand.

Purpose of the Study

This research is being conducted to investigate the effects of different frequencies of stimulation. We will use tACS (Transcranial Alternating Current Stimulation) at different frequencies or tDCS (Transcranial Direct Current Stimulation) paired with cognitive exercises. TACS and tDCS are techniques that stimulates the brain by a very small electrical current through two electrodes placed over the head.

Screening Visit

To participate in the study, we will check your eligibility to confirm your continuation in the study. The screening visit is normally in-person in our lab, while in some circumstances (e.g. for out-of-town volunteers) we can also run it by video conferencing using Zoom or TEAMS. A screening session may take up to one hour.

Study Design

Our study design is a double-blind, sham-controlled design. It means that you will receive all 4 different tACS/tDCS treatment protocols in a random order with cognitive exercises using MindTriggers app. Each treatment session block includes every day (except weekends) treatment in two sessions of 30 minutes each for 4 weeks consecutively with a break in between the two sessions. Between the different treatments, there is 8 weeks of no treatment sessions (washout period) up to 5 months. The table below shows the study timeline with the treatment protocols being one of the following: personalized theta tACS, personalized gamma tACS, tDCS, and sham stimulation. With our study design, every participant receives all 4 treatments, and after that we will add one more treatment block with a protocol based on promising research in Italy targeting the back of the brain (precuneus which is directly involved in episodic memory) and then we will continue with the frequency (type) of stimulation that has the highest efficacy for each participant. Sham stimulation is being used to measure the placebo effect. Sham stimulation is a very small amount of electrical stimulation only lasts for a couple of seconds and would have no effect on the brain's activity; thus, we can compare its effect that is considered placebo with the effect of the real stimulation.

In case you cannot tolerate tACS/tDCS (some people cannot focus on cognitive exercises while receiving tACS/tDCS), you will be assigned to a different protocol in which you will receive only cognitive exercises for 4 weeks, every day (except the weekends) with the help of a tutor.

Month 1	Months 2-4	Month 5	Months 6-8	Month 9	Months 10-12	Month 13
4 Weeks of Treatment Using Protocol 1	8-20 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 2	8-20 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 3	8-20 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 4
Months 14-16	Month 17					
8-20 Weeks Washout (No Treatment)	4 Weeks of Treatment Using Protocol 1					

tACS and tDCS Study Procedures

tACS and tDCS apply a very small electric current thorough two electrodes placed over the head. One of the study research assistants will need to measure your head size to identify the exact location of the electrodes.

At each day of treatment, you will receive tACS or tDCS while working on some cognitive games on an iPad or computer with the help of a tutor. There will be two sessions per day; each is about 30 minutes with 30 minutes break in between.

Assessments

Your cognitive functioning (ability to remember and make decisions) will be assessed. These assessments involve some questionnaires, games, and tests of memory and other thinking abilities. Some of your responses will be recorded and transcribed in order to analyze your speech patterns. A family member or friend will also be asked to complete questionnaires about symptoms or difficulties you may be having. The purpose of the tests and questionnaires is to measure any improvement that may occur with tACS/tDCS plus cognitive exercises treatment. We will also measure the treatment effects on balance, blood oxygenation changes, and the effects on the frequency bands from electroencephalography measurements.

The assessments of out-of-town participants could be performed online using either Zoom or TEAMS, whichever is more convenient.

The results of your assessments (individually) will be provided to you upon your request by the principal investigator of the study (Dr. Zahra Moussavi). Also, the results of the study in general will be disseminated to public once we reach our target number of participants.

You will also be asked to volunteer for EVestG assessment; that has a separate consent form, in which its plausible minimal risks are explained in detail. EVestG will also include a blood pressure measurement.

Time Commitment

There are two different time commitments: one is for daily treatment sessions and one is for the assessment sessions.

Treatment Sessions Time Commitment: The study has 4 periods of 4-weeks daily treatment (except weekends); each 4-weeks intervention include 20 daily sessions of 1.5 hours/day but given the preparation time allow 2 hours/day. Three treatment days within each treatment block may be selected to involve simple EEG recording immediately before and after the treatment, you will be notified ahead of time of the extra 30 minutes required for those treatment days. One treatment day within each treatment block may be selected

to involve fNIRS immediately before and after the treatment, you will be notified ahead of time of the extra 15 minutes required.

Assessment Sessions Time Commitment: Each block of treatment (repeated every 3 months) has 3 assessments: pre- and post-treatment and one month after the end of treatment (follow-up). The in-person assessments all together can take up to 5 hours. If you participate in EVestG assessment study, it will take another 2 hours. EVestG measures the signals in the ear canal by placement of electrodes inside the ear. It will be used to determine whether this recording technique can provide diagnostic information and help predict the efficacy of the treatment.

Medication Guidelines

By participating in this study, you agree not to start any new medication for Alzheimer's disease, dementia, or depression, nor changing your dementia or depression-related medications for the duration of one week prior to treatment block until the follow-up assessment, for each block of treatment. Overall we need you to be on a stable dose of medication during any treatment block (including its assessment weeks). If it is absolutely necessary to change a medication during the treatment block, please inform the study coordinator ASAP. Also if you start a new medication during the washout period between two blocks of treatment, please let us know as we may have to delay the next treatment block so that the effect of medication is stabilized.

Benefits

It is possible that you may experience better memory after a period of treatment, however it is not known if individuals will experience an improvement in memory. Other possible benefits include contributing to a better understanding of brain activity. We cannot guarantee or promise that you will receive any benefits from this project.

Costs

There will be no cost for the study treatment that you will receive.

Risks and Discomforts

The tACS and tDCS procedure used in this study is considered to be of minimal risk. These include mild pain, mild headaches or fatigue. Also, the electrodes may cause tingling, itching, burning sensation, or skin redness. There is however a serious risk of seizure from tACS in people with history of epilepsy or in people who have an increased risk of getting seizures. If you have a history of seizure, you should not receive tACS. You will be asked some questions regarding your or your family's medical history, if you have certain conditions. Please respond completely and accurately to these questions for your safety.

Also, if you have any medical head implant, your doctor will need to provide a written document stating tACS/tDCS can be safely applied for your continuation in the study.

There are no physical risks of performing the computer tasks and assessments. You may find some of the tasks dull or tiring.

As for assessments that use technologies, there is no risk associated to electroencephalography (EEG) other than discomfort with electrodes placed on the head. Another assessment is to attach a headband that has light electrodes; it is called functional near infra-red spectroscopy (fNIRS) to measure the blood flow to your brain. There is no risk in using fNIRS; you may only feel a bit pressure over your forehead due to the head band. Lastly, for the balance assessment, there is a small risk of falling but we will always have at least one research assistant ready to prevent any falls during the assessment.

While running a questionnaire to assess participants' depression level, if one expresses suicidal thoughts, we will encourage the participant to call his/her family doctor as well as calling the following help lines:

1. Mobile Crisis Services (204-940-1781),
2. Manitoba Suicide Prevention (1-877-435-7170),
3. Mental Health Crisis Line (204-786-8686)."

In addition to the above-mentioned risks, please read the important information about COVID-19 and its risks for research participation in the attached Appendix.

Confidentiality

Increasingly, the scientific community, the granting agencies and medical scientific journals require that data be stored and made available for secondary review and analyses. Data sharing will of course be de-identified in terms of confidential information. Your demographic information (e.g., age, sex, etc.) along with your performance data de-identified (without your name, contact information or any identifying information) may be sent outside of the University of Manitoba or Riverview Health Centre to other researchers, academic institutions, health care facilities, or organizations for further analysis, testing or as part of the research study. Information gathered in this research study may be published or presented in public forums, however your name and other identifying personal information will not be revealed.

Each participant will be assigned a unique code, a number, and your data will be labeled using this code rather than your name. A separate, secure file will link the code to your identity, which will be maintained by the research team either stored in locked cabinets or on a separate secure server. Only authorized members of the

research team will have access to these files. Any document containing your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. **De-identified audio speech recording will be kept for 5 years following the conclusion of the study. In the case of online assessments, the video conference recording will be kept for a period of 2 months on our secure server following the assessment date of analyzing the scores and verification and then will be deleted entirely.** However, despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave the Riverview Health Centre. In case of any publication of results of this study, information will be provided in such a way that you cannot be identified.

With your permission, your Family Physician (GP) may be notified if we find any concern and need consult.

This study is registered on a publically available Registry Databank. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://ClinicalTrials.gov>. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Also, if your study doctor feels that it is in your best interest to withdraw you from this study, your study doctor will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

As we also run some parallel studies to this one, you may be asked if you would be willing to participate in an additional study to investigate the efficacy of treatment, which you may or may not accept.

Results of the Project

All participants have the option of receiving a lay summary of their own assessments after the completion of all 4 protocols. If you wish to be informed of your results, please inform the research staff at the time of your participation or you may contact the principle investigator of this study, Dr. Zahra Moussavi by email (Zahra.Moussavi@umanitoba.ca).

Questions

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact Dr. Zahra Moussavi ([REDACTED]). For questions about your rights as a research participant, you may contact the University of Manitoba Biomedical Research Ethics Board at [REDACTED].

Statement of Consent

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. The University of Manitoba may look at your research records to see that the research is being done in a safe and proper way.

This research has been approved by the University of Manitoba Biomedical Research Ethics Board. If you have any concerns or complaints about this project you may contact any of the above-named persons or the University of Manitoba Bannatyne Campus at [REDACTED] 204-789-3389. A copy of this consent form has been given to you to keep for your records and reference.

I agree to being contacted in relation to this study. **Yes** ☐ **No** ☐

I agree to my family physician being notified of my participation in this study. **Yes** ☐ **No** ☐

Participant signature _____ **Date** _____

Participant printed name: _____ **(day/month/year)**

Date of Birth: _____

Contact Number: _____ **Email:** _____

In cases where a legal representative gives consent on behalf of participant:

Legal representative's signature _____ **Date** _____

Legal representative's printed name: _____
(day/month/year)

Relationship to Participant: _____

The study coordinator Part

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Coordinator's Signature: _____

Date

Coordinator's Printed Name: _____

(day/month/year)

Role in the study: _____

Relationship to study team members _____ *[eg. supervisor, teacher/professor or family member.]*

Assigned Code: _____

A.5 Weston rTMS Study

Title of Study: "Investigating the effect of repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for Alzheimer's Disease"

Protocol Version: "Version 12 Aug. 2020"

Principal Investigator: "Dr. Zahra Moussavi, Biomedical Engineering, University of Manitoba, [REDACTED]"

Co-Investigator: "Dr. Colleen Millikin, University of Manitoba, Deer Lodge Centre, Winnipeg, Canada"

Co-Investigator: "Dr. Craig Omelan, University of Manitoba, St. Boniface Hospital, Winnipeg, Canada"

Co-Investigator: "Dr. Behzad Mansouri, University of Manitoba, Internal Medicine, Winnipeg, Canada"

Co-Investigator: "Dr. Xikui Wang, University of Manitoba, Dept of Statistics, Winnipeg, Canada"

Funder: Weston Brain Institute – Canada

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

You are being asked to participate in a research study on investigating efficacy of a new treatment for Alzheimer's disease. You may discuss your decision about participating in this clinical trial with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand.

The study investigator and institution are receiving funds from the funder, **Weston Brain Institute, Canada** to conduct this study.

Purpose of Study

This research is being conducted to study whether rTMS (repetitive Transcranial Magnetic Stimulation) could be potentially used as a treatment for Alzheimer's disease. rTMS is a technique that stimulates the brain by rapidly switching a magnetic field in a coil placed over the head.

Screening Visit

To participate in the study, you need to be diagnosed with Alzheimer's at a mild or moderate stage by your psychiatrist/geriatrician/neurologist, or by one of our study doctors. Afterwards, by consultation with our study doctors, we will check your eligibility to confirm your continuation in the study.

We also need a MRI scan for research purposes. If you do not have a previous MRI scan, we will schedule a research MRI scan for you. Afterwards, if we still cannot retrieve a valid MRI scan, another reference MRI scan similar to your anatomy will be used.

If you require a research MRI scan, any implants, devices, or objects may be hazardous to you and/or may interfere with the MRI scan. Please let us know if you have any questions or concern regarding an implant, device or object. We will consult with the MRI radiologists before proceeding with a MRI scan.

We only retrieve MRI scans without any reports. If you wish to have your MRI scan interpreted, we can provide you a copy of your MRI scan on a USB drive or CD that you can give to your family doctor, psychiatrist or neurologist. They may have a MRI computer program to view and to interpret your MRI scan. We are not trained on reading any MRI scans.

rTMS Study Procedures

rTMS stands for Repetitive Transcranial Magnetic Stimulation, which uses short magnetic pulses from a coil placed over the head. Your MRI scan is used to apply rTMS to specific target brain regions. These magnetic pulses are able to cause neurons in the brain to activate, and hopefully this will train the neurons to be more active in the future.

Procedures for this study will include single pulse TMS and repetitive TMS (rTMS) treatment. If you agree to participate, you will be asked to participate in either one set of 10 treatment sessions (every day for 2 weeks excluding weekends) or 20 treatment sessions (every day for 4 weeks excluding weekends); each treatment session lasts about 25 minutes. In the first session, you and a family member or friend will be interviewed by a researcher associated with the study to assess your general health and aspects of your mood, anxiety, memory, other psychological symptoms, and your ability to carry out everyday activities.

You will be receiving either sham or active treatment. Sham treatment sessions are identical to active treatment sessions, except that there is no magnetic stimulation. As this is a double-blind study, you will not know whether you are receiving sham or active treatment. You will be assigned to one of these groups (sham or active treatment for either 2 or 4 weeks) randomly similar to flipping a coin. The purpose of sham treatment is to have a control group data that the plausible improvement as a result of rTMS can be compared to. If you are assigned to sham group, after 6 months, we will offer you active treatment with the same procedure if you wish.

Your cognitive functioning will be assessed at the beginning of each week and also at the end of the treatment, with additional assessments at every 4 weeks up to 6 months after the final rTMS treatment session. These assessments involve some questionnaires, games, and tests of memory and other thinking abilities. Some of your responses will be recorded and transcribed in order to analyze your speech patterns. A family member or friend will also be asked to complete questionnaires about symptoms or difficulties you may be having. The purpose of the tests and questionnaires is to measure any improvement that may occur with rTMS treatment. The

assessments will occur in our laboratory. If we are unable to run the assessment in-person due to pandemic, we will have it online, by video conferencing.

The results of your assessments will be provided to you upon your request by the principal investigator of the study (Dr. Zahra Moussavi) once we reach our target number of participants. Also, the results of the study in general will be disseminated to public once we reach our target number of participants.

Benefits

It is possible that you may experience better memory after a period of treatment, however it is not known if individuals will experience an improvement in memory. Other possible benefits include contributing to a better understanding of brain activity. We cannot guarantee or promise that you will receive any benefits from this project.

Costs

All clinic and professional fees, diagnostic, laboratory tests and MRI scans (if applicable) which will be performed as part of this study are provided at no cost to you. There will be no cost for the study treatment that you will receive. Please let us know if you need reimbursement for any transportation and/or accommodation costs.

Risks and Discomforts

The TMS procedure used in this study is considered to be of minimal risk. Since TMS applies a magnetic field similar to a MRI scan, we ask you to identify if you have any implants, devices, or objects that may be hazardous to you. If you have any concerns, you should consult with your doctor. Also, if you have any medical implants, devices or objects, your doctor will need to provide a written document stating TMS can be safely applied for your continuation in the study.

There is however a risk of seizure from TMS in people with history of epilepsy or in people who have an increased risk of getting seizures. If you have a history of seizure, you should not participate in this study. You will be asked some questions regarding your or your family's medical history and will be excluded from the study, if you have certain conditions. Please respond completely and accurately to these questions for your safety.

You may have a mild headache following rTMS application. This is believed to be due to muscle tension. In the case of a headache, you may take acetaminophen, a medication that in all prior cases of headaches induced by rTMS, has promptly resolved the discomfort. Toothaches and mild pain in the eye, scalp and neck are other common but mild and temporary side effects of rTMS treatments. Since the TMS device is an investigational instrument, there may be some other minor risks that are unknown.

There are no physical risks of performing the computer tasks and assessments. You may find some of the tasks dull or tiring.

Please note that if you come alone for treatments, we will have to call a taxi for you to go back home after the treatment.

In addition to the above-mentioned risks, please read the important information about COVID-19 and its risks for research participation in the attached Appendix.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however, your name and other identifying information will not be used or revealed. Medical records, including your MRI scans, that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Audio speech recordings will be kept for a period of 5 years following the conclusion of the study. In case of Online assessment, the video conference recording will be kept for a period of 2 months on our secure server following the assessment date for analyzing the scores and verification; then, it will be deleted entirely. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave the Riverview Health Centre. In case of any publication of results of this study, information will be provided in such a way that you cannot be identified.

With your permission, your Family Physician (GP) and/or your neurologist/psychiatrist will be notified about your participation in this study.

This study is registered on a publically available Registry Databank. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://ClinicalTrials.gov>. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Also, if your study doctor feels that it is in your best interest to withdraw you from this study, your study doctor will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

As we also run some parallel studies to this one, you may be asked if you would be willing to participate in an additional study to investigate the efficacy of treatment, which you may or may not accept.

Results of the Project

All participants have the option of receiving a lay summary of their own assessments once we reach our target number of participants. If you wish to be informed of your results, please inform

the research staff at the time of your participation or you may contact the principle investigator of this study, Dr. Zahra Moussavi by email (Zahra.Moussavi@umanitoba.ca).

Questions

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact Dr. Zahra Moussavi (). For questions about your rights as a research participant, you may contact the University of Manitoba Biomedical Research Ethics Board at .

Statement of Consent

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. The University of Manitoba may look at your research records to see that the research is being done in a safe and proper way.

This research has been approved by the University of Manitoba Biomedical Research Ethics Board. If you have any concerns or complaints about this project you may contact any of the above-named persons or the University of Manitoba Bannatyne Campus at 204-789-3389. A copy of this consent form has been given to you to keep for your records and reference.

I agree to being contacted in relation to this study. **Yes** ☐ **No** ☐

I agree to my family physician being notified of my participation in this study. **Yes** ☐ **No** ☐

I require reimbursement for transportation and/or accommodation costs. **Yes** ☐ **No** ☐

Participant signature _____ **Date** _____

Participant printed name: _____ **(day/month/year)**

Date of Birth: _____

Contact Number: _____ **Email:** _____

In cases where a legal representative gives consent on behalf of participant:

Legal representative's signature _____ **Date** _____

Legal representative's printed name: _____ **(day/month/year)**

Relationship to Participant: _____

The study coordinator Part

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Coordinator's Signature: _____

Date

Coordinator's Printed Name: _____

(day/month/year)

Role in the study: _____

Relationship to study team members _____ *[eg. supervisor, teacher/professor or family member.]*

Assigned Code: _____

A.6 Weston Maintenance rTMS Study

Title of Study: *"Investigating the effect of repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for Alzheimer's Disease"*

Title of Sub-Study: *"Investigating the effect of maintenance repetitive Transcranial Magnetic Stimulation (rTMS) and the Brain Fitness App as an ongoing treatment for Alzheimer's disease (linked to HS21624 (B2018:029))"*

Sub-Protocol Version: "Version 3 - March 24, 2019"

Principal Investigator: "Dr. Zahra Moussavi, Biomedical Engineering, University of Manitoba, [REDACTED]"

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

You are being asked to participate in a research study on investigating efficacy of a new treatment for Alzheimer's disease. You may discuss your decision about participating in this clinical trial with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand.

The cost of this maintenance treatment study is supported by a donation fund from the Puchniak family.

Purpose of Study

This research is being conducted to study whether scheduled maintenance rTMS (repetitive Transcranial Magnetic Stimulation) with our optional Brain Fitness App exercises could be potentially used as an ongoing treatment for Alzheimer's disease. rTMS is a technique that stimulates the brain by rapidly switching a magnetic field in a coil placed over the head. The Brain Fitness App consists of a series of memory and spatial orientation exercises.

Screening Visit

To participate in the ongoing maintenance treatment study, we will check your eligibility with some screening assessments. Also, a family member or friend will be asked to complete a questionnaire about symptoms or difficulties you may be having.

rTMS Maintenance Study Procedures

rTMS stands for Repetitive Transcranial Magnetic Stimulation, which uses short magnetic pulses (2000 pulses on each side per session) from a coil placed over the head. Your MRI scan from the main study is used to apply rTMS to specific target brain regions. These magnetic pulses are able

to cause neurons in the brain to activate, and hopefully this will train the neurons to be more active in the future.

Procedures for this study will include single pulse TMS, repetitive TMS (rTMS) treatment while naming objects/ actions displayed to you and playing our optional Brain Fitness App exercises. If you agree to participate, there are two maintenance treatment scheduling options:

Option 1: One block of 4 weeks, 5 days/ week of treatment repeated every 4 months for at least a year (About 60 sessions per year). Assessments will be completed before and after each treatment block.

Option 2: One block of 3 weeks, 5 days/week and then the following weeks with 2 days/ week up to 3 months of treatment. Afterwards, stop treatments for 3 months and then repeat the whole cycle for at least a year (About 76 sessions per year). Assessments will be completed before and after each treatment block with a follow-up assessment 2 months after the treatment block.

Participants may receive maintenance active treatments up to 4 years.

Our assessments involve some questionnaires, games, and tests of memory and other thinking abilities. A family member or friend will also be asked to complete questionnaires about symptoms or difficulties you may be having. The purpose of the tests and questionnaires is to measure any improvement that may occur with rTMS treatment.

You will also complete an assessment every 6 months to evaluate your overall memory and functional abilities, while we ask a family member or friend some related questions.

The results of your assessments will be provided to you upon your request by the principal investigator of the study (Dr. Zahra Moussavi) once we reach our target number of participants. Also, the results of the study in general will be disseminated to public once we reach our target number of participants.

Brain Fitness APP Exercises (Optional)

We also recommend participants to play our Brain Fitness APP exercises on the same days as their scheduled rTMS treatments. The Brain Fitness APP consists of a series of memory and spatial orientation brain exercises with several difficulty levels. Each participant will have a dedicated tutor (qualified trainee) for the brain exercises. If you are interested in participating, the tutor sessions will be twice on a scheduled treatment session day with a duration of maximum 45 minutes each. There will be a one-hour break between the two sessions. During each session, we will stop sooner than 45 minutes if the participant feels mentally fatigued.

The Brain Fitness APP Exercises are optional, and they are not a requirement to receive rTMS maintenance treatment.

Benefits

It is possible that you may experience better memory after a period of treatment, however it is not known if individuals will experience an improvement in memory. Other possible benefits include

contributing to a better understanding of brain activity. We cannot guarantee or promise that you will receive any benefits from this project.

Costs

There will be no cost for the study treatment that you will receive. All clinic and professional fees, diagnostic, laboratory tests which will be performed as part of this study are provided at no cost to you. Please let us know if you need reimbursement for any transportation and/or accommodation costs.

Risks and Discomforts

The TMS procedure used in this study is considered to be of minimal risk. Since TMS applies a magnetic field similar to a MRI scan, we ask you to identify if you have any implants, devices, or objects that may be hazardous to you. If you have any concerns, you should consult with your doctor. Also, if you have any medical implants, devices or objects, your doctor will need to provide a written document stating TMS can be safely applied for your continuation in the study.

There is however a risk of seizure from TMS in people with history of epilepsy or in people who have an increased risk of getting seizures. If you have a history of seizure, you should not participate in this study. You will be asked some questions regarding your or your family's medical history and will be excluded from the study, if you have certain conditions. Please respond completely and accurately to these questions for your safety.

You may have a mild headache following rTMS application. This is believed to be due to muscle tension. In the case of a headache, you may take acetaminophen, a medication that in all prior cases of headaches induced by rTMS, has promptly resolved the discomfort. Toothaches and mild pain in the eye, scalp and neck are other common but mild and temporary side effects of rTMS treatments. Since the TMS device is an investigational instrument, there may be some other minor risks that are unknown.

There are no physical risks of performing the Brain Fitness App exercises, computer tasks and assessments. You may find some of the tasks dull or tiring.

Please note that if you come alone for treatments, we will have to call a taxi for you to go back home after the treatment.

In addition to the above-mentioned risks, please read the important information about COVID-19 and its risks for research participation in the attached Appendix.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however, your name and other identifying information will not be used or revealed. Medical records, including your MRI scans, that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave the Riverview Health Centre. In case of any publication of results of this study, information will be provided in such a way that you cannot be identified.

With your permission, your Family Physician (GP) and/or your neurologist/psychiatrist may be notified about your participation in this study.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. Also, if your study doctor feels that it is in your best interest to withdraw you from this study, your study doctor will remove you without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

As we also run some parallel studies to this one, you may be asked if you would be willing to participate in an additional study to investigate the efficacy of treatment, which you may or may not accept.

Results of the Project

All participants have the option of receiving a lay summary of their own assessments once we reach our target number of participants. If you wish to be informed of your results, please inform the research staff at the time of your participation or you may contact the principle investigator of this study, Dr. Zahra Moussavi by email (Zahra.Moussavi@umanitoba.ca).

Questions

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact Dr. Zahra Moussavi ([REDACTED]). For questions about your rights as a research participant, you may contact the University of Manitoba Biomedical Research Ethics Board at [REDACTED].

Statement of Consent

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. The University of Manitoba may look at your research records to see that the research is being done in a safe and proper way.

This research has been approved by the University of Manitoba Biomedical Research Ethics Board. If you have any concerns or complaints about this project you may contact any of the above-named persons or the University of Manitoba Bannatyne Campus at 204-789-3389. A copy of this consent form has been given to you to keep for your records and reference.

I am interested in playing the Brain Fitness App exercises. Yes ☐ No ☐

I agree to being contacted in relation to this study. Yes ☐ No ☐

I agree to my family physician being notified of my participation in this study. Yes ☐ No ☐

I require reimbursement for transportation and/or accommodation costs. Yes ☐ No ☐

Participant signature _____ **Date** _____

Participant printed name: _____ **(day/month/year)**

Age at enrollment: _____

Contact Number: _____ **Email:** _____

In cases where a legal representative gives consent on behalf of participant:

Legal representative's signature _____ **Date** _____

Legal representative's printed name: _____ **(day/month/year)**

Relationship to Participant: _____

The study coordinator part:

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Coordinator's Signature: _____ **Date** _____

Coordinator's Printed Name: _____ **(day/month/year)**

Role in the study: _____

Relationship to study team members _____ *[eg. supervisor, teacher/professor or family member.]*

Assigned Code: _____

Appendix B – Assessments

This appendix provides detailed information of the standardized assessments analyzed in this thesis. Due to copyright restrictions, the original assessments manuals and validation studies are referenced and not reproduced in this section.

B.1 Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)

The ADAS-Cog is a well-established clinical assessment evaluating cognitive function in Alzheimer’s disease [1]. This assessment takes approximately 30 minutes, and it is clinician-administered performance-based test. It consists of word recall task, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition task, language, comprehension, word finding difficulty, and remembering test instructions. The score ranges from 0 to 70, with higher score indicating greater cognitive impairment.

B.2 Wechsler Memory Scale (WMS)

The WMS is a standardized comprehensive test designed to measure different aspects of memory, including immediate recall, delayed recall, and recognition [2]. This assessment takes approximately one hour, and it is clinician-administered performance-based test. It consists of the brief cognitive status exam, logical memory, verbal paired associates, designs, visual reproduction, spatial addition, symbol spam, auditory memory, visual memory, immediate memory, and delayed memory. The score ranges from 0 to 160, with lower scores indicating greater cognitive impairment.

B.3 Montreal Cognitive Assessment (MoCA)

The MoCA is a screening tool for cognition [3]. This assessment takes approximately 15 minutes. It consists of visuospatial, naming, memory, attention, language, abstraction, delayed recall, and orientation. The score ranges from 0 to 30, with lower scores indicating more severe depression. The categorized interpretations are as follows:

- 26-30: no cognitive impairment
- 18-25: mild cognitive impairment
- 10-17: moderate cognitive impairment
- 0-10: severe cognitive impairment

B.4 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a clinician-rated scale for depressive symptoms through a semi-structured interview [4]. This assessment takes approximately 15 minutes. It consists of apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The scale ranges from 0 to 60 with each item scored from 0 to 6, with higher scores indicating more severe depression. The categorized interpretations are as follows:

- 0-6: no depression
- 7-19: mild depression
- 20-34: moderate depression
- 35-60: severe depression

B.5 Neuropsychiatric Inventory Questionnaire (NPI-Q)

The NPI-Q is a questionnaire assessing 12 neuropsychiatric symptoms commonly observed in dementia [5]. The symptoms include delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, motor disturbance, nighttime behaviors, and appetite and eating. For each symptom, the presence and severity are recorded. Symptom severity is rated on a scale from 1 (mild) to 3 (severe), with a total severity score ranging from 0 to 36. This questionnaire is completed as a structured caregiver interview which takes approximately 10 minutes. The version used in the studies (Version 2, February 2008) does not include caregiver burden. The assessors of this assessment required obtaining NPI-Q Interviewer Certification.

B.6 References

- [1] W. G. Rosen, R. C. Mohs, and K. L. Davis, "A new rating scale for Alzheimer's disease," *American Journal of Psychiatry*, 1984, doi: 10.1176/ajp.141.11.1356.
- [2] D. Wechsler, "Wechsler Memory Scale," *PsycTESTS Dataset*, Feb. 2014, doi: 10.1037/T27207-000.
- [3] Z. S. Nasreddine et al., "The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment," *J Am Geriatr Soc*, 2005, doi: 10.1111/j.1532-5415.2005.53221.x.
- [4] A. M. Montgomery SA, "The Montgomery-Asberg Depression Scale (MADRS)," *British Journal Of Psychiatry*, vol. 134, 1979.
- [5] D. I. Kaufer et al., "Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory," *Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 12, no. 2, pp. 233–239, 2000, doi: 10.1176/jnp.12.2.233.

Appendix C – Study Documents

C.1. Standards of Practice

Tutoring Guide

MindTrigger Application

Top priority games that should be played every treatment day with the participant:

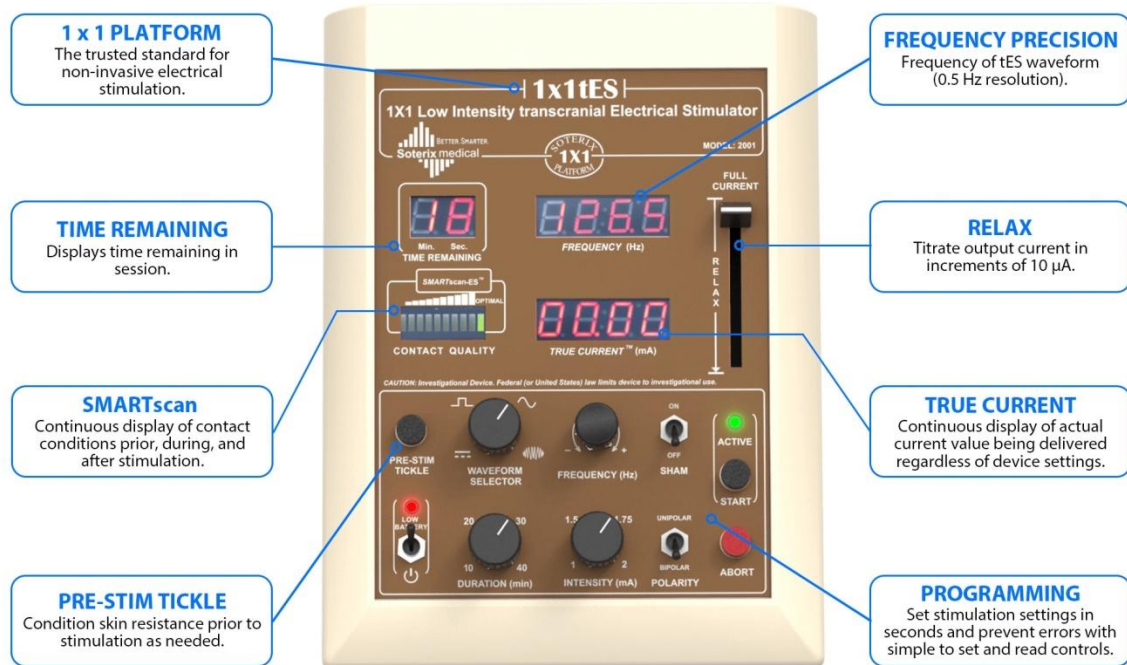
- Spatial Memory
- Associative Memory
- Image-Word Association
- Memorize and Rewrite

General Tips

The rule of thumb is to go to a higher level if a participant can obtain a perfect score on a level twice in a row. Also, do not skip a level. The goal is not to get the highest possible level but to find the level that challenges them to practice and improve.

- Explain the goal of the game. Participants may not remember the game from the day before so explain the goal of the game each time if they appear to forget.
- Work slowly. Certain games may be quite difficult so take small steps and slowly encourage participants to try things on their own. Other participants may need very little help.
- Encourage but do not push too hard. Always be aware of the participants' mood. Be positive and encourage them to try their best, but never push them to the point of causing stress. If they get very frustrated, bored, or tired, offer to switch the game or take a break for a minute to chat with them.
- Know where the participant is at all times. Some people easily get disoriented in the hallways. For example, keep an eye out on the participant when they go to the washroom.

Transcranial Electrical Stimulation Device



Precautions for applying tES

- Transcranial magnetic stimulation (TMS) machine should not be used around the tES machine.
- Participants should not have wet or oily hair (i.e. participants need to have clean and dry hair).
- Always check the battery light (located above the power switch)
 - If the light is on or flashing, stop the stimulation (using the “Abort” button), wait till the “True Current” goes to zero, disconnect the participant, turn off the device, and change the 9V batteries.
- Ensure the machine and the wires are not wet.
- Do not place sponges on previously irritated, burnt, or damaged skin.
- It is not recommended to use tES on someone with a pacemaker, metal implant, history of seizures, has had traumatic brain injury, or history of stroke.

Notes

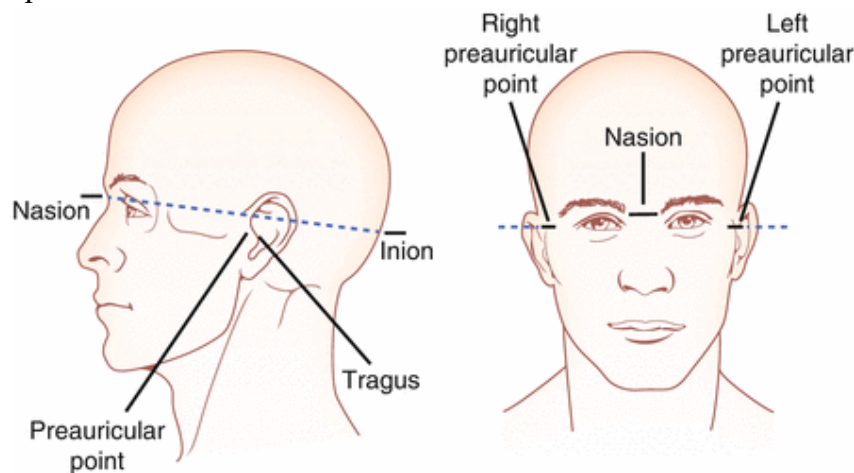
- Battery lasts around 3 hours.
- Sponges are for one time usage only.

Before the First Treatment Session

Head measurements occur at baseline assessment or first day of tutoring. The participant should be tested for their tolerance to tES before their first treatment session. Make sure that when testing for tolerance, to ensure good contact and try pre-stim tickle if they appear to not tolerate tES.

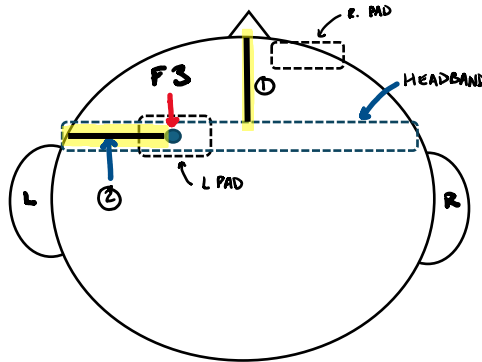
Part 1: Initial measurement to find F3 stimulation site

In the Appendix, there is a form to assist with measuring and recording the measurements for the participant to make it easier to determine F3 at every session quickly. On this form, there is a top view diagram of a head indicating the measurements colour coded. This section will go into detail on how to perform each measurement.



1. Measure distance between nasion and inion (**A**). Make sure to measure along the top middle of the head.
 - Mark **A-1**: 10% of distance **A** measured starting at the nasion
 - Mark **A-2**: 30% of distance **A** measured starting from the nasion (i.e. 20% of distance **A** measured starting at **A-1**)
 - Mark **A-3**: 50% of the distance **A** measured starting at the nasion
2. Measure distance between the right and left preauricular point (**B**). Make sure to measure by connecting the preauricular points and the marked **A-3**.
 - Mark **B-1**: 10% of the distance **B** measured starting at the left preauricular point
3. Measure distance between **B-1** and **A-1** (**C**).
 - Mark **C-1**: 40% of the distance **C** measured starting at **B-1**
4. Measure distance between **C-1** and **A-2**.
 - Mark **F3**: 50% of the measured distance

Part 2: Measurement to identify headband placement



Try on the head straps and find the size that fits best so that the top strap is above F3 and the frontal strap is above the right eyebrow.

- Record the strap size (small, medium or large) on the form in the Appendix.

First place headband over identified F3 location with a sponge pad.

1. Record distance between the nasion and the closest edge of headband (as seen in the diagram above labelled as number one).
2. Record measurement on strap where F3 is located.

L. Pad (Left Sponge Pad) is the active electrode (**Anode Red**).

- Placed with F3 at its centre

R. Pad (Right Sponge Pad) is the reference electrode (**Cathode Black**).

- Placed just above the right eyebrow (supraorbital area)

Common Symptoms/Sensations

- Tingling
- Itching
- Burning sensation
- Skin redness
- Mild pain
- Mild headaches
- Fatigue
- Phosphene (i.e. perceive flashes of light)

Tutors and research assistants need to pay close attention to symptoms and ask how the participant feels with the application of tES. Abnormal sensations or intolerance, the PI (Dr. Zahra Moussavi) needs to be immediately consulted on how to proceed.

These symptoms can be reduced with the following:

- Proper contact of the electrode on the scalp.
- Increasing the current slower with small breaks.
- Having the participant distracted with the cognitive exercise while increasing the current to the proper level.

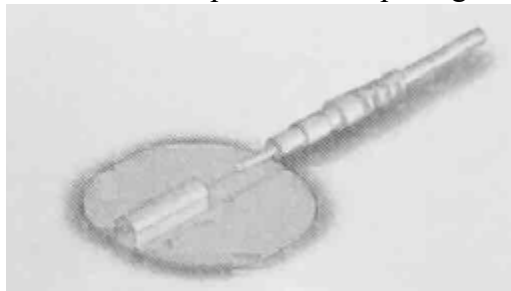
Treatment Sessions

Required Equipment

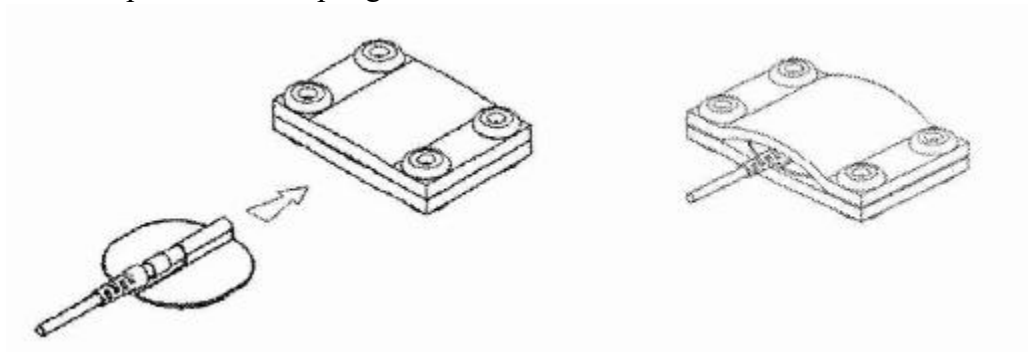
- tES machine
 - Batteries
 - Cables
 - Rubber electrodes
- Sponge pads
- Alcohol swabs
- Head straps
- Cup (for saline)
- Medicine dropper/syringe
- Plate
- Tablet

Preparation of Materials/Equipment

- Wet 2 sponge (8mL each sponge and 4mL each side of the sponge)
- Ensure the sponges are moist, but not dripping
- Insert connect cord pin into the opening of the rubber pads:



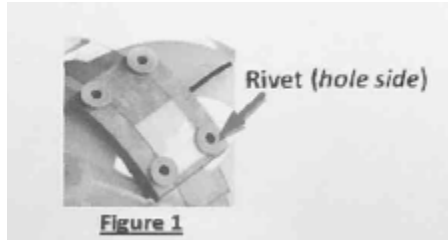
- Place rubber pads in moist sponges:



Procedure for Treatment

- Explain to the participant what will happen and the steps you are taking such as “I will measure your head”.
- Determine the location of F3 using the measurements found and documented on the Appendix form

- Thoroughly clean F3 and above the right eyebrow (contralateral supraorbital area) with alcohol swabs
 - Allow time for the alcohol to dry
- Place the appropriate head strap size and place wet sponges (electrodes inside) under the head strap
 - Rivet (hole side) should face outward and sponge should be centred under the headband:



- Make sure the sponges are not dripping but are completely wet
- Turn on machine
 - Check battery life light
- Check all the settings
 - Frequency: 40 Hz
 - Duration: 30 minutes
 - True Current: 0.75 mA (1.5 mA peak-to-peak)
 - Bipolar
 - Sine waveform
 - Sham:
 - Set to “ON” if the participant is scheduled to receive Sham tES
 - Set to “OFF” if the participant is scheduled to receive Active tES
 - Check SMARTscan-ES:
 - Provides electrode contact quality before, during and after tES
 - The right-most bar indicates the ‘Best’ electrode-skin contact
 - Do not stimulate if the one/two left-most bar are lit up



Proper contact improvements

- Tighten headband
- Fully soaked sponges
- Not dripping sponges
- Skin under sponges is not damaged or irritated
- Properly placed rubber electrodes inside sponge pads
- Clean area where sponges are placed with alcohol swabs

Begin tES and begin playing the MindTrigger app cognitive exercises:

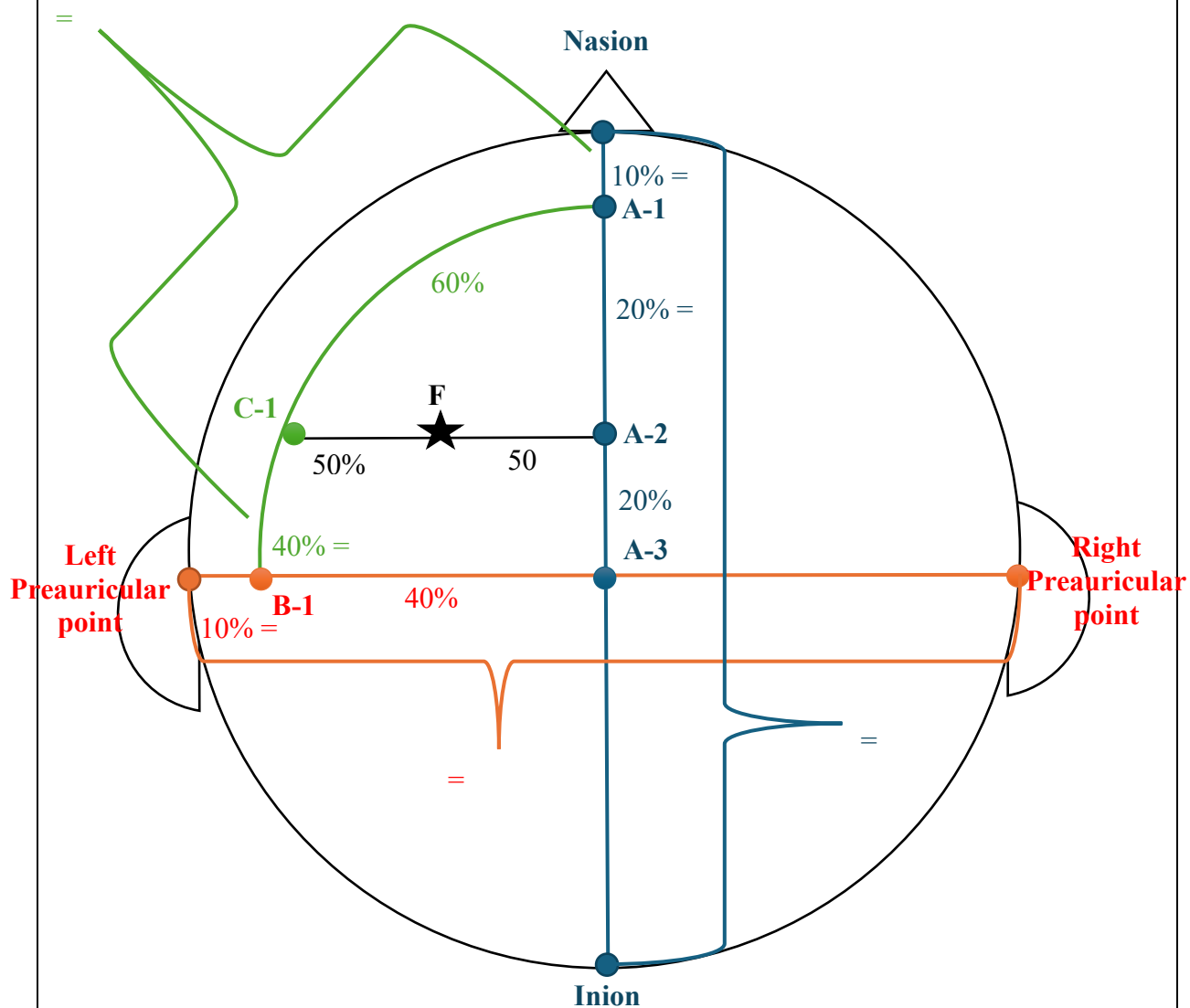
- Press the “Start” button and the “Active” light will begin flashing.
 - After approximately 30 seconds, the “active” light will remain on (i.e. should not be flashing) and the timer begins.
- The dial on the right side can be moved up and down to adjust the current.
- Generally we begin with the dial in the middle.
- Once the timer begins (i.e. after 30 seconds of beginning the treatment), move the dial up slowly to bring the “True Current” to reach 0.75 mA within the first minute of stimulation.
- **Important:** *If the current does not remain constant, the machine should not be used.*
- If the participant complains of burning or pain, stop increasing the dial for 5-10 seconds and then continue increasing the dial slowly.
 - Distracting the participant with the cognitive exercise will help reducing the symptoms.
- Check SMARTscan-ES throughout entire session for the contact quality and battery light.
- Once the current reaches 0.75 mA, play the cognitive exercise with the participant for approximately 30 minutes.

End of treatment session:

- After the timer ends, the “active” light will begin flashing again because the current is going down to zero.
- Once the “Time Remaining” is zero and the “True Current” has gone down to zero, you can turn off the device, remove the sponges, and remove the head strap.
- Clean the head straps with an alcohol swab.
- Throw out the used sponges in the garbage after the second session of the day of each participant.

Head Measurement for F3 Position

Participant code:	Headband size:
First Impression:	Distance between headband and nasion:
Date:	F3 position on headband for pad:
Notes:	



tES Summary Sheet

