The Effect of Transcranial Direct Current Stimulation Concurrent With Cognitive Training on Working Memory

by

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Abstract

Background

Working memory plays a crucial role in higher-level cognitive functions such as reasoning, learning, and comprehension. It also serves as a predictor of academic achievement and professional success in individuals. However, working memory may decline with ageing and/or acquired brain injury, including strokes. Cognitive training can counteract cognitive decline, particularly when complemented with Transcranial Direct Current Stimulation (tDCS). TDCS can modulate neural excitability and enhance neuroplasticity, making it a promising tool for enhancing working memory when combined with working memory training. Nevertheless, the efficacy of tDCS combined with working memory training may vary among healthy adults and the elderly, with limited research focusing on acute stroke patients.

Method

In this project, I leverage between-participant designs to investigate the efficacy of combined tDCS and working memory training intervention for modulating working memory function in three distinct groups: healthy adults, elderly participants, and acute stroke patients. The initial phase of the project aims to explore the impact of various factors, such as the choice of tDCS setup (high-definition tDCS vs. bipolar tDCS), the experimental protocol (online vs. offline tDCS), and external variables (e.g., age, initial working memory capacity, and cognitive strategy), on the outcomes of the intervention. To achieve this, I administered one or more sessions of 2mA tDCS for 20 minutes along with a working memory task (specifically, the nBack task), simultaneously engaging both the storage and processing components of working memory. In the project's second phase, I applied the insights gained from the initial

phase to design an intervention specifically tailored for a group of acute stroke patients.

Results

In healthy young adults, I found that the application of a single-session high-definition tDCS, either online or offline with a working memory task, did not have a significant impact on performance. However, when bipolar tDCS was utilized, and individual differences were considered, there was a significant benefit for young adults with lower working memory capacity. This trend was also evident in older adults, where I observed that an individual's initial working memory capacity played a pivotal role in the effectiveness of a combination of tDCS and working memory training over a short period.

Building upon these findings, I proceeded to investigate this specific setup, involving 20 minutes of anodal bipolar tDCS over the right dorsolateral prefrontal cortex, along with adaptive working memory training, in acute stroke patients, showing a working memory decline. In this context, I found that stroke patients with left-sided brain lesions exhibited notable improvements in working memory performance.

Conclusion

In summary, this comprehensive study underscores the notion that tDCS functions as a "state-dependent" intervention, showing discernible benefits for specific groups: healthy young adults with initially low working memory capacity who were given external strategy support, elderly individuals who are both older and have a low baseline working memory, and acute stroke patients with left-sided brain lesions. In the future, researchers should carefully take these factors into account and delve into the mechanisms underpinning the effectiveness of this intervention.

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Publications, Presentations, and Academic Contributions

Several papers were submitted, and conference presentations were delivered during my doctoral research study at the University of Birmingham, each of which is listed below. All research described in this thesis was conducted under the supervision and guidance of my supervisor, Professor Kim Shapiro and my tutor, Sara Assecondi.

Specifically, the research described in Chapters 3 and 6 was completed by myself, Rong Hu, under the guidance of Kimron Shapiro and Sara Assecondi, who supervised design implementation and data analysis.

The contents of Chapter 4 have been published, co-senior authored with Sara Assecondi. The experiment was designed by Sara Assecondi, Rong Hu and Kim Shapiro, and data were jointly collected by Rong Hu (75%) and Sara Assecondi (25%). I took the primary role in data analysis and drafting the thesis, whereas Sara assisted in the analysis and the drafting process for publication. In the manuscript preparation process for publication, I was actively involved in the design of the methodology, its subsequent validation, spearheading the investigation, curating the collected data, and the comprehensive review and editing of the manuscript. The results in Chapter 4 align closely with the outcomes of this published research. Importantly, this chapter's introduction and discussion have been developed to offer novel theoretical perspectives, framing the findings in an expansive scholarly context. Further details of the individual contributions to the publication are listed below.

Some of the content from Chapter 5 has been published. Sara Assecondi and Kim Shapiro designed the experiment in Chapter 5, and data were jointly collected by Rong Hu (75%) and Sara Assecondi (25%), analysed and written for the thesis by

Rong Hu and analysed and written for publication by Sara Assecondi. For the publication of the paper, I assisted in the collection of data and the subsequent review and editing of the written manuscript. Furthermore, this chapter delves deeper into the data from the capacity subgroups beyond that which has been published. The introduction and discussion in Chapter 5 have been restructured to deliver fresh analytical insights, situating the results within a more comprehensive academic discourse. Further details of the individual contributions for publication are listed below.

Papers Submitted for Publication From This Doctoral Research:

1. Assecondi Sara, **Hu Rong** (co-senior author), Eskes Gail, Pan Xiaoping, Zhou Jin, Shapiro Kim. *Impact of tDCS on working memory training is enhanced by strategy instructions in individuals with low working memory capacity*. Sci Rep. 2021 Mar 9;11 (1):5531. (Chapter 4). For this published paper, the author's contribution was as follows: R.H.: methodology, validation, investigation, data curation, writing review, editing. S.A.: conceptualisation, methodology, validation, data curation, formal analysis, investigation, writing — original draft, writing — review & editing. G.E.: methodology, writing — review & editing. X.P.: writing — review & editing, funding acquisition. J.Z.: writing — review & editing, funding acquisition. K.S.: conceptualisation, methodology, resources, supervision, writing — review & editing, funding acquisition.
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ABBREVIATIONS

ACC	anterior cingulate cortex
aNBACK	adaptive spatial *n*-back task
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BDNF	brain-derived neurotrophic factor
COVID-19	coronavirus disease 2019
CRUNCH	compensation-related utilisation of neural circuits hypothesis
CT	cognitive training
DA	dopamine
DLPFC	dorsolateral prefrontal cortex
DSB	digit span backward
DSF	digit span forward
DTI	diffusion tensor imaging
EEG	electroencephalography
ESS	Epworth Sleepiness Scale
fMRI	functional magnetic resonance imaging
fNBACK	fixed visual shape *n*-back task
FWT	familiarity with technology
GABA	γ-aminobutyric acid
HADS	Hospital Anxiety Depression Scale
HAMA	Hamilton Anxiety Scale
HAMD	Hamilton Depression Scale
HAROLD	hemispheric asymmetry reduction in older adults
HD-tDCS	high-definition transcranial direct current stimulation
LDSB	length of digit span backward
LDSF	length of digit span forward
LTD	long-term depression

LTP	long-term potentiation
MATLAB	matrix laboratory
MoCA	Montreal Cognitive Assessment
MRS	magnetic resonance spectroscopy
NIBS	non-invasive transcranial stimulation
NIC	neuroelectrics instrument controller
NIHSS	National Institute of Health Stroke Scale
NMDA	n-methyl-d-aspartate
PANAS	positive and negative affect schedule
PASA	posterior-anterior shift in ageing
PASS	power analysis and sample size
PC	parietal cortex
PET	positron emission tomography
PVT	psychomotor vigilance task
RT	reaction time
rTMS	repetitive transcranial magnetic stimulation
SD	standard deviation
SPSS	statistical package for the social sciences
STAC-r	scaffolding theory of ageing and cognition-revised
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
tES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
tPCS	transcranial pulse current stimulation
TrkB	tyrosine receptor kinase B
tRNS	transcranial random noise stimulation
WAIS-IV	Wechsler Adult Intelligence Scale-IV
WAIS-IV	Wechsler Adult Intelligence Scale - Fourth Edition
WHOQOL	World Health Organization Quality-of-Life Scale
WM	working memory

WMC	working memory capacity

Chapter 1 - Introduction

1.1 Memory

Concept and Classification of Memory

Memory is a process that includes encoding, storage and retrieval (Klein, 2015). Memory can also be divided into types according to time and function. This classification method was based on the landmark model developed by Richard Atkinson and Richard Shiffrin in 1968, which proposed three stages from information to memory (Atkinson & Shiffrin, 1968). Firstly, the information from the environment enters the sensory memory, which stores images, voices and other materials for milliseconds to seconds (Atkinson & Shiffrin, 1968). The information then enters the short-term memory for seconds to minutes after the attention system selects the materials (Atkinson & Shiffrin, 1968). Lastly, when the rehearsal process is enacted, the information can transfer from the short-term to the long-term memory, storing the information for minutes to years (Atkinson & Shiffrin, 1968). In 1971, Atkinson and Shiffrin brought the working memory together with the short-term stores (Atkinson & Shiffrin, 1971). Over the past 50 years, a considerable number of research studies have been based upon this model.

Today, memory is still classified into two different types. One is short-term forms of memory, including the sensory, short-term, and working memory (Gazzaniga, B.Ivry, & R.Mangun, 2019). Sensory memory can take in the information through our eyes or ears and hold it for milliseconds to seconds; when we go back to find the information from that period, we can still track it (Gazzaniga et al., 2019). Short-term memory holds some items for seconds to minutes in a section of the brain known as a buffer (in some cases, multiple buffers), and parts of these items will be committed

to the long-term memory after a period of rehearsal (Norris, 2017). Working memory means that we not only remember something, but also manipulate it to extend the concept of a short-term memory (Baddeley, 2010). The other type of memory is long-term memory, which stores information for minutes, months or years (Gazzaniga et al., 2019). This includes declarative (or explicit) memory and non-declarative (or implicit) memory, depending on whether it forms part of our conscious or unconscious memory collection (Squire, 1992). According to the materials we remember, explicit memory can be classified into episodic memory, related to specific events we have experienced, and semantic memory, which consists of the facts or knowledge taken from the world around us (Squire, 1992). Nondeclarative memory comprises four types: skills and habits or procedural memory, priming, simple classic condition, and nonassociative learning (Squire, 1992). The working memory and our short-term memory capacity are the most limited of the memory types. It is for this reason that this thesis focuses on the improvement of working memory.

Working Memory

Definition of Working Memory

The definition of “working memory” was developed by Miller, Galanter and Pribram in 1960 and was then further elaborated upon by other scientists (Baddeley, W.Eysenck, & C.Anderson, 2015). The term generally refers to a limited-capacity memory system which temporarily stores information (Baddeley, 2010). The definition of working memory modifies and extends the concept of short-term memory that is based on the model proposed by Atkinson and Shiffrin (1968) (Baddeley et al., 2015). In 1974, Baddeley and Hitch proposed a three-component model of working memory, which meant that central executives were supported

directly by a visuospatial sketchpad and a phonological loop (Baddeley, 2010). In 2000, this model added a fourth component, this being an “episodic buffer”, which temporarily stores integrated episodes or chunks from the phonological loop, visuospatial sketchpad and long-term memory (Baddeley, 2000). In 2012, Baddeley modified this model and proposed the episodic buffer as the upper stage of the phonological loop and visuospatial sketchpad, rather than being the paralleled stage of these two components (Baddeley, 2012). Additionally, the episodic buffers can control these two components without the direct engagement of a central executive (Baddeley, 2012). Some other theories of working memory focus on different elements. One is Cowan’s embedded-processes model, which proposes that working memory is activated from the sensory features in long-term memory and focuses on attention (Cowan, 1999). Engle developed an inhibitory control theory focused on proactive interference (Engle, 1996).

There are different views on how working memory works at the neurobiological level. A traditional theory is the persistent stimulus-selective activity theory, which means that neurons keep firing over certain delays even when the stimulus is absent (Zylberberg & Strowbridge, 2017). Two studies first proposed this theory in monkeys, which consistently reported that neurons increased their firing rate, not only during the cue presentation, but also during the delay period of a task (Fuster & Alexander, 1971; Kubota & Niki, 1971). Zylberberg and Strowbridge recently reviewed the potential mechanisms by which neurons can be persistently firing, including the Bistability Mediated by Voltage-Gated Inward Currents, Calcium-Dependent Intrinsic Mechanisms and Bistability in Feedforward Networks (Zylberberg & Strowbridge, 2017). However, this theory is challenged by a synaptic theory, which is based on the evidence that the activity was found to disappear during the delay of a task and

residual calcium played an essential part during that period (Mongillo, Barak, & Tsodyks, 2008; Silvanto, 2017). In addition, Fiebig and Lansner proposed a spiking working memory model based on the fast-expressing form of Hebbian short-term potentiation (Fiebig & Lansner, 2017). This model claims that working memory's neuron activity occurs in discrete oscillatory bursts (Fiebig & Lansner, 2017). Although there are many studies on the mechanisms of working memory, the evidence remains insufficient and further study is required.

Classification of Working Memory

There are studies which denote that working memory can be classified according to the content into verbal, visual, and spatial working memory (Baddeley, 2012). Verbal working memory is directly and primarily manipulated by the phonological loop dealing with speech, signs, lip reading, music and environmental sound (Baddeley, 2012). Visual and spatial working memory comes from the visual-spatial sketchpad (Baddeley, 2012). The former is the "what" pathway representing the visual process dealing with information from colour and shape, and the latter is the "where" pathway representing the spatial process dealing with information from shape and kinaesthetic (Zimmer, 2008).

Measurements of Working Memory

There is a wide range of tests or paradigms that can be used to evaluate working memory. In clinical work, the simple span task, which asks the participants to recall the material in a forward or backward sequence, is widely used. Forward and backward digit span and Letter Number Sequencing, included in the Wechsler Adult Intelligence Scale IV (WAIS-IV), are widely used to test the verbal working memory span (Wechsler, 2010a). In Wechsler's Memory Scale IV (WMS-IV), the symbol span subtest is used to evaluate visual working memory, while the spatial addition subtest

in WMS-IV is used to evaluate spatial working memory (Wechsler, 2010b). In addition to this, the Corsi block tapping test (forward and backward), developed by Corsi in 1972, tests the spatial working memory span (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000). However, these tests are simple span tasks and reflect some working memory components. The *n*-back task asks subjects to identify whether the present pattern is the same as the pattern presented 'n' steps before and depends more on the central executive, including updating and maintenance (Kirchner, 1958; Waris et al., 2017). It can be designed to evaluate verbal, visual or spatial working memory in a single or dual task. This task can also be used as a training tool to improve working memory and fluid intelligence (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Takeuchi, Taki, & Kawashima, 2010). A change detection task is an experimental paradigm used to measure the capacity of visual working memory (Luck & Vogel, 1997). There are some other tasks, including complex span, which asks participants to perform a particular task and at the same time to memorise stimuli in order to recall stimuli; memory updating, which presents stimuli and updating operations and asks participants to remember the results of the operations; running span, which asks participants to recall a specified number of the most recent stimuli when they are exposed to a series of stimuli of indeterminate length; and coordination, which asks participants to decide whether the stimuli meets a specific relational criterion (Scharfen, Jansen, & Holling, 2018). Researchers choose the task according to the component of working memory that they aim to investigate.

Anatomical Basis of Working Memory

A Positron Emission Tomography (PET) study revealed that hemisphere-specific activation patterns were associated with distinct working memory types. Specifically,

verbal working memory mainly engages the left hemisphere of the brain, while spatial working memory tasks predominantly activate the right hemisphere (Smith, Jonides, & Koeppe, 1996). These findings are corroborated by a meta-analysis undertaken by Wager and Smith (2003), which further substantiates that working memory is related to distinct frontal domains within the respective hemispheres (Wager & Smith, 2003). In 2018, Chai and colleagues suggested that the frontal-parietal network played an essential role in working memory and depicted a simplified anatomical network based on Baddeley's multicomponent model (Chai, Abd Hamid, & Abdullah, 2018). This network is composed of the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the parietal cortex (PC) (Chai et al., 2018). The DLPFC is mainly involved in central control, which itself is a master component in the working memory model (Chai et al., 2018). In Functional Magnetic Resonance Imaging (fMRI) studies in humans, this area is employed in working memory tasks which require central control, including decision-making, maintenance, manipulation, and updating (Chai et al., 2018). In monkeys, some studies claim that the ventral dorsolateral prefrontal cortex is critical in visuospatial working memory (Tsutsui, Oyama, Nakamura, & Iijima, 2016). Using low-frequency Repetitive Transcranial Magnetic Stimulation (rTMS), when ventral DLPFC were unilaterally inactivated, monkeys were found to present visuospatial working memory deficits (Tsutsui et al., 2016). ACC acts as an attention controller, while PC is related to the episodic buffer dealing with sensory or episodic information (Chai et al., 2018). The DLPFC is consistently highlighted in literature for its critical role in working memory, making it a prevalent site for tDCS or rTMS in working memory studies.

Working Memory Decline

A comprehensive review by Blasiman and Was reported 21 factors which have an impact on working memory. They categorise them into three primary domains: the biological effect (e.g. intelligence, gender, age, personality, exercise, diet, altitude/hypoxia, drug and brain stimulation), preoccupying thoughts (e.g. mental illnesses/medical conditions, dieting, craving, stress/anxiety, emotion/motivation, stereotype threat, temperature and mindfulness), and some factors linked with uncertain mechanisms (e.g. practice, sleep, bilingualism and musical training) (Blasiman & Was, 2018). Notably, working memory exhibits a linear decline with advancing age, commencing from approximately 20 years of age, and is predominantly associated with dysfunctions in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) (Borella, Carretti, & De Beni, 2008; Wang et al., 2011). Furthermore, various neurological disorders, including, but not limited to, strokes, Parkinson's disease, Alzheimer's disease, traumatic brain injury, epilepsy, and multiple sclerosis, have been implicated in working memory deficits (Chiaravalloti & DeLuca, 2008; Foster, Yung, Drago, Crucian, & Heilman, 2013; Kobylecki et al., 2018; McDowell, Whyte, & D'Esposito, 1997; Nyberg et al., 2018; Poole, Phillips, Stewart, Harris, & Lah, 2021). Among stroke patients, an alarmingly high prevalence rate of 87.6% has been reported for working memory impairment (Nyberg et al., 2018). This may be attributed to lesions damaging the fronto-parietal network and associated disruptions in attentional maintenance (Lugtmeijer, Lammers, de Haan, de Leeuw, & Kessels, 2021; Plancher, Naëgelé, Guinet, Portrat, & Colliot, 2023).

Significance of Working Memory

Working memory is related to higher cognition, including reasoning, learning and comprehension (Chuderski & Necka, 2012; Conway, Kane, & Engle, 2003). For example, when calculating numbers mentally or learning words, we need working memory to participate in this process as it is working memory that is responsible for maintaining previous results and updating information (Baddeley, 1996). An unambiguous relationship exists between working memory and a person's academic success and professional career (Alloway & Alloway, 2010; Gathercole, Pickering, Knight, & Stegmann, 2004). Therefore, the investigation into methods for improving working memory is an increasingly important area in cognitive rehabilitation, particularly in those experiencing working memory decline, such as the elderly and stroke patients.

1.2 Cognitive Training

Cognitive training (CT) is an intervention that asks subjects to practice specific tasks in order to improve their cognitive function or to reduce the effects of a cognitive impairment. It is applied widely, not only in neuropsychological patients but also in healthy elderly people or healthy young adults. In 2010, Gates and Valenzuela developed an operational definition of cognitive training with four requirements: 1) practice repeated tasks, 2) undertake tasks which involve an inherent problem, 3) use standardised tasks, 4) undertake tasks aimed at specific cognitive fields (Gates & Valenzuela, 2010).

The theory introduced by Hebb, which supports cognitive training, is known as the Hebbian learning theory (Hebb, 1949). It emphasises that neurons that are repeatedly active simultaneously will develop stronger associations than before (Hebb, 1949). Later, researchers developed the notion of "neuroplasticity" to

describe the modification of neuron organisation after an altered experience or environment (Bavelier & Neville, 2002). Cognitive training can change the brain through activation and connectivity (van Balkom, van den Heuvel, Berendse, van der Werf, & Vriend, 2020).

Cognitive training covers various cognitive domains: working memory, attention, executive function, long-term memory, vocabulary and neglect. Of these, working memory training has received the most attention in the existing literature.

Working memory training is an efficacious tool for enhancing working memory capabilities (Takeuchi et al., 2010; von Bastian & Oberauer, 2014). There are three main kinds of paradigms: single-paradigm regimes, which focus on working memory alone; multiple-paradigm regimes, which combine working memory and other tasks closely related to working memory; and multi-factorial regimes, which focus on working memory and other cognitive areas (von Bastian & Oberauer, 2014). The *n*-back task is the most common of the single paradigms and can be designed as a single or a dual *n*-back (Jaeggi et al., 2008). However, it is reported that there is no significant difference between single and dual *n*-back tasks on the transfer effect (Jaeggi et al., 2010).

Two potential mechanisms of working memory training can be used to improve its related performance (von Bastian & Oberauer, 2014). One is to expand working memory capacity, and the other is to gain knowledge and skills, for example, by using certain strategies, chunking subsets and automating the process to make working memory more efficient (von Bastian & Oberauer, 2014). It remains difficult to distinguish between these two mechanisms in terms of their underlying effect on working memory training.

It is reported that working memory training may have a “near transfer” effect and a “far transfer” effect, which can be dictated by changing the neuronal functional connectivity and by modulating dopamine release (Constantinidis & Klingberg, 2016). A recent research study which explores this issue indicates that individuals in the working memory training group exhibited enhanced functional connectivity compared with those in the control group (Thompson, Waskom, & Gabrieli, 2016). This functional connectivity is predominantly observed within the frontal-parietal network (Thompson et al., 2016). In addition, a Positron Emission Tomography (PET) study found that the concentration of dopamine receptors is related to working memory gains (McNab et al., 2009). The dopamine transporter, which is genetically coded and serves as a critical component for the release of dopamine, is significantly associated with the degree of working memory gains after training (Brehmer et al., 2009).

There is ongoing controversy about the efficacy of cognitive and working memory training. A primary point of contention pertains to the generalization of skills, questioning whether enhancements achieved through designated training tasks extend to untrained tasks or yield overall cognitive improvements. Some studies showed that it not only can transfer to untrained tasks but also improve the everyday function evaluated using instrumental activities of daily living (Mewborn, Lindbergh, & Stephen Miller, 2017; Rebok et al., 2014), while other studies showed that cognitive training was limited on the trained task and no transfer effect was found in the untrained tasks or real-world cognitive skills (Melby-Lervåg, Redick, & Hulme, 2016; Owen et al., 2010; Sala & Gobet, 2019). Another critical issue is the durability of the training's beneficial effects. Some studies showed that improvements are maintained over time, which even lasts for 5 to 10 years (Rebok et al., 2014; Willis et al., 2006),

while other studies failed to find the long-term effect of cognitive training (Anderson et al., 2018; Gire et al., 2023).

Several factors may influence these variations. Pre-existing cognitive function levels have been identified as a potential determinant of training efficacy, although there is disagreement over whether higher or lower baseline cognitive skills are more advantageous (Borella, Carbone, Pastore, De Beni, & Carretti, 2017; Jaeggi et al., 2008; Shaw & Hosseini, 2021; von Bastian & Oberauer, 2014; Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2012). Additionally, methodological variations, such as the intensity and duration of training programs and the nature of the tasks employed (e.g., n-back tasks versus other modalities), are believed to impact both training and transfer effects (Tracy Packiam Alloway, Bibile, & Lau, 2013; Jaeggi et al., 2008; von Bastian & Oberauer, 2014). The dosage-dependent effect was observed during the training (Jaeggi et al., 2008). Another study showed that participants in the high-frequency group (four times a week) had a transfer effect on working memory tasks (Tracy Packiam Alloway et al., 2013). In contrast, the low-frequency group (once a week) did not have such a transfer effect (Tracy Packiam Alloway et al., 2013). Age differences further influence cognitive training results. The meta-analysis showed that older individuals potentially benefitted more from training in line with the compensation theory, whereas younger individuals may see more significant improvements following the magnification theory (Shaw & Hosseini, 2021). The specific strategy in working memory tasks is also an essential modulator in the training performance, especially in the early sessions (Laine, Fellman, Waris, & Nyman, 2018). Participants' motivation and expectations have been shown to positively influence working memory performance (Parong, Seitz, Jaeggi, & Green, 2022; Schmiedek, Lövdén, & Lindenberger, 2010), whereas baseline mood states,

such as anxiety, have been identified as detrimental to training efficacy (Derakshan & Eysenck, 2009). The integration of cognitive training with other interventions, like transcranial electrical stimulation (tES), has shown potential for enhancing training effects in both healthy and elderly populations (Au et al., 2016; Berryhill & Jones, 2012), though this enhancement is not universally observed (Nilsson, Lebedev, & Lovden, 2015; Nilsson, Lebedev, Rydstrom, & Lovden, 2017).

1.3 Transcranial Electrical Stimulation

The Classification of TES

Non-invasive transcranial stimulation (NIBS) has developed considerably in recent decades. Transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES) are established techniques that use magnetic forces and electricity, respectively. TES can be divided into four types according to the modes of stimulation current: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), and transcranial pulse current stimulation (tPCS) (Kadosh, 2014).

TDCS is a prominent form of tES that applies a low intensity (0.5-2 mA), constant direct current to modulate neuronal activity (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). It has been divided into three types according to the placement of electrodes: bipolar tDCS, high-definition tDCS (HD-tDCS), and anode-only/cathode-only tDCS (Halakoo et al., 2023; Masina et al., 2021). Bipolar tDCS, the most common type, involves one anodal and one cathodal electrode (Hill, Rogasch, Fitzgerald, & Hoy, 2017). High-definition tDCS is where a central anodal electrode is encircled by multiple return electrodes in a ring-like structure to concentrate the current (Kuo et al., 2013). Anode-only/cathode-only tDCS, on the other hand, is applied only to a single anode or cathode electrode, with the return electrode positioned at a

considerable distance from the cortex (Halakoo et al., 2023). TDCS can alter the level of cortical excitability and modulate neuroplasticity, functional connectivity, and brain oscillations (Lefaucheur et al., 2017).

TACS uses a non-constant current in the form of sinusoidal waves at various frequencies (1, 10, 15, 30 and 45 Hz) (Antal et al., 2008). TACS entrains neuronal firing, affecting the brain oscillations in relation to amplitude, frequency or phase/phase coherence (He, Liu, Chen, Ke, & Ming, 2023; Reato, Rahman, Bikson, & Parra, 2013). It was reported that the tACS is more brain-state dependent, particularly the endogenous oscillations, compared with other tES (He et al., 2023).

TRNS, introduced in 2008, is considered to be a relatively new tool to be applied in human subjects which uses an alternate current but applies a randomised frequency (ranging from 0.1 to 640 Hz) (Yavari, Jamil, Mosayebi Samani, Vidor, & Nitsche, 2018). The stimulation effect depends on the frequency and intensity (Campana, Camilleri, Moret, Ghin, & Pavan, 2016; Moliadze, Atalay, Antal, & Paulus, 2012). Specifically, high-frequency tRNS decreases the motion after-effect, while low-frequency tRNS increases it (Campana et al., 2016). In contrast, the higher intensity stimulation (1 mA) triggers excitation while the lower intensity stimulation (0.4 mA) inhibits due to the lower intensity facilitating the intracortical inhibitory networks (Moliadze et al., 2012).

TPCS uses repeated pulses of current to change the deep brain structure (Datta, Dmochowski, Guleyupoglu, Bikson, & Fregni, 2013). TPCS can alter cortical excitability through the tonic depolarisation and phasic effects caused by the pulsatile currents (Jaberzadeh, Bastani, & Zoghi, 2014). In addition, tPCS can alter the connectivity on the frontal area using a computer model (Datta et al., 2013) and

the connectivity between two hemispheres based on an electroencephalography (EEG) study (Morales-Quezada et al., 2015). Another EEG study confirms that a 2 mA current stimulating for 20 minutes is the optimal intensity parameter (Morales-Quezada, Saavedra, Rozisky, Hadlington, & Fregni, 2014). The random frequency at 6-10 Hz could also increase the alpha bandwidth, while the 11-15 Hz decreases the alpha and beta bandwidth (Morales-Quezada et al., 2015).

Definition and Mechanism of TDCS

Transcranial direct current stimulation (tDCS) is a non-invasive transcranial stimulation with a low intensity (0.5-2 mA) and a constant direct current (Zaghi et al., 2010). The current flow arrives at the head, and part of the flow penetrates the skull, finally reaching the brain tissue (Zaghi et al., 2010). TDCS changes cortical excitability and alters neuroplasticity and functional connectivity (Lefaucheur et al., 2017). Electrodes of tDCS can be divided into two polarisations, these being anodal and cathodal. The anodal stimulation depolarises the neuronal membrane and increases excitability, while the cathodal stimulation hyperpolarises the neuronal membrane and reduces excitability (Nitsche & Paulus, 2000). Besides the local effect (online), tDCS has an after-effect (offline), which can last for hours or weeks after the cessation of the stimulation (Cocco, Podda, & Grassi, 2018; Lefaucheur et al., 2017). One explanation of the after-effect is neuroplasticity (Das, Holland, Frens, & Donchin, 2016). Certain neurotransmitters have been found to play an essential part in changing the strength of plasticity. A study showed that N-methyl-D-aspartate (NMDA) receptor blocker dextromethorphan diminished the effect of excitability which was induced by anodal tDCS (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003). Additionally, in a magnetic resonance spectroscopy (MRS) study, it was found that anodal tDCS decrease the γ-aminobutyric acid (GABA)

concentration in the sensorimotor cortex, and cathodal tDCS increases the concentration of glutamate (Stagg et al., 2009). However, another study showed that the level of GABA and receptor activity were not changed after stimulation in recurrent mild traumatic brain injury patients and healthy control participants, where the primary motor cortex was stimulated (Wilke et al., 2017). Studies have reported that anodal tDCS can increase long-term potentiation (LTP), while cathodal tDCS can decrease LTP, and this, in turn, induces long-term depression (LTD) (H. H. Liu et al., 2019; Nitsche et al., 2009). In recent years, brain-derived neurotrophic factor (BDNF) has gained more attention for its essential role in motor learning and memory. A study in animals showed an age-related change in BDNF and in tyrosine receptor kinase B (TrkB) could be modified by spatial memory training, which increased the concentration of BDNF and TrkB (Silhol, Arancibia, Maurice, & Tapia-Arancibia, 2007). The effect of LTP induced by tDCS was BNDF-dependent and was abolished in BDNF- and TrkB-mutant mice (Fritsch et al., 2010). TDCS may change the expression of BDNF through the stimulation of NMDA receptors and Ca2+ influx (Cocco et al., 2018). BDNF Val66Met polymorphism is related to the response of anodal tDCS stimulated by the motor cortex (Puri et al., 2015). Dopamine (DA), which plays a vital role in working memory, can also be affected by tDCS. Leffa and colleagues reported that anodal tDCS, which stimulated the frontal cortex in spontaneously hypertensive rats with short-term memory deficits, increased the DA in their striatum and hippocampus (Leffa et al., 2016). At the network level, tDCS can influence the network between different brain regions through oscillation activities, synchronisation and functional connectivity (Lefaucheur et al., 2017). Electroencephalography (EEG) studies in humans showed that anodal tDCS can increase the frequency of beta and gamma oscillations, while cathodal tDCS

decreases the frequency of these oscillations (Antal, Varga, Kincses, Nitsche, & Paulus, 2004). In rodents, low-intensity electric stimulation increased the gamma oscillations in the hippocampus (Reato, Rahman, Bikson, & Parra, 2010), and this effect lasted longer when the period of stimulation was prolonged (Reato, Bikson, & Parra, 2015). Certain other non-neuronal tissues may alter the effect of tDCS, e.g. gial cells, lymphocytes and endothelial cells (Lefaucheur et al., 2017; Ruohonen & Karhu, 2012).

The efficacy of tDCS is influenced by a complex interplay of methodological factors and participant-specific characteristics. The methodological aspects include the frequency and schedule of stimulations, the intensity of the current, the size of the electrodes, the polarity of electrodes, the stimulated sites, the period of stimulation, and concurrent cognitive training (Liu, Rau, Gallagher, Rajji, Lanctot, et al., 2017). On the individual level, factors such as cranial anatomy, psychological state, baseline cognitive level, and other notable state of the brain may influence tDCS efficacy (Liu, Rau, Gallagher, Rajji, Lanctot, et al., 2017).

The adoption of multi-session tDCS is noted for its consolidation and cumulative effect on excitability (Alonzo, Brassil, Taylor, Martin, & Loo, 2012; Ho et al., 2016). However, the practical implementation of such protocols presents clinical challenges, especially in the context of acute stroke rehabilitation. This has led to an exploration of single-session tDCS interventions, which yield inconsistent results. For instance, some studies have shown that a single session of tDCS could enhance response time or accuracy in working memory tasks (Hoy et al., 2013; Ohn et al., 2008). Conversely, other studies have failed to identify such improvements in healthy adults (Horvath, Forte, & Carter, 2015).

Regarding electrode polarity in transcranial Direct Current Stimulation (tDCS) for working memory enhancement, most research has employed either bipolar tDCS or anode-only tDCS. This approach is based on the theoretical premise that these modalities effectively excite the target brain region, thus improving cognitive task performance (Jo et al., 2009). HD-tDCS, on the other hand, is recognized for its ability to increase spatial locality, allowing for more focused current delivery and potentially longer-lasting effects than bipolar tDCS (Chein & Morrison, 2010; Kuo et al., 2013). Research outcomes in working memory improvement are mixed. Some studies showed that HD-tDCS benefits working memory in individuals (Ke et al., 2019; Weintraub-Brevda & Chua, 2019), whereas other studies had not observed significant improvements (Gan, Nikolin, Loo, & Martin, 2019; Weintraub-Brevda & Chua, 2019).

The selection of stimulation sites in tDCS studies is also an essential factor that significantly impacts the outcomes. The DLPFC is frequently targeted in tDCS studies due to its integral role in working memory processes (Tremblay et al., 2014). Within this context, the left DLPFC is often stimulated in verbal working memory tasks, while the right DLPFC is more commonly targeted for spatial working memory tasks (Smith et al., 1996). Beyond the DLPFC, several studies have explored the effects of stimulating the posterior parietal cortex on working memory, which found it was the same effect with DLPFC (Moghadas Tabrizi, Yavari Kateb, & Shahrbanian, 2023; Živanović et al., 2021).

The current intensity is a pivotal variable. Studies on working memory typically utilize intensities from 1 mA to 2 mA (Pergher et al., 2022). The comparative efficacy of these intensities is inclusive. The differences between 1mA and 2mA are inclusive. Some research indicates no substantial differences in cognitive outcomes between 1

mA and 2 mA (Nilsson, Lebedev, & Lövdén, 2015; Papazova et al., 2020), while others suggest a heightened effect at 2 mA (Boggio et al., 2006; Hoy, Bailey, Arnold, & Fitzgerald, 2015; Teo, Hoy, Daskalakis, & Fitzgerald, 2011). In contrast, there are findings suggesting that 1 mA may be more beneficial than 2 mA (Hoy et al., 2013). Notably, the utilization of 2 mA appears more prevalent than 1 mA in these studies (Pergher et al., 2022). The meta-analysis showed that the duration of stimulation varies from 10 to 30 minutes (Pergher et al., 2022). Most studies used 20 minutes of stimulation.

Most studies conventionally utilize sponge electrodes with dimensions of either 5 x 7 cm^2 or 5 x 5 cm^2 (Liu, Rau, Gallagher, Rajji, Lanctôt, et al., 2017). Additionally, a subset of research employs round electrodes, with diameters ranging from 2 cm to 5 cm^2 (Antonenko et al., 2022; Ke et al., 2019; Pergher et al., 2022). Despite the variation in electrode sizes used, there is a lack of direct comparative studies examining the impact of electrode size on working memory outcomes.

The sequence of tDCS administration relative to cognitive tasks is important in influencing study outcomes. This sequencing can be categorized into two distinct modes: online and offline. The online mode entails the simultaneous execution of working memory tasks with the administration of tDCS, whereas the offline mode involves performing these tasks after the tDCS session (Martin, Liu, Alonzo, Green, & Loo, 2014). Inconsistent perspectives regarding these tDCS modes exist in the literature, with studies indicating that online and offline approaches can yield similar, disparate, or even contradictory effects on cognitive outcomes (Martin et al., 2014).

In addition to the methodological design of tDCS, the individual factors also impact the outcome of tDCS. The brain anatomical structures include the thickness of the

cortex and cerebrospinal fluid and the depth of sulci (Liu, Rau, Gallagher, Rajji, Lanctôt, et al., 2017; Opitz, Paulus, Will, Antunes, & Thielscher, 2015). It has been observed that a thinner cortex and reduced cerebrospinal fluid volume, alongside shallower sulci, correlate with increased stimulation intensity (Opitz et al., 2015). The psychological states, such as expectation and motivation, may enhance the effect of tDCS (Jones, Gözenman, & Berryhill, 2015; Rabipour, Wu, Davidson, & Iacoboni, 2018), whereas anxiety may detract from its efficacy (Gibson et al., 2021). The baseline cognitive level also plays a pivotal role, although there is debate regarding whether individuals with lower or higher cognitive capacities derive significant benefits. Arciniega and colleagues report that the tDCS selectively benefited the elderly with low visual working memory compared with the high visual working memory elderly (Arciniega, Gozenman, Jones, Stephens, & Berryhill, 2018). In contrast, another study showed that participants with high working memory capacity benefited from tDCS (Jones, Gozenman, & Berryhill, 2015). Furthermore, specific conditions such as stroke, including the timing post-stroke, lesion characteristics, and stroke severity, may influence tDCS outcomes (Lefebvre & Liew, 2017).

These discrepancies highlight the need for a more nuanced understanding of the effect of tDCS and its variable impacts across different populations.

Safety of TDCS

Although the current flow stimulates the brain and alters the level of cortical excitability, tDCS remains a safe technique. In general, when we use a 5cm*7cm sponge and the current setting is 2 mA, the current density is 0.06 mA/cm^2, which is far below the safety threshold of tissue damage of 14.29 mA/cm^2 (Jackson et al., 2017). To analyse the side effects, Poreisz and colleagues recruited 102 subjects, comprised of 77 healthy subjects, 10 tinnitus patients, 9 migraine patients and 6

post-stroke patients (Poreisz, Boros, Antal, & Paulus, 2007). They reported that during tDCS stimulation, side effects involved a mild tingling sensation (70.6%), moderate fatigue (35.3%) and a light itching sensation (30.4%). After stimulation, 12 participants reported a headache; three healthy subjects reported nausea; and one migraine patient reported insomnia, considered to be a rare frequency (Poreisz et al., 2007).

1.4 Plasticity

Plasticity denotes the ability of organisms or individual cells to modify their phenotype in response to environmental variations (Skipper, Weiss, & Gray, 2010). Neuroplasticity, which refers to the capacity of the brain to undergo structural and functional changes, exhibits distinct characteristics during the developmental stages, compared to during adulthood (Innocenti, 2022). During development, neuroplasticity includes alterations in neurogenesis and the regulation of neuronal quantity, neuron migration, somatodendritic and axonal phenotypes differentiation, the establishment of neural connections, and cytoarchitectonic differentiation (Innocenti, 2022). These alterations may result in comprehensive modifications to brain structure and the development of specific functions (Innocenti, 2022). However, in adults, neuroplasticity is comparatively restricted and predominantly manifests as alterations in the strength of the excitatory and inhibitory synapses (Innocenti, 2022). Efforts to regenerate neural connections under these conditions have largely experienced limited success (Innocenti, 2022).

In 1949, Hebb proposed that when neuron A persistently and repeatedly plays a role in triggering neuron B, the strength of the inter-neuronal connection should be enhanced (Hebb, 1949). Synaptic plasticity is critical in the study of learning and memory (Mancini, de Iure, & Picconi, 2022). Cognitive training can induce

neuroplasticity from neuroimaging studies (Kelly & Garavan, 2005). Furthermore, an earlier study showed that working memory training can induce plasticity within the intraparietal-prefrontal neural circuitry (Klingberg, 2010).

Long-term potentiation (LTP) was found to be an essential element of synaptic plasticity (Bliss & Lomo, 1973). TDCS can modulate synaptic plasticity by enhancing long-term potentiation and regulating neuroplasticity proteins (Cavaleiro, Martins, Gonçalves, & Castelo-Branco, 2020). In animal models, tDCS enhanced long-term potentiation when it was combined with plasticity induction, particularly in the hippocampus and primary motor cortex (Fritsch et al., 2010; Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Rohan et al., 2020). Human studies indicate that tDCS can induce LTP-like plasticity when stimulating the motor cortex or visual cortex (Agboada, Mosayebi-Samani, Kuo, & Nitsche, 2020; Frase et al., 2021). At the molecular level, tDCS has been found to upregulate the expression of crucial neuroplasticity-related proteins, such as brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDA) receptors (Cavaleiro et al., 2020; Fritsch et al., 2010). Therefore, tDCS is a promising tool for augmenting the beneficial effect of cognitive training through modulating neuroplasticity.

1.5 The Necessity of Intervention in Stroke Patients

Stroke can lead to impairments across several cognitive domains, including language, reading and writing, numeric, limb praxis, visuospatial function, social use of language, emotional function, attention, executive and memory (Donovan et al., 2008). A review highlighted that the rate of memory impairment after a stroke in 3 months ranged from 23% to 55% (Snaphaan & de Leeuw, 2007). However, this review has yet to engage with a detailed classification of memory impairments, which can encompass short-term, long-term and working memory. Among long-term

memory, episodic memory impairment is apparent, with a prevalence of 25% to 46% (Godefroy, Roussel, Leclerc, & Leys, 2009), with some studies indicating rates as high as 64.4%. Working memory is one of stroke patients' most common cognitive impairments (Whyte, Skidmore, Aizenstein, Ricker, & Butters, 2011). It was found an 87.6% prevalence of working memory impairment in patients within two weeks post-stroke, highlighting the critical need for targeted cognitive rehabilitation strategies in the acute stroke recovery phase (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009).

Memory impairment can reduce patients' independence, including forgetting to take medications, hard-to-follow treatment regimens, difficulties in managing personal affairs, and loss in familiar places. Learning new skills or rehearsing old information is rather complicated for them. Verbal memory and visual memory are significant factors in the progression of dementia in stroke patients (Narasimhalu et al., 2009). Verbal memory is also associated with early cerebral-cardiovascular death (Lowry et al., 2014). It is estimated that 42% of stroke patients may evolve into Mild Cognitive Impairment, and 28.5% may progress to dementia (Hénon et al., 2001; Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012), which significantly predicts poor functional outcomes (Ozdemir, Birtane, Tabatabaei, Ekuklu, & Kokino, 2001), increases mortality associated with stroke (Gaynor et al., 2018), and hinders the recovery from disability (Cederfeldt, Gosman-Hedstrom, Perez, Savborg, & Tarkowski, 2010; Y. H. Park et al., 2015).

Addressing cognitive impairment following a stroke presents a significant clinical challenge. The pharmacotherapy, including acetylcholinesterase inhibitors and memantine, may offer some cognition improvements in vascular cognitive impairment, including those resulting from stroke (Battle, Abdul-Rahim, Shenkin,

Hewitt, & Quinn, 2021; McShane et al., 2019). However, the efficacy of these treatments remains limited. Cognitive training may be beneficial for post-stroke cognitive impairment (Xuefang, Guihua, & Fengru, 2021). However, it needs several weeks to train, and long-term effects are still inconclusive due to heterogeneity and methodological limitations (Marzolini, Oh, McIlroy, & Brooks, 2013; Niemeijer, Sværke, & Christensen, 2020). The patients' training sessions are too long, always lasting up to 4 weeks. Working memory is the keystone of global cognitive function and supports goal-directed behaviour (Baddeley et al., 2015; Chai et al., 2018). It is reported that tDCS could enhance the effect of cognitive training, especially on working memory, in healthy adults and can transfer to fluid intelligence and attention (Au et al., 2016; Chein & Morrison, 2010; Jaeggi et al., 2008). This leads to the hypothesis that tDCS could enhance the effect of cognitive training in stroke patients, which not only enhances cognitive rehabilitation but also benefits the overall recovery processes.

Following a stroke, the brain's capacity for neuroplasticity, through mechanisms such as homeostatic and Hebbian plasticity, is crucial for forming compensatory neural networks (Murphy & Corbett, 2009). Homeostatic plasticity upregulates the presynaptic release and the postsynaptic response to neurotransmitters in to restore activity to a set point, which results in excitability changes (Murphy & Corbett, 2009). Hebbian plasticity strengthens the activated presynaptic and postsynaptic neurons, a process complemented by homeostatic plasticity's regulatory actions (Murphy & Corbett, 2009). Cognitive training leverages Hebbian plasticity to reinforce learning and memory (Hebb, 1949; Kelly & Garavan, 2005). TDCS is a promising tool to disrupt the unbalanced excitability through upregulation and downregulation of excitability or neuroplasticity proteins, which can increase homeostatic plasticity and

promote Hebbian plasticity, highlighting its therapeutic potential in stroke recovery (Cavaleiro et al., 2020).

1.6 TDCS and Cognitive Training on Working Memory

An early study that applied tDCS in order to improve working memory was conducted by Fregni and colleagues (2005) using a cohort of 15 healthy young participants. They found that tDCS, when placed on DLPFC, can improve the accuracy of the *n*-back task (Fregni et al., 2005). This line of inquiry was further substantiated by a meta-analysis conducted by Brunoni and Vanderhasselt (2014). Their study included 33 experiments (19 for tDCS and 14 for rTMS) in healthy participants and neuropsychological patients, and highlighted the effect of non-invasive brain stimulation on working memory (Brunoni & Vanderhasselt, 2014). Specifically, tDCS could improve the response time of the *n*-back task, rather than the accuracy of this task (Brunoni & Vanderhasselt, 2014). Conversely, Horvath et al. (2015) posited conflicting evidence, claiming that single-session tDCS failed to improve cognition, including working memory (Horvath et al., 2015). Subsequent meta-analyses, however, conducted by Hill et al. (2016) and Mancuso et al. (2016) proposed that tDCS did yield small but statistically significant effects on both response time and accuracy (Hill, Fitzgerald, & Hoy, 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016). Furthermore, a recent meta-analysis has provided valuable insights into the long-term efficacy of tDCS in conjunction with multi-session working memory training (Pergher et al., 2022). The analysis revealed a small positive net transfer effect of tDCS on working memory, with the duration of the observed effect ranging from one week to one year after working memory training (Pergher et al., 2022). Medina and Cason claimed that previous tDCS studies on working memory lacked evidence with 5% power, meaning that 5% of studies would

be replicated (Medina & Cason, 2017). Researchers must consider many factors before and after an experiment, including sufficient sample size, the preregistration of the study design and the publication of null effect results (Medina & Cason, 2017).

Notably, most of these studies have targeted the left dorsolateral prefrontal cortex (DLPFC). Few have explored the effects on spatial working memory or considered the right DLPFC as a stimulation target. In addition to this, Jeon and Han's study found that stimulating the left prefrontal cortex tDCS could improve verbal working memory and naming, while stimulating the right prefrontal cortex tDCS could be beneficial for visuospatial working memory performance (Jeon & Han, 2012). Au and colleagues, therefore, chose to employ multi-day tDCS in conjunction with cognitive training focused on spatial working memory in young and healthy participants, and found that anodal tDCS can augment the effect of spatial working memory training (Au et al., 2016). Moreover, stimulation of the right dorsolateral prefrontal cortex (DLPFC) demonstrated transfer effects on visual *n*-back and backward block-tapping tasks, whereas stimulation of the left DLPFC yielded transfer effects on the digit span forward task (Au et al., 2016). However, Au and colleagues did not replicate the result in the later experiment when stimulating the right DLPFC (Au et al., 2021).

Among the elderly population, there is inconsistent evidence regarding the efficacy of tDCS in enhancing working memory. Some studies found that tDCS benefits participants with either a high level of education or with a low baseline visual working memory (Arciniega et al., 2018; Berryhill & Jones, 2012). Conversely, research conducted by Nilsson and colleagues challenges this assertion (Nilsson, Lebedev, & Lovden, 2015; Nilsson, Lebedev, Rydstrom, & Lovden, 2017). Furthermore, a recent multi-session study has revealed that tDCS's impact is more pronounced in long-term memory, with mixed effects in working memory, particularly benefiting those

with lower initial working memory capacity (Au et al., 2022). These findings highlight the necessity for research methodologies that integrate both between-participants and multi-session approaches, designed explicitly for elderly populations, to comprehensively understand the differential effects of tDCS in this age group.

One study employed a single-session tDCS in stroke patients to enhance verbal working memory, and found significant improvements after stimulation (Jo et al., 2009). Furthermore, a recent study has demonstrated that home-based tDCS could effectively ameliorate overall cognition in individuals with chronic stroke (Ko et al., 2022). However, there is a noticeable paucity of research investigating the effect of combined tDCS and cognitive training on spatial working memory in acute stroke patients.

Based on these findings, this study aims to investigate the immediate and transferable effects of tDCS stimulation on the right DLPFC, focusing on spatial working memory. This investigation is conducted across a variety of populations, including healthy young adults and the elderly, with an eventual application to individuals who have suffered from stroke.

1.7 Aims and Objectives of Thesis

This thesis aims to investigate the effect of combined tDCS and cognitive training in healthy young adults and the elderly, with a subsequent application of this intervention to stroke patients. The specific objectives are as follows:

1. To examine the effect of single-session HD-tDCS on working memory in healthy young adults, specifically examining the differing effects of online and offline tDCS modes.

2. To investigate the role of strategy instructions in combining tDCS and cognitive training.
3. To analyse the effect of multi-session tDCS combined with cognitive training in the elderly;
4. To apply the multi-session tDCS combined with cognitive training in clinical practice – specifically to acute stroke patients.

1.8 Overview of Thesis

Chapter 2 presents the general methodology, details on tDCS parameters, the tDCS model, cognitive tasks, and the employed questionnaires.

Chapter 3 investigates the effect of single-session HD-tDCS on working memory tasks in healthy adults (18-45 years of age) and examines the differences between online and offline modes of tDCS.

Chapter 4 explores the role of strategy when combining tDCS and cognitive training in healthy adults (18-45 years of age). The strategy-mediation theory is examined in this chapter.

Chapter 5 explores the application of tDCS in the elderly (55-75 years of age), hypothesising that right DLPFC activation via tDCS could enhance adaptability and compensation during cognitive training.

Chapter 6 delves into applying multi-session tDCS combined with cognitive training in a specific low-working memory population – acute stroke patients.

Chapter 7 concludes the thesis, summarising the essential findings and discussing the implications for research and practice.

Chapter 2 - General Method

2.1 Participants

All participants meet the inclusion criteria of tDCS: participants had no neurological and psychological disease, no history of epilepsy, were not suffering from migraines or colour-blindness, had not undergone tCS/TMS or cognitive training in the previous six months, had not used pacemakers, intracranial electrodes, defibrillators, had no implanted prosthesis and no kinky hair or dreadlocks, as this can obstruct the efficacy of the stimulation process due to the way the equipment is worn. Pregnant women were not recruited. Participants were asked not to drink alcohol on that day, to drink no more than three units of alcohol in the previous 24 hours, to drink no more than one cup of coffee on that day, to abstain from the use of recreational drugs for the preceding 24 hours and to sleep for a minimum of 6 hours the night before the experiment.

2.2 Brain Stimulation

TDCS was administered using Neuroelectrics Instrument Controller (NIC) software (Neuroelectrics, Barcelona, Spain). The NIC software administered a constant current, with 1 mA in Chapter 3 and 2 mA in Chapters 4, 5, and 6. The anodal was positioned over DLPFC in the right hemisphere, F4, according to the 10-20 EEG system. The return electrodes were placed over C4, F8, Fp2, Fc2 in Chapter 3 or Fp1 in Chapters 4, 5, and 6. The stimulation electrodes used were Pistim, characterised by a circular contact area of π cm^2 and a sintered Ag/AgCl pellet measuring 12 mm in diameter (Neuroelectrics, Barcelona, Spain). In Chapter 3, the first reference electrode was placed on the mastoid, and the second reference electrode was placed inferiorly to the first reference electrode using the sticktrode. In Chapters 4, 5, and 6, a dual reference electrode was clipped to the right earlobe. In a

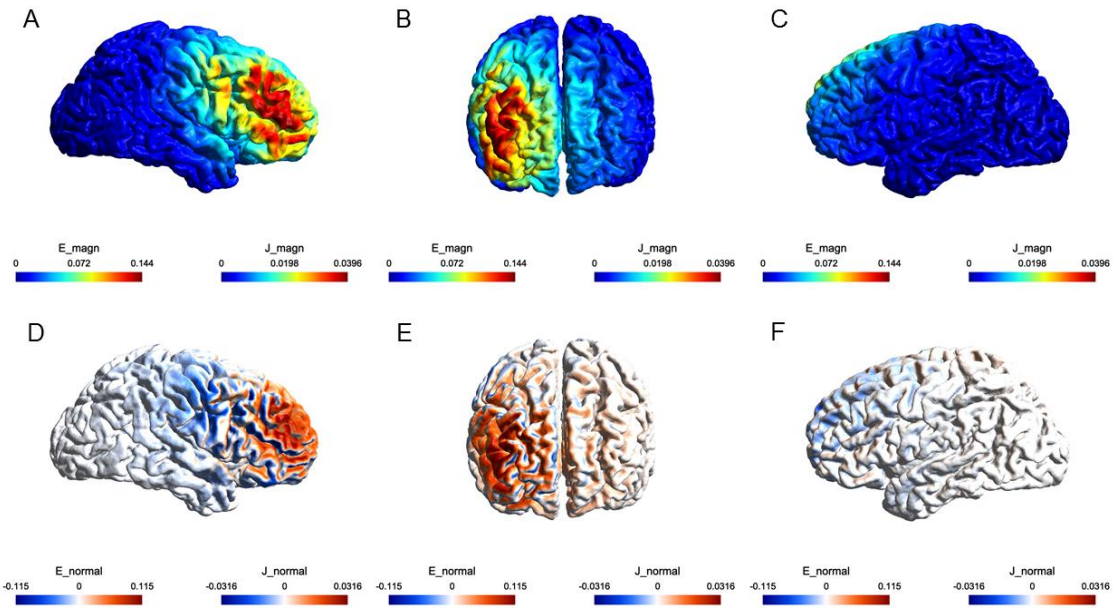
sham stimulation, the current was ramped up in the initial 30 seconds and was then ramped down to the baseline. During the final 30 seconds, the current was ramped up and down again.

The NIC software also has built-in safety measures, including the maximum current (2 mA), the maximum voltage (30 V), the continuous impedance check and the maximum stimulation time (1 h) (Neuroelectrics, 2016).

2.3 The Model of TDCS

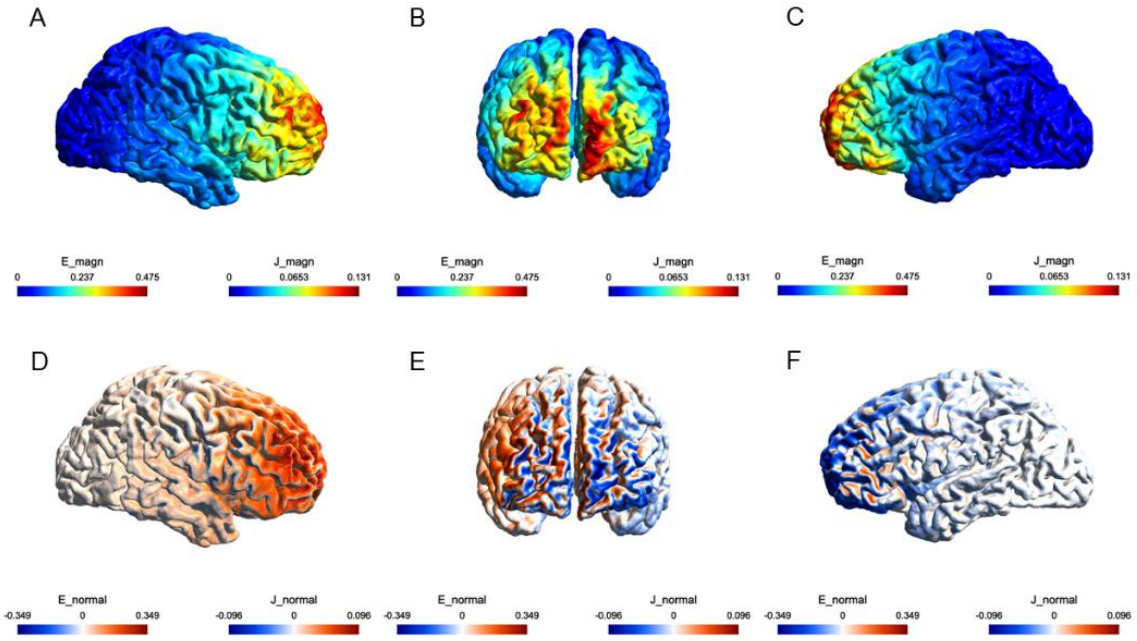
The current density and electric field patterns of tDCS were comprehensively simulated with SimNIBS 4.0.1 (Thielscher, Antunes, & Saturnino, 2015), illustrated in Figures 1 and 2. Pistim electrodes were represented in the model by an elliptical shape with a diameter of 2 cm. The specified thickness of these electrodes was 1 mm, with an accompanying gel layer of 2 mm. Panels A, B, and C in Figures 1 and 2 illustrate the distribution of current density and electric field within the Gmsh framework. The current density and electric field were normalised following an interpolation of the cortical surface centred with the grey matter sheet. Panels D, E, and F in these figures depict the subsequent interpolation onto the cortical surface.

Figure 1 - The Current Density and Electric Field Model of HD-TDCS in Chapter 3



Note. E_magn = Magnitude of the electric field (V/m). J_magn = Magnitude of the current density (A/m²). E_normal = Normalised Magnitude of the electric field (V/m). J_normal = Normalised Magnitude of the current density (A/m²).

Figure 2 - The Current Density and Electric Field Model of Bipolar TDCS in Chapters 4, 5, and 6



Note. E_magn = Magnitude of the electric field (V/m). J_magn = Magnitude of the current density (A/m²). E_normal = Normalised Magnitude of the electric field (V/m). J_normal = Normalised Magnitude of the current density (A/m²).

2.4 Trained *N*-Back Task in Young Adults in Chapters 3 and 4

The adaptive spatial *n*-back task application was from Brain Workshop 4.8.7, created by Paul Hoskinson and maintained by Paul Hoskinson and Jonathan Toomim (http://brainworkshop.sourceforge.net/). It was employed to train working memory in Chapters 3 and 4 (Jaeggi et al., 2008). In this task, the 3 × 3 grid comprising nine separate regions was presented on the screen. The centre of the grid was fixed with a cross, leaving eight regions to which the stimulus could be presented. The stimulus was a blue square that was presented in one of the eight regions for 500 milliseconds at a time. Participants had 1,500 milliseconds to decide whether the pattern of the present grid was the same as that of the one presented *n* steps back. If they were the same, they should press key “A”. If they were different, they did not

need to press any key. Each block had 20 + n trials. Every participant began from 2-back. After they finished one block, the next level would increase or decrease if they obtained an accuracy score of above 80% (in Chapter 3) or 70% (in Chapter 4) or below 50%, respectively. Otherwise, they would remain at the present level. The total time of the spatial *n*-back task varied depending on the levels that the participants had achieved, all of which were close to 20 minutes. This equalled the duration of the brain stimulation.

2.5 Trained *N*-Back Task in Elderly and Stroke Patients in Chapters 5 and 6

In Chapters 5 and 6, working memory was trained using an adaptive spatial *n*-back task, named N-IGMA (Assecondi, Hu, Kroeker, Eskes, & Shapiro, 2022; Jaeggi et al., 2008; Ploughman et al., 2019). Due to the reaction times were different healthy adults and elderly participants, stroke patients. The n-back task was explicitly designed for the elderly and stroke patients. The inter-trial duration in the elderly and stroke patients is 3,000 milliseconds, longer than that in healthy adults. In the elderly study, the stimuli were enacted for 500 milliseconds, and 2,500 milliseconds were given for decision-making. In the stroke study, the stimuli were enacted for 750 milliseconds, and 2,250 milliseconds were given for decision-making. The response keys were designed using the left and right arrows in the elderly and stroke stroke, which was more available for them to manipulate. Patients were asked to complete one session a day for five consecutive days. Each session included 15 blocks, and each block was comprised of 20 + n trials. N was the level of the task. In this task, a rectangle was divided into eight triangles, and the stimulus was a blue triangle that was presented in one of the eight white triangles. Participants were asked to decide whether the location of the present triangle was the same as that of the one that was present n steps back. If they were the same, participants were requested to press

the left arrow on the computer keyboard; if they were different, subjects responded by pressing the right arrow. Every participant started from Level one on the first block of the first session. The level would Increase to Level n + 1 if their accuracy at the Level n was higher than or equal to 90%. Otherwise, they remained at the present Level n. The total task time was approximately 20 minutes. The working memory training started at the same time as the tDCS.

2.6 Visual *N*-back Task

The visual-shape *n*-back task is a non-adaptive version of the *n*-back task with the n level held at n = 1 and n = 2. Participants were presented with a series of shapes and were asked to decide whether the present one was the same as the one presented *n* steps back. If they were the same pattern, participants needed to press key “A”; if not, participants needed to press key “L”.

2.7 Change Detection Task

A change detection task is a task used to evaluate visual working memory capacity (Luck & Vogel, 1997). The screen presented an array of squares with different colours for 500 milliseconds. The screen then presented one square after a 1,000 milliseconds fixation period. Participants needed to identify whether the colour of the present square was the same as the colour of the previous one that was presented at the exact same location. If they were the same, subjects needed to press key “Z”; otherwise, they needed to press key “/”. The stimulus array was 4, 6, and 8 in Chapter 3, and the array was 2, 4, and 6 in Chapter 5, presented in a randomised order and randomised locations.

2.8 Verbal Working Memory Span

Verbal working memory span consists of digit span forward (DSF) and digit span backward (DSB) from the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) (Wechsler, 2008), which asks participants to verbally repeat a series of numbers in a forward or backward sequence. Testing is stopped if the answers during a trial are incorrect, which includes two tests at one level. In the study of elderly participants presented in Chapter 5, the test was configured using Matrix Laboratory (MATLAB). Participants were asked to input their answers via the keyboard. Conversely, the study which focused on stroke patients in Chapter 6 employed a paper-based assessment format.

2.9 Questionnaires

2.9.1 Epworth Sleepiness Scale

In order to control the confounding effect of sleepiness in working memory, the 1997 version of the Epworth Sleepiness Scale (ESS) was self-administered (Johns, 1991). The daytime sleepiness during different activities was evaluated using a 4-point Likert scale ranging from 0 to 3. It includes eight items. The higher the score, the higher the participant's daytime sleepiness.

2.9.2 Hospital Anxiety Depression Scale

Emotional status was a factor which could affect working memory. Besides, stimulating DLPFC was reported to affect the emotional status. In order to investigate the emotional status on baseline, the Hospital Anxiety Depression Scale (HADS) was used to evaluate participants' depression and anxiety status during the past week (Zigmond & Snaith, 1983). It includes 14 items; each was scored on a 4-point scale from 1 to 4. In the stroke study, in order to confirm whether the beneficial

effect of tDCS was through the change of emotional status, the HADS was evaluated before and after the intervention.

2.9.3 Debriefing of Stimulation

In order to examine the success of blinding of stimulation, after experiments, participants were asked, “Do you feel you are in the sham group or stimulation group?” and “Why do you think you are in that group?”.

2.9.4 Side Effect Questionnaire

A questionnaire was used to evaluate side effects after tDCS. Participants were asked to report whether they experienced any side effects, including headache, pain in the neck, itching, sleepiness, trouble concentrating, acute mood change, fatigue, nausea, muscle twitches in the face or neck, tingling sensation (in the head or on the scalp), burning sensation (in the head or on the scalp), epileptic seizure, light flashes and any uncomfortable feeling (non-specific). They were asked to use a 1-4 point scale to evaluate their feelings (1 meant absent; 2 meant mild; 3 meant moderate; 4 meant severe). If they presented any feeling, they would be required to use a 1-5 scale to evaluate whether the feeling was related to tDCS. (1 meant none; 2 meant remote; 3 meant possible; 4 meant probable; 5 meant definite).

Chapter 3 - The Effect of Single-Session HD-TDCS with Working Memory Training on Working Memory in Healthy Adults

3.1 Abstract

Background

Working memory plays a crucial role in academic success and professional career and is attributed to intelligence, ageing and various other factors. Transcranial direct current stimulation (tDCS) presents a promising tool for adjusting brain excitability and plasticity. However, the efficacy of single-session high-definition tDCS (HD-tDCS) and the choice of online and offline modes in healthy participants continue to be debated.

Method

This is a randomised, single-blinded, between-subjects study. Forty-five participants were randomly assigned to four groups labelled as follows: Active HD-tDCS with Online Working Memory (WM) task, Active HD-tDCS with Calculation task, Sham HD-tDCS with Online WM task, and Sham HD-tDCS with Calculation task. Participants underwent one session of HD-tDCS paired with either an online or offline WM task, supplemented by a psychomotor vigilance task (PVT) task before and after brain stimulation. The primary objective was to understand the impact of HD-tDCS on online and offline working memory training tasks.

Results

Neither the effect of HD-tDCS nor the effect of the online/offline working memory task demonstrated significance (all *p*s > 0.05).

Conclusion

A single HD-tDCS session did not yield observable benefits for participants' working memory, whether online or offline. These findings suggest that a single HD-tDCS session does not modulate healthy participants' working memory performance.

3.2 Introduction

Working memory is a fundamental contributor to an individual's learning abilities and a strong predictor of academic attainment (Alloway & Alloway, 2010). Certain factors, including intelligence, age, emotional state, stress or anxiety levels, and sleep quality, have been identified as contributors to working memory capacity (Blasiman & Was, 2018). Thus, it is crucial to identify tools that can effectively improve working memory or counteract its decline.

Several methods for improving working memory in healthy adults have been explored, including working memory training, brain stimulation, and physical exercise. Evidence suggests that working memory training can improve healthy individuals' working memory and can transfer to other cognitive areas, including fluid intelligence and attention (Chein & Morrison, 2010; Jaeggi et al., 2008). However, the lengthy duration of the training and the debatable nature of its far-transfer effects pose challenges (Melby-Lervåg et al., 2016). Transcranial direct current stimulation (tDCS) is useful for modifying brain excitability and promoting brain connectivity (Lefaucheur et al., 2017). Some studies have combined brain stimulation with working memory training in healthy adults. It is reported that tDCS can augment the working memory training effect (Au et al., 2016; Ruf, Fallgatter, & Plewnia, 2017); while others have found no such effect (Shires, Carrasco, & Berryhill, 2020). Physical exercise has emerged as a promising tool to improve working memory. A recent meta-analysis demonstrated that physical exercise can improve visual working memory in children and the elderly but not in young adults (Zhu et al., 2023).

It is recommended that physical exercise should persist for at least 30 days, with greater benefits observed when undertaken for more than 90 days (Zhu et al., 2023).

The existing literature reveals controversies surrounding the parameters of brain stimulation and working memory training, such as the number of brain stimulation sessions, the sequencing of working memory training relative to tDCS (online vs. offline), and the specific configurations of brain stimulation (bipolar vs. high-definition tDCS). While some studies have shown that single-session tDCS could improve response time or accuracy in the conduct of working memory tasks (Hoy et al., 2013; Ohn et al., 2008), other studies have failed to identify such improvements in healthy adults (Horvath et al., 2015). The “Online” mode refers to conducting working memory tasks concurrently with tDCS administration, while the “offline” mode involves conducting working memory tasks after tDCS administration (Martin et al., 2014). Previous studies present different opinions regarding the tDCS modes and show that the online and offline designs can have the same, different, and even opposite effects (Martin et al., 2014). High-definition tDCS (HD-tDCS) uses an array of small electrodes, such as a “1 × 4” ring configuration (Kuo et al., 2013). This design increases the spatial focality, allowing the current to be more focused, thereby making the effect last longer than conventional bipolar tDCS (Chein & Morrison, 2010; Kuo et al., 2013). Some studies showed that HD-tDCS benefits working memory in individuals (Ke et al., 2019; Weintraub-Brevda & Chua, 2019), while other studies did not find significant working memory improvements stemming from the use of HD-tDCS (Gan et al., 2019; Hill et al., 2017).

This study, therefore, aims to explore the parameters of tDCS and working memory training. It examines the effect of single-session HD-tDCS on working memory tasks,

with a particular emphasis on discerning potential differences in outcomes between online and offline conditions.

3.3 Materials and Method

3.3.1 Study Design

This randomised, between-subjects and single-blinded study was conducted at the University of Birmingham. The ethical approval was confirmed by the University of Birmingham (ERN_12-1002AP18R).

3.3.2 Participants

Forty-five participants aged between 18 to 45 years old were recruited at the University of Birmingham. Participants were paid 16 pounds as compensation for participating in this study. In addition, before consenting to participate, participants were given information about this study and the possible side effects of HD-tDCS.

3.3.3 Randomisation and Masking

Before the experiment, subjects were randomly assigned to four groups: Active HD-tDCS and Online WM task, Active HD-tDCS and Mental Calculation task, Sham HD-tDCS and Online WM task, and Sham HD-tDCS and Mental Calculation task (See Figure 3). Participants did not know the details of the group allocation. In the present study, the “online” mode refers to conducting working memory tasks concurrently with tDCS administration, while the “offline” mode involves conducting working memory tasks after tDCS administration. In order to set the active control group and avoid the blinding failure, participants in the offline design group were asked to finish an easy mental calculation task concurrently with tDCS. This task was little working memory.

3.3.4 Materials

3.3.4.1 Brain Stimulation

The HD-tDCS used a “1 × 4” ring configuration. The active electrode was placed over region F4, and the return electrodes were placed over regions C4, F8, Fp2, and Fc2, according to the 10-20 EEG system. The NIC software administered a constant current of 1 mA. The details of brain stimulation are described in the Method section.

3.3.4.2 Trained Task

Spatial N-Back Task

This study used a spatial *n*-back task to train working memory (See Chapter 2). The level achieved in the spatial *n*-back task was also a primary outcome used to evaluate the effect of stimulation. Participants were required to complete one or two sessions of spatial *n*-back tasks due to the online and offline design. Participants in the online design completed HD-tDCS online with the spatial *n*-back task. After HD-tDCS, they were asked to complete another session of spatial *n*-back task to examine the offline effect of brain stimulation. However, participants in the offline design experiment completed the HD-tDCS with a calculation task and then completed one spatial *n*-back session after the HD-tDCS. Each session included 15 blocks of adaptive spatial *n*-back. After they completed each block, the next level would increase or decrease if they obtained an accuracy score of above 80% or below 50% respectively. Otherwise, they would remain at the present level.

Mental Calculation Task

The mental calculation task was used as a control task that kept participants engaged in a task which was not specific to working memory during brain stimulation. Participants in the Active HD-tDCS and Calculation task and Sham HD-tDCS and Calculation task groups were presented with mathematical operations

instead of online working memory tasks. They were required to press “A” if the answer was correct and “L” if incorrect. After responding, participants would receive feedback on their answers marked with either a “√” or a “×” for correct or incorrect, respectively.

3.3.4.3 Other Tasks

Change Detection Task

A change detection task was conducted before the intervention to evaluate the initial visual working memory capacity. Please see the details of the change detection task in the method section.

Psychomotor Vigilance Task (PVT)

The psychomotor vigilance task (PVT) was used to evaluate participants’ capacity for sustained attention before the *n*-back task (Dinges & Powell, 1985). Participants were requested to fixate upon a cross in the centre of the screen. When the cross turned into a dot, they needed to press the “down” key immediately. If they pressed the key in time, the dot turned green. If they pressed the key too late, it turned red. The reaction time was recorded.

3.3.4.4 Other Questionnaires

Four baseline questionnaires were completed by participants before the intervention (See Figure 3).

Positive and Negative Affect Schedule (PANAS)

The Positive and Negative Affect Schedule (PANAS) was used to rate positive and negative affect in participants using 20 items (Watson, Clark, & Tellegen, 1988). Each item used a 5-point Likert scale ranging from 1 to 5.

Epworth Sleepiness Scale

The Epworth sleepiness scale was employed to evaluate the status of sleep before intervention. Details of this scale are described in Chapter 2.

Expectancy

Four questions were applied to evaluate participants' alertness, motivation, expectation and sadness with a 5-point Likert scale ranging from 1 to 5.

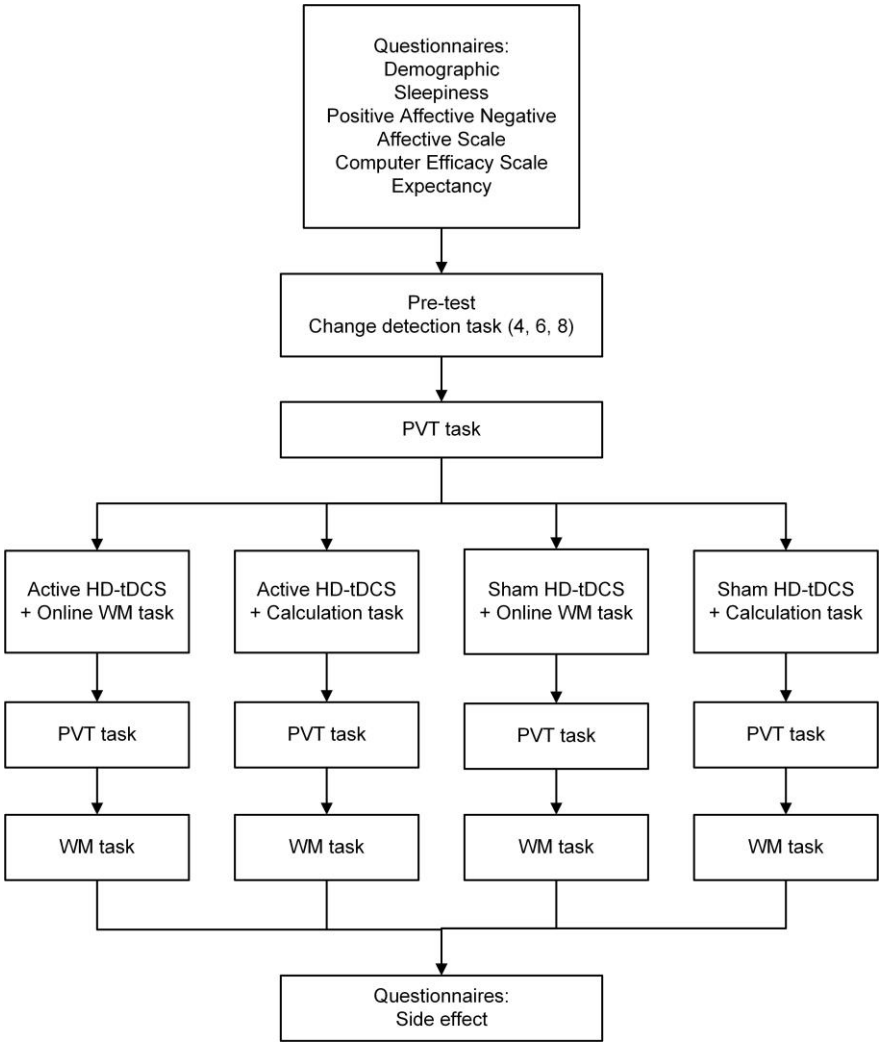
Computer Efficacy Scale

A questionnaire with 32 items was applied to evaluate participants' computer abilities.

3.3.5 Procedure

Figure 3 shows the diagram of this experiment.

Figure 3 - The Experiment Procedure in Chapter 3



3.3.6 Statistical Analysis

ANCOVA (Analysis of Covariance) was used to examine the difference between the four intervention groups on the spatial *n*-back task. Demographic and baseline characteristics were compared across the four groups using a one-way ANOVA or a chi-square test. An analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26. Data visualisations were generated using the package ggplot2 in R software (Hadley, 2016).

3.4 Results

3.4.1 Demographic and Baseline Characteristics

Forty-five patients were recruited and eligible. Of these, five participants withdrew before or during the experiment. Finally, the data from 40 participants were analysed. Of the 40 participants, the number of females was 28, and that of males was 12.

The one-way ANOVA analysis showed that the four groups did not differ in demographic characteristics and baseline performance, including in the K values of the change detection task, the positive affect score in PANAS, the negative affect score in PANAS, the sleepiness score in Epworth sleepiness scale, or alertness, motivation, expectation, sadness, and computer efficacy scores (all *p*s > 0.05, see Table 1). The chi-square test showed that the four groups did not differ in gender ($p = 0.085$). However, the age of the participants in the Sham HD-tDCS + Online WM task was higher than that of the other three groups ($p = 0.015$).

Table 1 - Baseline Characteristics by Treatment Group in Chapter 3

	Active HD-tDCS + Online WM task	Active HD-tDCS + Calculation task	Sham HD-tDCS + Online WM task	Sham HD-tDCS + Calculation task	p	η_p^2
N	10	10	10	10	—	—
Age	22.30 ± 3.89	22.60 ± 2.67	27.50 ± 7.78	20.70 ± 2.11	0.015*	0.248
Gender (M/F)	0/10	4/6	4/6	4/6	0.085[a]	—
K (setsize4)	2.61 ± 0.50	2.93 ± 0.54	2.04 ± 1.37	2.34 ± 1.01	0.191	0.122
K (setsize6)	2.31 ± 0.93	2.59 ± 1.18	1.82 ± 1.15	2.12 ± 1.11	0.467	0.067
K (setsize8)	2.53 ± 1.08	2.20 ± 1.45	1.48 ± 0.96	2.08 ± 1.60	0.346	0.087
Mean K	2.48 ± 0.67	2.57 ± 0.96	1.77 ± 1.04	2.18 ± 1.17	0.276	0.101
RT in PVT	330.01 ± 29.30	340.86 ± 42.47	334.96 ± 47.09	349.44 ± 35.36	0.715	0.037
Positive affect	24.70 ± 10.35	24.80 ± 8.47	22.50 ± 5.58	25.80 ± 6.30	0.818	0.025
Negative affect	13.90 ± 3.51	20.30 ± 11.04	12.90 ± 3.03	15.20 ± 5.33	0.074	0.173
Sleepiness	6.30 ± 3.65	6.50 ± 3.21	6.20 ± 3.36	7.80 ± 4.44	0.750	0.033
Alertness	3.40 ± 0.70	3.40 ± 1.35	3.60 ± 1.07	3.50 ± 0.85	0.966	0.007
Motivation	3.90 ± 0.74	3.70 ± 1.57	4.10 ± 0.88	3.40 ± 1.07	0.544	0.057
Expectation	3.20 ± 0.79	3.00 ± 1.41	3.10 ± 0.74	3.50 ± 0.97	0.716	0.036
Sadness	3.70 ± 0.82	3.30 ± 1.34	3.40 ± 1.17	3.20 ± 1.32	0.800	0.027
Computer efficacy	129.15 ± 24.07	129.05 ± 19.20	140.70 ± 15.35	135.21 ± 18.49	0.225	0.113

Note. RT = Reaction time.

[a] Chi-square test.

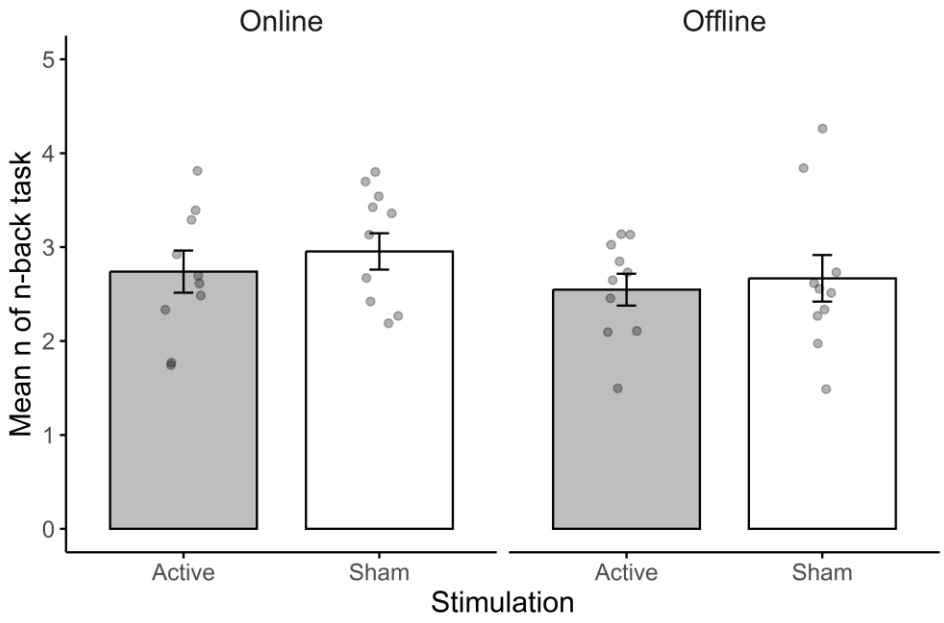
*p < 0.05.

3.4.2 The Active/Sham HD-TDCS Combined With Online/Offline Working Memory Task

Given the variance in ages across the four groups, a two-way Analysis of Covariance (ANCOVA) was employed, with age and k values of change detection as the covariates. This two-way ANCOVA with two between factors of Stimulation (Active,

Sham) and WM modes (Online WM task, Offline WM task) was used to analyse the potential effect of HD-tDCS and online/offline working memory tasks. The analysis did not reveal a significant main effect of Stimulation ($F_{(1,34)} = 1.366$, $p = 0.251$, $\eta_p^2 = 0.039$) or of the WM modes ($F_{(1,34)} = 1.363$, $p = 0.251$, $\eta_p^2 = 0.039$). Additionally, no interaction effect between Stimulation and WM modes was observed ($F_{(1,34)} = 0.045$, $p = 0.834$, $\eta_p^2 = 0.001$). The effect of covariate Age ($F_{(1,34)} = 0.113$, $p = 0.739$, $\eta_p^2 = 0.003$) and the k values of the change detection test ($F_{(1,34)} = 2.764$, $p = 0.106$, $\eta_p^2 = 0.075$) were also proved to be insignificant. The results are shown in Figure 4.

Figure 4 - The Effect of HD-TDCS and Online/Offline WM Task

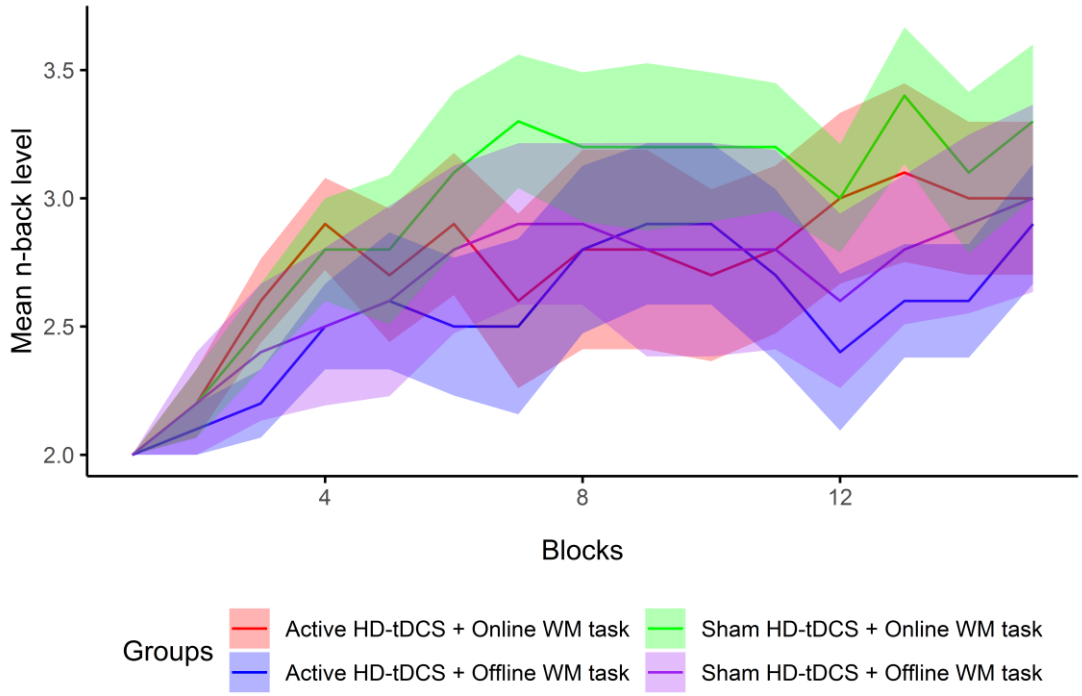


3.4.3 The Active/Sham HD-TDCS Combined With Online/Offline Working Memory Task Across Blocks

In order to examine the intervention effect across blocks, a three-way Analysis of Covariance (ANCOVA) was employed, with age and k values of change detection as the covariates. This three-way ANCOVA with two between factors of Stimulation (Active vs. Sham), WM modes (Online WM task vs. Offline WM task), and one within

factor of Blocks (ranging from Block 1 to Block 15) was used. The results indicated no significant main effects for Blocks ($F_{(4,144)} = 0.823$, $p = 0.518$, $\eta_p^2 = 0.024$), Stimulation ($F_{(1,34)} = 1.366$, $p = 0.251$, $\eta_p^2 = 0.039$), or WM modes ($F_{(1,34)} = 1.363$, $p = 0.251$, $\eta_p^2 = 0.039$). Additionally, there was no interaction effect between Block and Stimulation ($F_{(4,144)} = 0.689$, $p = 0.609$, $\eta_p^2 = 0.020$), no interaction effect between Block and WM modes($F_{(4,144)} = 0.512$, $p = 0.738$, $\eta_p^2 = 0.015$), and no interaction effect between Stimulation and WM modes ($F_{(1,34)} = 0.045$, $p = 0.834$, $\eta_p^2 = 0.001$). The effect of covariate Age ($F_{(1,34)} = 0.113$, $p = 0.739$, $\eta_p^2 = 0.003$) and the k values of the change detection test ($F_{(1,34)} = 2.764$, $p = 0.106$, $\eta_p^2 = 0.075$) were also proved to be statistically insignificant. The mean *n*-back levels across blocks are presented in Figure 5.

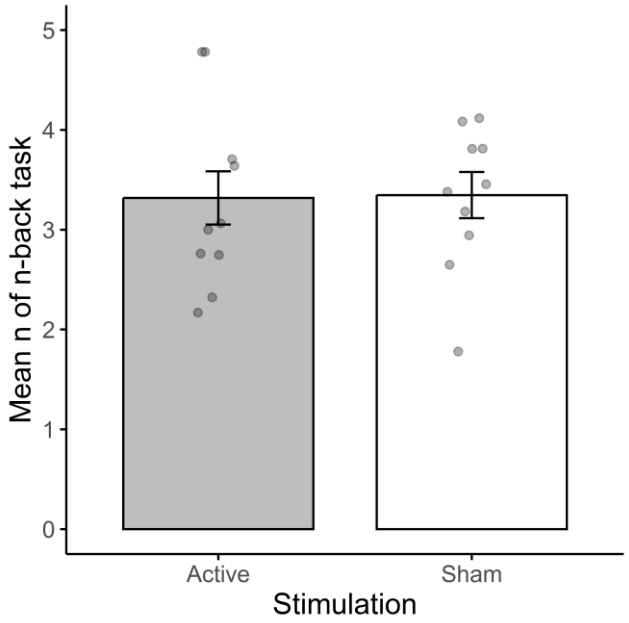
Figure 5 - The Effect of HD-TDCS Combined With the Online/Offline WM Task Across Blocks



3.4.4 The Offline Effect of HD-TDCS in Two Online Working Memory Task Groups

After the HD-tDCS and online working memory task, participants in the Active HD-tDCS + Online WM task and Sham HD-tDCS + Online WM task groups were asked to undertake another session of working memory task, which was offline. A t-test was used to analyse the offline effect of HD-tDCS between these two groups. No significant difference was found between these two groups (t = -0.076, p = 0.941). The data are shown in Figure 6.

Figure 6 - The Offline Effect of Stimulation Combined With the WM



3.4.5 The Effect on the Mathematics Calculation Task

An independent t-test was conducted to analyse the accuracy and reaction time of participants on the Mathematical calculation task in the Active HD-tDCS + Calculation task and Sham HD-tDCS + Calculation task groups. No significant difference was found in these two groups, both in terms of accuracy ($t_{(17)} = 1.721$, $p = 0.103$) and in reaction time ($t_{(17)} = -0.227$, $p = 0.823$).

3.4.6 The Performance of Psychomotor Vigilance Task (PVT)

The reaction time of PVT on baseline among the four groups was not significant as presented on baseline characteristics (See Table 1). In order to examine whether the arousal vigilance would decline between the two tasks, I analysed the reaction time in PVT, which was evaluated after the brain stimulation among the four groups. A 2-way ANOVA with two between-participant factors, Stimulation (Active, Sham) and Task (WM task, Calculation task), revealed that no significant main effect of Stimulation ($F_{(1,35)} = 0.971$, $p = 0.331$, $\eta_p^2 = 0.027$), no significant main effect of Task

($F_{(1,35)}$ = 2.548, p = 0.119, η_p^2 = 0.068), and no interaction effect of Stimulation × Task ($F_{(1,35)}$ = 2.297, p = 0.139, η_p^2 = 0.062).

3.4.7 Possible Adverse Effects of Brain Stimulation

Each participant was questioned about the possible adverse effects of brain stimulation after stimulation. The five most frequently observed adverse effects were sleepiness (55%), tingling (52.50%), itching (50%), burning (47.50%), and fatigue (47.50%). Chi-square tests were conducted to analyse the difference in the reported adverse effects between the four groups. It revealed no significant difference in any of the side effects between the four groups (all *p*s > 0.05). The results are presented in Table 2.

Table 2 - The Output Rate of Participants Reporting an Adverse Effect in Chapter 3

	Active HD-tDCS + Online WM	Active HD-tDCS+ Calculation	Sham HD-tDCS + Online WM	Sham HD-tDCS + Calculation	*p*
Headache	3 (30%)	1 (10%)	0	3 (30%)	0.256
Pain in the neck	0	1 (10%)	2 (20%)	2 (20%)	0.730
Itching	8 (80%)	5 (50%)	2 (20%)	5 (50%)	0.066
Sleepiness	7 (70%)	6 (60%)	3 (30%)	6 (60%)	0.431
Trouble Concentrating	4 (40%)	3 (30%)	2 (20%)	5 (50%)	0.691
Acute Mood Change	2 (20%)	1 (10%)	2 (20%)	1 (10%)	1.000
Fatigue	6 (60%)	4 (40%)	3 (30%)	6 (60%)	0.536
Nausea	1 (10%)	2 (20%)	0	2 (20%)	0.726
Muscle twitches in the face or neck	1 (10%)	4 (40%)	1 (10%)	2 (20%)	0.455
Tingling	7 (70%)	4 (40%)	4 (40%)	6 (60%)	0.540
Burning	5 (50%)	3 (30%)	4 (40%)	7 (70%)	0.409
Epileptic seizure	0	0	0	0	-
Light flashes	2 (20%)	0	0	1 (10%)	0.603
Uncomfortable feeling	3 (30%)	3 (30%)	2 (20%)	5 (50%)	0.645

Note. This table presents the number and rate of participants (%) in all four groups that reported any of the possible adverse effects.

3.5 Discussion

This study investigated the efficacy of a single HD-tDCS session combined with an online or offline working memory task in healthy young adults. These results reveal that a single HD-tDCS session could not improve participants' working memory, regardless of the mode of working memory task employed - online or offline.

The main finding of this research is that a single tDCS session did not produce any observable alterations in the working memory of healthy adults, even though HD-tDCS was employed. This finding is consistent with a meta-analysis undertaken by Horvath and colleagues, which reported the absence of benefits to a healthy population following a single-session tDCS (Horvath et al., 2015). This meta-analysis predominantly included studies focusing on verbal working memory through stimulation of the left DLPFC, along with a few studies that examined visual working memory via stimulation of the right posterior parietal cortex (Horvath et al., 2015). Conversely, other studies have shown that a single-session tDCS stimulating left DLPFC could improve adults' verbal working memory, particularly in terms of the accuracy and response times recorded in the *n*-back task (Fregni et al., 2005; Ohn et al., 2008; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011). Similarly, the meta-analysis conducted by Mancuso and her team revealed that tDCS targeting the left DLPFC, when done in combination with cognitive training, enhanced working memory (Mancuso et al., 2016). However, the stimulation of the right DLPFC or the right parietal cortex was not associated with significant improvements in working memory (Mancuso et al., 2016). The study did not differentiate between subtypes of working memory and predominantly included studies that implemented offline tDCS

protocols. Therefore, no definitive conclusions have been drawn regarding the effectiveness of stimulating the right DLPFC. The conflicting results surrounding the efficacy of single-session tDCS may likely be attributed to the significant role of individual differences in working memory performance. Factors such as age, baseline cognitive level, gender, and education are reported to influence outcomes (Roheger, Kalbe, Corbett, Brooker, & Ballard, 2020; Shaw & Hosseini, 2021). Consequently, the importance of these factors should be emphasised, even in light of this study's failure to detect the efficacy of single-session HD-tDCS when controlling for the factors of age and visual working memory capacity at the baseline. Another factor which may account for the absence of HD-tDCS in the current study is the shunting phenomenon (Rush & Driscoll, 1968; Thair, Holloway, Newport, & Smith, 2017). Although the HD-tDCS setting is theoretically predicted to cause the current to be localised and concentrated, the short distance between electrodes may cause the current to disperse across the scalp, a process described as shunting (Rush & Driscoll, 1968; Thair et al., 2017).

The second finding of this experiment is the absence of a discernible difference between online and offline working memory tasks when applied in conjunction with brain stimulation. This result is consistent with a meta-analysis conducted by Brunoni and Vanderhasselt, which suggests that the factor of online versus offline does not substantially alter the results, including response time, correct responses and incorrect responses (Brunoni & Vanderhasselt, 2014). However, an existing study with a crossover design found that online cognitive training combined with tDCS would improve skill acquisition on the post-test compared with offline design (Martin et al., 2014). The meta-analysis also further indicates differences in the mode of intervention between healthy adults and neuropsychiatric patients (Hill et al., 2016).

In healthy participants, the online intervention did not affect the response time and accuracy, whereas offline intervention can improve the response time and accuracy to a certain degree (Hill et al., 2016). It is speculated that a robust homeostatic control system in healthy participants helps to regulate excitability and inhibition, making behavioural performance less likely to be affected by altering the neuronal firing rates caused by the online intervention (Hill et al., 2016). The absence of a discernible difference between online and offline modes may be attributed to the non-detection of positive outcomes from brain stimulation. Thus, caution is warranted before concluding the absence of significant differences between online and offline modes.

Finally, the reported side effects were uniformly distributed across the four groups, consistent with previous studies showing that tDCS is a successful blinding tool, with participants unable to differentiate between the active and sham stimulation groups (Gandiga, Hummel, & Cohen, 2006). In this experiment, the most frequent side effect was sleepiness (55%), and the second was tingling (52.50%). Another study reported that tingling was the most frequent side effect, with a rate of 70.6%, and moderate fatigue was the second most frequent side effect, with a rate of 35.3% (Poreisz et al., 2007). However, the study of Poreisz and his colleagues did not record the prevalence of sleepiness. The rate of fatigue reported in the present experiment was 47.50%. It should be noted that the subjective experiences of sleepiness and fatigue can be challenging to distinguish.

The present study has several limitations. Firstly, the small sample size limits the impact of the experiment. Using Power Analysis and Sample Size (PASS) software, it is suggested that 36 participants in each group would be necessary to effectively detect differences between four groups using ANOVA with a two-way between-

participants design. Secondly, individual differences, including age, baseline working memory capacity, and strategy usage, play significant roles in tDCS and working memory tasks. While this study controlled for age and visual working memory capacity at the baseline, other influential factors, such as strategy usage, were not considered.

Further research is needed in order to consider the effect of individual differences between participants, including age, baseline working memory capacity, and strategy use. Although this study has not found a significant effect of a single session of HD-tDCS on working memory tasks, studies into multi-sessions of HD-tDCS should be undertaken.

3.6 Conclusion

To conclude, this experiment did not find a significant effect of a single-session HD-tDCS on working memory tasks, irrespective of whether they were administered online or offline. However, HD-tDCS serves as a successful blinding tool for participants. Future studies should consider individual differences and the potential impact of multi-session tDCS.

Chapter 4 - The Role of Strategy in the Effect of TDCS and Cognitive Training on Working Memory in Healthy Adults

4.1 Abstract

Background

Working memory, a foundational component of higher cognition including reasoning, learning and comprehension, can be improved by specified working memory training. Using strategy in working memory training has proved to be effective over the first few sessions. However, the impact of strategy on the outcomes of tDCS combined with working memory training is still unknown.

Method

A single-blinded, randomised, between-subjects study was conducted at the University of Birmingham. Ninety-two healthy adults were recruited. Participants received two sessions of cognitive training (with or without strategy) combined with tDCS (sham or active) to the right dorsolateral prefrontal cortex (DLPFC). Adaptive spatial *n*-back and visual *n*-back tasks were applied on the pre-test and post-test to evaluate the training and transfer effects. Individuals were divided into high-, mid-, and low-working memory capacity groups so that the impact of the initial capacity could be considered.

Results

Of the recruited participants, 84 participants completed the experiment. Among those with low working memory capacity, a statistically significant improvement of mean *n* level on the adaptive spatial *n*-back task was observed in the Active-Strategy group, exhibiting a significant deviation from zero ($p < 0.001$) and outperforming the other three groups ($p < 0.05$).

Conclusion

Adults with a low working memory capacity benefited from strategy-instructed working memory training and tDCS. This beneficial effect was evident during the training period and persisted in the post-test, highlighting that combining strategy-instructed working memory training and tDCS could prove to be highly beneficial for individuals with low working memory capabilities.

4.2 Introduction

”Working memory” generally means a limited-capacity memory system temporarily storing information. Working memory is related to higher cognition, including reasoning, learning and comprehension (Baddeley, 1996). An unambiguous relationship exists between working memory and a person’s academic success and professional career (Alloway & Alloway, 2010; Gathercole et al., 2004). Therefore, improving working memory is an increasingly important area in cognitive rehabilitation.

Transcranial direct current stimulation (tDCS) is a non-invasive transcranial stimulation using a low-intensity current (1-2 mA) and can alter the level of cortical excitability, enhance neuroplasticity and change functional connectivity (Lefaucheur et al., 2017). Several studies have demonstrated that tDCS improves working memory (Au et al., 2016; Fregni et al., 2005; Ruf et al., 2017). However, the findings of the meta-analyses are inconsistent and showed that the effect of tDCS on working memory was small yet significant (Hill et al., 2016; Mancuso et al., 2016), while others report either a partial effect (Brunoni & Vanderhasselt, 2014) or no effect. (Horvath et al., 2015). It is, therefore, important to explore the factors which will affect the impact of tDCS on cognitive training.

Two main mechanisms can mediate the improvement of working memory. One is to expand working memory capacity, and another is to gain knowledge and skills, for example, by using certain strategies, chunking subsets and automating the process to make working memory more efficient (von Bastian & Oberauer, 2014). It is difficult to distinguish whether the final effect of working memory training is through the former mechanism or the latter. Strategy is a mentally effective process directed by goals (Chan, Mueller, & Masson, 2019; Dunning & Holmes, 2014; Morrison & Chein, 2011). A wide range of strategies includes rehearsal, chunking, grouping, imagining visualisation, inhibiting irrelevant information and semantic linkage (Dunlosky & Kane, 2007; Dunning & Holmes, 2014). Based on the strategy mediation hypothesis, McNamara reported that strategy use was related to improving working memory on span tasks (McNamara & Scott, 2001). Strategy can enhance performance by facilitating information, encoding, maintenance, and retrieval (Chan et al., 2019). When tDCS combined with working memory training is applied to participants, it remains unknown as to whether strategy use affects brain stimulation on working memory performance. In addition, it is also unclear whether or not tDCS improves working memory through strategy changes. This issue aside, working memory capacity is an essential individual difference that may affect responses to tDCS and strategy (Arciniega et al., 2018; Bailey, Dunlosky, & Kane, 2008; Baldwin & Reagan, 2009). This study examines the effect on subgroups with different working memory capacity.

This part of the study explored the relationship between tDCS and strategy usage in cognitive training in healthy young adults. Specifically, it aimed to establish whether tDCS and working memory training incorporating strategy instructions would have an effect or an interaction effect in different working memory capacity subgroups.

Additionally, this section of the study examined the transferred effect of tDCS combined with working memory training.

4.3 Materials and Method

4.3.1 Study design

This is a randomised, between-subjects, single-blinded study conducted at the University of Birmingham. The ethical approval was confirmed by the University of Birmingham (ERN_12-1002AP18R).

4.3.2 Participants

For this study, 92 participants were recruited from the University of Birmingham. Eight participants withdrew before or during the experiment. Inclusion criteria included being aged between 18 to 45 years old and right-handed. Exclusion criteria included neurological and psychological disease, history of epilepsy, history of migraine, colour-blindness, having had tCS/TMS or cognitive training in the previous six months, having a pacemaker, having intracranial electrodes, having been treated with a defibrillator, having implanted prosthesis, kinky hair or dreadlocks, or women who were pregnant. Participants were asked not to drink alcohol on that day, not to drink more than three units of alcohol in the previous 24 hours, not to drink more than one cup of coffee on that day, to abstain from the use of recreational drugs for the preceding 24 hours, and to sleep for a minimum of 6 hours the night before the experiment. Participants were paid 20 pounds or three credits as compensation for completing this study. All participants provided written consent forms before the experiment.

4.3.3 Randomisation and Masking

Before the experiment, subjects were randomly aligned into four groups: active tDCS and cognitive training with a provided strategy, active tDCS and cognitive training without a provided strategy, sham tDCS and cognitive training with a provided strategy, and sham tDCS and cognitive training without a provided strategy. Participants were informed of the instructions for this study and the possible side effects of tDCS. Participants did not know the details of the group allocation.

4.3.4 Materials

4.3.4.1 Brain Stimulation

TDCS was administered using the Neuroelectrics Instrument Controller (NIC) software (Neuroelectrics, Barcelona, Spain) with a constant current (2 mA, 20 minutes). The anodal electrode was positioned over DLPFC on the right hemisphere, which is F4 according to the 10-20 EEG system. The return electrode was placed over Fp1. These stimulation electrodes were Pistim electrodes with a 12 mm diameter (Neuroelectrics, Barcelona, Spain). An Earclip, a dual reference electrode, was clipped to the right earlobe. During the sham stimulation, the current was ramped up and then ramped down to the baseline in the initial 30 seconds. During the final 30 seconds, the current was ramped up and down again.

4.3.4.2 Trained Task: Adaptive Spatial *N*-Back Task

A typical adaptive spatial *n*-back task (aNBACK) named “Brain Workshop” was applied in order to train the working memory (Jaeggi et al., 2008). The details of this are described in Chapter 2. All participants started from 2-back. After they finished one block, the next level would increase or decrease according to whether their accuracy score was above 70% or below 50%, respectively. Otherwise, they would remain at the present level.

If participants were assigned to a strategy group, they were provided with a strategy before cognitive training and stimulation. Those participants were asked to recall the location of the blue square and transfer it into a position on the grid in boxes numbered from 1 to 9, and to then create sets of *n* digits (*n* refers to the level of task), and to imagine one set below the other set. Participants paired up every two sets and compared whether the upper digit was the same as the digit below. They proceeded by holding the last set in mind and creating a new set of digits below it, while simultaneously comparing the digit pairs with each other (Laine et al., 2018).

4.3.4.3 Untrained *N*-Back Task

In order to investigate the transfer effect of tDCS and cognitive training, the fixed visual shape *n*-back task (fNBACK), which was an untrained task, was programmed through Psychtoolbox and MATLAB. One shape out of ten was presented randomly for 0.5 seconds, followed by fixation for 2.5 seconds. Participants were asked to compare the present shape with the shape presented *n* steps previously. If they were the same, participants needed to press key “A”; if they were different, they needed to press key “L”. A total of 20 + *n* shapes were presented during each block. Each block had 20 trials, including 30 % matches and 10 % interference. Participants were asked to complete six blocks of 2 back and six blocks of 3 back on the pre-test and post-test.

4.3.4.4 Other Questionnaires

Positive and Negative Affect Schedule (PANAS)

A PANAS survey (Merz et al., 2013) was used to evaluate mood and emotional experience before and after the intervention. There were 20 items: 10 to capture positive effects and 10 to negative effects. Participants used a 1 to 5 scale to rate

their mood (1 = very slightly, 2 = a little, 3 = moderately, 4 = quite a bit, and 5 = extremely).

Alertness, Sadness, Motivation and Expectation

A 1-5 scale questionnaire was used to rate alertness, sadness, motivation and expectation before every spatial *n*-back task. For alertness, motivation, and expectation, 1 meant very low and 5 meant very high. For sadness, 1 meant extremely sad and blue, and 5 meant extremely cheery and optimistic.

Side Effect Questionnaire

A questionnaire was used to evaluate side effects after tDCS. Participants were asked to report whether they experienced any side effects, including headache, pain in the neck, itching, sleepiness, trouble concentrating, acute mood change, fatigue, nausea, muscle twitches in the face or neck, tingling sensation (in the head or on the scalp), burning sensation (in the head or on the scalp), epileptic seizure, light flashes and any uncomfortable feeling (non-specific). They were asked to use 1-4 to evaluate their feelings (1 = absent; 2 = mild; 3 = moderate; 4 = severe). If they presented any feeling, they would be required to use a 1-5 scale to evaluate whether the feeling was related to tDCS. (1 = none; 2 = remote; 3 = possible; 4 = probable; 5 = definite).

Debriefing of Strategy

In the No Strategy groups, participants were asked whether they used a strategy and if they answered “Yes”, they had to choose the type that they used during each spatial *n*-back task session after finishing the experiment. Spontaneous strategies generated by the participants were divided into 16 types (see Table 3). After completing the experiment, participants in the Strategy groups were asked to report

whether they had used the strategy provided during each spatial *n*-back task session.

Table 3 - Options of Spontaneous Strategy Types and Definitions

Numbers	Strategy types	Definition of strategy use
1.	Rehearsal	I repeated the location of the target in my mind.
2.	Grouping	I remembered the location of a target in groups (e.g. two or more locations) together.
3.	Grouping	I created a group of locations in my mind and dropped the last location when a new location appeared.
4.	Grouping	I split the locations into different series and compared them to each other.
5.	Association	I used the meaning of the target to remember or connect them (such as top left, top middle, and top right).
6.	Imagery	I connected the location of targets with lines.
7.	Association	I thought about other things that could relate to the location (such as the time on a clock).
8.	Imagery	I created a visual image based on the location.
9.	Concentration	I concentrated on the location of the target.
10.	Association	I transferred the location of targets into numbers, such as 1,2,3,6,7,8 and 9.
11.	Association+ Grouping	I transferred the location of targets into numbers, such as 1,2,3,6,7,8 and 9, split the numbers into different sets, and compared them to each other.
12.	Look	I pictured the way the target looked on the screen.
13.	Familiarity	I answered based on the location which seemed recent or familiar.
14.	Checklist	I expected certain locations to appear and mentally checked them off as they appeared.

15.	Intuition	I used my intuition.
16.	Unspecified	Other (Please describe below).

Blinding of Stimulation

After the post-tests, participants were told of the existence of a sham brain stimulation group and an active stimulation group, and were then asked to guess the group allocation. Reasons were also recorded.

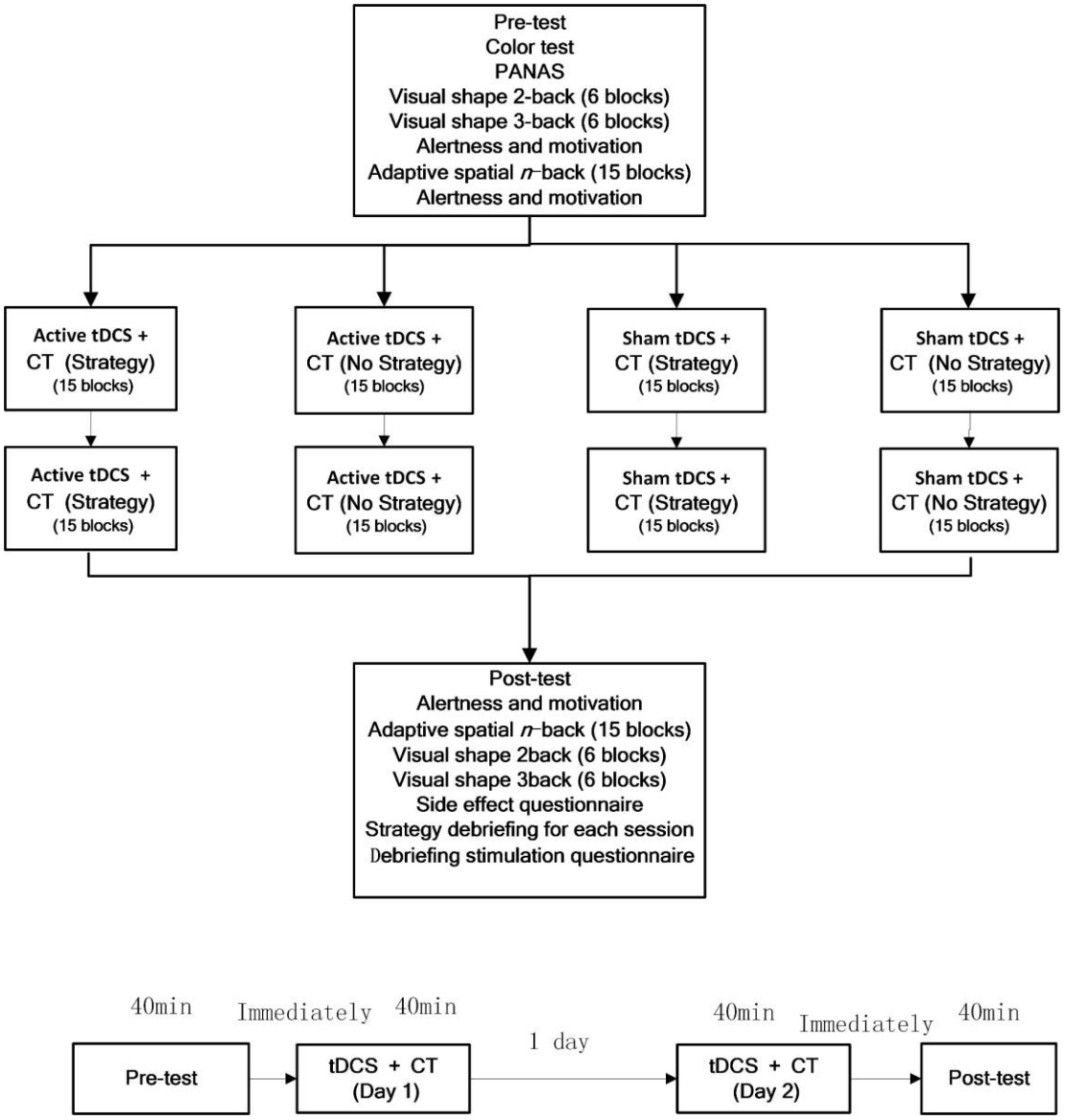
4.3.5 Procedure

Figure 7 shows the diagram of this experiment.

4.3.6 Statistical Analysis

A statistical analysis was performed using SPSS software (version 26). For baseline characteristics across the four groups, ANOVAs were carried out for continuous variables, and the chi-square test was used for categorical variables. A four-way ANOVA was used to analyse the primary efficacy endpoint, which was the improvement on the post-test. A three-way ANOVA was used to analyse the transfer effect on the visual shape *n*-back task, gains on PANAS scores and the levels of alertness, sadness, motivation and expectation. The difference in the blinding of the stimulation between the stimulation and sham stimulation groups was analysed using chi-square tests. All *p*-values were reported as two-sided; a *p*-value <0.05 was considered significant. Data visualisations were performed using the package ggplot2 in R software (Hadley, 2016). Bayesian model comparison was employed to select the best model in the working memory capacity subgroups, with Bayesian Factor BF_{10} reported for each subgroup. Bayesian analysis was run in JASP 0.14.1.0 (JASP, 2023).

Figure 7 - Overall Flowchart of Study Design in Chapter 4



4.4 Results

4.4.1 Outliers Analysis

Using a criterion of three Standard Deviations (*SD*) of the mean *n* level on a spatial *n*-back task over all four sessions for four groups, respectively, there was no outlier.

4.4.2 Demographic and Baseline Characteristics

A total of 92 participants were recruited and eligible. Eight participants withdrew before or during the experiment. Eighty-four participants were allocated to each

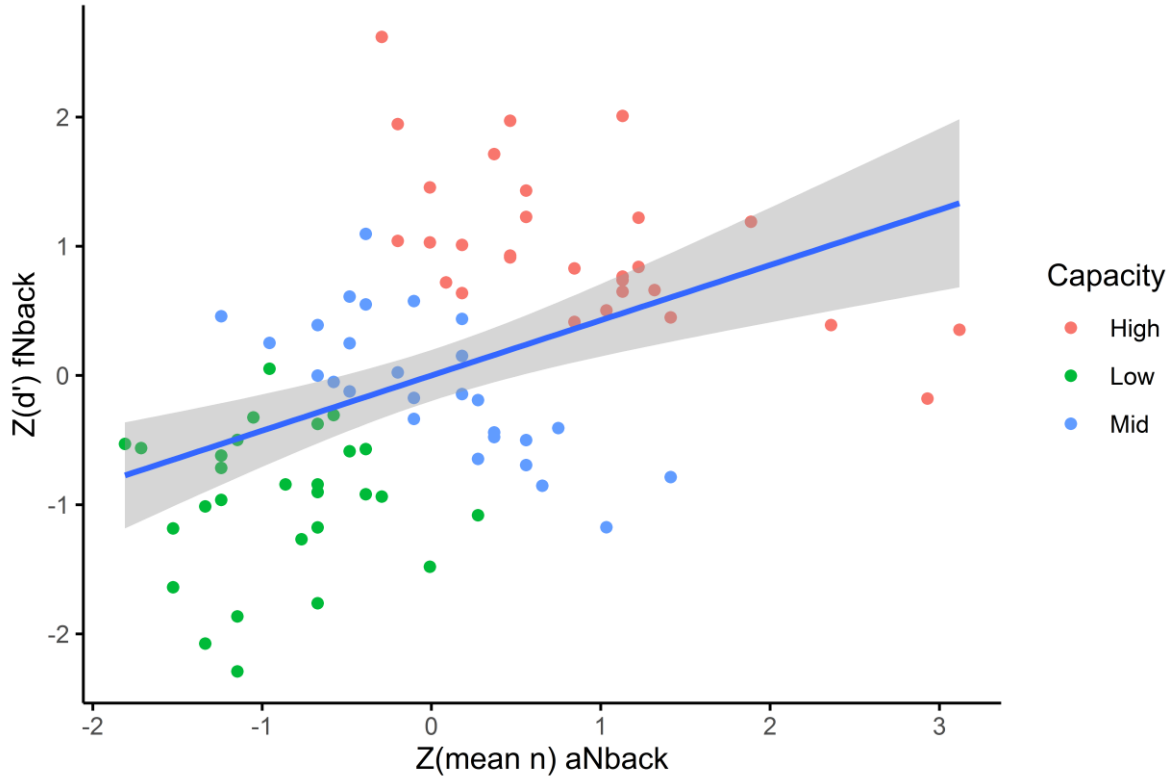
treatment group. Demographic and baseline characteristics, including age, gender, years of education, mood, and baseline performance were compared across the four groups, and the differences observed were not significant (all *p*s > 0.05) (Table 4). The demographic and baseline characteristics were also compared across four groups in the low, mid, and high working memory capacity subgroups (see Supplementary Tables 1, 2, and 3). The years of education, alertness, motivation, the expectation of tDCS and positive affect differed significantly between the mid-working memory capacity subgroups. The baseline performances recorded in the spatial *n*-back task, visual *n*-back task, and composite capacity scores did not differ between the intervention groups in the low, mid, and high working memory capacity subgroups, respectively. At the baseline, there was a significant correlation between the standardised adaptive spatial *n*-back task (aNBACK) and the fixed visual shape *n*-back task (fNBACK) ($r = 0.427$, $p = 0.000$). The correlation plot between the spatial *n*-back task and the visual *n*-back task is presented in Figure 8.

Table 4 - Baseline Characteristics by Treatment Group in Chapter 4

	Active tDCS + Strategy	Active tDCS + No Strategy	Sham tDCS + Strategy	Sham tDCS + No Strategy	*F* (3,80)	*p*	η_p^2
N	21	21	21	21	--	--	--
Age	21.66±5.62	20.90±3.71	19.09±0.94	20.85±3.64	1.673	0.179	0.059
Gender (M/F)	7/14	4/17	8/13	5/16	--	0.506[a]	--
Years of Education	17.05±3.17	15.95±3.93	15.28±1.65	15.57±2.96	1.362	0.260	0.049
Alertness	3.48±0.75	3.29±0.78	3.29±0.85	3.33±0.80	0.270	0.847	0.010
Motivation	3.76±0.77	3.66±0.66	3.48±0.87	3.67±0.66	0.544	0.654	0.020
Sadness	3.67±0.91	3.71±1.00	3.76±0.77	3.62±1.16	0.084	0.969	0.003
Expectation of CT	3.62±0.74	3.33±0.86	3.29±1.06	3.33±0.91	0.605	0.614	0.022
Expectation of tDCS	3.38±0.80	2.86±0.96	2.86±0.91	3.05±0.80	1.680	0.178	0.059
Positive affect	28.10±7.69	29.19±6.80	26.95±8.34	26.14±7.00	0.665	0.576	0.024
Negative affect	12.67±2.18	12.33±3.84	13.05±3.89	12.29±6.25	0.251	0.860	0.009
Z ($\bar{n}$) in aNback	0.26±1.24	-0.30±0.89	-0.07±0.72	0.11±1.05	1.235	0.303	0.044
Z (d') in fNback	0.01±1.04	0.00±1.00	-0.06±1.14	0.06±0.87	0.045	0.987	0.002
Composite capacity score	0.13±0.92	-0.15±0.80	-0.06±0.84	0.09±0.84	0.473	0.702	0.017

[a] Chi-square test.

Figure 8 - Correlation Plot Between Standardised Spatial N-Back Task (aNback) and Fixed Visual Shape N-Back Task (fNback) at Baseline on Different Capacity Groups



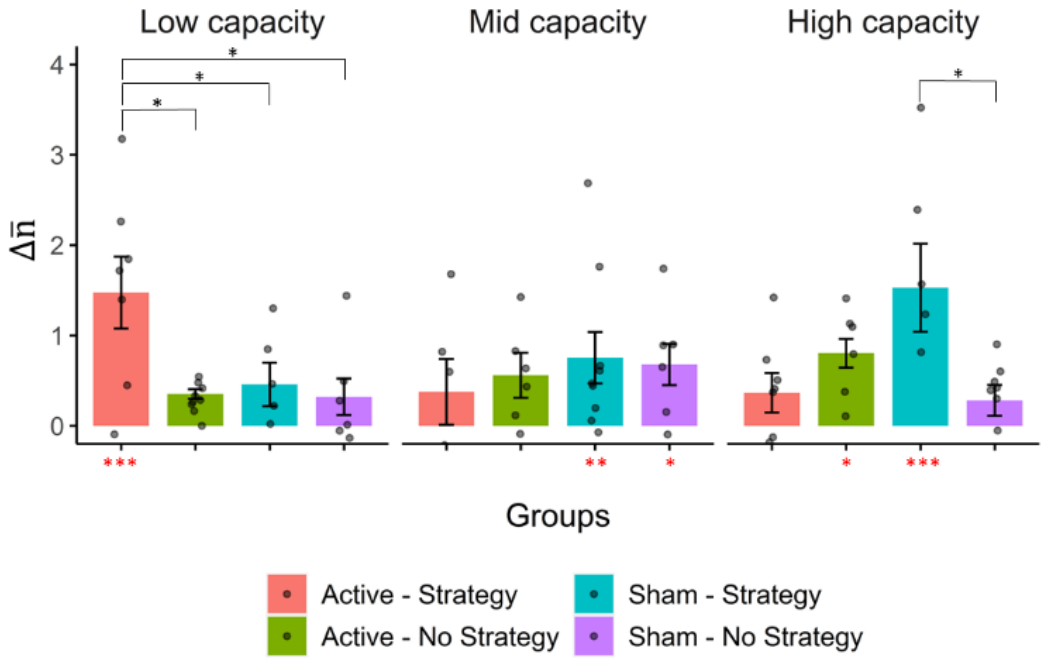
4.4.3 Online Effect of the Intervention on the Adaptive Spatial N-Back Task (aNBACK)

In this study, it was predicted that working memory capacity would modulate the effect of brain stimulation and working memory training. The $\Delta\bar{n}$ was analysed using a four-way ANOVA with three between-participant factors of Stimulation (Active vs. Sham), Strategy (Strategy vs. No Strategy), and Capacity (Low vs. Mid vs. High) and a within-participant factor of Time (Day 1 vs. Day 2). This analysis revealed that the main effect of Strategy was significant ($F_{(1,72)} = 4.797$, $p = 0.032$, $\eta_p^2 = 0.062$), and the main effect of Time was significant ($F_{(1,72)} = 35.076$, $p < 0.001$, $\eta_p^2 = 0.328$). Additionally, the interaction effect of Time × Strategy was significant ($F_{(1,72)} = 5.474$, $p = 0.022$, $\eta_p^2 = 0.071$) ,and the interaction effect of Stimulation × Strategy × Capacity

was significant ($F_{(2,72)}$ = 5.830, p = 0.005, η_p^2 = 0.139). As predicted, low working memory capacity participants benefitted more from stimulation and strategy instructions. After collapsing across Time, the three-way interaction is then analysed. The interaction was further investigated using t-tests (Holm-corrected) in individuals with differing working memory capacities. The optimal model delineating the variations in $\Delta\bar{n}$ encompasses the main effect of Strategy and Stimulation and the interaction effect of Stimulation × Strategy. For individuals with a low working memory capacity, the BF_{10} value was 6.320. For those with a high working memory capacity, the BF_{10} value was 1.971.

In participants with low working memory capacity, the improvement of the mean *n* level in the Active-Strategy group was significantly different from zero ($t_{(24)}$ = 6.098, p < 0.001) and larger than the other three groups (Active-No strategy: $t_{(14)}$ = 3.479, p_H = 0.012, d_{Cohen} = 1.490; Sham-Strategy: $t_{(11)}$ = 2.857, p_H = 0.035, d_{Cohen} = 1.191; Sham-No strategy: $t_{(11)}$ = 3.236, p_H = 0.018, d_{Cohen} = 1.400). No significant effect was observed among participants with mid-working memory capacity across the four groups (all p-values > 0.1). In participants with high working memory capacity, the improvement of the mean *n* level in the Sham-Strategy was larger than zero ($t_{(5)}$ = 5.020, p_H < 0.001), and was significantly larger than those in the Sham-No Strategy group ($t_{(13)}$ = 3.219, p_H = 0.021, d_{Cohen} = 1.286). The online performance changes after collapsing across Time in groups with different working memory capacities are shown in Figure 9.

Figure 9 - Change in Mean N Level Collapsed Across Days One and Two (Online TDCS Sessions) in Four Groups



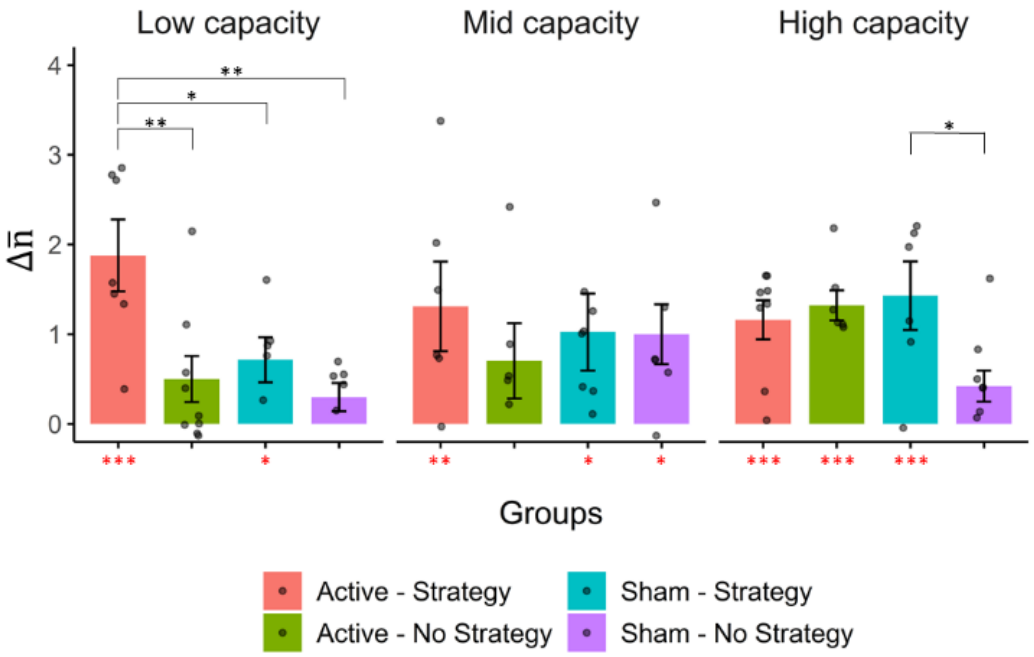
Note. Means with standard errors are reported for each intervention group and working memory capacity subgroup. Significant results are marked with asterisks (*indicates $p < 0.05$, **indicates $p < 0.01$, ***indicates $p < 0.001$). Changes which are more significant than 0 are marked in red.

4.4.4 Offline Effect of the Intervention on the Adaptive Spatial N-Back Task

In order to test the offline effect of brain stimulation and cognitive training, the $\Delta\bar{n}$, which equalled the mean *n* level on the post-test minus the mean *n* level on the baseline, was analysed. The $\Delta\bar{n}$ was analysed using a three-way ANOVA with the factors of Stimulation (Active vs. Sham), Strategy (Strategy vs. No Strategy), and Capacity (Low vs. Mid vs. High). This analysis revealed that the main effect of Strategy was significant ($F_{(1,72)} = 8.405$, $p = 0.005$, $\eta_p^2 = 0.105$), and the main effect of Stimulation tended to be significant ($F_{(1,72)} = 3.175$, $p = 0.079$, $\eta_p^2 = 0.042$). Additionally, the interaction effect of Stimulation × Strategy × Capacity tended to be significant ($F_{(2,72)} = 2.711$, $p = 0.073$, $\eta_p^2 = 0.070$). As predicted, participants with low working memory benefitted more from stimulation and strategy. The interaction was

further investigated using t-tests (Holm-corrected) in individuals with differing working memory capacities. In characterising the changes in the $\Delta\bar{n}$, the most fitting model integrates the main effect of Strategy and Stimulation and the interaction effect of Stimulation × Strategy. It is worth noting that for low working memory capacity individuals, the BF_{10} was 11.195, while for high working memory capacity individuals, the BF_{10} was 2.473. In participants with low working memory capacity, the improvement of the mean *n* level in the Active-Strategy group was significantly larger than zero ($t_{(24)} = 6.468$, $p < 0.001$) and larger than the other three groups (Active-No Strategy: $t_{(14)} = 3.562$, $p_H = 0.008$, $d_{Cohen} = 1.485$; Sham-Strategy: $t_{(11)} = 2.717$, $p_H = 0.048$, $d_{Cohen} = 1.338$; Sham-No Strategy: $t_{(11)} = 3.700$, $p_H = 0.007$, $d_{Cohen} = 1.977$). No significant effect was observed among participants with mid-working memory capacity across the four groups (all *p*-values > 0.1). In participants with high working memory capacity, the improvement of the mean *n* level was larger than zero in the Active-Strategy ($t_{(25)} = 5.274$, $p < 0.001$), the Active-No Strategy ($t_{(25)} = 4.868$, $p_H < 0.001$), and the Sham-Strategy ($t_{(25)} = 5.261$, $p_H < 0.001$). Additionally, the increase in the mean *n* level in the post-test in the Sham-Strategy group was significantly larger than in the Sham-No Strategy group ($t_{(13)} = 2.874$, $p_H = 0.049$, $d_{Cohen} = 1.328$). The performance changes after the intervention in groups with different working memory capacities are shown in Figure 10.

Figure 10 - Change in Mean N Level With Respect to Baseline on the Post-Test (Offline TDCS Session) in Four Groups



Note. Means with standard errors are reported for each intervention group and working memory capacity subgroup. Significant results are marked with asterisks (*indicates $p < 0.05$, **indicates $p < 0.01$, ***indicates $p < 0.001$). Changes which are more significant than 0 are marked in red.

4.4.5 Offline Effect of the Intervention on Fixed Visual Shape N-Back Task (fNBACK)

In order to examine the transfer effect of brain stimulation and strategy instructions on an untrained task, specifically the fixed visual shape *n*-back task (fNBACK), the d-prime changes on the post-test concerning the baseline in the fixed visual shape *n*-back task were analysed. D-prime was calculated according to the formula: d-prime = z (Hits) - z (False Alarm) (Haatveit et al., 2010). The changes in d-prime in the visual shape *n*-back task were analysed using a three-way ANOVA with the factors of Stimulation (Active vs. Sham), Strategy (Strategy vs. No Strategy), and Capacity (Low vs. Mid vs. High). This analysis revealed that the main effect of Capacity

tended to be significant ($F_{(2,72)} = 2.879$, $p = 0.063$, $\eta_p^2 = 0.074$), and there was no significant interaction between the three factors.

4.4.6 Mood, Expectation and Other Related Questionnaires

In order to test the effect of brain stimulation and strategy instructions on mood and other statuses, the level of alertness, motivation, optimism, and expectation were analysed. This was done using a three-way ANOVA with two between-participant factors of Stimulation (Active vs. Sham), and Strategy (Strategy vs No Strategy), and a within-participant factor of Time (Pre-test vs. Day 1 vs. Day 2 vs. Post-test). Results are shown in Table 5. It can be seen from the table that there was no significant effect on alertness, motivation and sadness (all *p*s > 0.05). A significant effect was found of Time on Expectation of WM performance ($F_{(3,193)} = 3.239$, $p = 0.031$, $\eta_p^2 = 0.040$). There was also a significant effect of Time ($F_{(2,165)} = 9.789$, $p < 0.001$, $\eta_p^2 = 0.112$) and a significant interaction effect of Time × Strategy × Stimulation ($F_{(2,165)} = 4.711$, $p = 0.009$, $\eta_p^2 = 0.057$) on Expectation of brain stimulation. After breaking down the time, a two-way ANOVA with two between-participants factors of Stimulation (Active vs. Sham) and Strategy (Strategy vs. No Strategy) was used for analysis purposes at different times. On the post-test, there was a significant effect of Stimulation ($F_{(1,80)} = 6.320$, $p = 0.014$, $\eta_p^2 = 0.073$), with participants in Active groups having higher expectations towards brain stimulation than those in Sham groups. However, within the Active group, the correlation between the expectation toward brain stimulation score and the $\Delta\bar{n}$ in aNBACK online did not yield statistical significance ($r = -0.075$, $p = 0.636$). The scores of positive attitude and negative attitude obtained in the PANAS were analysed using a three-way ANOVA with two between-participant factors of Stimulation (Active vs. Sham) and Strategy (Strategy vs. No Strategy) and a within-participant factor of

Time (Pre-test vs. Post-test). A significant effect of Time on Positive affect was found ($F_{(1,80)}$ = 8.402, p = 0.005, η_p^2 = 0.095) with scores lower on the post-test than on the pre-test. However, the intervention had no significant effect on Negative affect (all ps > 0.05).

In order to examine whether motivation modulates the performance of the spatial *n*-back task, a Pearson correlation test was used to test the relationship between the mean *n* of the spatial *n*-back task and the scores of motivation, scores of positive attitudes on PANAS, expectations of cognitive training and expectations of brain stimulation. No significant correlation was found between the mean *n* of the spatial *n*-back task and motivation items ($r_{(\text{Motivation})}$ = 0.042, p = 0.705; $r_{(\text{Positive attitudes})}$ = 0.060, p = 0.587; $r_{(\text{Expectation of CT})}$ = -0.020, p = 0.860; $r_{(\text{Expectation of brain stimulation})}$ = -0.001, p = 0.996).

Table 5 - Output of A Three-Way Mixed ANOVA on the Mood and Attitudes

	df	*F*	*p*	η_p^2
Alertness				
Time	3,199	1.239	0.296	0.016
Time × Strategy	3,199	0.377	0.740	0.005
Time × Stimulation	3,199	0.582	0.603	0.008
Time × Strategy × Stimulation	3,199	0.595	0.595	0.008
Strategy	1,77	0.223	0.638	0.003
Stimulation	1,77	1.663	0.201	0.020
Strategy × Stimulation	1,77	2.075	0.154	0.026
Motivation				
Time	3,207	2.541	0.057	0.032
Time × Strategy	3,207	0.794	0.488	0.005
Time × Stimulation	3,207	0.390	0.741	0.005
Time × Strategy × Stimulation	3,207	0.136	0.925	0.002
Strategy	1,76	0.318	0.575	0.004
Stimulation	1,76	1.180	0.281	0.015
Strategy × Stimulation	1,76	0.809	0.371	0.011
Sadness				
Time	2,168	0.065	0.949	0.001
Time × Strategy	2,168	0.154	0.874	0.002

Time × Stimulation	2,168	0.423	0.673	0.005
Time × Strategy × Stimulation	2,168	0.601	0.563	0.008
Strategy	1,77	0.242	0.624	0.003
Stimulation	1,77	0.056	0.814	0.001
Strategy × Stimulation	1,77	0.001	0.979	0.000
Expectations on WM				
Time	3,193	3.239	0.031*	0.040
Time × Strategy	3,193	0.479	0.663	0.006
Time × Stimulation	3,193	1.471	0.229	0.019
Time × Strategy × Stimulation	3,193	1.995	0.127	0.025
Strategy	1,77	0.142	0.708	0.002
Stimulation	1,77	2.975	0.089	0.037
Strategy × Stimulation	1,77	0.358	0.551	0.005
Expectations of brain stimulation				
Time	2,165	9.789	< 0.001*	0.112
Time × Strategy	2,165	1.424	0.243	0.018
Time × Stimulation	2,165	2.199	0.111	0.027
Time × Strategy × Stimulation	2,165	4.711	0.009*	0.057
Strategy	1,78	0.242	0.624	0.003
Stimulation	1,78	3.285	0.074	0.040
Strategy × Stimulation	1,78	0.006	0.939	0.000
Positive affect				
Time	1,80	8.402	0.005*	0.095
Time × Strategy	1,80	0.278	0.600	0.003
Time × Stimulation	1,80	1.275	0.262	0.016
Time × Strategy × Stimulation	1,80	0.512	0.477	0.006
Strategy	1,80	0.081	0.776	0.001
Stimulation	1,80	2.832	0.096	0.034
Strategy × Stimulation	1,80	0.090	0.765	0.001
Negative affect				
Time	1,80	0.741	0.392	0.009
Time × Strategy	1,80	0.398	0.530	0.005
Time × Stimulation	1,80	0.000	1.000	<0.001
Time × Strategy × Stimulation	1,80	0.013	0.909	0.000
Strategy	1,80	0.202	0.654	0.003
Stimulation	1,80	0.069	0.794	0.001
Strategy × Stimulation	1,80	0.069	0.794	0.001

*$p < 0.05$.

4.4.7 Retrospective Strategy Questionnaires

4.4.7.1 Strategy Use in Four Groups

In order to ensure that the strategy was used in the experiment, participants in the Strategy group were asked whether they used the provided strategy or not, and participants in the No Strategy group were asked whether they used a strategy and how they classified it according to the strategy options provided. In the Active-Strategy group, one participant failed to use the provided strategy. In the Sham-Strategy group, two participants failed to use it. The difference in the rate of strategy use between the Active-Strategy and Sham-Strategy groups was not significant (p = 1.000). One participant did not produce a spontaneous strategy in the Active-No Strategy and Sham-No Strategy groups. In order to examine the strategy used at baseline across the four intervention groups or three capacity groups, a Fisher exact test was used. It showed no significant difference between the four intervention groups (X^2 = 25.304, p = 0.646) or between the three capacity subgroups (X^2 = 21.864, p = 0.215).

4.4.7.2 Strategy Effectiveness and Brain Stimulation

A variety of strategy types were used. In order to examine the relationship between strategy effectiveness and brain stimulation, the strategy use was divided into effective (which was similar to the one provided in this experiment, including association and grouping) and ineffective (which was different from the one provided in this experiment). In the Active-No Strategy group, eight participants produced a spontaneous effective strategy; twelve participants produced a spontaneous effective strategy in the Sham-No Strategy group. The difference in the rate of effective strategy usage between the Active-Strategy and Sham-Strategy groups was not significant (X^2 = 1.527, p = 0.217).

4.4.7.3 Strategy Effectiveness and Baseline Motivation

In order to examine the relationship between strategy effectiveness and baseline motivation, the strategy used at the first block before the intervention was divided into groups of either effective or ineffective. An independent t-test was used to compare the score of baseline motivation between the effective strategy and ineffective strategy groups. The result showed no significant difference in baseline motivation between the effective and ineffective strategy groups (t = -0.357, p = 0.722).

4.4.8 Possible Side Effects of Brain Stimulation

A chi-square test was used to examine the side effects between Active groups and Sham groups. On Day 1, the rates of headache and fatigue reported in the Sham group were higher than those in the Active group ($X^2_{(1)\ \text{Headache}}$ = 11.012, p = 0.001; $X^2_{(20)\ \text{Fatigue}}$ = 4.421, p = 0.035). There was no significant difference between the Active and Sham groups in terms of the rate of other reported side effects on Day 1, or across all side effects reported on Day 2 (see Table 6).

Table 6 - Possible Side Effects of Brain Stimulation on Days 1 And 2

	Active	Sham	X^2	*p*
Day1				
Headache	1 (2.38%)	12 (28.57%)	11.01	0.001*
Pain in the neck	4 (9.52%)	0	2.363	0.124
Itching	25	24 (57.14%)	0.049	0.825
Sleepiness	11	18 (42.86%)	2.581	0.108
Trouble concentrating	14	18 (42.86%)	0.808	0.369
Acute mood change	3 (7.14%)	6 (14.29%)	0.498	0.480
Fatigue	9	18 (42.86%)	4.421	0.035*
Nausea	1 (2.38%)	1 (2.38%)	0.000	1.000
Muscle twitches in the face or neck	4 (9.52%)	2 (4.76%)	0.179	0.672
Tingling	37	36 (85.71%)	0.105	0.746
Burning	25	29 (69.05%)	0.830	0.362
Epileptic seizure	0	0	-	-
Light flashes	1 (2.38%)	1 (2.38%)	0.000	1.000
Uncomfortable feeling	21	20 (47.62%)	0.048	0.827
Day2				
Headache	4 (9.52%)	7 (16.67%)	0.941	0.332
Pain in the neck	2 (4.76%)	1 (2.38%)	0.000	1.000
Itching	18	18 (42.86%)	0.000	1.000
Sleepiness	21	17 (40.48%)	0.769	0.381
Trouble concentrating	19	15 (35.71%)	0.791	0.374
Acute mood change	4 (9.52%)	5 (11.90%)	0.001	0.970
Fatigue	17	18 (42.86%)	0.049	0.825
Nausea	1 (2.38%)	0	-	1.000
Muscle twitches in the face or neck	2 (4.76%)	1 (2.38%)	0.000	1.000
Tingling	33	35 (83.33%)	0.309	0.578
Burning	25	25 (59.52%)	0.000	1.000
Epileptic seizure	0	0	-	-
Light flashes	1 (2.38%)	0	-	1.000
Uncomfortable feeling	15	16 (38.10%)	0.051	0.821

*$p < 0.05$.

4.4.9 Blinding of Stimulation

One participant in the Sham stimulation group did not finish the questionnaire on blinding. The chi-square test was used to test the difference of rate of participants who guess that they were in the Active group between the Active and Sham groups.

There was no significant difference between these two groups ($X^2_{(1)} = 0.863$, $p = 0.353$).

4.5 Discussion

The primary finding of this study is that the combination of tDCS and strategy benefitted participants who initially had low working memory capacity. With a two-day intervention, this study fails to detect any transfer effect on untrained visual *n*-back tasks. Furthermore, there was no evidence that brain stimulation affected self-generated strategy. Moreover, tDCS affected the expectation of brain stimulation, but did not affect the level of alertness, motivation, sadness or the score of PANAS.

As summarised above, the main finding in this study was that the combination of tDCS and strategy-provided cognitive training selectively benefitted participants with low working memory capacity. The strategy mediation theory, which supports this, claims that strategy instruction can improve performance in working memory tasks (McNamara & Scott, 2001). Another study also revealed that strategy use mediates working memory capacity and performance in a matrix task, a fluid intelligence measure (Gonthier & Thomassin, 2015). The reason for this could be that strategy use can efficiently promote working memory storage (McNamara & Scott, 2001). It may make more cognitive resources available for the central executive system of working memory (Peng & Fuchs, 2017). However, participants with lower working memory capacity are likely to experience “utilisation deficiency”, which results in limited improvements, even with a provided strategy. TDCS may counteract “utilization deficiency” by enhancing the neuroplasticity, which synergises with strategy (Bjorklund, Schneider, Cassel, & Ashley, 1994; Chan et al., 2019). By contrast, participants with high working memory capacity have enough cognitive resources, either by using an external strategy or by producing a spontaneous

effective strategy, making the effect of tDCS unobservable (Jones, Gozenman, et al., 2015). However, the study by Jones and colleagues showed that the strategy combined with tDCS only benefitted high working memory capacity participants, while low working memory capacity participants did not benefit from this combination (Jones, Gozenman, et al., 2015). The inconsistent results may be ascribed to the different experimental designs that were used. This study adopted a between-participants design, while Jones et al. used a within-participants design (Jones, Gozenman, et al., 2015). Employing a within-participants design presents challenges in ensuring that participants do not apply the strategy given to them during the subsequent session, potentially impacting the outcome. In addition, the *n*-back task was used in this study, and a strategy was provided using association and grouping, while Jones et al. used the change detection task and provided a strategy using naming and rehearsal (Jones, Gozenman, et al., 2015). The finding in this study is consistent with Au and colleagues, who reported that tDCS and working memory training improved verbal and spatial *n*-back task performance (Au et al., 2016). However, Au's study did not consider the factor of working memory capacity. A previous study that divided working memory capacity into high and low subgroups found that older participants with low working memory capacity and young participants with high working memory capacity benefitted from tDCS in visual working memory tasks (Arciniega et al., 2018). This inconsistency may be due to the different working memory tasks and parameters, including the stimulated location. Although there are some inconsistencies between the findings in this study and others, it suggests that different levels of working memory capacity participants may have different response patterns, particularly where strategy is taken into account.

On the untrained visual shape *n*-back task, this study failed to find any transfer effect of tDCS and strategy-provided cognitive training. Even though the visual shape *n*-back task and the spatial *n*-back task are both *n*-back tasks, the provided strategy in the spatial *n*-back task could not be used in the visual *n*-back task due to the complex visual pictures used. Additionally, the visual *n*-back task stimuli are challenging for participants to encode or to create associations with, leading them to use spontaneous imaging, different strategies from those provided or spontaneous strategies used in the spatial *n*-back task. Finally, studies showed that the transfer effect is more likely to exist during the follow-up periods than during the post-test conducted immediately after the tDCS and working memory training (Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Teixeira-Santos et al., 2022).

The fronto-parietal and default networks, such as the medial prefrontal cortex, were related to discovering new strategies during tasks (Allegra et al., 2020). However, from the strategy questionnaire, this study found that tDCS, which stimulated DLPFC, does not affect the use of a spontaneous strategy. It was reported that both strategy selection and efficiency involved in the working memory task in children were modulated by individual differences, including processing speed, arithmetic skill, gender and maths anxiety (Imbo & Vandierendonck, 2007). No previous study has examined the relationship between tDCS and spontaneous strategy. It is possible that two sessions of tDCS would not significantly modulate the reported modulators, including processing speed and anxiety, meaning that it would fail to affect spontaneous strategy.

This study has shown that brain stimulation and working memory training do not improve working memory capacity through an emotional change. Although the DLPFC is related to emotion, the effect of tDCS on negative and positive attitudes is

yet to be seen. This is consistent with Au's study, which also showed that tDCS applied to DLPFC combined with working memory training did not change the score of the positive and negative attitudes of PANAS (Au et al., 2016). However, this study has revealed that the positive attitude score decreased when considered together with time. It may be due to the fatigue or boredom participants felt when they undertook the tasks on the second day.

Finally, this study found that participants in the tDCS group had higher scores of expectations on brain stimulation after the intervention. This finding is supported by a previous study that found frontal tDCS can promote dopamine release on the ventral striatum in humans (Fonteneau et al., 2018). It is well known that dopamine is associated with reward processing and will increase people's expectations when the activation increases (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Haber & Knutson, 2010). However, the analysis in Chapters 5 and 6 failed to identify the effect of tDCS on expectation in both the elderly and stroke patients. This absence may be attributed to the progressive dopamine decline associated with ageing (Volkow et al., 1994) and the influence of the dopaminergic system triggered by stroke lesions (Gower & Tiberi, 2018). Moreover, the higher expectation scores on brain stimulation were not related to improvement on the n-back task. These results need to be interpreted with caution. Further studies could be undertaken to explore the alterations in dopamine levels after tDCS across diverse populations.

The major limitation of this research is that the sample size was small for each subgroup when the analysis was conducted on three subgroups. These data, therefore, should be interpreted cautiously. In addition, a two-day intervention may not be powerful enough to detect the brain stimulation's transfer effect and long-term

effect. Further studies are needed to examine the relationship between brain stimulation and strategy during multi-week interventions with large samples.

4.6 Conclusion

This study has found that the combination of tDCS and strategy-instructed cognitive training is beneficial in healthy young adults with low working memory capacity. These results draw our attention to the importance of considering strategy and working memory capacity when designing brain stimulation studies.

Chapter 5 - The Effect of Multi-Day TDCS Concurrent With Cognitive Training on Working Memory in the Elderly

5.1 Abstract

Background

Working memory decline is linearly associated with ageing from the 20s through to the 70s. Long-term cognitive training is widely used in the elderly to improve working memory. TDCS is a promising tool to modulate the plasticity of the brain. However, whether multi-sessions of tDCS can promote the effect of cognitive training is still unknown.

Method

A randomised, between-subjects, single-blinded study was conducted at the University of Birmingham. Thirty healthy elderly participants were recruited and received five sessions of cognitive training combined with sham or active tDCS applied to the right DLPFC. On the pre-test and post-test, a fixed spatial *n*-back task, a visual *n*-back task, change detection, and digit span forward and backward were applied to evaluate the training and transfer effect. Individuals were divided into subgroups so that the effect of age and initial capacity could be considered.

Results

Twenty-eight participants completed the experiment. In the subgroup of participants of advanced age, the benefit of the training task was significant in the active group compared with the sham group ($p = 0.004$). A similar benefit was also found in the low-capacity subgroup ($p = 0.001$). This effect persisted in the spatial *n*-back task on the post-test measured two days after brain stimulation. However, the intervention could not be transferred to non-trained tasks.

Conclusion

The elderly participants of an advanced age or with low working memory capacity benefitted from tDCS. This effect lasted for at least two days. This study also shows that the effect of a five-day tDCS did not transfer to the untrained task. These findings indicate that tDCS would be of benefit to low working memory subjects, including those suffering from brain injury and stroke.

5.2 Introduction

Working memory is a mental workspace which plays an essential role in general cognition and is related to fluid intelligence. Therefore, there is an expectation that general cognition can be improved through working memory training. In Chapter 4, we see that tDCS can augment the beneficial effect of strategy-instructed cognitive training in healthy young adults. In this chapter, the established set-up from Chapter 4 was replicated in a sample of healthy elderly participants to investigate the potentially beneficial effect of tDCS on cognitive training in this demographic. This chapter did not incorporate strategy modulation due to the challenges for the elderly to execute complex strategy instructions. The information on strategy use was collected following the intervention.

Several studies have shown that ageing has contributed to the decline in working memory (Babcock & Salthouse, 1990; Borella et al., 2008; Cowan, Naveh-Benjamin, Kilb, & Saults, 2006). In an investigation into working memory and age groups, Borella and colleagues found that working memory decline was linearly associated with ageing from the 20s through to the 70s (Borella et al., 2008).

Some influential theories have been proposed to explain the age-related decline in working memory, such as the Hemispheric Asymmetry Reduction in Older Adults

(HAROLD) model (Cabeza et al., 2004), the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008), the Posterior-Anterior Shift in Ageing (PASA) model (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008) and the Scaffolding Theory of Ageing and Cognition-revised (STAC-r) (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). Specifically, the CRUNCH proposes that the elderly tend to activate other brain regions to compensate for the overloaded capacity of task-specific regions (Reuter-Lorenz & Cappell, 2008). Similarly, the PASA model highlights relative augmentation in frontal activity and a decline in occipital activity in the elderly (Davis et al., 2008). The STAC and STAC-r models suggest increased frontal activation indicating an adaptive brain which compensates for the decreased structure or function due to ageing (D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). In the HAROLD model, scientists found evidence that the elderly activated the bilateral hemisphere during working memory tasks, a pattern that contrasts with the unilateral activation observed in younger adults (Cabeza et al., 2004). Recent studies have also concluded that a diminished cortical surface area of the right frontal cortex, a decline in dopamine, emotional distractors, caffeine, and hormones all contribute to poor working memory performance in the elderly (Chai et al., 2018; Luciana & Collins, 1997; Nissim et al., 2017). Although there is no consensus regarding a predominant theory, identifying valuable tools to intervene in working memory decline is considered to be essential. As reviewed in Chapter 1, tDCS could increase excitability and enhance neuroplasticity. This study hypothesis stimulating right DLPFC via tDCS could help healthy elderly increase working memory capacity as a result of adaptive cognitive training.

The literature presents varied findings regarding the effect of tDCS on working memory capacity in the elderly. The protocols in such studies differ from one another leading to inconsistent conclusions. For instance, Jones and colleagues used a crossover design, revealing that participants in the more highly educated group could benefit from the tDCS, regardless of the stimulation hemisphere or the material of the working memory task (Berryhill & Jones, 2012). A subsequent study by the same group showed that visual working memory was improved by using unilateral tDCS, rather than bilateral tDCS, and was particularly beneficial for individuals with low baseline visual working memory capacity (Arciniega et al., 2018). Contradictory to these results, other studies have questioned the efficacy of tDCS on working memory in the elderly (Nilsson, Lebedev, & Lovden, 2015; Nilsson et al., 2017). These conflicting outcomes may be due to the absence of concurrent cognitive training or between-subject designs. These varied findings lead us to further investigate the potential of tDCS to accelerate working memory improvement in the elderly.

Individual differences, such as age, initial capacity and education, are essential for predicting the effect of training and brain stimulation (Arciniega et al., 2018; Berryhill & Jones, 2012). Lövdén and colleagues suggest that neuron plasticity depends on a mismatch between supply (capacity for cognitive function) and demand (the requirement of the environment) (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). This means that low-capacity participants on the baseline would have more room to improve. Zinke's study reports that baseline performance can be used to predict training gains (Zinke et al., 2014). Previous research also indicates that, compared with young adults, the influence of cerebral spinal fluid volume on the electric field was mitigated in the elderly (Antonenko et al., 2021). We can, therefore,

hypothesise that elderly participants with different working memory capacities and ages would benefit from different modes. Participants with low working memory capacity and advanced age would benefit more from tDCS and cognitive training.

The main aim of this study was to investigate the beneficial effect of tDCS combined with five training sessions in healthy elderly participants. It was also hypothesised that working memory capacity at the baseline and age could predict the beneficial effect following the intervention. Another objective was to examine the transfer effect of tDCS combined with cognitive training in healthy elderly people.

5.3 Materials and Method

5.3.1 Study Design

This is a randomised, between-subjects, single-blinded study conducted at the University of Birmingham. The ethical approval was confirmed by the University of Birmingham (ERN_12-1002AP18R).

5.3.2 Participants

Thirty participants were recruited and eligible. Two participants withdrew before or during the experiment, and 28 participants were then divided into two treatment groups. Of the 28 participants, the number of females was equal to that of males. All of them were between 55 to 75 years old. The other inclusion criteria are presented in Chapter 2. Researchers introduced the instructions for this study and the possible side effects of tDCS to participants. Participants were asked to complete a safety screening questionnaire to ensure that they were eligible to participate in this study, and were also required to sign a consent form. Participants were paid 100 pounds as compensation for completing this study.

5.3.3 Randomisation and Masking

Before the experiment, participants were randomly assigned to the active and sham groups. Participants in both groups performed the cognitive training tasks whilst they were doing the active or sham brain stimulation. The group allocation blinded all participants.

5.3.4 Materials

5.3.4.1 Brain Stimulation

See the details of the parameters of brain stimulation in Chapter 2.

5.3.4.2 Trained Task: Adaptive Spatial N-Back Task (N-IGMA)

The *n* level of the adaptive spatial *n*-back task (N-IGMA) began at Level 1 every day. The stimuli were enacted for 500 milliseconds, and 2,500 milliseconds were given for decision-making. The details of the N-IGMA are described in Chapter 2.

5.3.4.3 Transfer Measures

The pre- and post-tests comprised a fixed spatial *n*-back task, a visual-shape *n*-back task, a change detection task, and a verbal working memory span task. On the pre- and post-tests, the spatial *n*-back task was fixed, while on the training task, the spatial *n*-back task was adaptive. The visual-shape *n*-back task, while utilising different stimuli, demonstrated the near transfer effect. The change detection task and the verbal working memory span task were employed to illustrate the far transfer effect. The d-prime of the change detection task, the spatial *n*-back task, the visual-shape *n*-back task, and the maximum span for the Digital Span Forward (DSF) and Digital Span Backward (DSB) were calculated and subsequently standardised into a z-score for individual participants. Each task received an individual z-score, and a composite working memory capacity (WMC) score was determined by averaging the

mean z-score across these five tasks. These composite scores were calculated both at the baseline and in the post-test.

Fixed Spatial N-Back

The fixed spatial *n*-back task is a non-adaptive version of N-IGMA with the *n* level held at *n* = 1 and *n* = 2. Participants were asked to complete six blocks of the 1-back task and six blocks of the 2-back task in the pre-test and post-test.

Visual-Shape N-Back

Participants were asked to complete six blocks of 1-back and 6-blocks of 2-back in the visual-shape *n*-back task. See the details of the visual shape *n*-back task in Chapter 2.

Change Detection Task

Considering that working memory capacity in the elderly was lower than in adults, the number of squares was set into 2, 4, and 6 in this task. Other details of the change detection task are described in Chapter 2.

Digit Span Forward and Digit Span Backward

MATLAB programmed Digit Span Forward and Digit Span Backward from WAIS-IV, asking participants to repeat a series of numbers in a forward or backward sequence, respectively (Wechsler, 2008).

5.3.4.4 Other Questionnaires

Before the intervention, participants were asked to complete questionnaires, including the Epworth Sleepiness Scale (ESS), World Health Organization Quality-of-Life Scale (WHOQOL), Familiarity With Technology (FWT), and the Hospital Anxiety Depression Scale (HADS). The ESS and HADS are described in Chapter 2.

WHOQOL

World Health Organization Quality-of-Life Scale (WHOQOL) was employed to evaluate how participants felt about their quality of life, health, and other areas in their lives over the two weeks before they were recruited. It is a 26-item questionnaire using a 5-point Likert scale ranging from 1 to 5.

Familiarity With Technology

A six-item questionnaire was designed to evaluate the extent to which participants were familiar with standard modern technology. It includes being familiar with computers, laptops and tablets, smartphones, smart televisions and smartwatches, internet banking and online shopping, e-health applications, cash machines and ticket machines, and computer or tablet games.

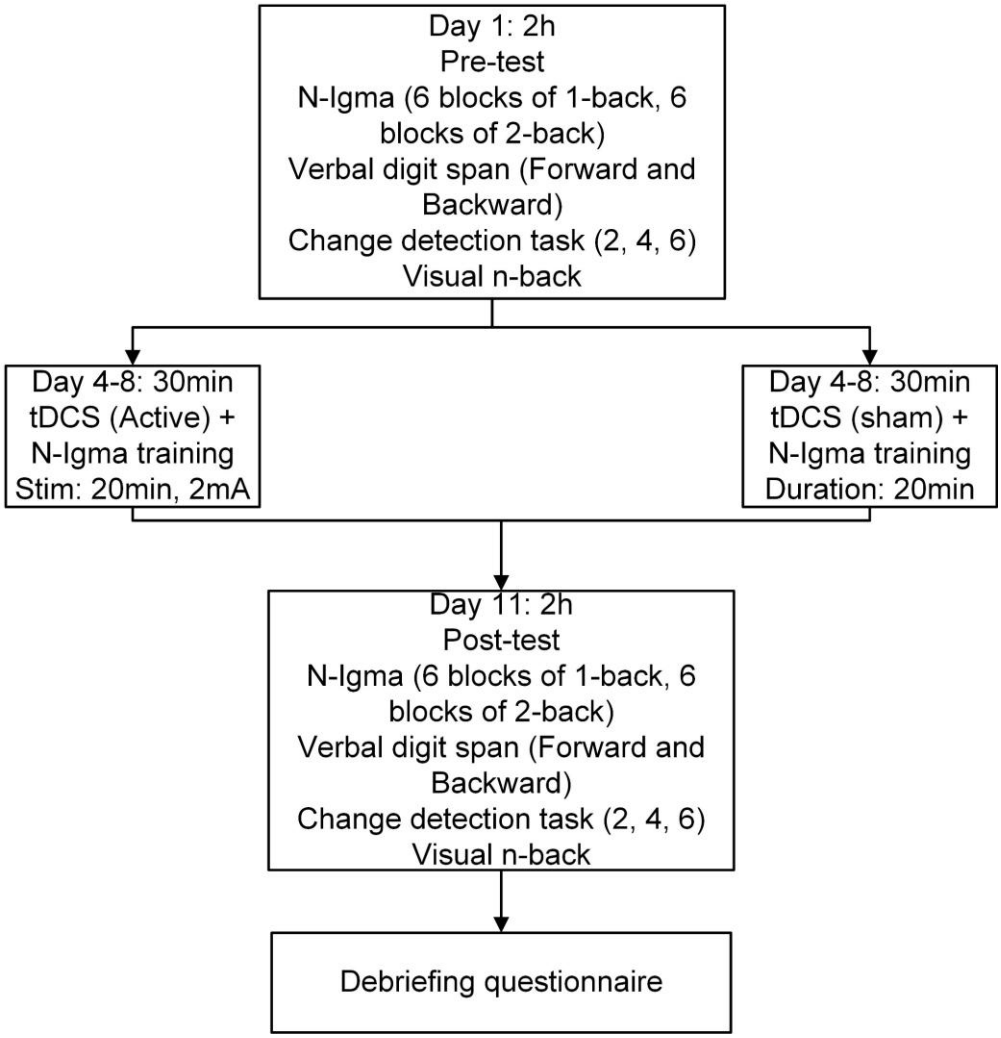
5.3.5 Procedure

Figure 11 shows the timeline of this experiment. On the first day (Friday), participants were asked to complete screening questionnaires and then finish the pre-tests in the following order: Fixed spatial *n*-back (6-blocks of Level 1, 6-blocks of Level 2), digit span forward, digit span backward, a change detection task, visual-shape *n*-back (6-blocks of Level 1, 6-blocks of Level 2). Participants then had a weekend on the second and third days. From the fourth day (Monday) to the eighth day (Friday), participants were subjected to cognitive training combined with tDCS (Active or Sham). After that, participants had a two-day break over the weekend and took the post-tests on the eleventh day, which was Monday. The tasks in the post-test were the same as those used in the pre-test. After the assessment, participants were asked about the strategy used during the spatial *n*-back task and the group allocation.

5.3.6 Statistical Analysis

A statistical analysis was performed in SPSS software (version 26). For baseline characteristics, side effects and a debriefing of the stimulation between the two groups, t-tests were carried out for continuous variables, and chi-square tests were used for categorical variables. ANOVA or ANCOVA was employed to analyse the training and transfer effect. The Greenhouse-Geisser correction was applied when it did not meet the assumption of sphericity. All *p*-values were reported as two-sided. A *p*-value < 0.05 was considered significant. Data visualisations were generated using the package ggplot2 in R software (Hadley, 2016).

Figure 11 - Procedure of the Experiment in the Elderly Study



5.4 Results

5.4.1 Outliers Analysis

Outliers were identified using a criterion of three SD for the average training performance (mean *n* level) over five sessions for both the Active and Sham groups. No outlier was detected.

5.4.2 Demographic and Baseline Characteristics

Analysis showed that the active and sham groups did not differ in age, gender, education and Moca (Montreal cognitive assessment) (all *p*s > 0.05; see Table 7). The baseline characteristics were then compared in different working memory capacity subgroups, and the results are shown in Supplementary Table 4. The years of education ($p = 0.037$) and the anxiety score ($p = 0.030$) differed significantly between the stimulation and sham groups in the high working memory capacity subgroup. On the other hand, no significant difference was found in the years of education between the stimulation and sham groups in the low- and mid-working memory capacity subgroups (all *p*s > 0.05, see Supplementary Table 4). The median age was 69. Participants were divided into two subgroups (Young-old and Advanced-old) according to median age. Participants between 70 and 75 were in the Advanced-old group, while those aged 55-69 were in the Young-old group. The baseline characteristics were compared between the Active and Sham groups in different age subgroups, and no significant differences were detected (all *p*s > 0.05; see Supplementary Table 4). In order to examine the composite working memory capacity (WMC) score in different age subgroups, an independent t-test was employed. Participants' WMC score on the baseline in the Advanced-old group was lower than in the Young-old group ($t_{(26)} = 2.107$, $p = 0.045$).

Table 7 - Baseline Characteristics by Overall Group in the Elderly Study

	Active	Sham	*t*	*p*
Overall groups				
N	14	14	—	—
Age	67.57 ± 6.16	68.35 ± 6.13	-0.338	0.738
Gender (M/F)	7/7	7/7	—[a]	1.000
Years of education	17.46 ± 6.10	15.42 ± 4.77	-1.071	0.294
Moca	28.71 ± 1.27	28.42 ± 1.45	0.555	0.584
WMC score	-0.08 ± 0.60	0.07 ± 0.60	-0.657	0.517
ESS	4.64 ± 2.62	5.14 ± 3.13	-0.458	0.651
FWT	21.79 ± 5.59	20.43 ± 5.02	0.676	0.505
QOL	58.13 ± 5.08	57.47 ± 5.77	0.321	0.751
Anxiety score	3.79 ± 2.52	4.71 ± 2.52	-0.975	0.339
Depression score	2.86 ± 2.98	2.79 ± 2.78	0.066	0.948

Note. Moca = Montreal cognitive assessment.

[a]Chi-square test.

[*]$p < 0.05$.

5.4.3 Online Trained Task – Spatial N-Back Task

5.4.3.1 Online Trained Task – Ageing Subgroup

Given the variance in composite working memory capacity score (WMC score) at the baseline between ageing subgroups, a three-way analysis of Covariance (ANCOVA) was employed, with the baseline WMC score as the covariate. This three-way ANCOVA with the two between-participant factors of Stimulation (Active, Sham) and Age (Young-old, Advanced-old), as well as a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5), was used to analyse the effect of brain stimulation.

The main effect of Time ($F_{(2,55)} = 11.276$, $p < 0.001$, $\eta_p^2 = 0.329$) and the interaction of Stimulation × Age ($F_{(1,23)} = 10.846$, $p = 0.003$, $\eta_p^2 = 0.320$) were significant. The effect of the covariate WMC score proved to be significant ($F_{(1,23)} = 10.736$, $p = 0.003$, $\eta_p^2 = 0.318$). However, the main effects of Age ($F_{(1,23)} = 0.172$, $p = 0.682$, $\eta_p^2 =$

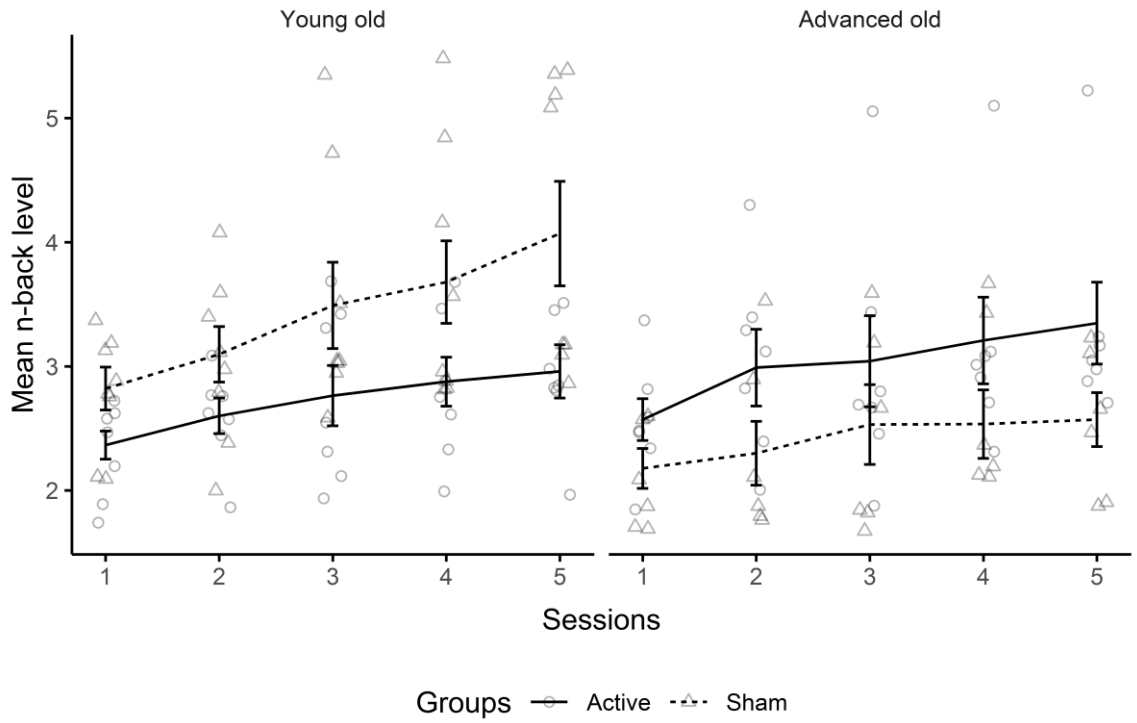
0.007) and Stimulation ($F_{(1,23)} = 0.004$, $p = 0.948$, $\eta_p^2 < 0.001$) were not significant.

The next stage then focused on the interaction effect. A two-way ANCOVA with a between-participant factor of Stimulation (Active, Sham) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5), with a covariate of the WMC score was conducted in the ageing subgroups (see Figure 12).

Within the advanced-old participants, the main effect of Stimulation ($F_{(1,10)} = 13.624$, $p = 0.004$, $\eta_p^2 = 0.577$) was significant, with participants in the active group benefitting more than those in the sham group. The main effect of Time ($F_{(3,28)} = 6.744$, $p = 0.002$, $\eta_p^2 = 0.403$), and the effect of the covariate of the WMC score ($F_{(1,10)} = 34.361$, $p < 0.001$, $\eta_p^2 = 0.775$) were significant. However, no interaction effect of Time × Stimulation was found ($F_{(3,28)} = 0.651$, $p = 0.580$, $\eta_p^2 = 0.061$).

Within the young-old participants, the main effect of Stimulation ($F_{(1,12)} = 5.249$, $p = 0.041$, $\eta_p^2 = 0.304$) was significant, with participants in the sham group benefitting more than those in the active group. The main effect of Time ($F_{(2,24)} = 5.036$, $p = 0.015$, $\eta_p^2 = 0.296$), the interaction effect of Time × Stimulation ($F_{(2,24)} = 0.805$, $p = 0.460$, $\eta_p^2 = 0.063$), and the effect of the covariate of the WMC score ($F_{(1,12)} = 0.193$, $p = 0.668$, $\eta_p^2 = 0.016$) were not significant.

Figure 12 - Change in Mean N Level in Different Age Subgroups After the Intervention



Note. Means with standard errors are reported for each intervention group and age subgroup.

5.4.3.2 Online Trained Task – Working Memory Capacity Subgroup

I predicted that participants with low working memory capacity would benefit from active brain stimulation. The mean *n* level was analysed using a three-way ANOVA with two between-participant factors of Stimulation (Active, Sham) and Capacity (Low, Mid, High) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5).

A main effect was found of Time ($F_{(2,51)} = 9.873$, $p < 0.001$, $\eta_p^2 = 0.310$) and Capacity ($F_{(2,22)} = 7.040$, $p = 0.004$, $\eta_p^2 = 0.390$), and an interaction of Stimulation × Capacity was found to be trending towards significance ($F_{(2,22)} = 2.907$, $p = 0.076$, $\eta_p^2 =$

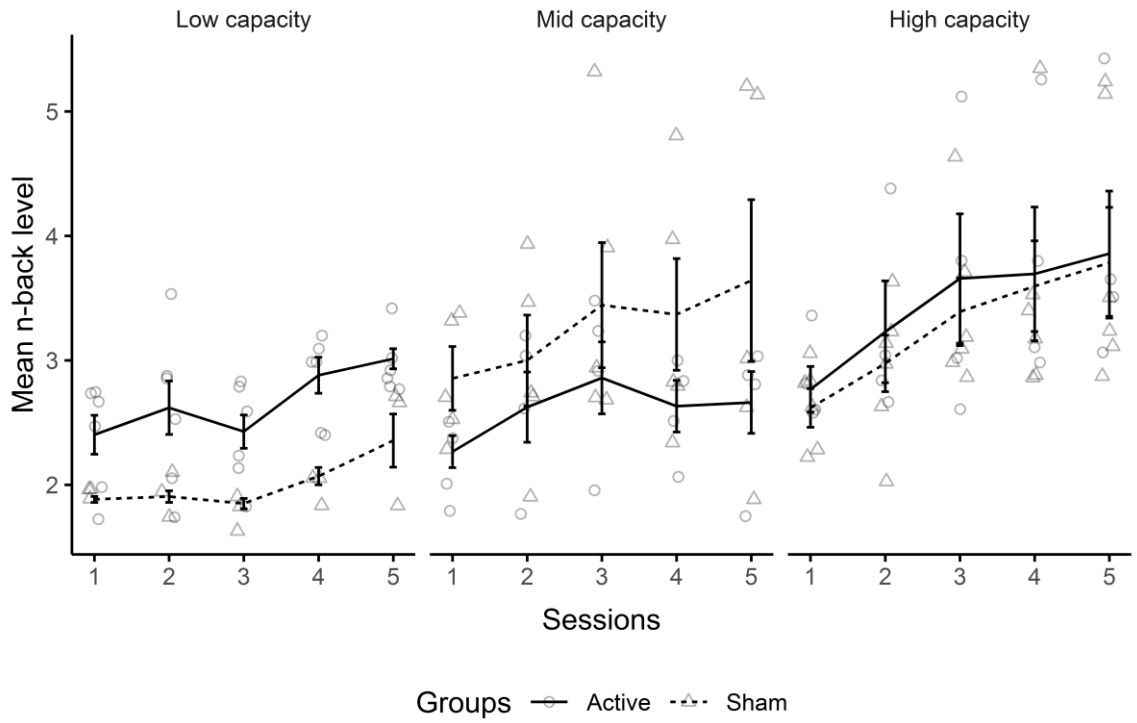
0.209). The next stage then focused on the interaction trend. A two-way ANOVA with a between-participant factor of Stimulation (Active, Sham) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5) was conducted in each of the three capacity subgroups (see Figure 13).

Within low-capacity participants, a main effect of Stimulation was found ($F_{(1,7)}$ = 27.896, p = 0.001, η_p^2 = 0.799), which showed that active group participants performed better than the sham group participants. There was a significant main effect of Time ($F_{(4,28)}$ = 4.566, p = 0.006, η_p^2 = 0.395). However, no interaction effect of Time × Stimulation was found in individuals with low-capacity ($F_{(4,28)}$ = 0.267, p = 0.897, η_p^2 = 0.037).

Within the group of mid-capacity participants, there was no significant main effect of Time ($F_{(2,13)}$ = 1.650, p = 0.230, η_p^2 = 0.191) and Stimulation ($F_{(1,7)}$ = 2.161, p = 0.185, η_p^2 = 0.236), and no interaction effect of Time × Stimulation ($F_{(2,13)}$ = 0.326, p = 0.709, η_p^2 = 0.044).

However, within the group of high-capacity participants, there was a significant main effect of Time ($F_{(2,16)}$ = 8.341, p = 0.003, η_p^2 = 0.510). No significant main effect of Stimulation ($F_{(1,8)}$ = 0.143, p = 0.143, η_p^2 = 0.715), and no interaction effect of Time × Stimulation ($F_{(2,16)}$ = 0.078, p = 0.924, η_p^2 = 0.010) were found in individuals with high capacity.

Figure 13 - Change in Mean N Level in Different Working Memory Capacity Subgroups After the Intervention



Note. Means with standard errors are reported for each intervention group and working memory capacity subgroup.

5.4.4 Offline Training Effect – Spatial N-Back Task

5.4.4.1 Offline Trained Task – Ageing Subgroup

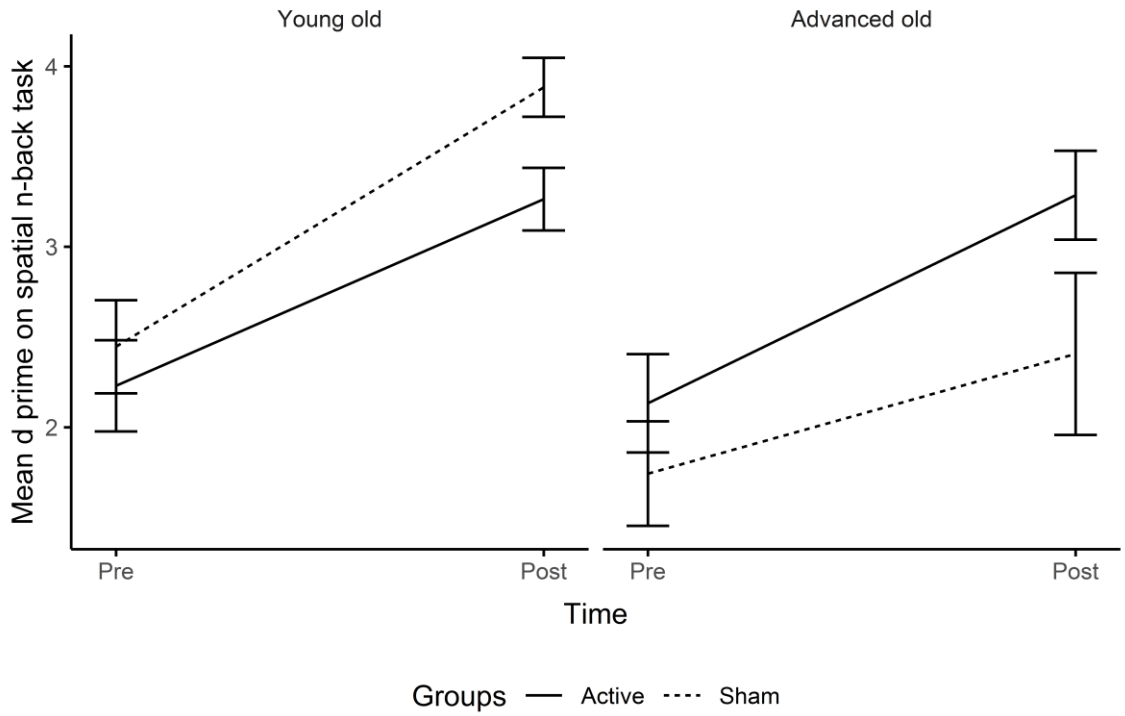
It was predicted that the advanced-old subgroup, in particular, would benefit from the brain stimulation. The mean d-prime analysed using a mixed three-way ANCOVA with two between-subject factors of Stimulation (Active, Sham) and Age (Young-old, Advanced-old) and one within-subject factor of Time (Pre, Post). The covariate was the Working Memory Composite score. The analysis revealed that the main effect of Time ($F_{(1,23)} = 86.641$, $p < 0.001$, $\eta_p^2 = 0.790$) and the interaction effect of Stimulation × Age ($F_{(1,23)} = 10.489$, $p = 0.004$, $\eta_p^2 = 0.313$) were significant. The effect of the

covariate WMC score was also significant ($F_{(1,23)} = 36.732$, $p < 0.001$, $\eta_p^2 = 0.615$). A two-way ANCOVA with a between-participant factor of Stimulation (Active, Sham) and a within-participant factor of Time (Pre, Post), with a covariate of WMC score, was conducted in each ageing subgroup. Results are presented in Supplementary Table 5 and Figure 14.

Within the group of advanced-old participants, the main effect of Stimulation ($F_{(1,10)} = 7.688$, $p = 0.020$, $\eta_p^2 = 0.435$) was significant, with participants in the active group achieving better results than the sham group participants. The main effect of Time ($F_{(1,10)} = 25.704$, $p < 0.001$, $\eta_p^2 = 0.720$), and the effect of the covariate of the WMC score ($F_{(1,10)} = 20.516$, $p = 0.001$, $\eta_p^2 = 0.672$) were also significant. However, no interaction effect of Time × Stimulation was found ($F_{(1,10)} = 0.651$, $p = 2.205$, $\eta_p^2 = 0.168$).

Within the group of young-old participants, the main effect of Time ($F_{(1,12)} = 57.773$, $p < 0.001$, $\eta_p^2 = 0.828$) was significant. However, the main effect of Stimulation ($F_{(1,12)} = 2.552$, $p = 0.137$, $\eta_p^2 = 0.175$) and the interaction effect of Time × Stimulation was found ($F_{(1,12)} = 2.248$, $p = 0.160$, $\eta_p^2 = 0.158$) were not significant. The effect of the covariate of the WMC score ($F_{(1,12)} = 12.899$, $p < 0.001$, $\eta_p^2 = 0.985$) was significant.

Figure 14 - Change in Mean D-Prime in the Non-Adaptive Spatial Task in Active and Sham Groups Collapsed Across Level 1 and Level 2 in Ageing Subgroups



5.4.4.2 Offline Trained Task – Working Memory Capacity Subgroup

It was predicted that the low working memory capacity subgroup would benefit from the brain stimulation. The $\Delta d'$ was analysed using a mixed three-way ANOVA with two between-subject factors of Stimulation (Active, Sham) and Capacity (Low, Mid, High), and one within-subject factor of Time (Pre, Post). The analysis revealed that the main effect of Time ($F_{(1,22)} = 86.962$, $p < 0.001$, $\eta_p^2 = 0.798$) and the interaction effect of Stimulation × Capacity ($F_{(2,22)} = 9.119$, $p = 0.001$, $\eta_p^2 = 0.453$) were significant. The study then focused on the interaction effect. A two-way ANOVA with a between-participant factor of Stimulation (Active, Sham) and a within-participant factor of Time (Pre, Post) was conducted in the three capacity subgroups, respectively. The changes in performance after the intervention in the different

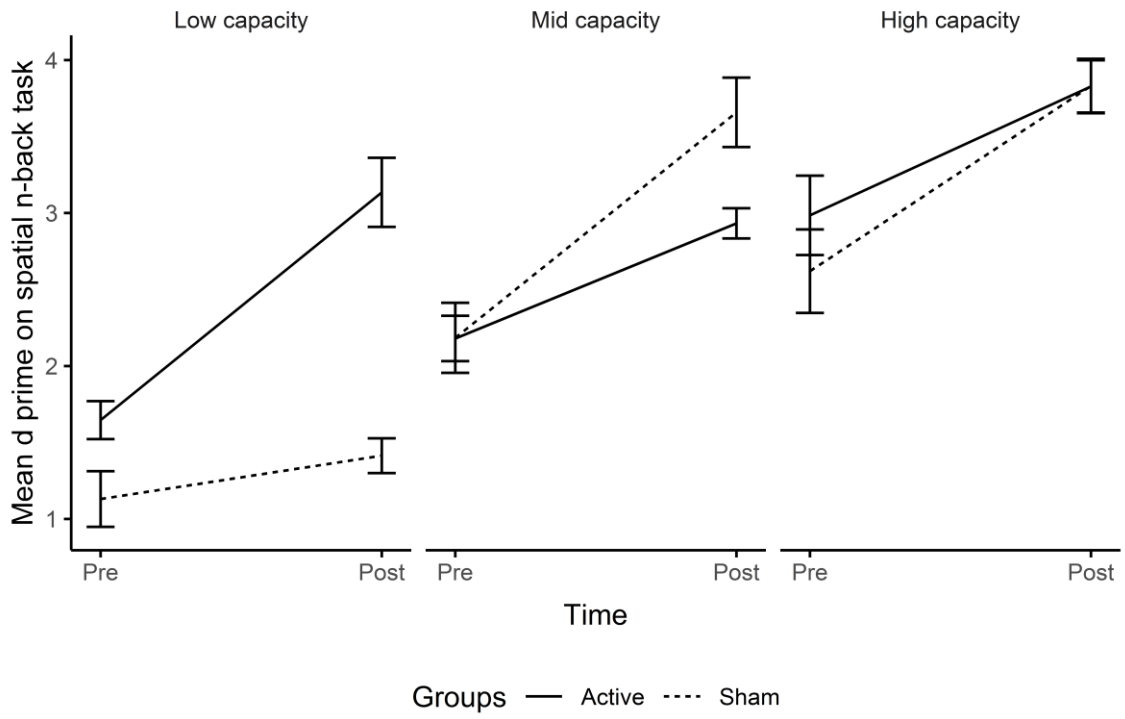
working memory capacity groups are shown in Figure 15, and the results are presented in Supplementary Table 6.

Within the group of low-capacity participants, a main effect of Stimulation was found ($F_{(1,7)}$ = 19.727, p = 0.003, η_p^2 = 0.738), which showed that active group participants performed better than the sham group participants. There was a significant main effect of Time ($F_{(1,7)}$ = 45.045, p < 0.001, η_p^2 = 0.865) and a significant interaction effect of Time × Stimulation ($F_{(1,7)}$ = 20.838, p = 0.003, η_p^2 = 0.749).

Within the group of mid-capacity participants, a main effect of Stimulation was found ($F_{(1,7)}$ = 9.154, p = 0.019, η_p^2 = 0.567), which showed that the sham group participants performed better than the active group participants. The main effect of Time was significant ($F_{(1,7)}$ = 19.178, p = 0.003, η_p^2 = 0.733). However, no significant interaction effect of Time × Stimulation was found ($F_{(1,7)}$ = 2.014, p = 0.199, η_p^2 = 0.223).

However, within the group of high-capacity participants, there was a significant main effect of Time ($F_{(1,8)}$ = 45.429, p < 0.001, η_p^2 = 0.850). No significant main effect of Stimulation ($F_{(1,8)}$ = 0.365, p = 0.562, η_p^2 = 0.044), and no interaction effect of Time × Stimulation ($F_{(1,8)}$ = 1.456, p = 0.262, η_p^2 = 0.145) were found in individuals with high capacity.

Figure 15 - Change in Mean D-Prime in the Non-Adaptive Spatial Task in Active and Sham Groups Collapsed Across Level 1 and Level 2 in Capacity Subgroups



5.4.5 Transfer Effect – Untrained Task

An analysis was conducted to test the offline effect of brain stimulation in untrained tasks in each of the different ageing and working memory capacity subgroups. The untrained tasks include the Visual *n*-back task, change detection task, digit span forward, and digit span backward task

In the ageing subgroups, the analysis was applied using a mixed three-way ANCOVA with two between-subject factors of Stimulation (Active, Sham) and Age (Young-old, Advanced-old) and one within-subject factor of Time (Pre, Post). The covariate was the Working Memory Composite score. In the Visual *n*-back task, there was a significant interaction effect of Time × Age × Stimulation ($F_{(1,23)} = 5.208$, $p = 0.032$, $\eta_p^2 = 0.185$). Further analysis showed that there was no significant main effect of Stimulation in the Young-old subgroups ($F_{(1,13)} = 3.237$, $p = 0.095$, $\eta_p^2 =$

0.199) or in the Advanced-old subgroups ($F_{(1,11)} = 0.066$, $p = 0.802$, $\eta_p^2 = 0.006$). No significant effect of Stimulation was found on the four untrained tasks. Results are presented in Supplementary Table 5.

In the working memory subgroups, the data were analysed using a mixed three-way ANOVA with two between-subject factors of Stimulation (Active, Sham) and Capacity (Low, Mid, High) and one within-subject factor of Time (Pre, Post). In the working memory subgroups, no significant effect of Stimulation was found on these four untrained tasks (all *p*s > 0.05). Results are presented in Supplementary Table 6.

5.4.6 Mood and Attitudes Towards the Stimulation

Mood and attitudes towards the intervention before each testing session were analysed in the different ageing and working memory subgroups. In the ageing subgroups, the scores of mood and attitudes were analysed separately using a three-way ANOVA with two between-participant factors of Stimulation (Active, Sham), and Age (Young-old, Advanced-old), and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). In the different working memory capacity subgroups, the scores of mood and attitudes were analysed separately using a three-way ANOVA with two between-participant factors of Stimulation (Active, Sham) and Capacity (Low, Mid, High), and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). No significant effect of Stimulation was found on the mood and attitude scores in ageing and working memory subgroups (all *p*s > 0.05). Results are shown in Supplementary Tables 7 and 8.

5.4.7 Debriefing of Strategy

After the experiment, all participants were asked whether they used a strategy during the cognitive training tasks. Chi-square tests were conducted to compare the ratio in each subgroup. The results showed that advanced-old participants in the active group had a higher rate of strategy use than those in the sham group ($p = 0.005$). Additionally, participants with low working memory capacity in the active groups had a higher rate of strategy use than those in the sham groups ($p = 0.012$). The results are presented in Table 8.

Table 8 - Count of Participants That Developed a Strategy in Active and Sham Groups for Overall Groups and Ageing and Capacity Subgroups in the Elderly Study

	Active (Yes/No)	Sham (Yes/No)	*p*
Overall groups	13/1	9/5	0.165
Ageing subgroups			
Young-old	6/1	8/0	0.467
Advanced-old	7/0	1/5	0.005*
Capacity subgroups			
Low-capacity	6/0	0/3	0.012*
Mid-capacity	3/1	4/1	1.000
High-capacity	4/0	5/1	1.000

*$p < 0.05$.

5.4.8 Possible Adverse Effects of Brain Stimulation

Participants were asked about the possible adverse effects of brain stimulation after each stimulation session. Chi-square tests were used to analyse the difference in the reported adverse effects between the active and sham groups. These two groups showed no significant difference in their reported adverse effects (all *p*s > 0.05). Results are presented in Table 9. The five most frequently observed adverse effects were tingling (64.28%), burning (27.14%), itching (22.85%), trouble concentrating (11.43%), and fatigue (12.86%).

Table 9 - Output of Chi-Square Tests on the Rate of Participants Reporting Each Possible Adverse Effect in the Elderly Study

	Active	Sham	X^2	*p*
Headache	3 (4.28%)	2 (2.85%)	0.000	1.000
Pain in the neck	1 (1.43%)	2 (2.85%)	0.000	1.000
Itching	19	13 (18.57%)	1.458	0.227
Sleepiness	6 (8.57%)	6 (8.57%)	0.000	1.000
Trouble concentrating	7 (10.00%)	9 (12.85%)	0.282	0.595
Acute mood change	0	0	—	—
Fatigue	9 (12.85%)	9 (12.85%)	0.000	1.000
Nausea	0	0	—	—
Muscle twitches in the face or neck	0	0	—	—
Tingling	40	50 (71.43%)	3.111	0.078
Burning	23	15 (21.43%)	2.312	0.128
Epileptic seizure	0	0	—	—
Light flashes	0	0	—	—
Uncomfortable feeling	2 (2.85%)	5 (%)	1.353	0.245

Note. Total times in five sessions and rate of participants (%) in the active and sham groups reporting each possible adverse effect.

5.4.9 Blinding of Stimulation

After the intervention, participants were asked to guess their group allocation. Two participants did not finish the questionnaire; one was in the active group, and the other was in the sham group. There was no significant difference in the rate of participants who guessed that they were in the active group between the active and sham groups, with 61.5% in the active group and 76.9% in the sham group using the Fisher's exact test ($p = 0.673$). This result indicates that participants were blinded to the group allocation successfully.

5.5 Discussion

This study examined the effect of multi-day tDCS administered concurrently with working memory training among the elderly. The results revealed that tDCS can augment the efficacy of working memory training in elderly people of advanced age or those with low working memory capacity. This effect persisted in the post-test conducted two days after the intervention. However, the enhancement of tDCS did not transfer to performance in the visual *n*-back task, the change detection task, or the digit span forward and backward tests. Furthermore, there was no discernible alteration in the levels of alertness, motivation, expectation or optimism due to tDCS.

The main finding in this study was that participants in the advanced-old subgroup benefitted from tDCS, while participants in the young-old subgroup did not gain from tDCS. While some studies highlighted that those in the elderly subgroup with higher education or with a low working memory capacity benefitted from tDCS when it was combined with cognitive training (Arciniega et al., 2018; Berryhill & Jones, 2012), the impact of age in the elderly towards this intervention has rarely been reported. Previous studies have shown that ageing corresponds with decreased cortical excitability (Oliviero et al., 2006; Rossini, Desiato, & Caramia, 1992). Given that tDCS can increase excitability and enhance neuroplasticity, it may compensate for age-induced declines. Crucially, tDCS serves as a “state-dependent” tool that is impacted by the ongoing neural activity in the targeted region (Masina et al., 2022; Silvanto & Pascual-Leone, 2008; Vergallito et al., 2023). The existing literature suggests an inverted U-shaped correlation between the excitation/inhibition balance and behavioural performance (Krause & Cohen Kadosh, 2014; Krause, Márquez-Ruiz, & Cohen Kadosh, 2013). Optimal performance appears to be achievable when the excitation and inhibition reach an ideal balance (Krause & Cohen Kadosh, 2014;

Krause et al., 2013). Consequently, participants within the advanced-old subgroup that were distant from the optimal point experienced improvement after tDCS, approximating this ideal state. Conversely, participants within the young-old subgroup that were close to the optimal point may be drawn further from it following the application of tDCS, thereby failing to obtain any benefit. Additionally, age-induced anatomical variations, particularly in the volume of cerebral spinal fluid, may contribute to the different responses to tDCS (Antonenko et al., 2021). Furthermore, the working memory capacity was lower in the advanced-old participants than in the young-old participants. The result that advanced-old participants benefitted from tDCS when combined with cognitive training could partially, but not wholly, be explained by their low working memory capacity. The impact of initial working memory capacity can be interpreted via the supply-demand mismatch theory, which will subsequently be discussed.

In this study, it was also found that the beneficial effect of brain stimulation and cognitive training was significant in the elderly with low working memory capacity. However, no significant promoting effect is observed in the medium and high working memory capacity subgroups. This finding is consistent with that of Hector and colleagues, who report that the low visual working memory elderly would benefit more than the high visual working memory elderly (Arciniega et al., 2018). The first reason may be that older adults' working memory capacity activates different neural activities when doing working memory tasks strategically (Arciniega et al., 2018). For example, young adults with high visual working memory capacity benefit from tDCS stimulating the posterior parietal lobe in complex tasks (Jones & Berryhill, 2012). Studies also report a compensatory effect of training, which suggests that participants with a lower initial cognitive ability benefitted more from the training (von

Bastian & Oberauer, 2014). This may be explained by the fact that low-level capacity individuals have more room to improve (von Bastian & Oberauer, 2014). Jaeggi and colleagues' research shows that participants with lower initial fluid intelligence benefit more from training (Jaeggi et al., 2008). This is also supported by Zinke and colleagues, who reported that low visuospatial working memory at the baseline could predict the training gains made in this task in the elderly (Zinke et al., 2014). In addition to this, neuron plasticity depends on the mismatch between the function system and the environmental demands (Lövdén et al., 2010). When there is a significant mismatch in the low working memory capacity participants, there is a greater impetus to change (Lövdén et al., 2010). It is well-known that tDCS can change plasticity through intracellular Ca2+ concentration (Das et al., 2016). Therefore, a possible explanation for this result is that, with the help of stimulation, the plasticity is altered, and the mismatch is decreased significantly in participants with low working memory. Based on this finding, it is advisable to apply tDCS and cognitive training to elderly people with a low working memory capacity. Overall, the finding shows that participants with a low working memory capacity benefitted more from tDCS when it is combined with cognitive training, than when subjected to cognitive training alone.

My study also found that the training effect still existed in the post-test two days later (more than 48 hours), regardless of whether they were in the stimulation or sham groups. Previous studies show that working memory training benefits the healthy elderly (Jones, Stephens, et al., 2015; Shatil, 2013). Furthermore, in this study, the improvement observed in the post-test where a benefit was derived from tDCS was significantly greater than the sham group in the low working memory subgroup or advanced-old subgroup. Recent evidence suggests that, in the elderly, the effect of

multi-session working memory training combined with tDCS could last up to one month after treatment (Jones, Stephens, et al., 2015). In young adults, researchers found that tDCS combined with cognitive training based on numerical abilities could last up to six months (Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010). The limitation of my study is that I did not follow up with participants after a month or longer. However, I observed that the offline effect of tDCS combined with cognitive training existed for at least two days.

It was observed that there existed no transfer effect of the tDCS in augmenting the effect of working memory training across various tasks, including in the visual shape *n*-back task, the change detection task, the digit span forward task, and the digit span backward task. One reason for this is the task correlations. Von Bastian suggested that the stronger the correlation between training tasks and testing tasks, the more significant the transfer effect that can be achieved by participants (von Bastian & Oberauer, 2014). Although both the visual *n*-back task and the spatial *n*-back task fall under the *n*-back paradigm, they employ different stimuli: the former uses an array of figures, while the latter utilises various locations of triangles. Such variations necessitate participants to use different cognitive strategies in order to complete each task. Moreover, the digit span forward and backward tests relate to verbal working memory capacity. The change detection task is related to visual working memory storage capacity (Feuerstahler, Luck, MacDonald, & Waller, 2019). The finding made in this thesis contradicts previous studies, which reported that tDCS changed the accuracy of the change detection task results in young adults, especially in those with low working memory capacity (Tseng et al., 2012). However, some experimental design differences exist between this study and my present experiment. This study focused on young adults and ran the change detection task

immediately after or just minutes post-stimulation, while my research was conducted in the elderly and the change detection task was undertaken two days post-stimulation. Another noteworthy consideration is that a five-day tDCS intervention may be insufficient to produce longer-term transfer effects.

This study found no modulatory effects of tDCS on emotional and motivational aspects, including alertness, motivation, expectation, and optimism. It suggested that the beneficial effect of tDCS on the low-capacity or advanced-old subgroup was not modulated through emotional regulation. This is supported by Au's research, which also shows that tDCS does not change the motivational and alertness status when it stimulates the DLPFC in young adults (Au et al., 2016). However, it was reported that tDCS could promote cognitive reappraisal by regulating emotional responsiveness (Feeser, Prehn, Kazzer, Mungee, & Bajbouj, 2014), because DLPFC plays an essential role in emotional regulation. A possible explanation may be that tDCS can modulate cognitive function and emotional state, but its impact on working memory is not via emotional regulation.

In this study, participants within the advanced-old age group or the low working memory group during the application of tDCS had a higher rate of strategy use than those in the sham group. TDCS may help advanced-old participants or those with a low working memory capacity to produce spontaneous strategies. However, as discussed in Chapter 4, there was no evidence to say that tDCS can help young adults to produce spontaneous strategies. The population and sessions in these two studies differed. The study described in this chapter focused on the elderly and involved five sessions of tDCS, while the study in Chapter 4 focused on young adults and involved two sessions of tDCS.

This study is limited by the small sample sizes, mainly when analysed in terms of the age and capacity subgroups, and so the results must be interpreted cautiously. Moreover, participants took the post-test 48 hours after the intervention without any subsequent follow-up assessments. It is, therefore, unknown whether the training effect would continue during the follow-up period.

Future studies are needed to combine an Electroencephalogram (EEG) or functional Magnetic Resonance Imaging (fMRI) in order to explore the brain changes which occur during or after tDCS in elderly people of advanced age or in groups with a low working memory capacity. In addition, adjustments to the design of strategy studies, including providing an external strategy and recording the details of the spontaneous strategies used, could be undertaken in relation to an elderly population. Finally, large-scale studies are needed to replicate this study's results.

5.6 Conclusion

Overall, the results of this study suggest that tDCS can augment the effect of working memory training in elderly participants of advanced age or those with a low working memory capacity. This enhancement is sustained for a duration of two days post-stimulation. However, the beneficial effects of this intervention do not extend to other cognitive tasks following a five-day training regimen.

Chapter 6 - The Effect of Multi-Day TDCS Concurrent With Cognitive Training on Working Memory in Stroke Patients

6.1 Abstract

Background

Working memory impairment is common following acquired brain injuries, such as stroke and traumatic brain injury. Transcranial direct current stimulation (tDCS) is a promising neurorehabilitation approach that modulates brain excitability and plasticity. However, the effectiveness of tDCS in enhancing working memory training outcomes in acute stroke patients remains undetermined.

Method

In this randomised, single-blinded, between-subjects study, ninety participants were randomised into four groups: Active tDCS and Adaptive cognitive training, Active tDCS and Non-adaptive cognitive training, Sham tDCS and Adaptive cognitive training, and Sham tDCS and Non-adaptive cognitive training. Participants conducted five consecutive daily intervention sessions accompanied by pre- and post-test assessments. As lesion sides were considered to be an essential factor, individuals were further classified into left and right-sided lesion subgroups. The primary endpoint was the training effect on working memory training tasks, while secondary outcomes included (1) the offline effect on fixed spatial *n*-back tasks, and (2) the transfer effect on clinical scales such as the digit span forward, digit span backward, Symbol span, and Spatial addition.

Results

Participants in the Active tDCS + Adaptive working memory group with left-sided lesions showed a more significant improvement in the training task than those in the

Sham tDCS + Adaptive working memory group (p = 0.007). The stimulation and training did not influence the mood of participants, including alertness, motivation, expectation, sadness, anxiety and depression. However, no transfer effect on clinical measures was observed.

Conclusion

Acute stroke patients with left-sided lesions experienced enhanced benefits to their working memory from tDCS combined with adaptive working memory training. In addition, the results show that the enhancement in working memory facilitated by tDCS does not arise from mood modifications in these patients. These findings suggest that tDCS combined with adaptive working memory training could serve as a valuable intervention for acute stroke patients.

6.2 Introduction

Stroke is one of the leading causes of mortality, which can increase the burden on the patient's family and society (Strong, Mathers, & Bonita, 2007). Post-stroke cognitive impairment negatively affects survivors' functional recovery and quality of life (Jokinen et al., 2015; Park et al., 2013). Several cognitive domains can be impaired after stroke, including language, reading and writing, numeric, limb praxis, visuospatial function, social use of language, emotional function, attention, executive function and memory (Donovan et al., 2008). Working memory, which temporarily holds and manipulates information, is the keystone of global cognitive function and supports goal-directed behaviour (Baddeley et al., 2015; Chai et al., 2018). During the acute phase, stroke patients have a high prevalence of working memory impairment (Jaillard et al., 2009). This impairment may be caused by stroke lesions in a widespread fronto-parietal network (Lugtmeijer et al., 2021).

Interventions for post-stroke cognitive impairment pose a considerable challenge. Several treatment tools for post-stroke cognitive impairment include pharmacotherapy, physical exercise, cognitive training, and non-invasive brain stimulation. Acetylcholinesterase inhibitors and memantine may offer some cognition improvements in vascular cognitive impairment, including stroke, while their effect is limited (Battle et al., 2021; McShane et al., 2019). Although physical exercises can optimise cognition function and decrease the likelihood of developing a mild cognitive impairment (Cumming, Tyedin, Churilov, Morris, & Bernhardt, 2012; Marzolini et al., 2013), they require a long-term commitment to training and do not specifically target the impaired cognitive areas. Cognitive training may be beneficial for post-stroke cognitive impairment (Xuefang et al., 2021), but its long-term effects are still inconclusive due to heterogeneity and methodological limitations (Marzolini et al., 2013; Niemeijer et al., 2020). In recent years, non-invasive transcranial stimulations, including transcranial direct current stimulation (tDCS) and transcranial magnet stimulation (TMS), have shown promise in cognitive rehabilitation by their ability to alter cortical excitability and promote neuroplasticity (Monte-Silva et al., 2013; Nitsche & Paulus, 2000; Siebner & Rothwell, 2003). Importantly, tDCS has a higher rate of tolerability in patients, and the equipment required is more portable than TMS (Poreisz et al., 2007), making the former more suitable for stroke patients, especially in the acute phase. However, applying tDCS in acute stroke patients requires robust evidence and well-designed trials to evaluate its therapeutic efficacy.

Adaptive plasticity is reported to play an essential role in spontaneous recovery in stroke patients (Dalise, Ambrosio, & Modo, 2014). Plasticity involves large-scale changes, an endogenous cell response and neuronal remodelling (Dalise et al., 2014). Some theories explained this process in the large-scale changes, including

contralateral hemisphere activity, diaschisis, cortical map reorganisations, inflammation and neurotrophic factors (Dalise et al., 2014). The contralateral hemisphere activity mechanism comes from an unbalanced interhemispheric inhibition theory, meaning the ipsilesional hemisphere is less excited and is inhibited by the overexcited contralesional hemisphere (Hummel & Cohen, 2006). This is the most common model used to recover functional impairment in chronic stroke patients using rTMS or tDCS. However, in the acute phase, activation of the contralateral hemisphere is associated with good functional recovery (Bütefisch et al., 2008). RTMS or tDCS are proposed to upregulate or/and downregulate excitability (Hummel & Cohen, 2006). As reviewed in an earlier section of the study, tDCS may also affect the LTP and LTD to change the neuroplasticity by various neurotransmitters, which may also modulate the large-scale changes. Finally, tDCS is reported to facilitate neurogenesis and modulate microglia responses in animal models, potentially improving the endogenous cell response (Braun et al., 2016).

Until recently, findings from meta-analyses have been inconsistent regarding the impact of tDCS on working memory. Some studies highlight that the effect is small yet significant (Hill et al., 2016; Mancuso et al., 2016), while others point towards a partial effect (Brunoni & Vanderhasselt, 2014) or no effect (Horvath et al., 2015). Nevertheless, several studies have demonstrated that tDCS combined with working memory training is more beneficial than working memory training alone in healthy adults (Au et al., 2016; Fregni et al., 2005; Ruf et al., 2017). Results in Chapters 4 and 5 reveal that young adults with low working memory capacity and elderly individuals of advanced age and with low working memory capacity benefit from tDCS when combined with working memory training (Assecondi et al., 2021; Assecondi et al., 2022). The latest meta-analysis showed that tDCS positively

affected working memory in patients suffering from brain disorders such as stroke, traumatic brain injury and dementia (Begemann, Brand, Ćurčić-Blake, Aleman, & Sommer, 2020). One study used tDCS to improve verbal working memory in stroke patients with cognitive problems, finding that verbal working memory improved after stimulation (Jo et al., 2009). However, the sample size of this study was small, and the study applied only one session of tDCS. Furthermore, it has been shown that home-based tDCS improves overall cognition in chronic stroke patients (Ko et al., 2022). However, research on the effect of tDCS on working memory in acute stroke is limited. With a dementia prevalence of 25.5% three months post-stroke (Rost et al., 2022) and evidence suggesting that post-stroke cognition within the first three weeks predicts the long-term functional outcome (Nys et al., 2005; Wagle et al., 2011), early intervention during the acute phase of a stroke may prove beneficial in preventing the progression to dementia.

In this chapter, the ability of tDCS to improve the effectiveness of working memory training in patients with acute stroke was investigated. Given that stroke lesions not only affect related fibres, but also change the functional network in both hemispheres (Murase, Duque, Mazzocchio, & Cohen, 2004) and increase neural activity in the non-lesioned hemisphere, which has been associated with better motor function recovery in the acute phase (Bütefisch, Wessling, Netz, Seitz, & Hömberg, 2008), it was hypothesised that applying tDCS to stroke patients would positively augment the effect of cognitive training.

6.3 Materials and Method

6.3.1 Study Design

The study was designed as a single-blinded, randomised, between-subjects experiment. It was conducted at Guangzhou First People's Hospital, which granted

ethical approval. This clinical study was registered at the Chinese Clinical Trial Registry (ChiCTR1900024955).

6.3.2 Participants

Participants were recruited in the Department of Neurology, Guangzhou First People's Hospital. All participants signed written informed consent forms before the experiment. The details of the inclusion and exclusion criteria are listed in Table 10. The average duration from the stroke onset to the initial tDCS treatment in participants was 5.62 days (SD = 2.36 days). The severity of stroke, as measured by the National Institute of Health Stroke Scale (NIHSS), yielded an average score of 2.1 (SD = 2.7). Anatomical distribution of stroke locations in participants revealed that 80.3% were in the cerebral hemispheres, while 19.7% were in the brainstem or cerebellum. Lateralization of stroke incidence showed 52.5% on the left side and 47.5% on the right side. These clinical characteristics among the four groups are presented in Table 11.

Table 10 - Inclusion and Exclusion Criteria of Participants

Inclusion criteria	
1.	Acute ischemic stroke patients;
2.	Ranging from 55 to 80 years old;
3.	Normal or corrected-to-normal vision and hearing;
4.	Providing informed consent;
5.	Having at least three days between their injury and starting the tDCS.
Exclusion criteria	
1.	Self-reported pre-stroke psychiatric or neurological disease (such as an anxiety disorder, ADHD, or Parkinson's disease);
2.	History of diagnosed severe depression (diagnosed pre-stroke);
3.	History of epilepsy (diagnosed pre-stoke);

4.	Family history of epilepsy;
5.	Fainting spells or syncope in the last three years pre-stroke;
6.	Significant hearing loss, vision or motor impairment that would prevent participants from performing the task;
7.	Known to be pregnant;
8.	Consuming medication affecting cortical excitability or recreational drugs;
9.	Metal (except titanium) or electronic implants in the brain /skull (e.g., splinters, fragments, clips, cochlear implant, deep brain stimulation, medication pump) ;
10.	Metal (except titanium) or any electronic device at other sites in body, such as a cardiac pacemaker or traumatic metallic residual fragments;
11.	Skin problems such as dermatitis, psoriasis or eczema at the stimulation sites;
12.	Brain stimulation in the past six months;
13.	Undergone transcranial electric or magnetic stimulation in the past (more than six months), which resulted in adverse effects;
14.	Skull fractures, significant skull defects, skull plates or large vessel occlusions in the site of electrode placement;
15.	Seizure at the time of the stroke or between the stroke and the start of the therapy;
16.	A severe cognitive problem which affects the understanding of the training task.

6.3.3 Randomisation and Masking

Before the experiment, participants were randomly allocated to four groups: Active tDCS and Adaptive cognitive training, Active tDCS and Non-adaptive cognitive training, Sham tDCS and Adaptive cognitive training, and Sham tDCS and Non-adaptive cognitive training. The group allocation blinded all participants.

6.3.4 Materials

6.3.4.1 Brain Stimulation

See details of the parameters of brain stimulation in Chapter 2.

6.3.4.2 Trained Task: Spatial N-Back Task – N-IGMA

This study's spatial *n*-back task employed N-IGMA, which is described in Chapter 2. Participants in adaptive cognitive training groups started from level one on the first block of the first session. The level would increase to $n + 1$ if their accuracy score at the *n* level was higher than or equal to 90%. Otherwise, they remained at the present *n* level. The level of the subsequent session was the same as that of the last block of the previous session. During all training sessions, participants in the non-adaptive cognitive training groups were kept at Level one. Stroke patients needed a longer reaction time than the healthy elderly participants, so the time given for the stimuli was 750 milliseconds, and for deciding, it was 2,250 milliseconds, which were longer times than those in the elderly study. The total task time was approximately 20 minutes. The working memory training began at the same time as the tDCS.

6.3.4.3 Transfer Measures

Pre- and post-tests were conducted on the first and seventh days, respectively. These tests included outcomes that evaluated the effect of the non-adaptive trained *n*-back task and the generalisation of training gains onto verbal working memory span and Visual Working Memory Test (including a symbol span and a spatial addition).

Spatial N-Back

The spatial *n*-back task is a non-adaptive version of N-IGMA with *n* levels at $n = 1$ and $n = 2$. Participants were asked to finish six blocks of the 1-back task and six blocks of the 2-back task during the pre- and post-tests.

Verbal Working Memory Span

Verbal Working Memory Span consists of digit span forward and digit span backward WAIS-IV (Wechsler, 2008), and asks participants to verbally repeat a series of numbers in a forward or backward sequence, respectively.

A Visual Working Memory Test

The visual working memory test includes a symbol span and a spatial addition from the Wechsler Memory Test-IV (Wechsler, 2009). In the symbol span task, participants were required to remember a series of abstract symbols, and after five seconds, they were required to recall the symbols they had seen in the same order from a wider set of symbols. The test was discontinued after four consecutive imperfect scores. The spatial addition task required participants to remember the location of circles. They would be shown the first page with blue or red circles on the grid, and five seconds later, they were shown a second page. They were asked to place a blue circle, if they saw a blue circle card, on only one of the pages and a white circle card, if they saw a blue circle, in the same place on both pages. They were asked to ignore the red circles and not to use a red circle card. The Working Memory Index was then calculated based on the scores of the symbol span and spatial addition tasks according to the manual of the Wechsler Memory Test-IV.

6.3.4.4 Other Questionnaires

Affect Rating

The Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Hospital Anxiety and Depression Scale (HADS) were employed to evaluate the mood and emotional experiences of participants before and after the intervention. HAMD is measured using 24 items, and each question uses a 1-5 scale rating in order of more severe symptoms. HAMA consists of 12 items, each rated on a 1-5

scale in order of more severe symptoms. The patients were evaluated by HADS, which included 14 items.

Alertness, Optimism, Motivation and Expectation

A bar scale from 1 to 100 was used to rate the level of alertness, motivation, expectation, and optimism before every session of the N-IGMA task. Participants were asked to use the mouse to move the bar to show the individual levels of their alertness, optimism, motivation, and expectation.

Side Effect Questionnaire

See the details of the questionnaire in Chapter 2.

Debriefing of Strategy

After these tests, participants were asked whether they used a strategy to complete the cognitive training. If they had used a strategy, they would be asked to describe it in detail.

Blinding of Stimulation

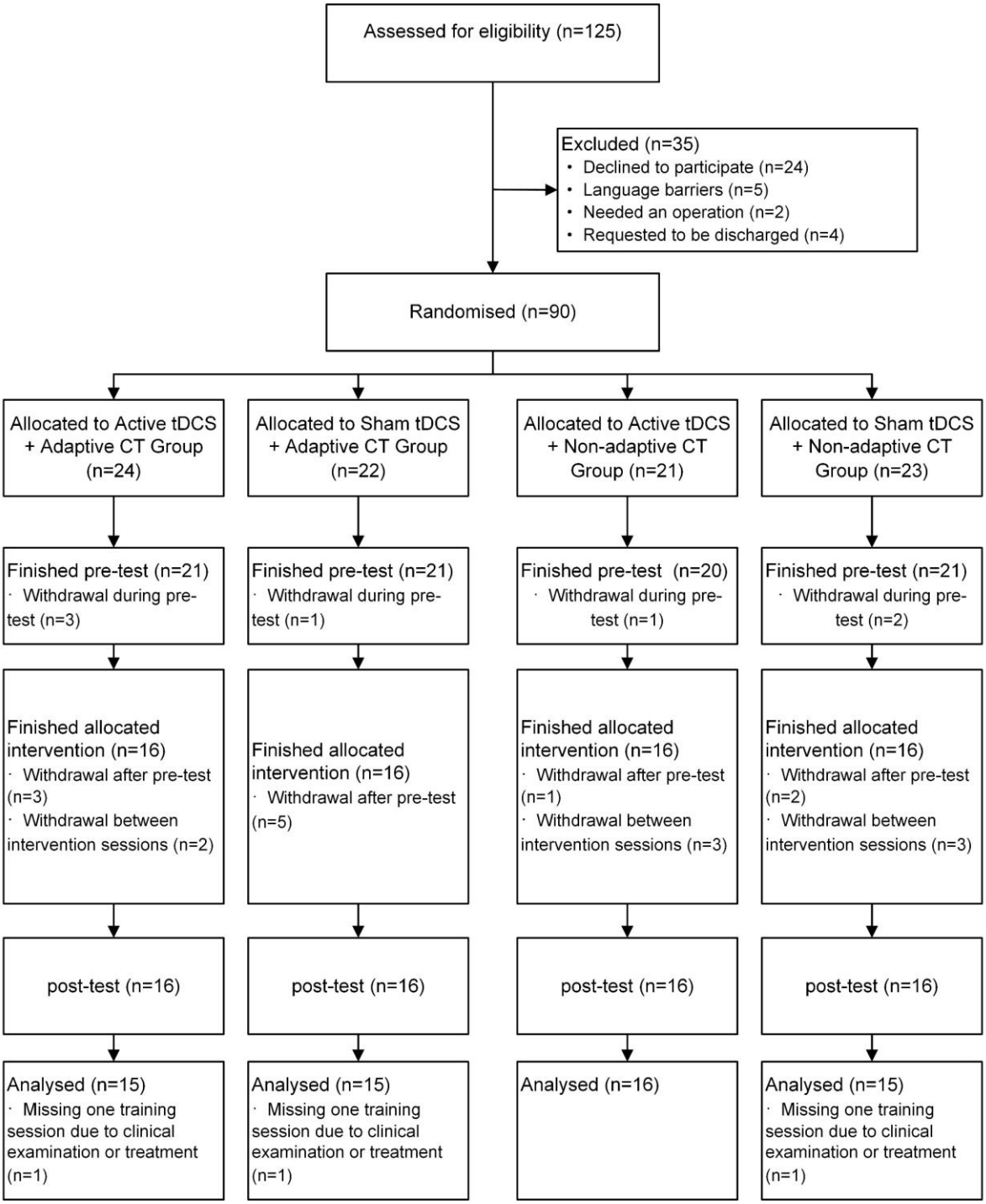
After the post-tests, participants were told of the existence of the sham and active stimulation groups, and they were then asked to guess the group allocation. Reasons were also recorded.

6.3.5 Procedure

Figure 16 shows the timeline of this experiment. On the first day, participants were asked to finish the screening questionnaires and the pre-tests in the following order: spatial *n*-back (six blocks of 1-back, six blocks of level 2-back), digit span forward, digit span backward, symbol span, and spatial addition. The participants were then asked to be subjected to brain stimulation combined with the training session from the second to the sixth day. Following this, participants took the post-tests on the

seventh day. The tasks in the post-test were the same as those in the pre-test. After the assessment, participants were asked about the strategy used during the cognitive training and the blinding of group allocation.

Figure 16 - Flow Diagram in the Stroke Study



Note. CT = Cognitive training.

6.3.6 Statistical Analysis

A statistical analysis was performed using SPSS software (version 26). For baseline characteristics across the four groups, ANOVA was carried out for continuous variables, and a chi-square test was used for categorical variables. ANOVA was carried out for online and offline effects and mood and attitudes. To examine the online effect, the analysis of variance used a three-way mixed ANOVA with two between-participant factors of Stimulation (Active, Sham) and Lesion (Left, Right), and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). To examine the offline effect and transfer effect, the analysis of variance also used a mixed three-way ANOVA with two between-subject factors of Stimulation (Active, Sham) and Lesion (Left, Right) and within-subject factor of Time (Pre, Post). The Greenhouse-Geisser correction was applied when it did not meet the assumption of sphericity. The difference in the blinding of group allocation was analysed using a chi-square test. All *p*-values were reported as two-sided. A *p*-value < 0.05 was considered significant. Data were visualised using the package ggplot2 in R software (Hadley, 2016).

6.4 Results

6.4.1 Outliers Analysis

Outliers were identified separately using a criterion of three SD for the average training performance over five sessions for the four groups. In the Active tDCS + Adaptive group and Sham tDCS + Adaptive group, the mean *n* level is calculated as the average training performance; in the Active tDCS + Non-adaptive and Sham tDCS + Non-adaptive groups, the mean accuracy is calculated as the average training performance. No outlier was found.

6.4.2 Demographic and Baseline Characteristics

Analysis showed that four groups did not differ in demographic characteristics and baseline performance, including in terms of age, gender, education, Moca (Montreal Cognitive Assessment), days from stroke onset to the initial of tDCS treatment, NIHSS (National Institute of Health Stroke Scale), rate of lesion location (left or right side), spatial *n*-back, length of digit span forward (LDSF), length of digit span backward (LDSB), symbol span and spatial addition (all *p*s > 0.05, see Table 11). The rate of lesion location (hemisphere vs brainstem/cerebellum) was significant between the four groups ($p = 0.006$). However, the rate of lesion location (hemisphere vs brainstem/cerebellum) was not significant in adaptive and non-adaptive subgroups, respectively (all *p*s > 0.05, see Supplementary Tables 9 and 10). Supplementary Tables 9 and 10 present the demographic characteristics and baseline performance in the adaptive and non-adaptive subgroups. No significant difference in demographic characteristics and baseline performance between the four groups was found in the adaptive subgroup. Across the non-adaptive subgroup, significant differences in the ratio of gender ($p = 0.010$) and NIHSS ($p = 0.037$) were found. It was observed that none of the participants exhibited a Working Memory Index exceeding 100, suggesting that individuals who have suffered a stroke experience a decline in working memory performance when compared to normative data.

Table 11 - Demographic and Baseline Characteristics of the Overall Sample, Divided by Stimulation and Cognition Training Groups

Overall Groups	Active + Adaptive	Sham + Adaptive	Active + Non-adaptive	Sham + Non-adaptive	*p*	η_p^2
N	15	15	16	15	—	—
Age (years)	65.60 ± 6.19	66.93 ± 6.67	64.56 ± 5.32	66.13 ± 8.28	0.794	0.018
Gender	6/9	9/6	11/5	7/8	0.372[a]	—

Years of education	10.86 ± 1.66	11.29 ± 2.61	10.87 ± 4.00	8.73 ± 3.15	0.102	0.108
Moca	20.53 ± 4.69	18.93 ± 5.61	20.07 ± 3.26	19.27 ± 4.59	0.770	0.020
Days from onset	5.86 ± 1.81	6.13 ± 2.59	5.69 ± 2.75	4.80 ± 2.17	0.450	0.045
NIHSS	1.47 ± 0.92	2.60 ± 2.26	1.50 ± 1.21	2.73 ± 3.06	0.172	0.083
Lesion (Left/Right)	7/8	6/9	12/4	7/8	0.204	—
Lesion (Hemisphere/ Brainstem and cerebellum)	9/6	10/5	15/1	15/0	0.006* [a]	—
Spatial *N*-	0.68 ± 0.16	0.57 ± 0.13	0.59 ± 0.14	0.62 ± 0.21	0.298	0.063
LDSF	6.13 ± 1.25	6.33 ± 1.50	6.38 ± 1.31	6.66 ± 1.23	0.744	0.021
LDSB	3.47 ± 1.12	3.67 ± 0.98	3.44 ± 1.15	3.33 ± 1.54	0.898	0.010
Symbol	11.80 ± 4.55	11.86 ± 5.41	12.56 ± 3.52	9.87 ± 3.20	0.344	0.056
Spatial	6.27 ± 2.58	6.73 ± 2.66	6.69 ± 1.49	6.13 ± 2.33	0.854	0.013

Note. Moca = Montreal Cognitive Assessment. NIHSS = National Institute of Health Stroke Scale scale. LDSF = length of digit span forward. LDSB = length of digit span backward.

*p < 0.05.

[a]Chi-square test.

6.4.3 Online Trained Task – Spatial N-Back Task

6.4.3.1 Online Trained Task in Adaptive Groups

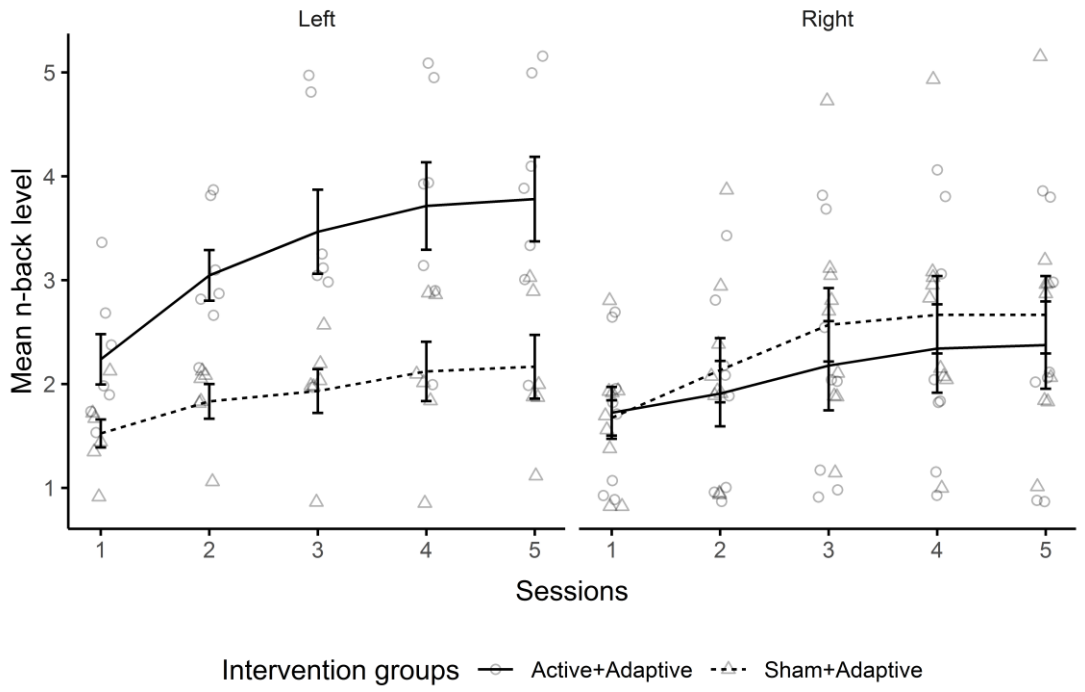
6.4.3.1.1 Online Trained Task in Adaptive Groups – Lesion Subgroup

To examine the online effect of brain stimulation in the adaptive groups, the mean *n* level in the spatial *n*-back task was calculated for each day. It was predicted that participants would benefit from active tDCS. Additionally, the hypothesis extended to

the expectation that individuals with stroke lesions localised on either the left or right would yield differential responses to tDCS. The mean *n* level was analysed using a three-way mixed ANOVA with two between-participant factors of Stimulation (Active, Sham) and Lesion (Left, Right) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). A significant main effect of Time was observed ($F_{(1,38)} = 39.795$, $p < 0.001$, $\eta_p^2 = 0.605$), as well as significant interactions of Stimulation × Lesion ($F_{(1,26)} = 5.913$, $p = 0.022$, $\eta_p^2 = 0.185$) and Stimulation × Lesion × Time ($F_{(1,38)} = 4.680$, $p = 0.024$, $\eta_p^2 = 0.153$). The experiment then focused on the highest level three-way interaction with a two-way mixed ANOVA with a between-participant factor of Stimulation (Active, Sham) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5) in the left and right lesion subgroups, respectively.

Within the left-lesion individuals, a significant main effect of Stimulation was found ($F_{(1,11)} = 11.060$, $p = 0.007$, $\eta_p^2 = 0.501$), with participants in the active group benefitting more than the sham group participants. In addition, there was a significant main effect of Time ($F_{(1,15)} = 19.979$, $p < 0.001$, $\eta_p^2 = 0.645$), and no interaction of Stimulation × Time ($F_{(1, 15)} = 3.668$, $p = 0.063$, $\eta_p^2 = 0.251$). For right-lesion individuals, there was a significant main effect of Time ($F_{(2,23)} = 19.574$, $p < 0.001$, $\eta_p^2 = 0.566$), and no interaction of Stimulation ($F_{(1,15)} = 0.252$, $p = 0.623$, $\eta_p^2 = 0.017$), and no interaction of Stimulation × Time ($F_{(2, 23)} = 1.135$, $p = 0.324$, $\eta_p^2 = 0.070$). Figure 17 shows the performance changes during five training sessions, split by lesion location.

Figure 17 - Training Performance (Mean N) Across Five Training Sessions Within Each Lesion Location Subgroup



Note. Error bars represent the standard error of the mean.

Given the small size of the sample, single-case statistics on the mean *n* for five sessions in the adaptive groups were run to support previous findings. In addition, the sham groups were used as control groups within the exact lesion location. Table 12 shows that six out of seven participants with a left lesion in the Active tDCS + Adaptive group had a significant performance improvement compared with individuals with a left lesion in the Sham tDCS + Adaptive group. However, in the Active tDCS + Adaptive group, where participants had a right lesion, some participants performed better, and others performed worse, compared with those in the Sham tDCS + Adaptive group with a right lesion (see Table 12).

Table 12 - Single Case Statistics for Each Individual in the Active TDCS + Adaptive Group

Lesion	sID	*t*	*df*	*p*
Left	sub20	0.131	5	0.901
	sub41	-6.700	5	0.001*
	sub44	-11.521	5	<0.001*
	sub48	-12.726	5	<0.001*
	sub61	-5.092	5	0.004*
	sub68	-6.440	5	0.001*
	sub73	-4.440	5	0.007*
Right	sub08	-3.994	8	0.004*
	sub43	-3.830	8	0.005*
	sub56	-1.211	8	0.261
	sub62	3.227	8	0.012*
	sub69	4.365	8	0.002*
	sub72	4.365	8	0.002*
	sub84	-0.481	8	0.644
	sub90	1.308	8	0.227

* $p < .05$.

6.4.3.1.2 Online Trained Task in Adaptive Groups – Ageing Subgroup

Age is an essential factor in the potential effect of tDCS combined with working memory training, as found in Chapter 5. In order to examine whether age was a modulator in the stroke study, this study employed a three-way mixed ANOVA with two between-participant factors of Stimulation (Active, Sham) and Age (Young, Old) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). A significant main effect of Time was found ($F_{(1,36)} = 35.360$, $p < 0.001$, $\eta_p^2 = 0.576$). There was no main effect of Age ($F_{(1,26)} = 0.062$, $p = 0.805$, $\eta_p^2 = 0.002$), no interactions of Stimulation × Age ($F_{(1,26)} = 0.420$, $p = 0.523$, $\eta_p^2 = 0.016$), no interaction effect of Stimulation × Time ($F_{(1,36)} = 0.360$, $p = 0.624$, $\eta_p^2 = 0.014$), no

interactions of Stimulation × Age × Time ($F_{(1,36)}$ = 0.217, p = 0.724, η_p^2 = 0.008), and no other significant effect.

6.4.3.2 Online Trained Task in Non-Adaptive Groups

6.4.3.2.1 Online Trained Task in Non-Adaptive Groups – Lesion Subgroup

To examine the online effect of brain stimulation in the non-adaptive groups, the mean accuracy in the spatial *n*-back task for every session was calculated. The mean accuracy was analysed using a three-way mixed ANOVA with two between-participant factors of Stimulation (Active, Sham) and Lesion (Left, Right) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). A significant main effect of Time was found ($F_{(2,43)}$ = 8.848, p = 0.001, η_p^2 = 0.247). There was no main effect of Stimulation ($F_{(1,27)}$ = 0.076, p =0.785, η_p^2 = 0.003) or Lesion ($F_{(1,27)}$ = 1.570, p =0.221, η_p^2 = 0.055), and no interaction of Stimulation × Time ($F_{(2,43)}$ = 0.108, p = 0.857, η_p^2 = 0.004), Stimulation × Lesion ($F_{(1,27)}$ = 0.012, p = 0.913, η_p^2 < 0.001), Time × Lesion ($F_{(2,43)}$ = 0.821, p = 0.423, η_p^2 = 0.029), or Stimulation × Time × Lesion ($F_{(2, 43)}$ = 0.171, p = 0.797, η_p^2 = 0.006).

6.4.3.2.2 Online Trained Task in Non-Adaptive Groups – Ageing Subgroup

In order to examine whether age was a modulator in the stroke study in the non-adaptive groups, the study also employed a three-way mixed ANOVA with two between-participant factors of Stimulation (Active, Sham) and Age (Young, Old) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). A significant main effect of Time was found ($F_{(2,42)}$ = 8.962, p = 0.001, η_p^2 = 0.249). There was no main effect of Age ($F_{(1,27)}$ = 3.009, p = 0.094, η_p^2 = 0.100), no interactions of Stimulation × Age ($F_{(1,27)}$ = 0.560, p = 0.461, η_p^2 = 0.020), no

interaction effect of Stimulation × Time ($F_{(2,42)}$ = 0.115, p = 0.844, η_p^2 = 0.004), no interactions of Stimulation × Age × Time ($F_{(2,27)}$ = 0.660, p = 0.487, η_p^2 = 0.024), and no other significant effect.

6.4.4 Offline Training Effect – Spatial N-Back

In order to examine the offline effect of brain stimulation in the non-adaptive spatial *n*-back task in the Adaptive groups and the Non-adaptive groups, the accuracy was analysed using a mixed three-way ANOVA with two between-subject factors of Stimulation (Active, Sham) and Lesion (Left, Right), and one within-subject factor of Time (Pre, Post).

In the Adaptive groups, a significant main effect of Stimulation was found ($F_{(1,26)}$ = 4.845, p = 0.037, η_p^2 = 0.157), with participants in the active tDCS groups benefitting more than the sham tDCS participants. There was a significant effect of Time ($F_{(1,26)}$ = 18.668, p < 0.001, η_p^2 = 0.418). There was no significant effect of Lesion ($F_{(1,26)}$ < 0.001, p = 0.989, η_p^2 < 0.001), no interaction effect of Stimulation × Time ($F_{(1,26)}$ = 0.078, p = 0.782, η_p^2 = 0.003), and no interaction of Stimulation × Lesion × Time ($F_{(1,26)}$ = 1.518, p = 0.229, η_p^2 = 0.055). It was hypothesised that individuals with stroke lesions localised on the left or right side in the adaptive groups would yield differential responses to tDCS. A two-way mixed ANOVA with a between-participant factor of Stimulation (Active, Sham) and a within-participant factor of Time (Pre, Post) was employed in both the left and right lesion subgroups. For left-lesion individuals, a significant main effect of Stimulation was found ($F_{(1,11)}$ = 8.115, p = 0.016, η_p^2 = 0.425), with participants in the active group benefitting more than sham group participants. In addition, there was a significant main effect of Time ($F_{(1,11)}$ =

9.689, p = 0.010, η_p^2 = 0.468), and no interaction of Stimulation × Time ($F_{(1, 11)}$ = 0.420, p = 0.530, η_p^2 = 0.037). Within right-lesion individuals, there was a significant main effect of Time ($F_{(1,15)}$ = 9.232, p = 0.008, η_p^2 = 0.381), and no main effect of Stimulation ($F_{(1,15)}$ = 0.138, p = 0.715, η_p^2 = 0.009), or of Stimulation × Time ($F_{(1, 15)}$ = 1.275, p = 0.277, η_p^2 = 0.078).

In the Non-adaptive groups, there was a significant main effect of Lesion ($F_{(1,26)}$ = 6.554, p = 0.017, η_p^2 = 0.201), with left-sided lesion participants benefitting more than the right-lesion participants. Further to this, there was a significant main effect of Time ($F_{(1,26)}$ = 55.732, p < 0.001, η_p^2 = 0.682). No significant main effect of Stimulation was found ($F_{(1,26)}$ = 3.289, p = 0.081, η_p^2 = 0.112), no interaction effect of Stimulation × Time ($F_{(1,26)}$ = 0.098, p = 0.757, η_p^2 = 0.004), and there was also no interaction of Stimulation × Lesion × Time ($F_{(1,26)}$ = 0.081, p = 0.778, η_p^2 = 0.003).

6.4.5 Transfer Effect – Untrained Task

Analysis was applied to test the transfer effect of brain stimulation and cognition on untrained tasks in adaptive and non-adaptive groups. The outcomes were analysed using a mixed three-way ANOVA with two between-subject factors of Stimulation (Active, Sham) and Lesion (Left, Right), and one within-subject factor of Time (Pre, Post). Results are presented in Supplementary Tables 11 and 12.

In the adaptive groups, there was a significant interaction effect of Lesion × Stimulation ($F_{(1,26)}$ = 5.389, p = 0.028, η_p^2 = 0.172) in the digit span backward task. Further analysis showed there was no significant main effect of Stimulation in the left lesion subgroup ($F_{(1,11)}$ = 2.410, p = 0.149, η_p^2 = 0.180) or in the right lesion subgroup ($F_{(1,15)}$ = 2.914, p = 0.108, η_p^2 = 0.163).

6.4.6 Mood and Attitudes Toward the Stimulation

Mood and attitudes towards the intervention were analysed in the adaptive groups. The scores of mood and attitudes were analysed separately using a three-way ANOVA with two between-participant factors of Stimulation (Active, Sham) and Lesion (Left, Right) and a within-participant factor of Time (Session 1, Session 2, Session 3, Session 4, Session 5). The levels of anxiety and depression were also analysed using a three-way ANOVA with two between-participant factors of Stimulation (Active, Sham) and Lesion (Left, Right) and a within-participant factor of Time (Pre, Post). Results are shown in Supplementary Table 13. In the adaptive groups, there was no significant main effect of Stimulation, no interaction effect of Time × Lesion × Stimulation, and no interaction effect of Lesion × Stimulation (all *p*s > 0.05).

6.4.7 Debriefing of Strategy

All participants were asked whether they used a strategy during the cognitive training. The difference in the rate of participants who used the strategy among the four groups was insignificant ($p = 0.512$). The rate of strategy use in the lesion subgroups subgroups was also analysed. No significant difference was detected among the four groups in the lesion subgroups. The data are presented in Table 13.

Table 13 - Count of Participants That Developed a Strategy in the Active and Sham Groups for the Overall Groups and Lesion Subgroups in the Stroke Study

Groups	Active + Adaptive (Yes/No)	Sham + Adaptive (Yes/No)	Active + Non-adaptive (Yes/No)	Sham + Non-adaptive (Yes/No)	*p*
Overall groups	2/13	5/10	4/12	2/13	0.512
Lesion subgroups					
Left	0/7	1/5	3/9	2/5	0.614

Right	2/6	4/5	1/3	0/7	0.255

6.4.8 Possible Adverse Effects of Brain Stimulation

Participants were asked about the possible adverse effects of brain stimulation after each stimulation session. Chi-square tests were used to analyse the difference in the reported adverse effects across the four groups. The results showed a significant difference in itching ($X^2_{(1)} = 10.331$, $p = 0.016$), sleepiness ($p = 0.016$), tingling ($X^2_{(1)} = 21.056$, $p < 0.001$), and burning ($X^2_{(1)} = 12.474$, $p = 0.006$) between these four groups (all ps > 0.05). Results are presented in Table 14. In order to test whether the significance was affected by stimulation, the cognition groups were collapsed and analysed in two groups (Active and Sham). This showed that the rate of itching ($X^2_{(1)} = 4.914$, $p = 0.027$), tingling ($X^2_{(1)} = 16.935$, $p < 0.001$), and burning ($X^2_{(1)} = 6.409$, $p = 0.011$) in the Stim group was significantly higher than for those in the Sham group, while the rate of sleepiness ($X^2_{(1)} = 5.308$, $p = 0.021$) in the Active group was significantly lower than in the Sham group.

Table 14 - The Output of Chi-Square Tests on the Rate of Participants Reporting Each Possible Adverse Effect in the Stroke Study

	Active + Adaptive	Sham + Adaptive	Active + Non-adaptive	Sham + Non-adaptive	X^2	p
Headache	0	1 (1.33%)	0	0	—	0.733[a]
Pain in the neck	0	1 (1.33%)	0	0	—	0.737[a]
Itching	49	32 (42.66%)	51 (63.75%)	49 (65.33%)	10.33	0.016*
Sleepiness	0	3 (4%)	1 (1.25%)	6 (8%)	—	0.022*[a]
Trouble concentrating	0	0	0	0	—	—
Acute mood	0	0	0	0	—	—
Fatigue	1 (1.33%)	1 (1.33%)	0	2 (2.67%)	—	0.475[a]
Nausea	0	0	0	0	—	—

Muscle twitches in the face or neck	0	0	0	1 (1.33%)	—	0.734[a]
Tingling	24 (32%)	15 (20%)	37 (46.25%)	12 (16%)	21.05	< 0.001*
Burning	14	3 (4%)	6 (7.5%)	4 (5.33%)	12.47	0.006*
Epileptic seizure	0	0	0	0	—	—
Light flashes	0	0	0	0	—	—
Uncomfortable feeling	1 (1.33%)	0	0	0	—	0.738[a]

Note. Total times in five sessions and rate of participants (%) in four groups reporting each possible adverse effect.

[a] Fisher exact test.

[*] $p < .05$.

6.4.9 Blinding of Stimulation

After the intervention, participants were asked to guess their group allocation. There was no significant difference in the rate of participants who guessed that they were in the active group across the four groups ($X^2_{(3)} = 6.526$, $p = 0.089$). This result showed that participants were successfully blinded to the intervention groups.

6.5 Discussion

This chapter has investigated the efficacy of tDCS combined with adaptive working memory training to improve working memory in acute stroke patients. The results reveal that this combination benefitted participants with a stroke lesion on the left side when the right DLPFC was stimulated. Importantly, the benefit was not present when stimulation occurred in the ipsilesional hemisphere or when participants undertook non-adaptive working memory training. Results also reveal that the benefit still existed on the post-test one day after the training task. However, training benefits could not transfer to related clinical tasks. Finally, the stimulation did not

influence mood, specifically alertness, motivation, expectation, sadness, anxiety and depression.

The main significant finding of this chapter is that tDCS can improve the effectiveness of working memory training in acute stroke patients with left-sided lesions when they are stimulated in the right DLPFC. Notably, these findings from the acute phase diverge from those observed in the chronic phase. In the chronic phase, most study designs are based on the inter-hemisphere model, which uses anodal tDCS to excite the lesioned side and/or cathodal tDCS to depress the contralateral hemisphere (Lefaucheur et al., 2017; Murase et al., 2004). My results are consistent with previous studies showing that activation of the contralateral hemisphere in the acute phase is associated with good functional recovery (Bütefisch et al., 2008). A stroke severely disrupts the excitation/inhibition (E/I) balance, and a lower E/I ratio on the lesioned side was reported in the acute phase (Grigoras & Stagg, 2021). Increasing activation in the contralateral hemisphere with tDCS may decrease the lesioned side's excitation/inhibition (E/I) ratio. A previous study suggested that the inhibition in the acute phase may be protective (Grigoras & Stagg, 2021). The precise mechanism underpinning the shifts in E/I balance, especially in the context of tDCS interventions, needs further exploration. Another possible explanation for the effect of tDCS is its potential to enhance neuroplasticity, including alteration of functional connectivity and organization (Polanía, Nitsche, & Paulus, 2011). Specifically, when tDCS targets the right DLPFC, it may facilitate neuronal reorganization or connectivity in the right hemisphere, compensating for disruptions caused by lesions in the left hemisphere. Conversely, in cases with right hemisphere lesions, stimulation of the right DLPFC may not elicit comparable compensatory mechanisms from the left hemisphere. Baseline working memory

assessments revealed no significant disparity between patients with left and right-sided lesions, indicating that the differences in tDCS efficacy are unrelated to the initial severity of working memory impairment. Single-case statistics revealed that a small proportion of participants in the right-sided lesion group (two out of eight) did derive benefit from tDCS, indicating variability in response among patients with right-sided lesions. This variability may be influenced by factors such as the size and specific location of the lesion. Although the current findings do not conclusively explain why tDCS is selectively beneficial for patients with left-sided stroke lesions, my finding is essential for treating commonly reported working memory decline in patients who have suffered a stroke.

A further important finding is that the beneficial synergistic effect of tDCS and working memory training is absent in the non-adaptive working memory training groups. This result is in agreement with that of Gill et al. (2015), who also found that the synergistic effect of tDCS and working memory training did not exist when they applied a one-back working memory training task in young adults (Gill, Shah-Basak, & Hamilton, 2015). As described in their study, non-adaptive one-back training was less effective in improving working memory than adaptive *n*-back training (Gill et al., 2015). It is noteworthy that studies have shown that tDCS alone can improve working memory performance (Berryhill & Jones, 2012; Hoy et al., 2013). However, after publication bias was controlled for in a meta-analysis, the effect of tDCS alone on working memory was relegated to being considered insignificant (Mancuso et al., 2016). The results of this study suggest that tDCS only benefits stroke patients in adaptive working memory training because tDCS promotes brain plasticity when the task is cognitively demanding (Miniussi, Harris, & Ruzzoli, 2013). When a non-taxing working memory task is employed, tDCS seems unable to activate the neural

network responsible for working memory. This finding suggests that, to a certain extent, the impact of brain stimulation on cognitive performance is task-dependent and thus may account for reports of negative results when tDCS is used.

This study found an offline effect of tDCS combined with training on spatial working memory when administered one day after the final tDCS session. This result is consistent with Chapters 4 and 5, corroborating the enduring impact of tDCS on offline training tasks, whether assessed immediately after stimulation or after 48 hours. It is supported that the benefit of tDCS on motor function in stroke patients could last for two weeks after stimulation (Boggio et al., 2007). There was a lack of existing studies that examined the effect of tDCS on cognitive function in stroke studies. Previous studies revealed that in a neuropsychiatric cohort, performance improved in online tasks but not in offline tasks (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Hill et al., 2016); An opposing pattern was observed in the healthy cohort (Dedoncker et al., 2016; Hill et al., 2016). Direct current-induced neuroplasticity can change spontaneous discharge rates and alter the N-methyl-D-aspartate-receptor activation, contributing to the after-effect of tDCS (Liebetanz et al., 2002). A further study could examine the longer-term tDCS benefits on cognition in stroke patients.

This study could not demonstrate a transfer effect of tDCS combined with cognitive training on clinical measures, such as digit span, spatial addition and symbol span. This finding agrees with previous research that reports a lack of transfer from working memory training to “real-world” cognitive skills (Melby-Lervåg et al., 2016). In contrast, some studies have shown that tDCS combined with cognitive training can improve digit span forward scores (Au et al., 2016; Park, Seo, Kim, & Ko, 2014). One possible explanation for these inconsistent results is measurement variation. It

has been suggested that transfer effects are more robust during a latent follow-up than immediately following the intervention (Jones, Stephens, et al., 2015)

Finally, it was found that tDCS did not alter mood dimensions, including alertness, motivation, expectation, sadness, anxiety and depression. This finding is consistent with that of Au et al. (2016), who also found that tDCS did not alter mood and emotional experience in healthy adults (Au et al., 2016). A recent study showed that tDCS, which stimulated left DLPFC, improved cognitive function in chronic stroke patients (Chu et al., 2022). This improvement was associated with the activation of the prefrontal cortex, a region related to motivation, as evidenced by functional near-infrared spectroscopy (Chu et al., 2022). However, in the study conducted by Chu et al., a direct measurement of motivation was absent (Chu et al., 2022). Despite reports indicating that anxiety could contribute to a working memory decrease in stroke patients (Grosdemange et al., 2015) and the notion that tDCS may mediate mood alterations to enhance working memory (Feeser et al., 2014), the findings of this study did not corroborate that tDCS combined with cognitive training improves working memory via mood modulation. Two factors may account for this result. Firstly, the placement of the active electrode was on the right DLPFC in the present study, while most tDCS research on depression has targeted the left DLPFC (Lefaucheur et al., 2017). Secondly, the limited sessions of tDCS stimulation may have influenced the outcome.

Several limitations to this study need to be acknowledged. Firstly, the sample size is small when I analyse the training data in different subgroups, e.g., left vs. right lesion side and stimulation site. Additionally, although it is observed that the lesion side can selectively affect brain stimulation, I did not analyse neuroimaging data, including the lesion size and the impact of lesion location on the current in the present study.

Neuroimaging data will be modelled and analysed in my future research. Another limitation is that it was not possible to follow up with patients after hospital discharge due to the Coronavirus Disease 2019 (COVID-19). Finally, based on the previous studies, the right DLPFC was stimulated in order to investigate the effect on cognitive training; however, the effect of stimulating the left DLPFC remains unclear.

To conclude, this study reveals that, among acute stroke patients, tDCS applied to the right DLPFC, combined with working memory training, selectively benefits patients with left-sided lesions. Furthermore, tDCS, when combined with non-adaptive working memory training did not positively affect spatial working memory. This study highlights the influence of lesion location on the efficacy of combined brain stimulation and training in acute stroke patients, providing valuable insights for clinical treatment.

Further research is needed to incorporate neuroimaging techniques, such as functional Magnetic Resonance Imaging (f MRI) and Diffusion Tensor Imaging (DTI), to better understand brain function and network connectivity during or after stimulation and training in the acute phase. Additionally, the findings from this study suggest that future research should consider the phase of stroke recovery and the location of the lesion when designing clinical studies involving tDCS. It is theoretically possible to achieve even better results by applying an anodal tDCS to the contralateral hemisphere simultaneously with a cathodal tDCS application to the lesioned side in the hyperacute and acute phases. Moreover, where this study focuses on spatial working memory, examining the effect of combined training and brain stimulation on verbal working memory is also crucial. Finally, large-scale, multi-centre clinical trials are warranted.

6.6 Conclusion

In conclusion, this investigation has established the feasibility and tolerability of tDCS in the acute stroke patient population. My study demonstrates that tDCS combined with adaptive working memory training yields benefits in working memory capacity for stroke patients with left-sided lesions. Notably, the enhancement in working memory facilitated by tDCS does not arise from mood modifications in these patients. Future studies could employ neuroimaging techniques to reveal the potential mechanisms behind these observed outcomes.

Chapter 7 - General Discussion

Working memory is intrinsically linked to people's academic ability and is known to deteriorate with ageing and brain injury, such as post-stroke. Therefore, it is vital to identify practical tools to improve working memory. TDCS represents a promising tool to enhance brain excitability and induce neuroplasticity. The aim of the thesis was to investigate the application of tDCS and cognitive training in healthy young adults and elderly populations, and to subsequently apply the established knowledge to acute stroke patients. This chapter begins by presenting a comprehensive summarisation of the key findings. This is followed by interpretations of these findings, elaborating on how they fit within the context of the existing literature. Finally, it will delineate the strengths and limitations of this thesis, along with recommendations for future research.

7.1 Summary of Findings

This thesis comprises four experiments. Chapter 3 details an experiment designed to evaluate the effect of a single-session high-definition tDCS (HD-tDCS) and the parameters of online and offline modes of brain stimulation in healthy young adults. Unexpectedly, the single-session HD-tDCS did not yield significant results, and there was no significant difference between online and offline modes of brain stimulation.

Consequently, the aim of the experiment in Chapter 4 was to test the effects of two sessions of bipolar tDCS and the provision of strategy in healthy adults. In this experiment, participants with low working memory capacity benefitted from tDCS combined with strategy provision. In addition, tDCS could not elicit a spontaneous strategy.

In Chapter 5, the implication of five consecutive sessions of bipolar tDCS in the elderly was investigated, revealing that participants with low working memory capacity or those who were older benefitted more from tDCS combined with working memory training, than those who received the training alone. Participants who benefitted reported a higher rate of strategy use than other participants.

Finally, the combination of tDCS and cognitive training was applied to acute stroke patients who experienced working memory decline. The effects of five consecutive sessions of bipolar tDCS and working memory training in acute stroke patients were examined in Chapter 6. The results showed that combining training and stimulation improved working memory in stroke patients with left-sided lesions. Only a small number of stroke patients reported strategy use during the working memory tasks.

Overall, the combination of tDCS and cognitive training selectively benefitted healthy adults with initially low working memory capacity who were given external strategy support, elderly individuals who are both older and have a low baseline working memory, and acute stroke patients with left-sided lesions.

7.2 Interpretation and Implications of Findings

7.2.1 TDCS is a "State-Dependent" Intervention

As presented in Chapters 4, 5, and 6, tDCS selectively conferred benefits on healthy adults with low working memory capacity, elderly participants with low working memory capacity or those of advanced age, and stroke patients with left-sided lesions. These results are consistent with the theory that tDCS, a form of noninvasive brain stimulation, is a "state-dependent" intervention tool influenced by the ongoing neural activity in the targeted area (Masina et al., 2022; Silvanto & Pascual-Leone, 2008; Vergallito et al., 2023). The existing literature suggests that

tDCS is influenced by stimulus parameters and inter-individual or intra-individual variations, such as baseline performance, age, gender, and physiological characteristics (Dubreuil-Vall, Chau, Ruffini, Widge, & Camprodon, 2019; Hsu, Juan, & Tseng, 2016; Hsu, Tseng, Liang, Cheng, & Juan, 2014; Krause & Cohen Kadosh, 2014). These factors collectively impact the balance of excitation/inhibition (E/I) driven by glutamate and gamma-aminobutyric acid (GABA) (Krause et al., 2013). The relationship between the E/I balance and behavioural performance is suggested to follow an inverted U-shaped curve (Krause & Cohen Kadosh, 2014; Krause et al., 2013). When the levels of excitation and inhibition reach a perfect balance, an optimal performance will be achieved (Krause & Cohen Kadosh, 2014; Krause et al., 2013). In Chapters 4 and 5, healthy adults and the elderly with low working memory capacity experienced an improvement and moved closer to the optimal point after tDCS enhanced their cortical excitability. This is corroborated by research indicating that low working memory capacity participants benefitted from tDCS, with significant changes observed in N2-posterior-contralateral (N2pc) and contralateral delay activity (CDA). In contrast, high-capacity participants exhibited no such benefits from tDCS (Hsu et al., 2014; Tseng et al., 2012). However, those considered to be young-elderly, who initially were at the optimal point, could be pushed beyond it by tDCS, resulting in a decreased performance. Stroke patients were predicted to benefit from tDCS due to their low working memory capacity. Notably, the E/I balance in stroke patients was severely disrupted, making their responses dependent on the side of the lesion in addition to their low working memory capacity (Grigoras & Stagg, 2021).

7.2.2 Compensation Theory or Magnification Theory

There are two predominant hypotheses concerning the benefits of cognitive training: the compensation theory and the magnification theory (Lövdén, Brehmer, Li, &

Lindenberger, 2012; Teixeira-Santos et al., 2022). The compensation theory suggests that participants with a low baseline performance experience a significant improvement due to the greater margin for enhancement, than participants with a high baseline performance (Lövdén et al., 2012). Conversely, the magnification theory posits that individuals with a high baseline performance benefit from cognitive training because they have more cognitive resources (Lövdén et al., 2012). Findings from Chapters 4 and 5 of this thesis revealed that low working memory capacity participants benefitted from the combination of working memory training and tDCS, supporting the compensation theory in the context of combined working memory training and tDCS. This is consistent with the supply-demand mismatch theory, which proposes that the greater the mismatch between functional organic supplies available and the demands exerted by the environment, the greater the improvement participants will exhibit (Lövdén et al., 2010). The training task discussed in Chapters 4 and 5 is adaptive, and due to the low working memory capacity at the baseline, the mismatch in low-capacity subgroups was larger than in the mid- or high-working memory capacity subgroups. Consequently, in the high working memory capacity subgroups, the inherent improvement in working memory through practice is evident, leaving limited room for additional enhancement via tDCS. These findings support the compensation theory when cognitive training and tDCS are combined.

7.2.3 Relationship Between Strategy and the Combination of TDCS with Cognitive Training

As revealed in Chapter 4, the combination of tDCS and strategy-based cognitive training was beneficial for young adults with a low working memory capacity. However, the benefit was derived from the strategy provision rather than tDCS in participants with a high working memory capacity. Significantly, tDCS was not found

to induce the use of a spontaneous strategy. In Chapter 5, the experimental design did not include the strategy provision, but participants were queried regarding strategy usage after the experiment. Interestingly, participants of advanced-old age who benefitted from tDCS reported higher strategy use rates than the young-old participants. This is consistent with the Strategy Mediation hypothesis (Laine et al., 2018; McNamara & Scott, 2001), suggesting that external strategies can boost working memory among those with a low working memory capacity. Utilising a strategy is an example of knowledge acquisition which, when externally provided, leaves participants with more resources to devote to the task at hand and improves the flexibility of their capacity, which can be further augmented by tDCS-induced neuroplasticity changes (Lövdén et al., 2010). Conversely, for participants with a high working memory capacity, the improvement achieved through the provision of effective strategies was not further enhanced by tDCS, likely due to a minor supply-demand mismatch (Lövdén et al., 2010). In the elderly, those considered to be of advanced-old age and with low capacity benefitted from tDCS. These participants also reported a higher spontaneous strategy usage than those without tDCS. It is unknown whether the strategy used is a cause or an effect of this improvement. It is noteworthy that older adults tend to activate bilateral hemispheres, while young adults mainly activate unilaterally (Bäckman et al., 1997). These distinct activations may lead to different responses to tDCS and cognitive training, such as the use of spontaneous strategy.

7.2.4 Absence of Transfer Effects in Current Studies

The four experiments conducted within this study failed to identify transfer effects to untrained tasks or scales. Literature indicates that transfer effects are often observed in the follow-up phases (Jones, Stephens, et al., 2015; Pergher et al., 2022).

However, in my studies, participants were evaluated only one or two days post-intervention, without any subsequent follow-up after one month or a year, which may have been a limiting factor in observing transfer effects. Additionally, this lack of transfer effect might be partially ascribed to insufficient sessions. The initial two experiments, involving young adult participants, consisted of only one or two sessions. Despite the third and fourth experiments including more sessions, they were limited to just five sessions each. According to the latest meta-analysis in this field, the mean of sessions is five to observe transfer effects in healthy adults (Pergher et al., 2022). However, it is uncertain if stroke patients and the elderly require more extensive training than healthy adults. Furthermore, within the context of the stroke study, the selection of clinical scales, specifically Spatial Addition and Symbol Span from the Wechsler Memory Scale-Fourth Edition (WMS-IV), may have exhibited limitations in their sensitivity to detect transfer effects. This selection of scales also impacted the study's ability to detect any transfer effects that might have occurred.

7.2.5 Implications for Practice

This thesis explores the application of tDCS combined with cognitive training in different populations, from healthy young adults to the elderly and acute stroke patients. The findings suggest that tDCS is a “state-dependent” intervention, influenced by baseline performance, strategy use, age, and stroke lesion side. Future research is needed to account for each of these factors when designing tDCS studies. Clinicians must pay more attention to clinical factors, such as brain lesion hemifield in stroke, brain injury hemifield in acquired brain injury, and hemifield onset side in Parkinson’s disease, when integrating tDCS into clinical practice. Multiple

training sessions coupled with long-term follow-up is imperative to ascertain the extent of transfer effects to tasks or scales outside the scope of direct training.

Today, some people purchase tDCS devices and use them independently without medical supervision. My findings suggest that tDCS is not a “one-size-fits-all” solution, but is rather a “state-dependent” intervention. This suggests that its effectiveness and impact would vary across different user demographics. It is crucial to generate more evidence and develop comprehensive guidelines. Such guidelines should include recommendations for medical staff concerning tDCS use, emphasise the potential risks associated with unsupervised use, outline applications for different populations to ensure that individual characteristics, such as age, baseline capacity, and healthy conditions, are taken into account, and provide the details of the parameters of tDCS including electrode placement, current density, and duration of stimulation.

7.3 Strengths and Limitations

A key strength of this thesis is its systematic exploration of tDCS combined with cognitive training from a laboratory environment to real-world clinical applications, accomplished through progressive and step-by-step design optimisations. In healthy adults, it was found that the provision of strategy and baseline performance influenced the effect of tDCS. It is innovative to explore strategy use in the context of tDCS. In the elderly study, it was found that both ageing and working memory capacity impacted the efficacy of tDCS. Based on these findings, the research was then advanced to real-world clinical settings, making the present thesis the first study to explore the combination of tDCS and cognitive training in acute stroke patients. The results demonstrated that the sides of the lesion could affect the benefits

derived from tDCS. A comprehensive framework for applying tDCS in different populations has been developed throughout the entire thesis.

A primary limitation of the thesis relates to the analyses being divided into subgroups. As factors such as capacity, age and lesion sides were not confirmed to be the factors affecting the tDCS in healthy young adults, elderly and stroke patients prior to my research, the randomisation of participants was determined by the intervention rather than these factors. Further studies should be conducted using more exact allocation principles to recruit and allocate participants. Subgroup analysis, though necessary, resulted in a smaller sample size.

Another limitation is that it was not possible to follow up with patients after discharge due to COVID-19. Most participants were unwilling to return for subsequent follow-up tasks due to the risk of infection.

Furthermore, given that the entire thesis focuses on applying tDCS from laboratory to clinical settings, and the uncertainty as to whether stroke patients would benefit from the intervention, I did not include experiments to explore the mechanisms underlying brain change after the intervention. Based on the present work, detailed studies with neuroimaging, such as functional Magnetic Resonance Imaging (f MRI) and Diffusion Tensor Imaging (DTI), should focus on the brain network or frontal activity relative to lesion sites in stroke patients in response to combined cognitive training and tDCS.

Finally, this study has specifically concentrated on tDCS and did not extend to contrasting it with other brain stimulation techniques, such as the tACS and tRNS.

7.4 Future Research

This thesis demonstrated the behavioural improvement associated with combining tDCS and cognitive training. As a neurologist, my future research will explore the mechanisms underlying this behavioural improvement using neuroimaging to transfer these findings into clinical practice. Firstly, I intend to identify brain biomarkers in the elderly, using MRI before, during and after tDCS, to observe the alterations in glutamine and gamma-aminobutyric acid and subsequent changes in the brain's networks. I then will examine the same brain biomarker in acute stroke patients, taking lesion localisation into consideration. Finally, I aim to extend the application of this intervention to neurological diseases such as Mild Cognitive Impairment, Alzheimer's Disease, and Post-stroke Aphasia.

7.5 Conclusions

In summary, this comprehensive study underscores the notion that tDCS functions as a "state-dependent" intervention, showing discernible benefits for specific groups: healthy young adults with initially low working memory capacity who were given external strategy support, elderly individuals who are both older and have a low baseline working memory, and acute stroke patients with left-sided brain lesions. In the future, researchers should carefully take these factors into account and delve into the mechanisms underpinning the effectiveness of this intervention.

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Appendices

Appendix 1: Supplementary Materials in Chapter 4

Supplementary Table 1 - Baseline Characteristics of Low Working Memory Subgroup in Chapter 4

	Active tDCS + Strategy	Active tDCS + No Strategy	Sham tDCS + Strategy	Sham tDCS + No Strategy	*F* (3,24)	*p*	η_p^2
N	7	9	6	6	--	--	--
Age	23.86 ± 2.01	20.56 ± 2.35	19.00 ± 0.89	18.83 ± 0.75	1.986	0.143	0.199
Gender (M/F)	3/4	2/7	0/6	1/5	--	0.405	--
Years of Education	17.86 ± 2.97	15.22 ± 2.17	15.50 ± 0.84	14.83 ± 2.40	2.521	0.082	0.240
Alertness	3.29 ± 0.95	3.33 ± 0.71	3.67 ± 0.82	3.17 ± 0.75	0.427	0.735	0.051
Motivation	3.43 ± 0.98	3.67 ± 0.87	3.83 ± 0.75	3.50 ± 0.84	0.280	0.840	0.034
Sadness	3.57 ± 0.79	3.67 ± 1.00	4.17 ± 0.75	3.17 ± 1.17	1.140	0.353	0.125
Expectation on CT	3.71 ± 0.95	3.44 ± 0.88	3.50 ± 1.05	3.50 ± 0.84	0.121	0.947	0.015
Expectation on tDCS	3.14 ± 1.07	3.56 ± 0.73	3.00 ± 0.89	2.83 ± 0.41	1.103	0.367	0.121
Positive affect	28.00 ± 9.83	28.66 ± 7.19	25.83 ± 8.30	27.50 ± 10.63	0.126	0.944	0.016
Negative affect	12.71 ± 2.29	12.11 ± 2.85	14.00 ± 4.94	13.33 ± 3.39	0.412	0.746	0.049
Z ($\bar{n}$) in aNback	-0.81 ± 0.55	-1.1 ± 0.39	-0.78 ± 0.58	-0.83 ± 0.56	0.694	0.565	0.080
Z (d') in fNback	-0.96 ± 0.41	-0.72 ± 0.46	-1.42 ± 0.70	-0.93 ± 0.58	2.080	0.130	0.206

Composite capacity score	-0.88 ± 0.27	-0.91 ± 0.30	-1.10 ± 0.56	-0.88 ± 0.47	0.434	0.731	0.051

Supplementary Table 2 - Baseline Characteristics of Medium Working Memory Subgroup in Chapter 4

	Active tDCS + Strategy	Active tDCS + No Strategy	Sham tDCS + Strategy	Sham tDCS + No Strategy	*F* (3,23)	*p*	η_p^2
N	6	6	9	6	--	--	--
Age	20.67 ± 4.63	19.17 ± 0.41	19.00 ± 0.71	23.00 ± 4.56	2.393	0.095	0.238
Gender (M/F)	1/5	0/6	3/6	1/5	--	0.480	--
Years of Education	17.83 ± 4.07	14.50 ± 1.05	14.67 ± 0.87	17.67 ± 4.03	2.895	0.057	0.274
Alertness	4.00 ± 0.63	2.83 ± 0.98	2.67 ± 0.50	3.00 ± 0.89	4.193	0.017*	0.354
Motivation	4.17 ± 0.75	3.50 ± 0.55	2.89 ± 0.60	3.67 ± 0.82	4.492	0.013*	0.369
Sadness	3.33 ± 1.37	3.83 ± 0.41	3.33 ± 0.50	3.33 ± 1.37	0.416	0.743	0.051
Expectation on CT	3.67 ± 0.52	2.67 ± 0.82	3.00 ± 0.87	3.33 ± 1.21	1.451	0.254	0.159
Expectation on tDCS	3.50 ± 0.55	2.17 ± 0.41	2.78 ± 0.97	3.17 ± 1.17	2.725	0.068	0.262
Positive affect	30.00 ± 5.10	24.33 ± 4.46	26.56 ± 5.29	22.17 ± 5.64	2.542	0.081	0.249
Negative affect	12.50 ± 2.59	13.33 ± 6.41	13.22 ± 4.18	11.83 ± 2.99	0.171	0.915	0.022
Z ($\bar{n}$) in aNback	0.13 ± 0.87	0.02 ± 0.59	0.01 ± 0.46	-0.18 ± 0.70	0.247	0.863	0.031
Z (d') in fNback	-0.16 ± 0.69	-0.05 ± 0.67	-0.03 ± 0.38	-0.02 ± 0.37	0.090	0.965	0.012

Composite capacity score	-0.01 ± 0.18	-0.02 ± 0.23	0.00 ± 0.24	-0.15 ± 0.17	0.725	0.547	0.086

*$p < 0.05$.

Supplementary Table 3 - Baseline Characteristics of High Working Memory Subgroup in Chapter 4

	Active tDCS + Strategy	Active tDCS + No Strategy	Sham tDCS + Strategy	Sham tDCS + No Strategy	*F* (3,25)	*p*	η_p^2
N	8	6	6	9	--	--	--
Age	20.50 ± 3.59	23.17 ± 6.01	19.33 ± 1.37	20.78 ± 3.63	1.015	0.403	0.109
Gender (M/F)	3/5	2/4	5/1	3/6	--	0.234	--
Years of Education	15.75 ± 2.49	18.50 ± 6.47	16.00 ± 2.76	14.67 ± 1.73	1.428	0.258	0.146
Alertness	3.25 ± 0.46	3.67 ± 0.52	3.83 ± 0.75	3.67 ± 0.71	1.179	0.338	0.124
Motivation	3.75 ± 0.46	3.83 ± 0.41	4.00 ± 0.89	3.78 ± 0.44	0.263	0.851	0.031
Sadness	4.00 ± 0.53	3.67 ± 1.50	4.00 ± 0.89	4.11 ± 0.93	0.256	0.857	0.030
Expectation on CT	3.50 ± 0.76	3.83 ± 0.41	3.50 ± 1.38	3.22 ± 0.83	0.567	0.642	0.064
Expectation on tDCS	3.50 ± 0.76	2.50 ± 1.05	2.83 ± 0.98	3.11 ± 0.78	1.623	0.209	0.163
Positive affect	26.75 ± 7.91	34.83 ± 3.92	28.67 ± 12.61	27.89 ± 3.92	1.487	0.242	1.151
Negative affect	12.75 ± 2.05	11.67 ± 1.75	11.83 ± 2.32	11.89 ± 1.90	0.440	0.727	0.050

Z ($\bar{n}$) in aNback	1.28 ± 1.12	0.58 ± 0.63	0.53 ± 0.58	0.94 ± 0.88	1.173	0.340	0.123
Z (d') in fNback	0.94 ± 0.79	1.15 ± 0.85	1.25 ± 0.42	0.84 ± 0.28	0.675	0.575	0.075
Composite capacity score	1.11 ± 0.44	0.86 ± 0.29	0.89 ± 0.19	0.89 ± 0.38	0.840	0.485	0.092

Appendix 2: Supplementary Materials in Chapter 5

Supplementary Table 4 - Baseline Characteristics by Capacity Subgroups and Age Subgroups in the Elderly Study

	Active	Sham	*t*	*p*
Low-capacity subgroup				
N	6	3	—	—
Age	70.50 ± 3.14	74.00 ± 1.73	-1.758	0.122
Gender (M/F)	1/5	2/1	—[a]	0.226
Years of education	14.17 ± 4.12	18.67 ± 8.08	1.147	0.289
Moca	28.67 ± 1.51	27.00 ± 1.73	1.498	0.178
WMC score	0.62 ± 0.20	0.73 ± 0.36	0.605	0.564
ESS	4.33 ± 2.50	5.67 ± 2.08	-0.789	0.456
FWT	19.67 ± 5.85	18.67 ± 2.08	0.279	0.788
QOL	56.90 ± 6.02	54.44 ± 5.88	0.580	0.580
Anxiety score	4.50 ± 2.07	5.00 ± 2.65	-0.314	0.763
Depression score	2.67 ± 2.94	3.67 ± 3.79	-0.441	0.673
Mid-capacity subgroup				
N	4	5	—	—
Age	66.00 ± 9.38	68.20 ± 4.44	-0.432	0.688
Gender (M/F)	3/1	3/2	—[a]	1.000
Years of education	17.75 ± 5.85	14.60 ± 2.97	-1.058	0.325
Moca	28.75 ± 1.71	28.40 ± 1.14	0.370	0.723
WMC score	-0.01 ± 0.20	-0.10 ± 0.10	0.791	0.471
ESS	4.25 ± 3.50	3.60 ±1.82	0.363	0.728
FWT	21.75 ± 7.14	21.00 ± 4.69	0.191	0.854
QOL	57.03 ± 3.93	69.51 ± 6.46	-0.941	0.378
Anxiety score	5.25 ± 2.36	4.20 ± 2.95	0.577	0.582
Depression score	5.25 ± 3.10	2.00 ± 1.73	2.008	0.085

High-capacity subgroup				
N	4	6	—	—
Age	64.75 ± 5.38	65.67 ± 7.28	-0.214	0.836
Gender (M/F)	3/1	2/4	—[a]	0.524
Years of education	22.75 ± 6.29	14.50 ± 4.23	-2.505	0.037*
Moca	28.75 ± 0.50	29.17 ± 1.17	-0.663	0.526
WMC score	0.68 ± 0.31	0.62 ± 0.32	0.304	0.769
ESS	5.50 ± 2.38	6.17 ± 4.17	-0.287	0.782
FWT	25.00 ± 2.16	20.83 ± 6.62	1.197	0.266
QOL	61.08 ± 4.42	56.45 ± 4.83	1.532	0.164
Anxiety score	1.25 ± 1.50	5.00 ± 2.53	-2.640	0.030*
Depression score	0.75 ± 0.96	3.00 ± 3.29	-1.580	0.164
Young-old subgroup				
N	7	8	—	—
Age	62.85 ± 4.85	64.25 ± 4.59	-0.569	0.579
Gender (M/F)	3/4	2/6	—[a]	0.608
Years of education	18.14 ± 7.69	15.00 ± 2.78	-1.083	0.299
Moca	28.85 ± 1.35	29.00 ± 1.20	-0.218	0.831
WMC score	0.12 ± 0.46	0.28 ± 0.49	-0.641	0.533
ESS	6.00 ± 2.58	4.00 ± 1.51	1.797	0.104
FWT	21.86 ± 5.46	22.25 ± 4.80	-0.147	0.886
QOL	57.41 ± 5.57	56.57 ± 4.17	0.335	0.743
Anxiety score	3.43 ± 2.44	5.50 ± 1.93	-1.837	0.089
Depression score	4.00 ± 3.70	2.38 ± 2.45	1.017	0.328
Advanced-old subgroup				
N	7	6	—	—
Age	72.29 ± 2.63	73.83 ± 2.32	-1.117	0.288
Gender (M/F)	4/3	5/1	—[a]	0.559
Years of education	17.14 ± 4.56	16.00 ± 6.90	-0.358	0.727
Moca	28.57 ± 1.27	27.67 ± 1.50	1.176	0.265
WMC score	-0.27 ± 0.69	-0.20 ± 0.66	-0.188	0.854
ESS	3.28 ± 1.98	6.67 ± 4.18	-1.915	0.082
FWT	21.71 ± 6.16	18.00 ± 4.56	1.216	0.249
QOL	58.85 ± 4.86	58.68 ± 7.69	0.049	0.961
Anxiety score	4.14 ± 2.73	3.67 ± 3.01	0.299	0.771
Depression score	1.71 ± 1.60	3.33 ± 3.33	-1.089	0.313

Note. Moca = Montreal cognitive assessment.

[a]Chi-square test.

*$p < 0.05$.

Supplementary Table 5 - Output of a Three-Way Mixed ANCOVA on the Offline and Transfer Effect of TDCS Considering Age as a Factor in the Elderly Study

	df	*F*	*p*	η_p^2
SNBACK				
Time	(1,23)	86.641	<0.001*	0.790
Time × Age	(1,23)	3.469	0.075	0.131
Time × Stimulation	(1,23)	0.001	0.971	<0.001
Time × Age × Stimulation	(1,23)	4.018	0.057	0.149
Age	(1,23)	1.376	0.253	0.056
Stimulation	(1,23)	1.836	0.189	0.074
Age × Stimulation	(1,23)	10.489	0.004*	0.313
WMC score	(1,23)	36.732	<0.001*	0.615
Time × WMC score	(1,23)	2.027	0.168	0.081
VNBACK				
Time	(1,23)	22.990	0.001*	0.500
Time × Age	(1,23)	0.549	0.466	0.023
Time × Stimulation	(1,23)	0.060	0.808	0.003
Time × Age × Stimulation	(1,23)	5.208	0.032*	0.185
Age	(1,23)	0.585	0.452	0.025
Stimulation	(1,23)	0.164	0.690	0.007
Age × Stimulation	(1,23)	1.642	0.213	0.067
WMC score	(1,23)	16.817	<0.001*	0.422
Time × WMC score	(1,23)	2.106	0.160	0.084
Change detection				
Time	(1,23)	12.274	0.002*	0.348
Time × Age	(1,23)	0.393	0.537	0.017
Time × Stimulation	(1,23)	1.025	0.322	0.043
Time × Age × Stimulation	(1,23)	0.174	0.681	0.007
Age	(1,23)	<0.001	1.000	<0.001
Stimulation	(1,23)	0.905	0.351	0.038
Age × Stimulation	(1,23)	0.262	0.614	0.011
WMC score	(1,23)	5.843	0.024*	0.203
Time × WMC score	(1,23)	0.194	0.663	0.008
DSF				
Time	(1,23)	0.847	0.367	0.036
Time × Age	(1,23)	0.095	0.760	0.004
Time × Stimulation	(1,23)	0.045	0.834	0.002
Time × Age × Stimulation	(1,23)	0.263	0.613	0.011
Age	(1,23)	0.001	0.982	<0.001
Stimulation	(1,23)	0.892	0.355	0.037

Age × Stimulation	(1,23)	1.358	0.256	0.056
WMC score	(1,23)	2.757	0.110	0.107
Time × WMC score	(1,23)	0.373	0.547	0.016
DSB				
Time	(1,23)	2.252	0.147	0.089
Time × Age	(1,23)	0.018	0.895	0.001
Time × Stimulation	(1,23)	0.728	0.402	0.031
Time × Age × Stimulation	(1,23)	0.600	0.446	0.025
Age	(1,23)	0.197	0.661	0.008
Stimulation	(1,23)	0.755	0.394	0.032
Age × Stimulation	(1,23)	0.230	0.636	0.010
WMC score	(1,23)	20.192	<0.001*	0.467
Time × WMC score	(1,23)	1.015	0.324	0.042

*$p < 0.05$.

Supplementary Table 6 - Output of a Three-Way Mixed ANOVA on the Offline and Transfer Effect of TDCS Considering Working Memory as a Factor in the Elderly Study

	df	*F*	*p*	η_p^2
SNBACK				
Time	(1,22)	86.962	<0.001*	0.798
Time × Capacity	(2,22)	0.358	0.703	0.031
Time × Stimulation	(1,22)	0.032	0.860	0.001
Time × Capacity × Stimulation	(2,22)	7.116	0.004*	0.393
Capacity	(2,22)	37.441	<0.001*	0.773
Stimulation	(1,22)	4.960	0.036*	0.184
Capacity × Stimulation	(2,22)	9.119	0.001*	0.453
VNBACK				
Time	(1,22)	16.387	0.001*	0.427
Time × Capacity	(2,22)	0.541	0.590	0.047
Time × Stimulation	(1,22)	0.020	0.889	0.001
Time × Capacity × Stimulation	(2,22)	2.194	0.135	0.166
Capacity	(2,22)	13.671	<0.001*	0.554
Stimulation	(1,22)	0.004	0.951	<0.001
Capacity × Stimulation	(2,22)	0.131	0.878	0.012
Change detection				
Time	(1,22)	11.207	0.003*	0.337
Time × Capacity	(2,22)	0.242	0.787	0.022
Time × Stimulation	(1,22)	0.713	0.407	0.031

Time × Capacity × Stimulation	(2,22)	0.195	0.825	0.017
Capacity	(2,22)	4.755	0.019*	0.302
Stimulation	(1,22)	1.566	0.224	0.066
Capacity × Stimulation	(2,22)	0.773	0.474	0.066
DSF				
Time	(1,22)	0.578	0.455	0.026
Time × Capacity	(2,22)	0.625	0.544	0.054
Time × Stimulation	(1,22)	0.019	0.892	0.001
Time × Capacity × Stimulation	(2,22)	1.275	0.299	0.104
Capacity	(2,22)	0.863	0.436	0.073
Stimulation	(1,22)	0.874	0.360	0.038
Capacity × Stimulation	(2,22)	1.095	0.352	0.090
DSB				
Time	(1,22)	2.426	0.134	0.099
Time × Capacity	(2,22)	0.453	0.641	0.040
Time × Stimulation	(1,22)	0.775	0.388	0.034
Time × Capacity × Stimulation	(2,22)	0.560	0.579	0.048
Capacity	(2,22)	4.947	0.017*	0.310
Stimulation	(1,22)	0.209	0.652	0.009
Capacity × Stimulation	(2,22)	1.072	0.360	0.089

*$p < 0.05$.

Supplementary Table 7 - Output of a Three-way Mixed ANOVA on the Mood and Attitudes Considering Age as a Factor in the Elderly Study

	df	*F*	*p*	η_p^2
Alertness				
Time	4,96	0.299	0.878	0.012
Time × Age	4,96	0.745	0.563	0.030
Time × Stimulation	4,96	0.458	0.767	0.019
Time × Age × Stimulation	4,96	2.018	0.098	0.078
Age	1,24	0.290	0.595	0.012
Stimulation	1,24	0.029	0.866	0.001
Age × Stimulation	1,24	0.022	0.884	0.001
Motivation				
Time	3,73	0.308	0.822	0.013
Time × Age	3,73	0.647	0.589	0.026
Time × Stimulation	3,73	0.343	0.797	0.014
Time × Age × Stimulation	3,73	0.254	0.860	0.010
Age	1,24	0.075	0.787	0.003

Stimulation	1,24	0.477	0.496	0.020
Age × Stimulation	1,24	0.219	0.644	0.009
Sadness				
Time	2,54	0.682	0.527	0.028
Time × Age	2,54	1.641	0.201	0.064
Time × Stimulation	2,54	0.331	0.744	0.014
Time × Age × Stimulation	2,54	0.066	0.951	0.003
Age	1,24	0.961	0.337	0.038
Stimulation	1,24	0.616	0.440	0.025
Age × Stimulation	1,24	1.148	0.295	0.046
Expectation				
Time	2,54	0.137	0.895	0.006
Time × Age	2,54	0.381	0.711	0.016
Time × Stimulation	2,54	0.416	0.687	0.017
Time × Age × Stimulation	2,54	1.368	0.264	0.054
Age	1,24	0.145	0.707	0.006
Stimulation	1,24	0.718	0.405	0.029
Age × Stimulation	1,24	1.921	0.178	0.074

Note. $^{*}p < 0.05$.

Supplementary Table 8 - Output of a Three-Way Mixed ANOVA on the Mood and Attitudes Considering Working Memory Capacity as a Factor in the Elderly Study

	df	*F*	*p*	η_p^2
Alertness				
Time	4,88	0.230	0.921	0.010
Time × Capacity	8.88	0.747	0.650	0.064
Time × Stimulation	4,88	0.408	0.802	0.018
Time × Capacity × Stimulation	8.88	1.062	0.397	0.088
Capacity	2,22	1.111	0.347	0.092
Stimulation	1,22	0.021	0.887	0.001
Capacity × Stimulation	2,22	0.364	0.699	0.032
Motivation				
Time	3,66	0.690	0.561	0.030
Time × Capacity	6,66	1.582	0.166	0.126
Time × Stimulation	3,66	0.339	0.797	0.015
Time × Capacity × Stimulation	6,66	1.474	0.201	0.118
Capacity	2,22	0.037	0.964	0.003
Stimulation	1,22	0.441	0.514	0.020
Capacity × Stimulation	2,22	2.669	0.092	0.195

Sadness				
Time	2,44	0.477	0.625	0.021
Time × Capacity	4,44	0.581	0.679	0.050
Time × Stimulation	2,44	0.426	0.657	0.019
Time × Capacity × Stimulation	4,44	0.698	0.598	0.060
Capacity	2,22	0.660	0.527	0.057
Stimulation	1,22	0.357	0.556	0.016
Capacity × Stimulation	2,22	1.903	0.173	0.147
Expectation				
Time	2,48	0.142	0.885	0.006
Time × Capacity	4,48	0.320	0.878	0.028
Time × Stimulation	2,48	0.379	0.705	0.017
Time × Capacity × Stimulation	4,48	0.442	0.794	0.039
Capacity	2,22	0.092	0.913	0.008
Stimulation	1,22	0.634	0.435	0.028
Capacity × Stimulation	2,22	3.263	0.057	0.229

Appendix 3: Supplementary Materials in Chapter 6

Supplementary Table 9 - Demographic and Baseline Characteristics of the Adaptive Group, Divided by Stimulation and Lesion Groups in the Stroke Study

Adaptive	Active+Left	Sham+Left	Active+Right	Sham+Right	*p*	η_p^2
N	7	6	8	9	—	—
Age (years)	65.29 ± 8.52	64.50 ± 7.87	65.88 ± 3.76	68.56 ± 5.64	0.632	0.063
Gender (M/F)	4/3	3/3	2/6	6/3	0.425[a]	—
Years of education	11.29 ± 1.80	10.67 ± 3.20	10.43 ± 1.51	11.75 ± 2.12	0.663	0.063
Moca	20.86 ± 5.90	15.17 ± 4.49	20.25 ± 3.73	21.44 ± 4.98	0.098	0.212
Days from onset	6.71 ± 1.80	7.17 ± 3.82	5.13 ± 1.55	5.44 ± 1.13	0.238	0.147
NIHSS	1.00 ± 0.82	3.33 ± 2.25	1.88 ± 0.83	2.11 ± 1.50	0.130	0.192
Lesion(Hemisphere/ Brainstem and cerebellum)	6/1	3/3	5/3	7/2	0.528[a]	—
Spatial N-Back	0.71 ± 0.11	0.53 ± 0.15	0.66 ± 0.20	0.60 ± 0.12	0.069	0.235
LDSF	6.14 ± 1.46	5.33 ± 0.82	6.13 ± 1.13	7.00 ± 1.50	0.128	0.193
LDSB	3.57 ± 1.13	3.00 ± 0.89	3.38 ± 1.19	4.11 ± 0.78	0.213	0.156
Symbol Span	11.14 ± 3.39	8.83 ± 4.36	12.38 ± 5.55	13.89 ± 5.28	0.264	0.140
Spatial Addition	6.57 ± 2.29	6.50 ± 2.66	6.00 ± 2.93	6.89 ± 2.80	0.926	0.018

[a] Fisher exact test.

[*] $p < .05$.

Supplementary Table 10 - Demographic and Baseline Characteristics of the Right Lesion Subgroup, Divided by Stimulation and Lesion Groups in the Stroke Study

Non-adaptive subgroup	Active+Left	Sham+Left	Active+Right	Sham+Right	*p*	η_p^2
N	12	7	4	8	—	—
Age (years)	64.42 ± 6.10	65.86 ± 7.84	65.00 ± 2.16	66.38 ± 9.18	0.937	0.015
Gender (M/F)	10/2	3/4	1/3	4/4	0.010[*a]	—
Years of education	10.50 ± 4.17	9.71 ±3.10	12.33 ± 3.51	7.88 ± 3.14	0.268	0.138
Moca	20.54 ± 3.24	19.57 ± 5.53	18.75 ± 3.40	19.00 ± 3.96	0.818	0.034
Days from onset	5.58 ± 3.10	3.29 ± 0.49	6.00 ± 1.83	6.13 ± 2.23	0.109	0.197
NIHSS	1.42 ± 1.16	4.29 ± 3.82	1.75 ± 1.50	1.37 ± 1.30	0.037[*]	0.266
Lesion(Hemisphere/ Brainstem and cerebellum)	12/0	7/0	3/1	8/0	0.128[a]	—
Spatial N-Back	0.65 ± 0.13	0.71 ± 0.22	0.44 ± 0.06	0.56 ± 0.19	0.141	0.186
LDSF	6.58 ± 1.31	7.14 ± 1.35	5.75 ± 1.26	6.25 ± 1.04	0.320	0.120
LDSB	3.42 ± 1.16	3.57 ± 2.07	3.50 ± 1.29	3.13 ± 0.99	0.932	0.016
Symbol Span	12.83 ± 2.89	10.86 ± 3.53	11.75 ± 5.50	9.00 ± 2.83	0.125	0.188
Spatial Addition	6.83 ± 0.94	6.28 ± 2.08	6.25 ± 2.75	6.00 ± 1.77	0.819	0.033

[a] Fisher exact test.

[*] $p < .05$.

Supplementary Table 11 - Output of a Three-Way Mixed ANOVA on the Offline and Transfer Effect of TDCS in Adaptive Groups in the Stroke Study

	df	*F*	*p*	η_p^2
SNBACK				
Time	(26,1)	18.668	< 0.001[*]	0.418
Time × Lesion	(26,1)	0.064	0.803	0.002
Time × Stimulation	(26,1)	0.078	0.782	0.003

Time × Lesion × Stimulation	(26,1)	1.519	0.229	0.055
Lesion	(26,1)	< 0.001	0.989	< 0.001
Stimulation	(26,1)	4.845	0.037*	0.157
Lesion × Stimulation	(26,1)	2.822	0.105	0.098
Spatial addition				
Time	(26,1)	2.423	0.132	0.085
Time × Lesion	(26,1)	0.643	0.430	0.024
Time × Stimulation	(26,1)	0.208	0.652	0.008
Time × Lesion × Stimulation	(26,1)	1.450	0.239	0.053
Lesion	(26,1)	0.221	0.642	0.008
Stimulation	(26,1)	0.440	0.513	0.017
Lesion × Stimulation	(26,1)	1.181	0.287	0.043
Visual symbol				
Time	(26,1)	0.561	0.461	0.021
Time × Lesion	(26,1)	0.002	0.961	< 0.001
Time × Stimulation	(26,1)	0.012	0.912	< 0.001
Time × Lesion × Stimulation	(26,1)	0.002	0.961	< 0.001
Lesion	(26,1)	3.127	0.089	0.107
Stimulation	(26,1)	0.024	0.879	0.001
Lesion × Stimulation	(26,1)	1.274	0.269	0.047
DSF				
Time	(26,1)	0.038	0.848	0.001
Time × Lesion	(26,1)	3.540	0.071	0.120
Time × Stimulation	(26,1)	1.491	0.233	0.054
Time × Lesion× Stimulation	(26,1)	3.194	0.086	0.109
Lesion	(26,1)	1.474	0.236	0.054
Stimulation	(26,1)	0.265	0.611	0.010
Lesion × Stimulation	(26,1)	1.707	0.203	0.062
DSB				
Time	(26,1)	0.043	0.838	0.002
Time × Lesion	(26,1)	0.261	0.614	0.010
Time × Stimulation	(26,1)	0.935	0.343	0.035
Time × Lesion× Stimulation	(26,1)	0.439	0.513	0.017
Lesion	(26,1)	1.190	0.285	0.044
Stimulation	(26,1)	0.080	0.780	0.003
Lesion × Stimulation	(26,1)	5.389	0.028*	0.172

*$p < 0.05$.

Supplementary Table 12 - Output of a Three-Way Mixed ANOVA on the Offline and Transfer Effect of TDCS in Non-Adaptive Groups in the Stroke Study

	df	*F*	*p*	η_p^2
SNBACK				
Time	(26,1)	55.732	< 0.001*	0.682
Time × Lesion	(26,1)	3.044	0.093	0.105
Time × Stimulation	(26,1)	0.098	0.757	0.004
Time × Lesion × Stimulation	(26,1)	0.081	0.778	0.003
Lesion	(26,1)	6.554	0.017*	0.201
Stimulation	(26,1)	3.289	0.081	0.112
Lesion × Stimulation	(26,1)	0.162	0.691	0.006
Spatial addition				
Time	(27,1)	1.895	0.180	0.066
Time × Lesion	(27,1)	1.342	0.257	0.047
Time × Stimulation	(27,1)	0.045	0.833	0.002
Time × Lesion × Stimulation	(27,1)	3.065	0.091	0.102
Lesion	(27,1)	1.377	0.251	0.049
Stimulation	(27,1)	0.087	0.770	0.003
Lesion × Stimulation	(27,1)	1.515	0.229	0.053
Visual symbol				
Time	(27,1)	3.610	0.068	0.118
Time × Lesion	(27,1)	0.959	0.336	0.034
Time × Stimulation	(27,1)	0.099	0.756	0.004
Time × Lesion × Stimulation	(27,1)	0.099	0.756	0.004
Lesion	(27,1)	2.317	0.140	0.079
Stimulation	(27,1)	2.000	0.169	0.069
Lesion × Stimulation	(27,1)	0.186	0.670	0.007
DSF				
Time	(27,1)	1.314	0.262	0.046
Time × Lesion	(27,1)	0.187	0.669	0.007
Time × Stimulation	(27,1)	2.204	0.149	0.075
Time × Lesion× Stimulation	(27,1)	2.797	0.106	0.094
Lesion	(27,1)	3.236	0.083	0.107
Stimulation	(27,1)	0.445	0.510	0.016
Lesion × Stimulation	(27,1)	0.445	0.510	0.016
DSB				
Time	(27,1)	0.066	0.799	0.002
Time × Lesion	(27,1)	1.942	0.175	0.067
Time × Stimulation	(27,1)	0.005	0.947	< 0.001
Time × Lesion× Stimulation	(27,1)	1.142	0.295	0.041

Lesion	(27,1)	1.270	0.270	0.045
Stimulation	(27,1)	0.048	0.828	0.002
Lesion × Stimulation	(27,1)	0.005	0.946	< 0.001

*$p < 0.05$.

Supplementary Table 13 - Output of a Three-Way Mixed ANOVA on the Mood and Attitudes in Adaptive Groups in the Stroke Study

	df	*F*	*p*	η_p^2
Alertness				
Time	(3,69)	5.318	0.003*	0.175
Time × Lesion	(3,69)	0.685	0.554	0.027
Time × Stimulation	(3,69)	0.415	0.728	0.016
Time × Lesion × Stimulation	(3,69)	1.728	0.173	0.065
Lesion	(1,25)	1.732	0.200	0.065
Stimulation	(1,25)	0.015	0.904	0.001
Lesion × Stimulation	(1,25)	0.006	0.938	<0.001
Motivation				
Time	(3,69)	4.889	0.005*	0.164
Time × Lesion	(3,69)	0.087	0.960	0.003
Time × Stimulation	(3,69)	0.413	0.729	0.016
Time × Lesion × Stimulation	(3,69)	1.866	0.147	0.069
Lesion	(1,25)	0.041	0.841	0.002
Stimulation	(1,25)	0.185	0.671	0.007
Lesion × Stimulation	(1,25)	0.523	0.476	0.021
Expectation				
Time	(3,69)	4.475	0.007*	0.152
Time × Lesion	(3,69)	0.170	0.905	0.007
Time × Stimulation	(3,69)	0.542	0.643	0.021
Time × Lesion × Stimulation	(3,69)	2.639	0.060	0.095
Lesion	(1,25)	0.081	0.778	0.003
Stimulation	(1,25)	0.275	0.605	0.011
Lesion × Stimulation	(1,25)	1.296	0.266	0.049
Sadness				
Time	(3,75)	3.441	0.021*	0.121
Time × Lesion	(3,75)	0.439	0.729	0.017
Time × Stimulation	(3,75)	0.365	0.780	0.014
Time × Lesion × Stimulation	(3,75)	0.676	0.570	0.026
Lesion	(1,25)	1.103	0.304	0.042
Stimulation	(1,25)	0.061	0.807	0.002
Lesion × Stimulation	(1,25)	0.224	0.640	0.009

HAMA				
Time	(1,25)	0.609	0.442	0.024
Time × Lesion	(1,25)	0.072	0.791	0.003
Time × Stimulation	(1,25)	2.948	0.098	0.105
Time × Lesion × Stimulation	(1,25)	0.282	0.600	0.011
Lesion	(1,25)	0.304	0.586	0.012
Stimulation	(1,25)	0.187	0.669	0.007
Lesion × Stimulation	(1,25)	0.410	0.528	0.016
HAMD				
Time	(1,25)	0.325	0.574	0.013
Time × Lesion	(1,25)	0.087	0.771	0.003
Time × Stimulation	(1,25)	1.107	0.303	0.042
Time × Lesion × Stimulation	(1,25)	0.106	0.748	0.004
Lesion	(1,25)	1.875	0.183	0.070
Stimulation	(1,25)	0.407	0.529	0.016
Lesion × Stimulation	(1,25)	1.608	0.216	0.060
HAD				
Time	(1,23)	0.100	0.755	0.004
Time × Lesion	(1,23)	0.417	0.525	0.018
Time × Stimulation	(1,23)	1.497	0.234	0.061
Time × Lesion × Stimulation	(1,23)	0.798	0.381	0.034
Lesion	(1,23)	0.224	0.640	0.010
Stimulation	(1,23)	0.968	0.335	0.040
Lesion × Stimulation	(1,23)	1.116	0.302	0.046

$^{*}p < 0.05$.